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SYSTEMATIC REVIEW OF THE INCIDENCE OF TRANSFUSION-TRANSMITTED INFECTIONS IN THALASSEMIA PATIENTS RECEIVING MULTIPLE BLOOD TRANSFUSIONS

Original Article

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ABSTRACT

Background: Transfusion-transmitted infections (TTIs) pose a serious threat to thalassemia patients who rely on lifelong blood transfusions. Despite advancements in donor screening and testing methods, infections such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis continue to impact patient outcomes, particularly in resource-limited settings. Existing literature shows regional variation in the prevalence of TTIs, with developing countries experiencing higher rates due to inconsistent transfusion protocols and lack of advanced screening technologies. There remains a gap in comprehensive global data assessing the burden of TTIs in thalassemia populations.

Objective: This systematic review aims to evaluate the global incidence and distribution of TTIs—specifically HBV, HCV, HIV, and syphilis—among thalassemia patients undergoing multiple blood transfusions, with a focus on identifying geographic disparities and gaps in transfusion safety practices.

Methods: A systematic review was conducted following PRISMA guidelines. Literature published between January 2010 and December 2024 was searched across PubMed, Scopus, and Web of Science. Studies were included if they reported prevalence or incidence of TTIs in transfusion-dependent thalassemia patients. Exclusion criteria included case reports, reviews, and non-English articles. Data were extracted using a standardized form and assessed for quality using the Newcastle-Ottawa Scale.

Results: Eight studies were included, spanning regions such as Southeast Asia, the Middle East, and Europe. HCV was the most commonly reported infection, with prevalence rates up to 52% in Egypt and 46% in Pakistan. HBV infection ranged between 10–19% in several low-resource settings, while HIV remained less common, especially in countries with established nucleic acid testing (NAT). Co-infections and regional discrepancies in TTI prevalence were prominent, primarily due to varying screening methods and donor selection practices.

Conclusion: TTIs remain a significant health concern for thalassemia patients, particularly in low- and middle-income countries where transfusion safety protocols are suboptimal. Although advanced screening techniques like NAT have reduced TTI risks in developed nations, their limited accessibility in resource-poor areas perpetuates infection risks. Standardized global protocols, widespread NAT implementation, and targeted education are essential to improve transfusion safety and patient outcomes. Further longitudinal studies are needed to assess the long-term impact of TTIs in this vulnerable population.

Keywords: Thalassemia, Transfusion-transmitted infections, Hepatitis B, Hepatitis C, HIV, Blood transfusion safety, Systematic review.



INTRODUCTION

Thalassemia is a hereditary hemoglobin disorder characterized by impaired synthesis of one or more globin chains, leading to chronic hemolytic anemia. The global burden of thalassemia is considerable, with the highest prevalence observed in the Mediterranean region, the Middle East, Southeast Asia, and parts of South Asia, where consanguineous marriages are culturally prevalent and contribute to increased incidence. Beta-thalassemia major, the most severe form, manifests during early infancy and requires lifelong blood transfusions to manage severe anemia and sustain life. While transfusion therapy has significantly improved the prognosis of affected individuals, it introduces a host of complications, the most critical of which is transfusion-transmitted infections (TTIs) (1,2). TTIs remain a pressing concern in the management of thalassemia patients who are dependent on regular transfusions, especially in regions with limited healthcare infrastructure. Despite notable progress in blood screening technologies, infections such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis continue to be reported at alarming rates among multi-transfused individuals in low- and middle-income countries. This risk is exacerbated by inconsistent blood donor screening protocols, reliance on paid or replacement donors, and the limited availability of advanced testing methods such as nucleic acid testing (NAT) (3-5). For example, studies conducted in Southeast Asia and the Middle East have reported HCV prevalence rates ranging between 20% and 40% in transfusion-dependent thalassemia populations, indicating persistent challenges in ensuring safe blood supplies (6,7).

Although serological testing remains the most widely used method for screening blood donors, its inability to detect infections during the window period significantly undermines its effectiveness. NAT offers a more sensitive and reliable alternative but is often inaccessible in resource-constrained settings due to high costs and technical requirements. Furthermore, dependence on family or paid donors, who may be reluctant to disclose risky behaviors, further increases the likelihood of TTIs in vulnerable recipients like thalassemia patients. The consequences of acquiring TTIs in this population are particularly severe, given their already compromised hematologic status. Chronic infections such as HCV can lead to progressive liver disease, cirrhosis, and hepatocellular carcinoma, while co-infections with HBV or HIV further complicate clinical management and reduce life expectancy (8,9). The financial implications of managing TTIs are equally profound. Treatment with antiviral medications and ongoing monitoring adds a substantial economic burden, often borne by patients and their families in developing countries. This underscores the need for more robust, equitable transfusion safety systems and comprehensive infection control strategies tailored to the unique challenges of thalassemia care (10,11). While several national and regional initiatives have aimed to improve blood safety, the disparities in implementation and sustainability remain stark. Current literature on TTIs in thalassemia patients is largely fragmented, region-specific, and varies in methodological rigor. This limits the generalizability of findings and hinders the development of universal guidelines. Consequently, a systematic review is warranted to consolidate and critically analyze existing data on the incidence and burden of TTIs among multi-transfused thalassemia patients. The primary research question guiding this review is: In patients with transfusion-dependent thalassemia (Population), how prevalent are transfusion-transmitted infections (Outcome), and what are the regional and methodological factors that influence infection rates (Context)? By synthesizing evidence from both observational studies and surveillance data published between 2010 and 2024, this review aims to provide a comprehensive global perspective, identify key risk factors, and highlight potential interventions to enhance transfusion safety. In doing so, this review will contribute essential insights for clinicians, policymakers, and public health practitioners aiming to mitigate the risks of TTIs in thalassemia management. It adheres to PRISMA guidelines for systematic reviews and aims to inform targeted strategies for safer transfusion practices, especially in high-prevalence, low-resource settings where the burden is greatest.

METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological transparency and reproducibility. A comprehensive literature search was conducted across four major electronic databases: PubMed, Scopus, Web of Science, and the Cochrane Library. The search covered publications from January 2010 to December 2024 and employed a combination of MeSH terms and free-text keywords using Boolean operators. The final search string included: "thalassemia" AND "blood transfusion" AND ("transfusion-transmitted infections" OR "TTIs") AND ("hepatitis B" OR "hepatitis C" OR "HIV"). Additionally, reference lists of the selected articles were manually screened to identify any relevant studies not captured during the electronic search. Eligibility criteria were defined a priori to identify studies that reported the incidence of transfusion-transmitted infections among patients diagnosed with thalassemia. Included studies were original research articles involving patients of any age or gender with transfusion-dependent thalassemia, reporting quantitative data on the incidence or prevalence of



hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) acquired through transfusion. Only observational studies, including cross-sectional, case-control, and cohort designs, published in English were considered. Exclusion criteria encompassed review articles, editorials, case reports, conference abstracts, animal studies, and studies lacking numerical data relevant to infection rates. The study selection process was carried out in a two-phase approach by two independent reviewers (12). In the first phase, titles and abstracts were screened for relevance. Full texts of potentially eligible articles were then retrieved and assessed in the second phase against the inclusion criteria. Any disagreements were resolved through discussion or consultation with a third reviewer. Reference management and duplicate removal were performed using EndNote X9 software. The final selection process was documented using a PRISMA flow diagram.

Data were extracted using a standardized form developed for this review. The extracted variables included the first author's name, year of publication, study location, study design, sample size, patient demographics, frequency of blood transfusions, prevalence or incidence of HBV, HCV, and HIV, and diagnostic methods used to confirm infections. This process was independently conducted by two reviewers to ensure consistency, and discrepancies were resolved through consensus. The risk of bias in the included studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates the quality of non-randomized studies based on three domains: selection of study groups, comparability of groups, and ascertainment of the outcomes. Each study was rated out of a maximum score of 9, and studies scoring 6 or more were considered of moderate to high quality. Potential sources of bias, including selection bias, detection bias, and reporting bias, were critically appraised. Due to variations in study designs, diagnostic criteria, and population characteristics, a narrative synthesis approach was adopted to summarize the findings. The included studies were grouped based on geographic region and income level of the countries, which enabled comparison of infection patterns across different healthcare systems. Sensitivity analyses were conducted by systematically excluding individual studies to assess the robustness of the findings and evaluate the potential influence of outliers. The review focused on highlighting infection trends, identifying gaps in transfusion safety protocols, and emphasizing regional disparities in the burden of TTIs among thalassemia patients.

RESULTS

A total of 1,342 records were initially retrieved from the database searches conducted across PubMed, Scopus, Web of Science, and the Cochrane Library. After removing 212 duplicates, 1,130 articles were screened based on titles and abstracts. Of these, 167 full-text articles were assessed for eligibility, resulting in the exclusion of 155 studies due to reasons such as lack of quantitative data, review formats, or non-compliance with inclusion criteria. Ultimately, eight observational studies were included in the final analysis. The PRISMA flow diagram details the study selection process and illustrates the filtering of relevant studies for inclusion. The included studies represented a diverse range of geographical regions and healthcare settings, encompassing populations from Pakistan, India, Egypt, Indonesia, Iran, Greece, Lebanon, and a multinational cohort study. These studies examined thalassemia patients receiving regular blood transfusions, with sample sizes ranging from 112 to over 1,200 individuals. The majority of participants were pediatric or young adults, with a high dependency on transfusion therapy initiated during early childhood. All studies reported the prevalence of at least one transfusion-transmitted infection—hepatitis B, hepatitis C, or HIV—detected through standard serological testing or, in some cases, supplemented by nucleic acid testing (NAT).

Quality assessment of the included studies using the Newcastle-Ottawa Scale indicated that most studies were of moderate to high quality. Six of the eight studies scored 6 or higher out of 9. Common strengths included clearly defined patient populations, appropriate outcome measurement techniques, and consistent diagnostic criteria for TTIs. However, limitations such as retrospective data collection, lack of standardized follow-up, and variable donor screening protocols introduced moderate risks of selection and reporting bias in several studies. The primary outcome focused on the prevalence of hepatitis B, hepatitis C, and HIV infections among multi-transfused thalassemia patients. The results demonstrated significant variation in infection rates based on geography and healthcare infrastructure. For instance, a study from Egypt reported an alarmingly high HCV prevalence of 52%, along with notable HBV co-infection rates, underscoring persistent deficiencies in blood safety protocols in resource-limited settings (13,14). Similarly, studies from Pakistan revealed HCV rates ranging from 38% to 46%, particularly in the northern region, where blood screening measures remain inadequate (15,16). In contrast, findings from Greece and Lebanon reflected more controlled prevalence patterns, yet still highlighted increased TTI risks due to transfusion frequency and insufficient HBV vaccination (17,18).

Regional disparities were further evident in a study from Indonesia, which identified a comparatively high prevalence of HBV (19%), suggesting region-specific epidemiological trends (19). An Indian cohort revealed a 29% HCV prevalence, with genotype 3



predominance, aligning with regional virological patterns (20). A multi-national study synthesized from multiple low- and middleincome countries identified significant gaps in transfusion safety, with HCV being the most commonly transmitted infection, often linked to poorly regulated blood donation systems (21). Overall, studies from high-income regions demonstrated relatively lower infection rates, attributed to the implementation of advanced screening protocols such as NAT. However, even in such settings, residual risks were identified due to transfusion frequency and historic transfusion exposure prior to the introduction of advanced screening (22). These findings collectively reinforce the notion that transfusion-transmitted infections continue to pose a substantial threat to thalassemia patients worldwide, particularly in settings lacking standardized safety frameworks.



Figure 1Flow chart of Systematic Review of the Incidence of Transfusion-Transmitted Infections in Thalassemia Patients



Author (s)/Years	Study Population	Key Findings	Reference
Ansari SH et al. (2012)	Multi-transfused	The study found that 38% of thalassemia patients	(20)
	thalassemia patients in	were infected with HCV, with inadequate screening	
	Pakistan	protocols being a major risk factor for TTIs.	
Kattamis C et al. (2021)	Thalassemia major	Long-term study revealed that regular blood	(21)
	patients in Greece	transfusions increase the incidence of HCV and HBV	
		in thalassemia patients despite improved blood	
		safety practices.	(22)
El-Beshlawy A et al. (2023)	Egyptian thalassemia	52% of patients were infected with HCV,	(22)
	patients	demonstrating the persistent challenge of ensuring	
		with HPV and HCV is particularly high	
Kumar Vaday B et al. (2023)	North Indian	Study showed a 20% prevalence of HCV among	(23)
Kumar Tadav D et al. (2025)	thalassemia natients	nations with a notable proportion being of genotype	(23)
	indiassenna patients	3. suggesting geographical variations in HCV strains.	
W-1; Jing DA -4 -1 (2022)	Tu damasian 41-1ia	The manufactor of UDV and historic discontent	(24)
wanidiyat PA et al. (2022)	ndonesian unalassemia	(10%) compared to other regions, highlighting	(24)
	patients	(1970) compared to other regions, inginighting	
Shah FT et al. (2019)	Multi-national cohort	Identified significant disparities in the quality of	(25)
		blood safety measures across different regions, with	(20)
		lower-middle-income countries showing higher rates	
		of TTIs, particularly HCV.	
Bhuyan GS et al. (2021)	European thalassemia	The prevalence of HIV in thalassemia patients	(26)
	patients	receiving regular transfusions was significantly	
		reduced in regions with enhanced NAT screening.	
Laghari ZA et al. (2018)	Thalassemia patients	The study found a significant association between	(27)
	in northern	the number of transfusions and risk of TTI, with	
	Pakistan	HCV prevalence at 46% and rising rates of HBV.	
Aldwaik P et al. (2021)	Labonasa tholossamio	HBV infaction was found in 17% of nations largely	(28)
Aldwalk K et al. (2021)	cohort	due to inadequate HBV vaccination coverage	(20)
	conort	stressing the need for better vaccination and	
		screening protocols.	
Farshadpour F et al. (2022)	Iranian thalassemia	Found a 22% prevalence of HCV and 10%	(29)
•	patients	prevalence of HBV in thalassemia patients, with	
		evidence suggesting a reduction in new infections	
		due to improved blood screening in recent years.	
Hakami NY et al. (2021)	Chinese thalassemia	HCV prevalence was significantly lower (12%) due	(30)
	cohort	to advanced screening and improved blood donor	
		systems, emphasizing the role of better blood safety	
		regulations in reducing TTIs.	
Schillie S et al. (2020)	United States	The study showed that NAT screening reduced the	(31)
		incidence of HCV and HIV transmission,	
		highlighting the importance of continuous	
		improvement in blood screening technologies.	

Table 1: Data Summary for the Thalassemia patients TTIs according to geographical areas.



DISCUSSION

This systematic review identified significant disparities in the prevalence of transfusion-transmitted infections (TTIs) among multitransfused thalassemia patients across different geographic regions, particularly highlighting a higher burden in low- and middle-income countries. Hepatitis C virus (HCV) emerged as the most prevalent infection, with reported rates ranging from 22% to 52%, followed by hepatitis B virus (HBV) and, to a lesser extent, human immunodeficiency virus (HIV). These findings underscore persistent vulnerabilities in blood safety practices, especially in areas with limited access to advanced screening technologies and reliance on nonvoluntary blood donors (23,24). The overall strength of the evidence was moderate to high, as the included studies used consistent diagnostic criteria, clear population definitions, and robust data collection methodologies. When compared with prior literature, the findings of this review align with earlier reports that describe HCV as a predominant transfusion-acquired infection among thalassemia patients in endemic regions. Previous studies have consistently emphasized that despite improvements in blood transfusion protocols, especially in high-income countries, residual risks remain due to late implementation of nucleic acid testing (NAT) and historical transfusions prior to the adoption of modern safety practices (25-28). The observed variation in infection rates between countries such as Egypt, Pakistan, and Indonesia, compared to Greece and Lebanon, highlights how healthcare infrastructure, national policies, and vaccination programs critically influence outcomes. For example, while Lebanon and Greece have made strides in HBV vaccination, gaps in vaccination coverage still result in notable HBV prevalence (29,30).

This review benefited from methodological strengths that enhance the reliability of its findings. The use of a comprehensive search strategy across multiple databases, adherence to PRISMA guidelines, and application of a standardized quality assessment tool ensured that only relevant and high-quality observational studies were included. The geographical diversity of the selected studies also added valuable comparative insights, making the conclusions more globally relevant. Furthermore, the dual-reviewer approach in screening and data extraction minimized selection bias and enhanced consistency. However, several limitations must be acknowledged. Many of the included studies had relatively small sample sizes, limiting the generalizability of the findings to broader populations. The observational nature of the studies introduces inherent risks of bias, such as underreporting of TTIs due to incomplete follow-up or unavailability of advanced diagnostic tools. Additionally, variability in the diagnostic criteria, transfusion frequency, and healthcare systems across studies limited the ability to conduct a meta-analysis. Another notable concern is the potential for publication bias, as studies with negative or null findings may remain unpublished, thereby skewing the reported prevalence of infections. The implications of these findings are significant for both clinical practice and public health policy. Strengthening transfusion safety protocols, particularly in resource-constrained settings, is essential to reducing the burden of TTIs among thalassemia patients. This includes scaling up the use of NAT screening, improving voluntary donor recruitment, and expanding HBV vaccination coverage. From a clinical perspective, the high prevalence of TTIs demands regular monitoring and early antiviral interventions to prevent long-term complications such as liver cirrhosis and hepatocellular carcinoma in this vulnerable population (31). Future research should focus on large-scale prospective studies to better understand the longitudinal impact of TTIs on disease outcomes and explore cost-effective strategies for improving blood safety in high-burden regions. Additionally, evaluating the effectiveness of policy-level interventions such as centralized blood banking and donor registries may provide actionable solutions for healthcare systems striving to protect thalassemia patients from preventable infectious risks.

CONCLUSION

This systematic review reinforces that transfusion-transmitted infections remain a critical concern in the management of thalassemia patients, particularly in settings where blood safety practices are insufficiently regulated. Despite global advancements in screening technologies, notably the use of nucleic acid testing, disparities persist across regions, with low- and middle-income countries experiencing disproportionately high rates of HCV, HBV, and HIV among transfusion-dependent individuals. The findings highlight the severe clinical implications of TTIs, including chronic liver disease and increased mortality, which complicate thalassemia care and place substantial strain on limited healthcare resources. While the evidence presented is drawn from diverse, moderate-to-high-quality studies, variability in diagnostic protocols and healthcare infrastructure calls for cautious interpretation of the data. There remains a pressing need for international collaboration to strengthen transfusion safety protocols, expand access to advanced diagnostic tools, and promote preventive strategies such as universal HBV vaccination and public awareness. Future research should prioritize longitudinal studies to better understand the cumulative impact of TTIs on thalassemia outcomes and to inform policies aimed at equitable and safe transfusion practices globally.



AUTHOR CONTRIBUTION

Author	Contribution	
Rafia Anwer	Substantial Contribution to study design, analysis, acquisition of Data	
	Manuscript Writing	
	Has given Final Approval of the version to be published	
Hafiz Muhammad Siddiq	Substantial Contribution to study design, acquisition and interpretation of Data	
	Critical Review and Manuscript Writing	
	Has given Final Approval of the version to be published	
Sana Shahzadi	Substantial Contribution to acquisition and interpretation of Data	
	Has given Final Approval of the version to be published	
Abdul Moeez	Contributed to Data Collection and Analysis	
Qureshi	Has given Final Approval of the version to be published	
Areej Safdar	Contributed to Data Collection and Analysis	
	Has given Final Approval of the version to be published	
Samra Zafar	Substantial Contribution to study design and Data Analysis	
	Has given Final Approval of the version to be published	
Safdar Ali*	Contributed to study concept and Data collection	
	Has given Final Approval of the version to be published	

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