Review
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The global survival rate of patients with beta-thalassemia major: A systematic review and meta-analysis

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Abstract

Objective Thalassemia is a public health challenge in the countries entitled belt thalassemia, but there is no pooled estimate of the survival rate on thalassemia major patients. The aim of this meta-analysis was to evaluate the pooled 10-, 15-, 20-, and 30-year survival rates of the patients with beta-thalassemia major around the world.

Methods A comprehensive literature search of five international databases including Medline/PubMed, Scopus, Embase, Web of knowledge, and ProQuest was conducted to identify studies reporting survival rate of beta-thalassemia major until March 2020.

Results From 714 retrieved studies, 7 studies with 8777 subjects were included in the meta-analysis. Base on random effect model, the 10-, 15-, 20-, and 30-year survival rates were 98.39, 95.07, 90.41, and 82.93 percent, respectively.

Conclusions This meta-analysis provided acceptable results for estimating survival rate of beta-thalassemia compared to other studies. Hence, these results can be effectively used to develop and implement prevention and treatment interventions for policymakers.

Keywords Survival rate; Beta-thalassemia major, Systematic review, Meta-analysis

Introduction

Two main forms of beta-thalassemia have been differentiated by their clinical severity, first severe anemia that occur in the initial year of life as thalassemia major (TM) and the second mild anemia as thalassemia intermedia.[1-3] The TM consequences occurred in diverse range in developing countries, from lack of public access to blood screening tests to timely iron removal from patients.[4,5] The two main causes of death in patients with TM were excess serum ferritin and iron overload followed by complications that occur including liver and endocrine disorders, cardiac disease, anemia, infection, and eventually death.[6-8]

The survival rate of TM in the last few decades has progressively increased in order that only 2% of TM died before 10 years after diagnosis.[9] Some factors affect on this increasing picture of TM survival including improving of surveillance in some parts of the world, improved treatment of cardiac complications, better accessibility to blood donor, blood screening for pathogens, treatment of infections, and treatment with deferoxamine.[10, 11]

In the Modell et al. study, decreasing of cardiac disease in TM was reported as the main factor in increasing of survival.[12] Lower survival rate in some reigns in the world associated with availability of deferoxamine treatment and also related to burdensome iron chelation regimen refusal by TM patients.[13] Studies about survival in TM patients reported different rates in which these differences may be due to several factors, but some factors such as clinical phenotype of patients in different reign possibly are important.[14]

To assess the current survival rate in patients with TM worldwide, to appraise the long-term survival (10-, 15-, 20-, and 30-year), and to obtain the important limitations toward long-term survival in thalassemia patients, this systematic review and meta-analysis was conducted.

Materials and methods

This is a systematic review and meta-analysis of patients with beta-thalassemia major. This study was designed in 2020. The methodology of the present study is based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement.[15]

Search strategy

The researchers searched five international databases including Web of knowledge, PubMed, Embase, Scopus, and ProQuest until March 2020. We also searched the Google Scholar for detecting gray literature. Selected keywords for international databases included: "beta-Thalassemia", survival rate", "survival analysis" and "Kaplan–Meier estimate"

The initial search was conducted by two researchers (ShR and SH). The searched record entered the EndNote X7 software, and duplicate articles were removed automatically.

Inclusion and exclusion criteria

All observational studies (cross-sectional, case–control, and cohort) stated the survival rate of patients with beta-thalassemia major, published in English language without time period restriction were included in the study. It should be noted that studies that did not report the confidence interval or sample size were not included into the final analysis.

Quality assessment

The Newcastle-Ottawa Quality Assessment checklist was used to evaluate the quality of selected papers. This tool has three different parts including Selection (4 questions), Comparability (1 question) and Outcome (3 questions), and based on the final scores divided into three categories: good, fair, and poor.[16-19]

Screening of studies

Screening of studies, extraction of results, and evaluation of quality control of articles were performed separately by two authors (ShR and SH). If there was no agreement between the two, the supervisor would announce the decision on that article.

Data extraction form

All final articles entered into the study process were provided by a checklist and were arranged to extract the data. This checklist includes the name of the author, the year of publication, the period of the study, the country of origin, the survival rate by year for each survival period.

Statistical analysis

The heterogeneity of the studies was assessed by Cochran test (with significance less than 0.1). Also, I^2 statistics was used for heterogeneity assessment. In the case of heterogeneity, the random effects model was utilized. All analyses were performed by the STATA (version 13) software.

Results

Study selection

After searching all the international databases, 524 articles were selected and after deleting duplicate articles, 431 studies entered the review phase in terms of title and abstract. After reviewing the abstract of articles, 15 articles entered the next stage, at which point the full text was examined and 7 studies entered the final analysis. It should be noted that the referenced articles were also reviewed to add related articles. In the screening stages of studies, some articles were removed for a variety of reasons, which included the unrelated topic (N=406), the unrelated population (N=10), inadequate information (N=6), and the repeated results (N=2). The study selection process is outlined in Fig. 1.

Result of quality assessment

Based on our results, six studies have good and one study had a fair quality. The result of quality assessment presented in Table 1.

Study characteristics

The included studies were published from 1994 to 2018. Base on geographical location, five studies conducted in Iran[9, 20-23], one in Italy,[24] and one in Cyprus.[25] Characteristics of the included studies presented in Table 2.

Heterogeneity

The result of chi-squared test and the I^2 index indicated that there was a considerable difference between-study heterogeneity. For 10- (I^2= 88.1 %, P<0.001), 15- (I^2= 94.1%, P<0.001), 20- (I^2= 93.8%, P<0.001), and 30-year survival rate (I^2= 98.2%, P<0.001).

Results of the meta-analysis

First, the articles were sorted according to the year of publication and then analyzed by 1-, 10-, 15-, 20-, and 30-year

Table 1. **Quality assessment of included studies.**

Author (year)	Selection	Comparability	Outcome	Total	Quality
Telfer, 2006	2	1	2	5	Fair
Kosaryan, 2007	2	2	2	6	Good
Di Bartolomeo, 2008	3	1	2	6	Good
Roudbari, 2008	3	2	2	7	Good
Rajaeefard, 2015	3	1	2	6	Good
Zamani, 2015	2	2	2	6	Good
Ansari-Moghadam, 2018	3	2	2	7	Good

Table 2. **Basic information of included studies.**

Author (year)	Location	Time period	Sample size	Survival rate			
				10	15	20	30
Telfer, 2006	Cyprus	1980-2004	539	100	98.5	-	92.7
Kosaryan, 2007	Iran	1984-2006	1010	98	-	88	70
Di Bartolomeo, 2008	Italy	1983-2006	115	-	-	89.2	-
Roudbari, 2008	Iran	1998-2006	578	97	92.1	-	-
Rajaeefard, 2015	Iran	-	911	97	92	-	-
Zamani, 2015	Iran	1997-2013	133	98.3		88.4	80.5
Ansari-Moghadam, 2018	Iran	1971-2015	5491	99	97	95	88

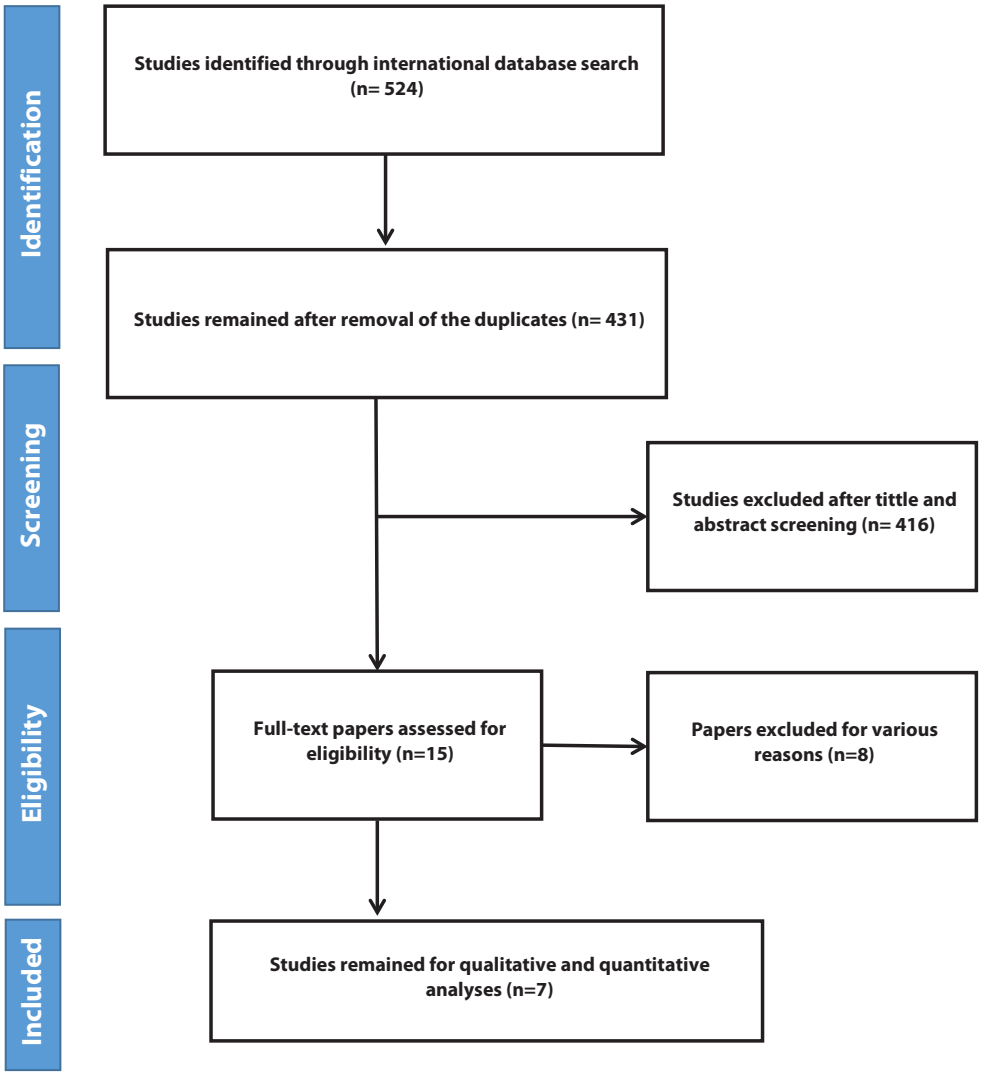

Fig. 1 **Flowchart of the included eligible studies in systematic review.**

survival. It should be noted that the number of papers of 5, 25, and other survival rate was very low.

10-year survival rate

Based on the random-effect model, the results of the study demonstrated that 10-year survival rate of BTMP was 98.39% (95 % CI; 97.51–99.26, I^2=88.1%, P<0.001). The highest survival was reported from Cyprus (100%, 95% CI; 99.12–100) by Telfer et.al. 10-year survival rate of BTMP has been shown in Fig. 2.

15-year survival rate

The results of the study show that 15-year survival rate was 95.07% (95 % CI; 92.50–97.64, I^2=94.1%, P<0.001). The highest survival was reported from Cyprus (98.5%, 95% CI, 96.74–99.18) by Telfer et.al. 15-year survival rate of BTMP has been shown in Fig. 3.

20-year survival rate

Based on the random-effect model, the 20-year survival rate was 90.41% (95 % CI; 85.43–95.40, I^2=93.8%, P<0.001). The highest survival was reported from Iran (95%, 95% CI, 94.37–95.54) by Ansari-Moghadam et.al. 20-year survival rate of BTMP has been shown in Fig. 4.

30-year survival rate

The results of the study show that 30-year survival rate was 82.93% (95 % CI; 74.21–91.66, I^2=98.2%, P<0.001). The highest survival was reported from Cyprus (92.7%, 95% CI, 90.15–94.74) by Telfer et.al. 30-year survival rate of BTMP has been shown in Fig. 5.

Publication bias

Given that the number of articles entered in each of analyses was less than 10, investigating the publication bias was not rational.[26]

Discussion

The present meta-analysis was carried out to determine the survival rate of patients with beta-thalassemia major until 10, 15, 20, and 30 years of age. The 10-, 15-, 20-, and 30-year survival rates were 98.39, 95.07, 90.41, and 82.93 percent, respectively. The findings of this study show that about 82% of the patients with beta-thalassemia major survived until the age of 30 years. In recent decades, several factors have been shown to improve survival rate of beta-thalassemia patients including implementation of thalassemia prevention program, increased

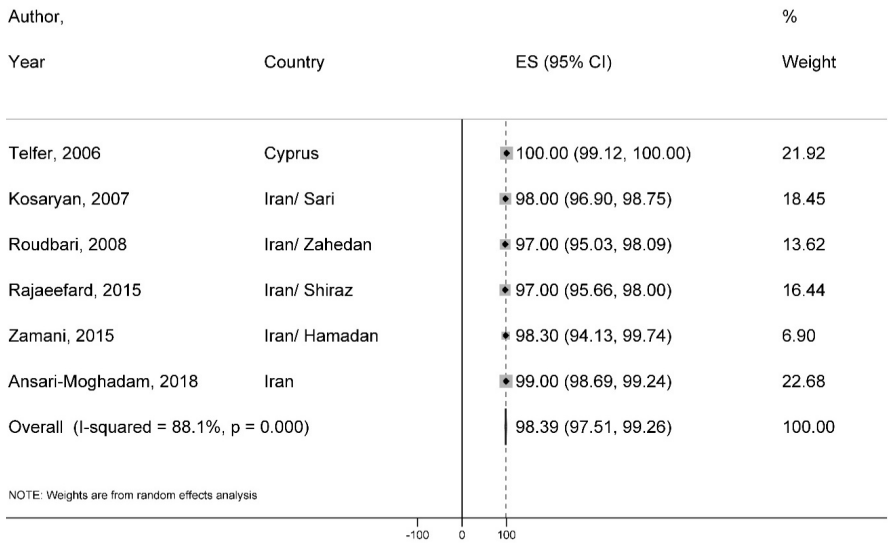

Fig. 2 **Forest plot of 10- year survival rate.**

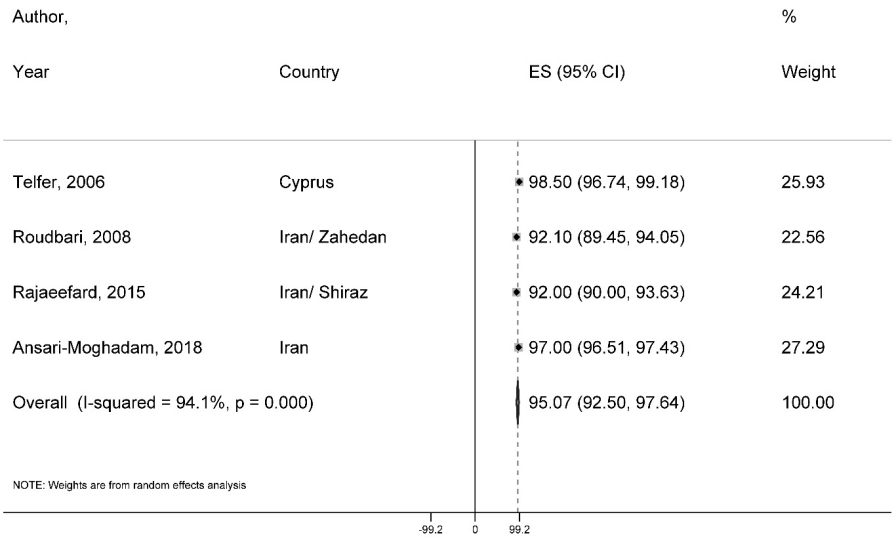

Fig. 3 **Forest plot of 15- year survival rate.**

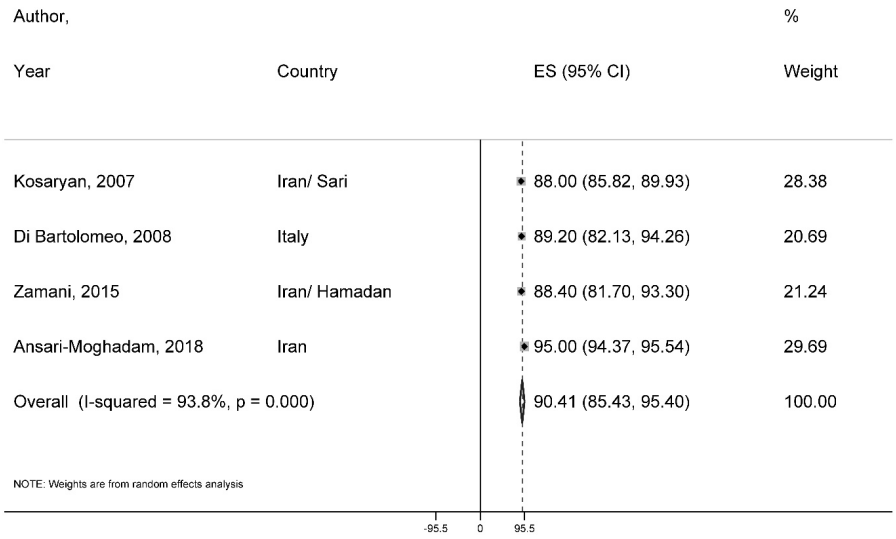

Fig. 4 **Forest plot of 20-year survival rate.**

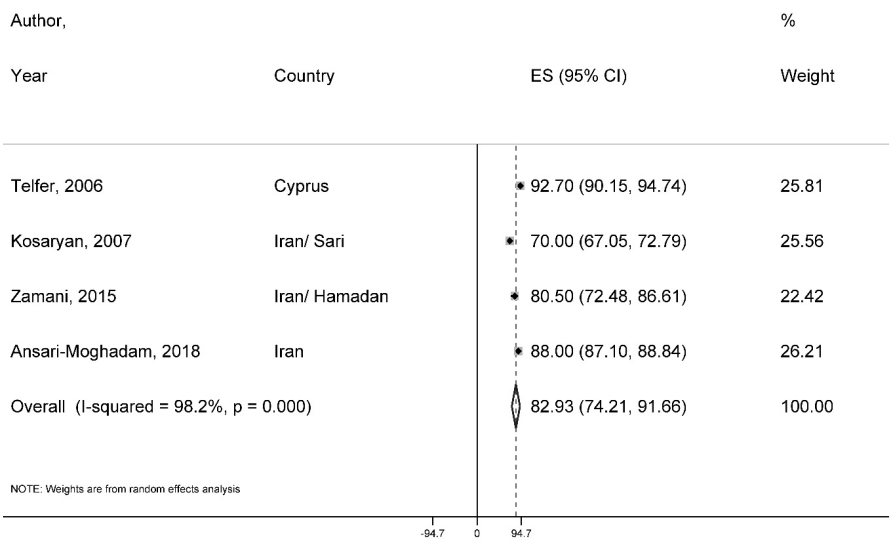

Fig. 5 **Forest plot of 30-year survival rate.**

quality of healthcare services, provision of appropriate treatment, and essential services for these patients, such as blood transfusions, administration of appropriate drugs, and screening of donated blood before blood transfusion.[22, 27-30]

Telfer and colleagues investigated factors associated with long-term survival of TM, and showed an unexpected increasing trend of survival rate since 2000 compared to before 1999. They also stated that excessive exposure of patients to toxins produced in iron chelation therapy, and subsequently increased rates of cardiac complications, the survival rate of thalassemia patients was significantly lower until 2000.[27] The findings of previous studies showed that delayed documentation of TM cases in registration system and delayed diagnosis in these patients are associated with low survival rate for beta-thalassemia major over the past years.[31-33]

The results of this study show that the highest 10- and 15-year survival rates for beta-thalassemia major were reported in Cyprus, and the highest 20-year survival rate was reported in Iran. Efthimiadis and colleagues reported the 15-year survival rate for beta-thalassemia major patients as 58%, and 88% for all.[34] Bartolomeo and colleagues also revealed that the 20-year survival rates for beta-thalassemia major patients and for all as 89.2%, and 85.7%, respectively.[35] Rajaeefard and colleagues reported the 20-, 40-, and 60-year survival rates of beta-thalassemia major patients as 85%, 63%, and 54%, respectively.[22] Wu et al.[36] also reported the survival rate of TM patients as higher than 97% due to improvements in treatment and growth of chelation therapy between 2007 and 2011. Although, excess iron due to long-term blood transfusion among these patients is the main cause of various complications, especially cardiac complications (as one of the main causes of death in beta-thalassemia major patients), nowadays optimal iron chelation therapy and administration of Deferiprone as a chelator in the treatment of iron overload in thalassemia patients, considerably increased survival rate among these individuals.[37-39]

Limitations

This meta-analysis had some limitations. The high proportion of retrieved studies were conducted in Iran due to high prevalence of beta-thalassemia major in this country. In the two studies, the combined survival rate has been reported for both major and intermedia thalassemia patients, and then these studies were excluded in the analysis. The meta regression was not done because of small sample of retrieved studies. In addition, due to various reports of survival rates in the retrieved studies, we failed to obtain an overall survival rate from all collected survival reports.

Conclusion

In conclusion, this meta-analysis provided acceptable results for estimating survival rate of beta-thalassemia compared to other studies. Hence, these results can be effectively used to develop and implement prevention and treatment interventions.

Conflicts of Interest Disclosure

All authors declare no conflicts of interest.

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