Review Article

Prevalence of Depression among Iranian Patients with Beta-Thalassemia Major: A Systematic Review and Meta-analysis

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Abstract

Background: Patients with beta-thalassemia (BT) are susceptible to psychological disorders such as depression. The present study was conducted to estimate the pooled prevalence of depression among patients with BT in Iran.

Methods: Domestic and international databases were searched for relevant articles published from 1991 until June 2019. We searched international databases such as Scopus, ISI, and Embase; Iranian databases such as SID, Magiran, and IranDoc; and Google Scholar and PubMed search engines. The MeSH keywords used were "depression", "mental health", "depressive disorder", "thalassemia", "beta-thalassemia major", "prevalence", "epidemiology", and "Iran". Relevant cross-sectional or cohort studies were included in the analysis. Cochran's Q test and the I^2 index were used to assess heterogeneity. The pooled prevalence and its 95% confidence interval (CI) were calculated using "metaprop" commands in Stata 14. In cases, where the I^2 statistic was greater than 50%, the random-effects model was used.

Results: Eighteen eligible studies were included. The pooled prevalence of depression was 42% (95% CI: 33% to 52%), whereas the pooled prevalence of mild, moderate, severe, and extremely severe depression was 16% (95% CI: 11% to 22%), 13% (95% CI: 9% to 18%), 13% (95% CI: 9% to 17%), and 3% (95% CI: 0% to 8%), respectively. The pooled prevalence of depression in moderate- and high-quality studies was 45% (95% CI: 29% to 61%), and 39% (95% CI: 27% to 51%), respectively.

Conclusion: The high prevalence of depression highlights the urgent need for the establishment of interventions for the prevention, early detection, and treatment of depression among Iranian patients with BT.

What's Known

• The psychological health of patients with beta-thalassemia major is of great importance, as it has been linked to their treatment compliance and long-term survival.
• Depression is the most common psychiatric disorder among patients with beta-thalassemia major and may lead to mental disorders.

What's New

• Nearly half of Iranian patients with beta-thalassemia major suffer from depression.
• Mild depression is more common (16%) in patients with beta-thalassemia major.

Introduction

Thalassemia is the most common form of inherited anemia worldwide.[1] Beta-thalassemia (BT) major is a thalassemia type characterized by anomalies in the synthesis of the beta chains of hemoglobin, which results in various phenotypes ranging from clinically asymptomatic to severe anemia.[2] The World Health Organization (WHO) in 2019 reported that around 50,000 infants were born with BT every year.[3] Iran, with a thalassemia gene

prevalence rate of 4%, is among the countries located on the thalassemia belt. It is estimated that there are between two to three million BT carriers and 25,000 patients in Iran.[4]

Patients with BT suffer from various physical and psychiatric problems. Although various aspects of physical health have been considered in these patients, little attention has been paid to their psychological status.[5] The psychological health of patients with BT is of great importance, as it has been linked to their treatment compliance and long-term survival. Depression is the most common psychiatric disorder among these patients[6] and could occur due to the chronic nature of the disease, prolonged treatment periods, expectations of premature death, changes in appearance, and feelings of deprivation.[7] Depression may cause sadness, loss of interest or pleasure, feelings of guilt or low self-esteem, sleep or appetite disorders, feelings of tiredness, and poor concentration in affected patients.[8] The prevalence of depression among patients with BT varies from 10% to 35% in different regions of the world.[1, 9-13] In Iran, there is a huge variation in the prevalence of depression in this population. It is reported that 12% to 100% of Iranian patients with BT experience depression.[14-16] Previous studies in some regions of Iran have shown that patients with BT have a low quality of life, and a high percentage of them suffer from moderate-to-severe depression, anxiety, and stress.[17, 18] As BT is a relatively rare disease, most studies conducted on this population have small sample sizes, which in turn decrease the precision of estimates. Accordingly, the main objective of this systematic review and meta-analysis was to assess the prevalence of depression among Iranian patients with BT. Furthermore, we addressed factors that may introduce heterogeneity in the prevalence. The results of this review may be beneficial to policy-making regarding the early detection of depression in this population.

Materials and Methods

Study Protocol

The present study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[19] The search steps, the selection of studies, quality assessment, and data extraction were independently performed by two researchers (J. Z. and A. Z.) to avoid bias, and in the case of controversies, the issue was referred to a third person (Sh. A.).

Search Strategy

Google Scholar and PubMed search engines and Scopus, Web of Science (ISI), and Embase databases were searched to find English articles. Additionally, Iranian databases such as Scientific Information Database (SID), Magiran, and the Iranian Research Institute for Information Science and Technology (IranDoc) were searched to find Farsi articles. The search date was restricted to articles published from 1991 until June 2019. The key Medical Subject Headings (MeSH) were combined using Boolean operators: (depression OR "mental health» OR "depressive disorder" OR "mental health") AND (thalassemia OR "beta-thalassemia major") AND (prevalence OR epidemiology) AND (Iran). Since Iranian databases do not allow for a search using Boolean operators, we performed a search in these databases by using only the keywords.

Inclusion and Exclusion Criteria

Cross-sectional or cohort studies that reported the prevalence of depression in individuals with BT and were published in either English or Farsi were eligible. Studies were excluded, if they had the following criteria: 1) they were published before 1991, 2) the prevalence was not reported or could not be calculated based on the data (e.g., studies that only reported the mean depression score), 3) their full-text was inaccessible, and 4) they were duplicated. Two independent reviewers (S. N. and A. Z.) meticulously scanned all the titles, abstracts, and keywords of every published article for their relevance and eligibility. Any disagreement between the two reviewers was resolved by further investigation and discussion among the authors. If the information in the title or abstract was insufficient, the full text was reviewed.

Quality Assessment

For the quality assessment of the articles, the Newcastle-Ottawa Scale (NOS) checklist was used.[20] This checklist contains seven items in three sections: 1) Selection of the Study (four items), 2) Comparability (one item), and 3) Outcome (two items). In this study, two authors (A. Z. and S. N.) reviewed the full text of the articles. Studies with NOS scores of seven or greater were regarded as high-quality, studies with a score of 5-6 were considered moderate-quality, and studies with a score of less than five were deemed poor-quality and were excluded from the meta-analysis.

Data Extraction

The data extraction procedure was performed

by two reviewers (J. Z. and Sh. A.) using a digital data extraction form. The extracted data were "study location and setting", "publication year", "participants' characteristics" (gender and age), "sample size", "reported prevalence of depression and its 95% confidence interval (CI)", "year of study", "type of study", and "type of questionnaire used for depression measurement".

Definition

The main outcome was defined as the diagnosis of depression in patients with BT based on the following questionnaires: the Beck Depression Inventory (Beck),[21, 22] the General Health Questionnaire (GHQ-28),[23] the Depression Anxiety Stress Scale (DASS),[24] the Hospital Anxiety Depression Scale (HADS),[22] the Children Depression Inventories (CDI),[25] the Children Depression Scale (CDS),[26] and the Kiddie-SadS (K-SADS).[27]

Statistical Analysis

Pooled prevalence was calculated using the "metaprop" command in Stata software, version 14 (StataCorp LP, 1985–2015, USA). The standard error of prevalence was calculated for each study based on the binomial distribution formula. For the assessment of heterogeneity across the studies, Cochran's Q test and the I^2 statistic were calculated. For I^2 values over 50%, the random-effects model was employed to estimate the pooled measures and 95% CIs. The effect of heterogeneity on depression prevalence was addressed through sub-groups analyses based on geographical regions, quality of studies, and type of questionnaire. In addition, a meta-regression model was used to control the effect of geographical regions, quality of studies, and type of questionnaire on depression prevalence. The possibility of publication bias was addressed through the depiction of a funnel plot illustrating the standard error. All the analyses were performed using Stata software, version 14 (Stata Corp LP, 1985-2015, USA), and P values of less than 0.05 were considered significant. The funnel plot was drawn using Microsoft MedCalc Software, version 19.1.7 (MedCalc software Ltd., Ostend, Belgium).

Results

Literature Search Result

The initial search identified 1175 articles, of which 385 duplicates were excluded. The
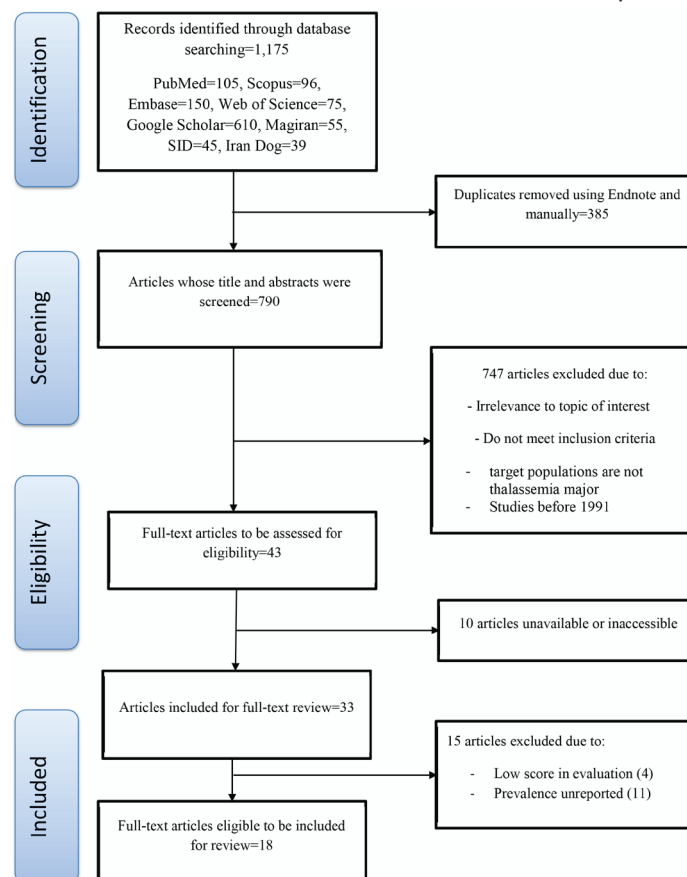

Figure 1: This figure shows the flow diagram of study selection in this systematic review and meta-analysis of depression prevalence among Iranian patients with beta-thalassemia major.

remaining 790 studies underwent title and abstract screening, which resulted in the identification of 43 eligible articles. At this stage, 10 articles were excluded, because their full-text was inaccessible. After the review of the full text of the remaining 33 articles, 18 articles with medium or high quality were entered into the meta-analysis process (figure 1). Overall, these articles recruited 3053 Iranian patients at a mean age of 22.21 years (95% CI: 19.46% to 24.95%). The sample size of the studies varied from 33 to 480 patients. The most commonly used type of questionnaire was Beck (35%) (table 1).

The Pooled Prevalence of Depression

The overall pooled prevalence (95% CI) of depression among patients with BT was 42% (95% CI: 33% to 52%) (figure 2). The sensitivity analysis for the prevalence of depression showed that after the application of the leave-one-out method, the result was still robust (figure 3).

Subgroup Analysis Based on the Geographical Region

The subgroup analysis according to the geographical region is shown in table 2. The south of Iran had the highest pooled prevalence of depression (50% [95% CI: 44% to 56%]), followed by east (39% [95% CI: 36% to 43%]), center (33% [95% CI: 20% to 48%]), and north (30% [95% CI: 13% to 50%]) (table 2). Since just one study was performed in the west of Iran, the calculation of the pooled prevalence for this region was impossible.

Table 1: Characteristics of the 18 studies recruited in the current systematic and meta-analysis of depression among Iranian patients with beta-thalassemia major

Author	Publication Year	Study Design	Place	Sample Size	Age (mean±SD)	Questionnaire	Quality Scores (NOS)[*]	Prevalence of Depression (%)[**]
Hooshmandi and colleagues[7]	2015	Cross-sectional	Bushehr	177	23.45±5.59	Beck[a]	7	45
Shafiee and colleagues[28]	2014	Cross-sectional	Tehran	56	-	Beck	6	38
Naderi and colleagues[16]	2012	Cross-sectional	Zahedan	164	18.70±2.20	GHQ-28[b]	7	12
Salehi and colleagues[29]	2014	Cross-sectional	Gorgan	163	19.60±5.30	GHQ-28	7	40
Poormansouri and colleagues[18]	2016	Cross-sectional	Ahvaz	142	25±5.13	DASS[c]	6	60
Adib-Hajbaghery and colleagues[17]	2015	Cross-sectional	Ahvaz	173	23.34±5.90	DASS	8	58
Maheri and colleagues[30]	2018	Cross-sectional	Tehran	389	30.23±8.30	HADS[d]	7	20
Azizzadeh Forouzi and colleagues[14]	2015	Cross-sectional	Kerman	480	22.60±4.50	DASS	7	51
Mohammadzadeh and colleagues[31]	2018	Cross-sectional	Bandar Abbas	264	-	Beck	8	42
Izadyar and colleagues[32]	2006	Cross-sectional	Tehran	135	-	CDI[e]	6	26
Izadyar and colleagues[32]	2006	Cross-sectional	Tehran	33	-	Beck	6	12
Ghanizadeh and colleagues[6]	2006	Cross-sectional	Shiraz	110	-	K-SADS[f]	7	49
Moafi and colleagues[33]	2008	Cross-sectional	Isfahan	50	14.80±2.85	Beck	5	52
Haji SeyedJavadi and Shafikhani[34]	2017	Cross-sectional	Qazvin	147	-	HADS	5	59
Ghafari Saravi and colleagues[35]	2004	Cross-sectional	Sari	165		CDS[g]	6	14
Aziznejad and colleagues[36]	2008	Cross-sectional	Babol	100	-	Beck	5	39
Hashemi and colleagues[37]	2012	Cross-sectional	Yazd	34	-	Beck	5	29
Marvasti and colleagues[38]	2006	Cross-sectional	Shiraz	208	-	Beck	5	47
Khamoushi and colleagues[15]	2015	Cross-sectional	Kermanshah	63	-	DASS	6	100

[*]Newcastle-Ottawa Scale; [**]Proportion test was used by "metaprop" command in Stata software. [a]Beck Depression Inventory; [b]General Health Questionnaire; [c]Depression Anxiety Stress Scale; [d]Hospital Anxiety Depression Scale; [e]Children Depression Inventories; [f]Kiddie-Sads; [g]Children Depression Scale
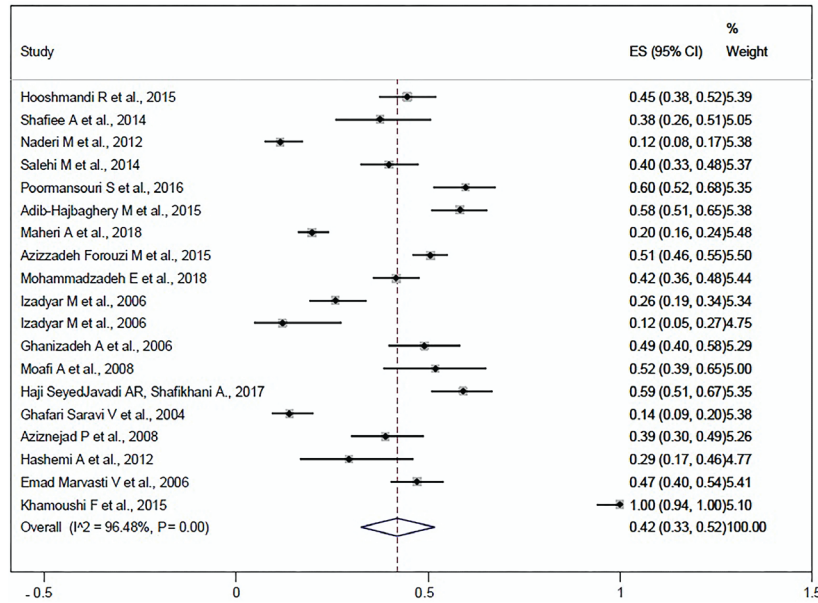
Figure 2: This figure shows the pooled prevalence of depression among Iranian patients with beta-thalassemia major.
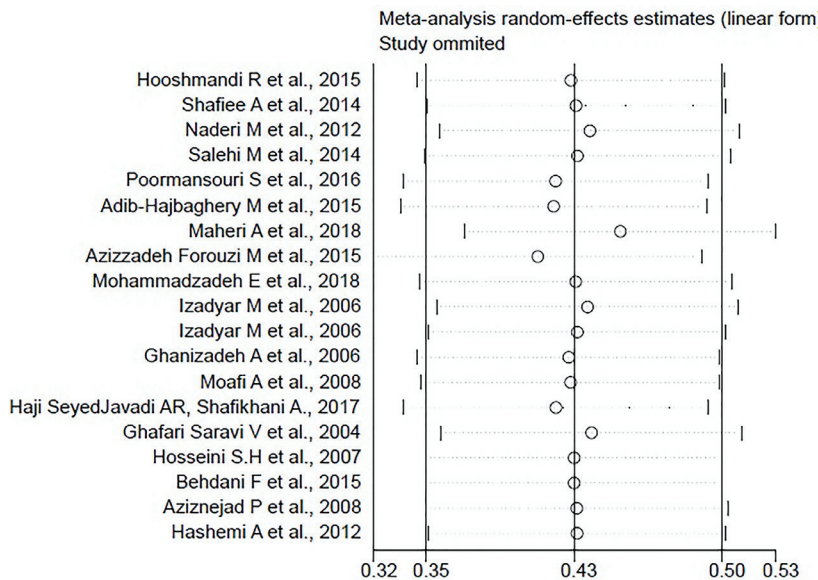

Figure 3: This figure shows the sensitivity analysis to explore the influence of each study on the pooled prevalence of depression among Iranian patients with beta-thalassemia major using the leave-one-out method.

Subgroup Analysis Based on Questionnaires

According to the type of questionnaires used, the lowest pooled prevalence was estimated for studies that utilized GHQ-28 (24% [95% CI: 20% to 29%]), while the highest pooled prevalence was estimated for studies that used DASS (72% [95% CI: 49% to 90%]) for the detection of depression (table 2). The fact that only one study used the CDS questionnaire precluded an estimation of the pooled prevalence based on this questionnaire.

Subgroup Analysis Based on the Quality of Studies

The pooled prevalence of depression in high-quality studies (39% [95% CI: 27% to 51%]) was

lower than that in moderate-quality studies (45% [95% CI: 29% to 61%]) (table 2).

Subgroup Analysis Based on the Intensity of Depression

The pooled prevalence of mild, moderate, severe, and extremely severe depression in Iranian patients with BT was 16% (95% CI: 11% to 22%), 13% (95% CI: 9% to 18%), 13% (95% CI: 9% to 17%), and 3% (95% CI: 0% to 8%), respectively (table 2).

Meta-regression

Based on the meta-regression, the pooled prevalence of depression did not vary by geographical region (meta-regression

Table 2: Subgroup analysis of the pooled prevalence of depression among Iranian patients with beta-thalassemia major by region, type of questionnaire, quality of studies, and depression intensity

Variable		Studies	Sample (n)[*]		Heterogeneity		95% CI[**]	Pooled Prevalence (%)[***]
			All	Event	I²[****]	P value		
Region	Center	7	844	260	93.50%	<0.001	20-48	33
	East	2	644	224	0	-	36-43	39
	West	1	63	63	-	-	94-100	100
	North	3	428	127	0	-	13-50	30
	South	6	1074	527	72.18%	<0.001	44-56	50
Type of questionnaire	Beck[a]	8	922	387	69.02%	<0.001	33-46	39
	GHQ-28[b]	2	327	84	0	-	20-29	24
	DASS[c]	4	858	492	97.40%	<0.001	49-90	72
	HADS[d]	2	536	164	0	-	26-34	30
	CDI[e]	1	135	35	-	-	19-34	26
	K-SADS[f]	1	110	54	-	-	40-58	49
	CDS[g]	1	165	23	-	-	9-20	14
Quality of studies	High	8	1920	748	96.49%	<0.001	27-51	39
	Moderate	11	1133	491	96.70%	<0.001	29-61	45
Intensity	Mild	10	2990	280	88.16%	<0.001	11-22	16
	Moderate	10	2969	279	83.94%	<0.001	9-18	13
	Severe	10	3053	205	83.43%	<0.001	9-17	13
	Extremely severe	10	2091	72	95.60%	<0.001	0-8	3

[a]Beck Depression Inventory; [b]General Health Questionnaire; [c]Depression Anxiety Stress Scale; [d]Hospital Anxiety Depression Scale; [e]Children Depression Inventories; [f]Kiddie-Sads; [g]Children Depression Scale; [*]Number; [**]Confidence interval; [***]Proportion test was used by "metaprop" command in Stata software; [****]Higgins test; P<0.05 was considered statistically significant.
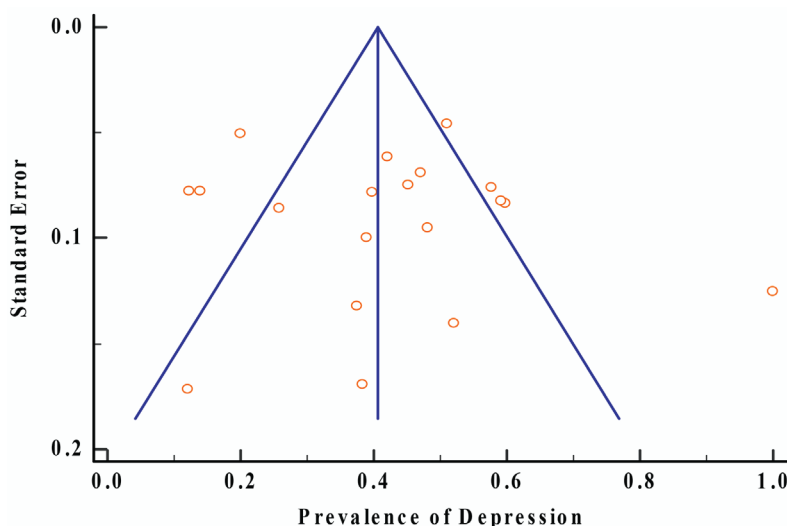

Figure 4: This figure shows the funnel plot of the studies included in the present meta-analysis of depression among Iranian patients with beta-thalassemia major.

coefficient: −0.022 [95% CI: −0.100% to 0.054%, P=0.542]), quality of studies (meta-regression coefficient: 0.011 [95% CI: −0.162% to 0.185%, P=0.889]), and type of questionnaires (meta-regression coefficient: −0.017 [95% CI: −0.069% to 0.034%, P=0.485]).

Publication Bias

A funnel plot was employed to assess the publication bias (figure 4). Asymmetry in the plot is indicative of publication bias.

Discussion

To the best of our knowledge, this study is the first systematic review and meta-analysis on the prevalence of depression among patients with BT. We showed that nearly half of Iranian patients with BT suffer from depression, with the prevalence varying from 30% to 50% in different regions of the country.

We found that approximately one out of two patients with BT in Iran had depression. There is no similar review in other countries of the Eastern Mediterranean Region (EMR); we, however, compared our results with those of the original studies on patients with BT in Lebanon (35%),[10] Egypt (32.1%),[13] and Iran's western neighbor, Turkey (20.5%),[39] indicating that the prevalence of depression in Iranian patients is

higher. This difference may be due to cultural and ethnic differences, diversities in the quality of prevention, and treatment services in different countries. The role of cultural differences in the expression of depression and psychological disorders has been well-considered in previous studies. Indeed, the association between the cultural and social backgrounds of a community with the emotional characteristics of individuals may result in differences in the expression of depression.[40, 41] Furthermore, stigma attached to psychological disorders, including depression, may result in the under-reporting of these disorders in some communities.[42, 43]

A comparison of our result with the rate in the general population indicates that the prevalence of depression is higher in patients with BT. In a review article conducted in 2016, the pooled prevalence of depression in the Iranian general population was estimated to be 37.2% in the studies that used the Beck questionnaire and 9% in the investigations that utilized the Symptom Checklist-90 (SCL-90) questionnaire.[44] Various factors may explain the higher prevalence of depression in patients with BT. BT is a disabling chronic disease, and the feeling of being different may predispose the affected population to depression. Changes in the physical appearance of patients occurring as a result of iron overload or bone expansion may decrease their self-esteem, which is followed by depression.[13] Besides, a case study suggested a link between BT and depression, which may be implicative of genetic susceptibility to depression in patients with BT.[45] Patients with BT, who suffer from depression may face difficulties in all aspects of life. Depression in this population may lead to weakness in education and job performance, social isolation, lack of independence, and reduced physical ability.[46]

Regarding the intensity of depression, mild depression was the most common (16%) among patients with BT, followed by moderate (13%), severe (13%), and extremely severe (3%) depression. Concerning prevention and early diagnosis, the detection of patients at the early stages of depression and reducing the intensity, duration, and frequency of depressive symptoms, before progression to the late stages of the disease are key interventions in controlling the disease in these patients and should be reinforced in future planning.[47]

There was a high level of heterogeneity in the findings of different studies. We tried to address this issue using the random-effects model, doing a subgroup analysis, and entering the possible sources of heterogeneity as a variable in a meta-regression model. In the subgroup analysis, we observed a geographical variation in the prevalence of depression. Since only one study was conducted in the west of Iran,[15] estimating the pooled prevalence for this region was not possible. Considering other regions, the highest prevalence was related to the south of Iran (50%), while the lowest prevalence was related to the north of Iran (30%). Differences in ethnicity, climates, socioeconomic factors, quality of health care, and access to services may explain this variation. Additionally, the subgroup analysis based on the quality of studies did not substantially affect the prevalence. The prevalence in high- and moderate-quality articles was 39% and 45%, which is close to the overall estimate of 42%. Nonetheless, apropos the type of instrument used, the pooled prevalence of depression extensively varied from 24% (for GHQ-28) to 72% (for DASS). Nevertheless, in the meta-regression, none of the mentioned variables (geographical region, type of instrument, and study quality) explained the heterogeneity in the prevalence reported in different studies. Still, lack of appropriate power due to the low number of the included studies compared with the number of predictors may explain the non-significant results of the meta-regression. Likewise, as the number of studies in most subgroups was low, the results of the subgroup analysis should be interpreted with caution. It is also still possible that other unobserved/unmeasured factors such as the sampling method, sex, and gender distribution caused bias in the design and implementation of the study. Significant variations in the prevalence of depression in different populations may be responsible for the observed heterogeneity.

We would like to acknowledge the limitations of the present study. Firstly, we did not adjust the estimated prevalence based on the size of the target population. Secondly, as the prevalence based on the age, gender, and marital status of participants were not reported in most studies, we did not conduct a subgroup analysis based on these variables. Thirdly, as national databases are insensitive to Boolean operators, we could not combine the keywords to search in Iranian databases. Fourthly, because of the possibility of publication bias, the estimated prevalence may not accurately show the real status of depression in patients with BT. Finally, heterogeneity was high across studies. We tried to address this issue by performing a meta-regression, a subgroup analysis, and the random-effects model to estimate the pooled prevalence. However, considering the low number of included studies, the findings should be interpreted with caution.

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Conclusion

The high prevalence of depression among Iranian patients with BT is worrisome. Therefore, effective strategies should be formulated in relation to the prevention and early detection of depression in these patients. Routine screening, appropriate education of patients' families and caregivers, and the integration of mental health services with medical services available for these patients may be appropriate strategies to reduce the burden of depression in this population.

Acknowledgement

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