



A Systematic Review and Meta-Analysis on the Epidemiology of Hepatitis B and Hepatitis C Virus among Beta-Thalassemia Major Patients in Pakistan

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Abstract

Beta-thalassemia major patients are the leading consumers of blood transfusions in Pakistan and, therefore, have a greater risk of acquiring transfusion-transmitted infections, most notably hepatitis B and C virus (HBV and HCV). The present study includes a comprehensive review on the status of HBV and HCV in beta-thalassemia major patients in Pakistan. For this purpose, we examined original articles assessing the epidemiology of HBV and HCV in transfusion-dependent thalassemia patients.

We searched 10 major subscription databases from January through February 2020, that is, Medline, PakMediNet, CINAHL, Scopus, PubMed, Web of Science, Embase, Science Direct, Google Scholar, and Directory of Open Access Journals. The World Health Organization resources were also explored for relevant reports. The search criteria included published articles up to December 31, 2019, with no language restrictions. Articles identified were introduced into the Endnote version X9 software and then screened for relevance and duplication. The results were stated as the pooled prevalence for the overall study and also for region-wise subgroups.

A total of 33 studies conducted from 1995 to 2019 were included in the review. All 33 articles yielded information on HCV prevalence, while 19 of them provided information on HBV prevalence. The overall sample size was 8,554 that tested the prevalence of HCV in thalassemia patients. The sample size from the 19 studies that tested the prevalence of HBV was 6,184. The overall pooled prevalence of HBV was computed to be 4.13%, while the pooled prevalence of HCV was 29.79%. The majority of the studies were obtained from the Punjab Province (33.33%), followed by Khyber Pakhtunkhwa Province (24.24%).

Keywords

- ▶ thalassemia
- ▶ hepatitis B
- ▶ hepatitis C
- ▶ epidemiology
- ▶ Pakistan

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The total sample size of 33 studies was less than 10% of the total number of estimated thalassemic patients, that is, 100,000. Further studies or a national baseline survey are imperative to confirm the actual frequency of HBV and HCV in thalassemia patients across the country.

Introduction

Beta-thalassemia is a monogene hereditary blood disorder resulting due to alteration of globin chain synthesis, characterized by reduced hemoglobin in erythrocytes and anemia.¹ The disease is predominantly present in regions where malaria incidence is high as thalassemic erythrocytes are responsible for immunity against the organism.² A high frequency of thalassemia carriers is seen in the Middle East, the Indian subcontinent, Southeast Asia, and South China. Cyprus (14%) has the highest carrier rate followed by Sardinia (10.3%).³ In the past few decades, migration of population and intermarriages among various ethnic groups have led thalassemia to almost every country around the globe.

Beta-thalassemia in its homozygous state (i.e., thalassemia major) is characterized by profound anemia and death before the age of 3 years.⁴ However, the life expectancy of thalassemic patients has increased because of the availability of regular blood transfusion and iron chelation therapy.⁵ The objective of the blood transfusion regimen in beta-thalassemia major is to treat anemia that prevents stunted growth, organ damage, and bone deformities, increasing the quality of life.⁶ However, this therapy has its side effects and results in several complications namely iron overload,⁷ alloimmunization,⁸ adverse transfusion reactions,⁹ and the transmission of transfusion-transmitted infections (TTIs) mostly notably hepatitis B and hepatitis C virus (HBV and HCV).^{10,11}

First reported in 1960,¹² thalassemia is the most frequent genetic disorder seen in the country¹³ and a major health care challenge for Pakistan.¹⁴ About 5%¹⁵ of the population is heterozygous for beta-globin gene (thalassemia minor) and the number of patients with thalassemia major is estimated to be 100,000.¹⁶ However, as no baseline survey has ever been conducted, the exact burden of the disease is unknown.¹⁶ Thalassemia incidence is seeing an upward trend despite being a preventable disease, attributed mainly to the absence of a national strategy. As a result, there are no national prevention, control, or management plans.

Thalassemia individuals are the leading consumers of blood transfusions in the country. These patients are not hospitalized yet require regular transfusions placing an enormous burden on the families as well as on the fragmented demand-driven¹⁷ blood transfusion system in the country. It is pertinent to mention that two of the provinces (Sindh¹⁸ and Balochistan¹⁹) have enacted legislation to prevent and control thalassemia in their respective jurisdictions. However, due to weak regulatory oversight and implementation mechanisms, they have not been enacted in earnest.

There are limited facilities for thalassemia patients in the government hospitals and thalassemic patients were the primary reason for the proliferation of nongovernmental organization (NGO) sector thalassemia centers in the country.²⁰ These patients are mostly treated by these NGOs whose standard of services varies. Some of these centers are not adequately equipped, have poor technical expertise, and place major emphasis on getting the blood transfusions neglecting other interventions including quality-assured screening for TTIs, among others. Many studies have reported a high incidence of TTIs in transfusion-dependent thalassemia patients. However, there is significant variation present in the individually published articles with regard to the number of patients tested, the number of positive patients, and the type of screening technique. Therefore, it is challenging to estimate the current pooled prevalence from those individual studies.

In addition, the reduction of hepatitis burden in the country is high on the Pakistan government's agenda. The government formulated and implemented a national hepatitis strategic framework (2017–2021).²¹ Hence, estimating the latest figures regarding HBV and HCV pooled prevalence in thalassemia cohort is necessary to understand prevalence dynamics and risk factors to formulate targeted and cost-effective preventative and treatment interventions to attain the target of hepatitis elimination.

We conducted this study with the objective to summarize and assess the epidemiology of HBV and HCV among thalassemic patients by performing a comprehensive systematic review and meta-analysis of relevant published studies from Pakistan.

Methodology

We searched the PROSPERO database and database of abstracts of reviews of effects (<http://www.library.UCSF.edu>) to see if the published or ongoing projects are present related to our topic. The methodological framework articulated by the Cochrane Collaboration Handbook²² was used to guide the current study. The study was based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 guidelines.²³ The detailed methodology of the study is briefed in the succeeding sections.

Data Sources and Article Identification

We searched 10 major subscription databases from January through February 2020, that is, Medline, PakMediNet, CINAHL, Scopus, PubMed, Web of Science, Embase, Science Direct, Google Scholar, and Directory of Open Access Journals. The World Health Organization (WHO) resources were also

explored for relevant reports. Medical subject heading terms with free text words were utilized in research equations with Boolean operators (AND, OR, and NOT). The keywords employed to search the mentioned databases included hepatitis C, hepatitis B, hepatitis B surface antigen, virus hepatitis, epidemiology, prevalence, seroprevalence, thalassemia major, transfusion-transmitted, Pakistan, as well as variations thereof. The search criteria included published articles up to December 31, 2019, with no language restrictions.

Article Selection and Eligibility Criteria

All articles identified through our above-mentioned databases were introduced into the Endnote version X9 software (reference manager), where duplicate publications were recognized and excluded independently by two of the authors (UW, NS). The remaining articles underwent a two-stage screening process, to determine eligibility and relevancy. This included the title and abstract screening, followed by a full-text review using our inclusion and exclusion criteria. Eligible articles were included and others excluded. Identification of additional articles was made through screening of references in full-text articles (i.e., handcomb search) as well as the gray literature, for example, country- or province-level reports. After the identification of articles that met inclusion criteria, two authors (UW, AW) independently reviewed all full-text articles. When agreement on inclusion was not reached between the two reviewers, a third reviewer arbitrated to reach a consensus.

The inclusion criteria used in the current study were any article with full-text reporting HBV or HCV prevalence in thalassemia major patients in Pakistan based on primary data. Review articles were not included but all data present in them were checked and matched to the present search results. Any additional study identified in reviews and not retrieved by the present search was included. All other articles were excluded such as case report, editorial, correspondence, commentary, original articles whose full texts are not retrievable or include study population outside Pakistan, unclear prevalence, or methodological errors.

Data Extraction and Screening

Each study was allotted a number for identification. The following data (based on ad hoc Excel spreadsheet) were later extracted from every article in the following domains: reference details (this included surname of author, title, journal, year of publication), city and province, study population, sample size, number of thalassemia patients screened for HBV and HCV (in case different from the sample size), number of thalassemia patients who tested positive, screening technique used, and the reported prevalence and incidence of HBV and HCV. Any discrepancy regarding the extracted data was resolved by discussion and mutual consensus.

Article Quality Appraisal

Two authors independently judged the quality of the included articles using the Joanna Briggs Institute quality assessment tool for prevalence and epidemiological studies²⁴ with 10 questions. The answer to each question was yes, no, not

clear, or not applicable. The quality of each included article was scored as poor (below the mean score) and good (mean score and above).

Data Analyses

To summarize the characteristics of included studies, numeric analysis was applied. The result was reported as pooled prevalence for the overall study and also for region-wise subgroups.

Results

Literature Search

► **Fig. 1** shows the steps for the selection of studies into this systematic review after adapting the PRISMA flow diagram. Briefly, a total of 94 citations were obtained using the search strategy for the identified databases. After the removal of 20 duplicate articles, the remaining 74 articles underwent title and abstract screening. Based on title and abstract scan, 46 articles were excluded not fulfilling the inclusion criteria and 28 remained for full-text review. One full-text article was further removed due to methodological errors. From the handcomb search, six potentially eligible articles were identified and added to the systematic review. Thus, a total of 33 articles qualified for inclusion in the review.²⁵⁻⁵⁷ All 33 articles yielded information on HCV prevalence, while 19 of them provided information on HBV prevalence.

Characteristics of Included Studies

► **Table 1** shows the features of studies included in the systematic review. The studies were published from January 1995 to December 2019. Regarding the province-wise coverage, majority of the studies were obtained from Punjab Province 11 (33.33%),^{25,34,35,40,42,43,46,48,50,53,55} Khyber Pakhtunkhwa Province 8 (24.24%),^{29,32,36,41,44,51,54,57} Sindh Province 6 (18.18%),^{26-28,37,39,49} Islamabad Capital Territory 3 (9.09%),^{30,45,52} Balochistan Province 1 (3.03%),³⁸ and mixed-province samples 4 (12.12%).^{31,33,47,56} No studies were identified from Azad Jammu and Kashmir and Gilgit-Baltistan regions.

Most of the selected studies performed screening through enzyme-linked immunosorbent assay 23 (69.69%), while rest through rapid diagnostic test (RDT) devices 4 (12.12%), chemiluminescence immunoassay 3 (9.09%), and polymerase chain reaction 3 (9.09%).

HBV and HCV Epidemiology Overview

From the 33 studies included in this systematic review, the overall sample size was 8,554 that tested the prevalence of HCV in thalassemia patients. The sample size from the 19 studies that tested the prevalence of HBV was 6,184. The sample size across the studies ranged from 35²⁵ to 1,440.⁵² The overall pooled prevalence of HBV was computed to be 4.13%, while the pooled prevalence of HCV was 29.79%. There was a wide variation in HBV and HCV prevalence among individual studies. For HBV, it ranged from 0.70% in Rawalpindi (Punjab Province)³⁴ to 8.40% in Peshawar (Khyber Pakhtunkhwa Province).³² For HCV, it ranged from 5.55% in Hazara (Khyber

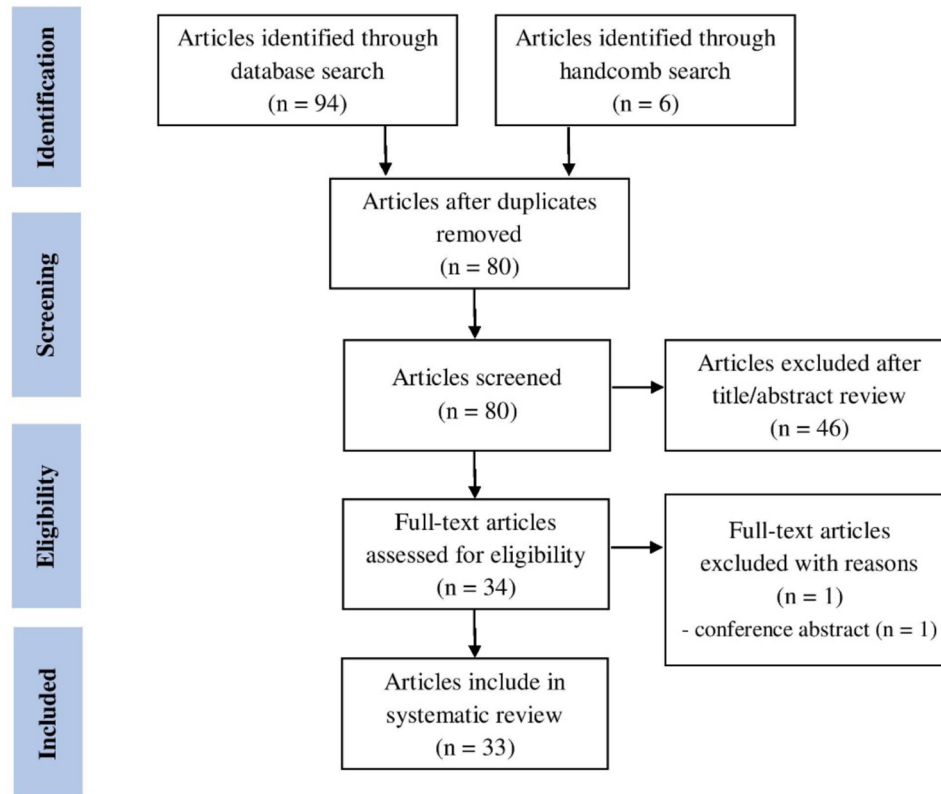


Fig. 1 Flowchart of the process through which articles were selected based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines.

Pakhtunkhwa Province)⁵⁴ to 65% in Faisalabad (Punjab Province).³⁵ Refer to **Table 1** for further details of study characteristics.

HBV and HCV Epidemiology Province-wise

The pooled subgroup prevalence stratified by geographical location (province) revealed that the prevalence of HCV among beta-thalassemia patients was high 41.34% in Punjab (based on 11 studies with a sample size of 2,090), compared with 24.17% of Khyber Pakhtunkhwa (based on 8 studies with a sample size of 1,518), 25.94% of Sindh (based on 6 studies with a sample size of 1,056), 26.61% of Islamabad Capital Territory (based on 3 studies with a sample size of 1,777), and 30% of Balochistan (based on 1 study with a sample size of 150).

The pooled subgroup prevalence of HBV was high 10.14% in Punjab (based on 6 studies with a sample size of 483), compared with 5.10% of Khyber Pakhtunkhwa (based on 5 studies with a sample size of 1,254), 3.80% of Sindh (based on 4 studies with a sample size of 709), and 3.05% of Islamabad Capital Territory (based on 2 studies with a sample size of 1,702).

Discussion

A number of hepatotropic viruses cause viral hepatitis. Among these, HBV and HCV are by far the most important viruses causing both acute and chronic hepatitis. These

viruses are still a serious public health concern across the globe, especially among the low-income countries including Pakistan.

The planning to implement appropriate and effective programs to prevent and control these viral syndromes requires the presence and use of scientific evidence that are up-to-date. Therefore, the goal of this review was to determine the pooled prevalence of HBV and HCV among the transfusion-dependent beta-thalassemia major patients, a well-known high-risk group needing regular transfusion to maintain quality of life. We observed highly variable prevalence estimates for both HBV and HCV from different studies in a similar population, even within the same province. The findings of this study indicated that the pooled prevalence of HBV and HCV was 4.13 and 29.79%, respectively. The observed pooled prevalence of HBV and HCV is higher in contrast to prevalence in the general population of the country that stands at 2.5 and 4.9%, respectively.⁵⁸

Safe blood transfusion increases the quality of life and survival of recipients. However, they also expose the recipients to the risk of acquiring TTIs. The probability of acquiring TTIs is linked to the probability of being exposed to the contaminated blood and blood components. This probability is influenced by the prevalence of TTIs in the blood donor population and the number of units being transfused. Thus, the rate of acquiring TTIs increases with age in subsequent years that is the case in chronic recipients of blood such as thalassemia. As the blood collections in Pakistan are predominantly “family

Table 1 Studies included in the systematic review that assessed the epidemiology of HBV and HCV among Pakistani beta-thalassemia major patients

Author and year of publication	City (region)	Sample size	HCV positive (%)	HBV positive (%)
Bhatti et al, 1995 ²⁵	Rawalpindi (Punjab)	35	21 (60%)	2 (5.71%)
Abdul Mujeeb et al, 1997 ²⁶	Karachi (Sindh)	91	46 (50.54%)	NA
Shamsi et al, 1998 ²⁷	Karachi (Sindh)	370	60 (16.21%)	18 (4.86%)
Akhtar et al, 2002 ²⁸	Karachi (Sindh)	256	86 (33.59%)	NA
Mohammad et al, 2003 ²⁹	Peshawar (KP)	80	29 (36.25%)	6 (7.5%)
Younus et al, 2004 ³⁰	ICT	75	32 (42.66%)	NA
Burki et al, 2005 ³¹	ICT and Peshawar (KP)	180	75 (41.66%)	NA
Shah et al, 2005 ³²	Peshawar (KP)	250	142 (56.80%)	21 (8.40%)
Hussain et al, 2008 ³³	ICT and Peshawar (KP)	180	75 (41.66%)	NA
Iqbal et al, 2010 ³⁴	Rawalpindi (Punjab)	141	50 (35.46%)	1 (0.70%)
Ain et al, 2011 ³⁵	Faisalabad (Punjab)	300	195 (65%)	NA
Ali et al, 2011 ³⁶	Peshawar (KP)	40	6 (15%)	NA
Riaz et al, 2011 ³⁷	Karachi (Sindh)	79	34 (43.03%)	4 (5.06%)
Rehman et al, 2011 ³⁸	Quetta (Balochistan)	150	45 (30%)	NA
Ansari et al, 2012 ³⁹	Karachi (Sindh)	160	21 (13.12%)	2 (1.25%)
Iqbal et al, 2013 ⁴⁰	Rawalpindi (Punjab)	95	40 (42.10%)	NA
Khattak et al, 2013 ⁴¹	Swat (KP)	170	37 (21.76%)	10 (5.88%)
Din et al, 2014 ⁴²	Rawalpindi (Punjab)	95	47 (49.47%)	3 (3.15%)
Nazir et al, 2014 ⁴³	Lahore (Punjab)	200	82 (41%)	NA
Khan et al, 2015 ⁴⁴	Bannu (KP)	180	14 (7.77%)	NA
Saeed et al, 2015 ⁴⁵	ICT	262	146 (55.72%)	8 (3.07%)
Ali et al, 2016 ⁴⁶	Faisalabad (Punjab)	379	123 (32.45%)	NA
Kiani et al, 2016 ⁴⁷	ICT, Rawalpindi (Punjab) and Karachi (Sindh)	1,253	273 (21.78%)	38 (3.03%)
Khalil et al, 2016 ⁴⁸	Rawalpindi (Punjab)	80	31 (38.75%)	4 (5%)
Sultan et al, 2016 ⁴⁹	Karachi (Sindh)	100	27 (27.0%)	3 (3.0%)
Khan et al, 2017 ⁵⁰	Lahore (Punjab)	470	216 (45.95%)	37 (7.87%)
Bari et al, 2017 ⁵¹	Mardan (KP)	44	19 (43.18%)	NA
Farooq et al, 2018 ⁵²	ICT	1,440	295 (20.4%)	44 (3.05%)
Raza et al, 2018 ⁵³	Lahore (Punjab)	200	53 (26.50%)	NA
Shah et al, 2019 ⁵⁴	Hazara (KP)	324	18 (5.55%)	6 (1.85%)
Abid et al, 2019 ⁵⁵	Lahore (Punjab)	95	6 (6.31%)	2 (2.17%)
Yasmeen et al, 2019 ⁵⁶	Lahore, Multan (Punjab), Karachi (Sindh) and Peshawar (KP)	350	103 (29.42%)	26 (7.42%)
Al-Moshary et al, 2019 ⁵⁷	Peshawar (KP)	430	102 (23.72%)	21 (4.88%)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; ICT, Islamabad capital territory; KP, Khyber Pakhtunkhwa; NA, not available.

replacement” instead of the WHO recommended regular voluntary donations,⁵⁹ the probability of acquiring the infection increases. The rampant use of poor quality RDTs⁶⁰ for screening purposes intensifies the situation. Hence, unsafe blood transfusions remained an important driver of the hepatitis epidemic in the country.

The findings of this study showed that the maximum pooled prevalence of HBV and HCV among thalassemia patients was observed in Punjab Province (10.14 and 41.34%, respectively). On the other hand, the least pooled prevalence for HBV was seen in Islamabad Capital Territory (3.05%), while

for HCV it was in Khyber Pakhtunkhwa Province (24.17%). The transfusion system in general and the screening system in specific could explain, at least partially, such findings.

Countries like Iran, Cyprus, and Italy⁶¹⁻⁶³ have a successful experience of eradicating thalassemia and it is vital that Pakistan should learn and follow a similar strategy. This strategy should then be adapted to local needs and requirements to formulate a national consensus for thalassemia prevention policy.

To the best of our understanding, this was the first systematic review to assess the pooled prevalence of HBV and

HCV among thalassemia patients in Pakistan. It is pertinent to mention that the total sample size of 33 studies was less than 10% ($n = 8,554$) of the total number of estimated thalassaemic patients, that is, 100,000.

Further studies or a national baseline survey are imperative to confirm the actual frequency of HBV and HCV in thalassaemia patients across the country in various settings that in turn may lead to better management of the problem.

Limitations

More than 90% of the studies incorporated in this systematic review reported the prevalence on the basis of serological tests; hence, there is a likelihood of missing occult HBV and HCV infections. Regional biasness is present as studies were not conducted in some geographical areas.

Conflict of Interest

None.

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