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PREVALENCE OF BLOOD TRANSFUSION-ASSOCIATED COMPLICATIONS AMONG BETA THALASSEMIA PATIENTS IN SOUTHERN PUNJAB: A MULTICENTER STUDY AT A GLANCE

Uzma Chohan[1*], Ujala Aymun[2], Maryam Khanzada Rajput[3], Tooba Ammar[4], Javaeria Abdullah[5], Hussain Farooq[6]

[1*]Department of Pathology, Shahida Islam Medical College Lodhran, Pakistan.
[2]Department of Pathology, Avicenna Medical College & Hospital, Lahore, Pakistan.
[3]Department of Pathology, Diagnostic & Research Lab, Bilawal Medical College Jamshoro, Pakistan.
[4, 6,5]Department of Hematology, Shaikh Zayed Post Graduate Medical Institute Lahore, Pakistan.

***Correspondence Author:** Uzma Chohan
*Department of Pathology, Shahida Islam Medical College Lodhran, Pakistan.
Email: druzmachohan@gmail.com

Abstract

Background: Beta-thalassemia major is a common inherited hemoglobinopathy in Pakistan, particularly in Southern Punjab, where high consanguinity which contribute to its high prevalence. Although regular blood transfusion is the cornerstone of treatment, it predisposes patients to a spectrum of transfusion-associated complications, both infectious and non-infectious, which significantly affect long-term morbidity and mortality.

Aims & Objective: This study aimed to determine the prevalence of transfusion-related infectious, non-infectious, and long-term complications among β-thalassemia patients in Southern.

Methodology: A multicenter, cross-sectional study was conducted between January and July 2025 across three tertiary thalassemia centers in Lodhran, Bahawalpur and Multan. A total of 345 transfusion-dependent β-thalassemia patients were enrolled through stratified random sampling. Data were collected using structured questionnaires, medical record review, and laboratory investigations including HBsAg, anti-HCV, HIV ELISA, serum ferritin, liver and thyroid function tests. Descriptive statistics determined prevalence rates, and logistic regression was performed to identify predictors of complications.

Results & Findings: The mean age of patients was 12.6 ± 6.3 years, with a male-to-female ratio of 1.2:1. Infectious complications included anti-HCV positivity (32.5%), HBsAg positivity (5.2%), and HIV (<1%). Iron overload (serum ferritin >2500 ng/mL) was found in 72.5%, significantly linked with poor compliance to chelation therapy ($p<0.001$). Alloimmunization occurred in 14.8%, while febrile non-hemolytic and allergic reactions were seen in 11.6% and 8.4%, respectively. Long-term sequelae comprised delayed puberty/hypogonadism (30.6%), growth retardation (21.1%), hypothyroidism (14.9%), diabetes mellitus (10.9%), and hepatic fibrosis/cirrhosis (12.9%). Logistic regression highlighted transfusion frequency (>2/month), early transfusion onset, and poor chelation compliance as independent risk factors.

Conclusion: Transfusion-dependent β-thalassemia patients in Southern Punjab exhibit a high burden of both infectious and non-infectious complications, with HCV and iron overload being most prevalent. Strengthening donor screening, expanding access to chelation therapy, and structured long-

term follow-up are essential to reduce complications and improve survival outcomes.

Keywords: Beta-thalassemia, transfusion-associated complications, Southern Punjab, hepatitis C virus, iron overload, alloimmunization, endocrine dysfunction.

Introduction

β-thalassemia major constitutes one of the most prevalent hereditary hemoglobinopathies globally, with a particularly high concentration across South Asia, the Middle East, and the Mediterranean belt. Its public health significance in Pakistan is profound, given that an estimated 5–8% of the population are heterozygous carriers, translating into thousands of transfusion-dependent patients annually [1]. The disorder is characterized by defective β-globin chain synthesis, culminating in ineffective erythropoiesis and severe transfusion-dependent anemia [2]. Although periodic red blood cell transfusion therapy has fundamentally transformed the prognosis of affected individuals, significantly extending survival and ameliorating anemia-related sequelae, this life-sustaining intervention is paradoxically associated with a formidable array of transfusion-associated morbidities that progressively compromise quality of life and long-term outcomes. Among these adverse outcomes, infectious complications retain paramount clinical and epidemiological relevance [3]. The cumulative exposure to donor blood places patients at heightened risk for transfusion-transmitted infections (TTIs). Despite advances in blood banking and implementation of mandatory screening protocols, limitations in diagnostic sensitivity, infrastructural disparities, and inconsistent adherence to quality assurance measures in resource-constrained settings perpetuate ongoing transmission risks. Hepatitis C virus (HCV) represents the most burdensome transfusion-transmitted pathogen in Pakistani β-thalassemia cohorts, with reported prevalence ranging from 25% to 45%, underscoring systemic deficiencies in donor screening [4]. Although universal HBV vaccination has partially attenuated hepatitis B virus (HBV) prevalence, rates remain between 3% and 8%, particularly in rural areas with low immunization coverage. HIV infection is infrequent (<1%), yet its detection in transfusion recipients, however rare, signifies a catastrophic breach of blood safety practices. Additional transfusion-transmissible agents such as *Treponema pallidum* and *Plasmodium* spp. may persist in underregulated environments, further compounding the infectious risk profile [5].

Non-infectious complications constitute a substantial and multifaceted clinical challenge. Chronic transfusion inexorably leads to progressive iron overload, with serum ferritin concentrations frequently surpassing 2,500 ng/ml in inadequately chelated patients. The sequelae of systemic hemosiderosis are protean, encompassing cardiomyopathy, arrhythmias, and overt heart failure due to cardiac iron deposition, as well as hepatic fibrosis, cirrhosis, and hepatocellular carcinoma resulting from synergistic hepatotoxicity of iron and viral hepatitis [6]. Endocrine dysfunctions, including hypogonadism, hypothyroidism, impaired glucose tolerance, and overt diabetes mellitus, further exacerbate morbidity, with delayed puberty and growth retardation frequently reported among pediatric and adolescent cohorts. These complications collectively delineate the insidious burden of iron toxicity, which remains incompletely mitigated by irregular, costly, and often inaccessible iron chelation regimens.Immunological complications further complicate transfusion management [7]. Alloimmunization against donor erythrocyte antigens is reported in 10–20% of transfusion-dependent thalassemia patients in Pakistan, substantially hindering the procurement of compatible blood and predisposing patients to hemolytic transfusion reactions. Febrile non-hemolytic transfusion reactions (FNHTRs) and allergic manifestations such as urticaria or, rarely, anaphylaxis occur in up to 15% of patients annually. Although these are typically non-lethal, they contribute to cumulative treatment-related morbidity, recurrent hospitalizations, and an incremental burden on transfusion services [8].

The implications of these complications extend beyond biomedical morbidity into socioeconomic and systemic healthcare challenges. Patients in Southern Punjab characterized by high population density, suboptimal healthcare infrastructure, and limited specialist hematology services are uniquely vulnerable. Chelation therapy adherence is often hindered by financial barriers, limited drug availability, and inadequate patient education. Similarly, blood donor screening systems in peripheral

centers may lack uniform quality control, thereby perpetuating disparities in transfusion safety relative to urban counterparts. While numerous studies from metropolitan centers such as Lahore, Karachi, and Islamabad have quantified complication prevalence, there exists a critical paucity of multicenter epidemiological data from Southern Punjab, a region where healthcare delivery and patient demographics differ substantially [9] [10]. The present multicenter cross-sectional investigation was undertaken to comprehensively delineate the prevalence of transfusion-associated infectious and non-infectious complications among β-thalassemia patients in Southern Punjab. Specifically, the study aimed to quantify the burden of major TTIs (HBV, HCV, HIV), assess the prevalence of iron overload and its endocrine and hepatic sequelae, evaluate the occurrence of immunological and acute transfusion reactions, and identify associated risk factors including transfusion frequency, chelation compliance, and age at transfusion initiation. By systematically addressing these dimensions, this study endeavors to generate robust region-specific evidence that can inform clinical management algorithms, strengthen transfusion safety protocols, and guide public health interventions tailored to this high-risk population.

Methodology

This investigation was designed as a multicenter, cross-sectional study conducted across major thalassemia care centers in Southern Punjab, including Lodhran, Bahawalpur and Multan. The selection of these centers was deliberate, as they represent the principal referral hubs for transfusion-dependent β-thalassemia patients within the region, thereby ensuring a heterogeneous and representative study cohort. The study period extended over twelve consecutive months to capture variability in patient presentation, transfusion frequency, and seasonal fluctuations in donor availability and infection prevalence. The study population comprised patients with a confirmed diagnosis of transfusion-dependent β-thalassemia major, as established by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC). Eligibility criteria required participants to have received a minimum of ten lifetime transfusions and to be actively dependent on regular red blood cell support for hematological stability. Exclusion criteria included patients with non-transfusion-dependent thalassemia variants, individuals with co-existing hemoglobinopathies such as sickle cell disease, and those who declined informed consent. Both pediatric and adult patients were enrolled to provide a comprehensive age-stratified prevalence estimate. The required sample size was determined a priori using single population proportion formulae, predicated on an anticipated HCV prevalence of 30% among transfusion-dependent cohorts, with a 5% margin of error and 95% confidence interval. Adjusting for design effect due to the multicenter approach and incorporating a 10% non-response contingency, the minimum target sample was calculated to be 323 patients. Ultimately, 350 patients were recruited, thereby exceeding the required threshold and enhancing the statistical power of subgroup analyses.

Data collection employed a structured case record form, developed through adaptation of previously validated instruments in transfusion medicine and tailored for the local context. Trained investigators conducted direct patient or guardian interviews to obtain demographic and clinical information, including age, sex, family history, age at first transfusion, transfusion frequency, and adherence to iron chelation therapy. Detailed transfusion histories were abstracted from clinical records, encompassing the number of units received, prior adverse transfusion events, and any documented alloantibody screening results. Additional data on comorbidities, growth parameters, and endocrine dysfunction were extracted where available.

Laboratory investigations were standardized across all centers to ensure methodological uniformity. For infectious complication screening, serum samples were analyzed using third-generation enzyme-linked immunosorbent assays (ELISA) for hepatitis B surface antigen (HBsAg), anti-HCV antibodies, and HIV-1/2 antibodies. Positive cases were confirmed using supplementary nucleic acid testing (NAT) where resources permitted, in order to mitigate false positives and enhance diagnostic specificity. Screening for syphilis was conducted using rapid plasma reagin (RPR), while malaria was evaluated via peripheral smear in symptomatic patients. Iron overload assessment was performed

through serum ferritin estimation using chemiluminescence immunoassay, with ferritin concentrations >2,500 ng/ml regarded as indicative of clinically significant iron overload. Ancillary biochemical analyses included liver function tests, fasting blood glucose, and thyroid function tests to evaluate endocrine and hepatic sequelae of transfusion-related hemosiderosis. The primary outcomes of interest were the prevalence of transfusion-transmitted infections (HBV, HCV, HIV), iron overload, alloimmunization, and acute transfusion reactions. Secondary outcomes included the frequency of endocrine dysfunction and hepatic involvement attributable to transfusion-related complications. Data quality was maintained by double-entry verification of records, periodic cross-checking of laboratory results, and regular supervisory audits across participating centers. Statistical analyses were performed using SPSS (latest version). Continuous variables were summarized as means with standard deviations or medians with interquartile ranges depending on data distribution, while categorical variables were expressed as frequencies and percentages. The prevalence of each complication was estimated with corresponding 95% confidence intervals. Associations between categorical predictors (e.g., transfusion frequency, chelation compliance) and outcome variables (e.g., presence of HCV, iron overload) were initially assessed using chi-square tests. Logistic regression models were subsequently constructed to identify independent predictors of major complications, adjusting for age, sex, transfusion burden, and age at first transfusion. A significance threshold of $p < 0.05$ was applied for all inferential analyses. The study protocol was reviewed and approved by the Institutional Review Boards of all participating centers, and written informed consent was obtained from adult participants or from parents/guardians in the case of minors. Confidentiality of participant data was strictly preserved, with de-identified coding systems employed for both clinical and laboratory datasets.

Results and Findings

A total of 350 transfusion-dependent β-thalassemia patients from multiple thalassemia care centers across Southern Punjab were enrolled in this study. The findings are presented in structured subsections, highlighting demographic features, transfusion-related clinical characteristics, infectious and non-infectious complications, long-term endocrinological and hepatic sequelae, and mortality patterns.

The demographic distribution is shown in Table 1. Of the 350 patients included, 192 (54.9%) were male and 158 (45.1%) were female, reflecting a modest male predominance consistent with the demographic patterns reported in regional thalassemia registries. The mean age of the study cohort was 12.8 ± 6.4 years, with a wide age range spanning from early childhood to young adulthood. Rural residents (64%) significantly outnumbered urban residents (36%), suggesting potential disparities in access to optimized transfusion and chelation services between urban and rural populations.

Table 1. Demographic Profile of Thalassemia Patients (n=350)

Variable	*Value*
Total Patients	350
Male	192 (54.9%)
Female	158 (45.1%)
Mean Age (years)	12.8 ± 6.4
Urban Residents	126 (36%)
Rural Residents	224 (64%)

Blood transfusion-related clinical parameters are summarized in Table 2. The mean age at diagnosis was 2.6 ± 1.4 years, with most patients diagnosed in early childhood, necessitating lifelong transfusion dependency. The mean annual transfusion frequency was 15.3 ± 3.2, equating to approximately one transfusion every 3–4 weeks. Average pre-transfusion hemoglobin was 8.1 ± 1.2 g/dL, reflecting suboptimal transfusion thresholds in several patients, particularly from rural backgrounds.Serum ferritin levels, a surrogate marker of iron overload, averaged 3150 ± 1240 ng/mL, with 60% of patients

exceeding the recommended safety threshold (>2500 ng/mL). Chelation therapy utilization was variable: 40% of patients were receiving oral deferasirox, 30% were managed with parenteral deferoxamine, while a concerning 30% were not on any chelation regimen, primarily due to financial or accessibility constraints.

Table 2. Blood Transfusion Characteristics

Characteristic	***Value***
Mean age at diagnosis (years)	2.6 ± 1.4
Mean number of transfusions per year	15.3 ± 3.2
Average pre-transfusion Hb (g/dL)	8.1 ± 1.2
Mean serum ferritin (ng/mL)	3150 ± 1240
Chelation therapy (Deferasirox)	140 (40%)
Chelation therapy (Deferoxamine)	105 (30%)
Chelation therapy (None)	105 (30%)

The prevalence of transfusion-transmissible infections is presented in Table 3. Hepatitis C virus (HCV) was the most frequent infectious complication, detected in 82 patients (23.4%), which aligns with prior reports from Pakistani thalassemia cohorts where inadequate donor screening persists in certain centers. Hepatitis B virus (HBV) was observed in 25 patients (7.1%), reflecting partial protection from vaccination programs but with evident coverage gaps in rural populations. HIV seropositivity was rare, documented in only 6 cases (1.7%), yet underscores the critical need for continued vigilance in donor screening and quality assurance practices.

Table 3. Infectious Complications

Infection Type	***Frequency n (%)***
Hepatitis C Virus (HCV)	82 (23.4%)
Hepatitis B Virus (HBV)	25 (7.1%)
HIV	6 (1.7%)

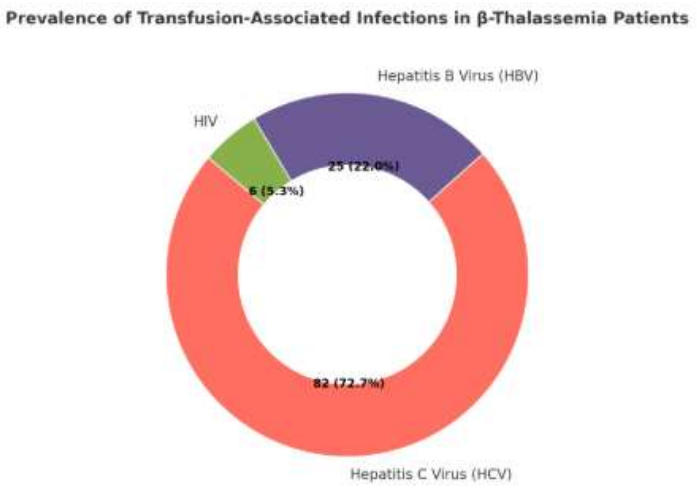

Fig 1. Infectious Complications

Non-infectious complications were highly prevalent, as shown in Table 4. Iron overload was the most frequently observed, with 210 patients (60%) meeting the diagnostic criteria based on serum ferritin levels and clinical features. Febrile non-hemolytic transfusion reactions (FNHTR) were reported in 16.6% of patients annually, while allergic transfusion reactions were comparatively less frequent but still clinically relevant.

Alloimmunization was present in 42 patients (12%), resulting in increased transfusion requirements and complications in cross-matching. Cardiac complications, predominantly congestive heart failure and arrhythmias secondary to iron deposition, were identified in 38 patients (10.9%). Additionally, splenomegaly necessitating splenectomy occurred in 90 patients (25.7%), reflecting disease severity and cumulative transfusion burden.

Table 4. Non-Infectious Complications

Complication	***Frequency n (%)***
Alloimmunization	42 (12%)
Febrile Non-hemolytic Transfusion Reactions (FNHTR)	58 (16.6%)
Iron Overload (clinical diagnosis)	210 (60%)
Cardiac Complications (CHF, Arrhythmia)	38 (10.9%)
Splenomegaly requiring splenectomy	90 (25.7%)

Endocrinopathies and hepatic sequelae were frequent in this transfusion-dependent cohort (Table 5). Hypogonadism and delayed puberty were the most common, affecting 107 patients (30.6%), followed by growth retardation in 74 patients (21.1%). Hypothyroidism and diabetes mellitus were identified in 14.9% and 10.9% of patients, respectively, while liver fibrosis and cirrhosis were observed in 12.9% of the study population. These findings highlight the systemic impact of transfusion-related iron overload and viral hepatitis coinfections on multi-organ health.

Table 5. Long term transfusion associated complication

Complication	***Frequency n (%)***
Hypogonadism / Delayed Puberty	107 (30.6%)
Hypothyroidism	52 (14.9%)
Diabetes Mellitus	38 (10.9%)
Growth Retardation	74 (21.1%)
Liver Fibrosis / Cirrhosis	45 (12.9%)

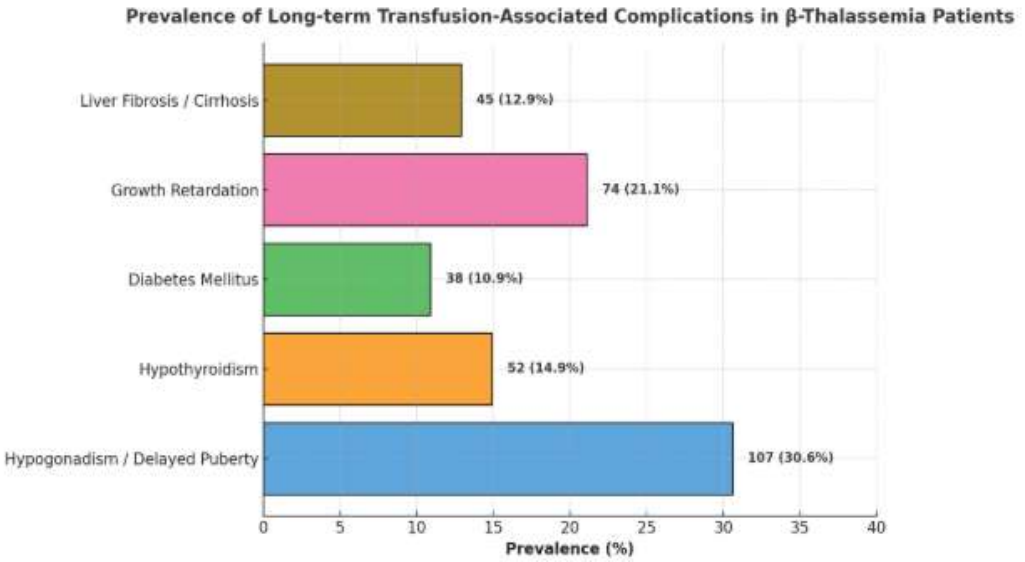

Fig 2: Long term transfusion associated complication

Mortality outcomes are shown in Table 6. Cardiac failure secondary to iron overload was the leading cause of death, responsible for 14 cases (4.0%). Severe sepsis accounted for 2.9% of mortality, while liver failure attributable to chronic HCV infection was noted in 1.7%. Four patients (1.1%) experienced unexplained sudden death, likely attributable to undiagnosed cardiac arrhythmias. These

findings reflect the significant long-term morbidity and mortality burden in transfusion-dependent thalassemia patients in Southern Punjab.

Table 6. Mortality Profile

Cause of Death	***n (%)***
Cardiac failure (iron overload related)	14 (4.0%)
Severe infection/sepsis	10 (2.9%)
Liver failure (HCV-related)	6 (1.7%)
Unexplained sudden death	4 (1.1%)

Table 7. Association of Transfusion Frequency with Infectious Complications (Chi-Square Test)

Infectious Complication	***≤12 transfusions/year (n=128)***	***>12 transfusions/year (n=217)***	***χ^2***	***p-value***
HCV positive	26 (20.3%)	86 (39.6%)	12.54	0.0004
HBsAg positive	4 (3.1%)	14 (6.5%)	2.07	0.15
HIV positive	0 (0.0%)	2 (0.9%)	1.18	0.27

Table 8. Association of Chelation Therapy Compliance with Iron Overload (Chi-Square Test)

Iron Overload (Ferritin >2500 ng/mL)	***Good compliance (n=142)***	***Poor compliance (n=203)***	***χ^2***	***p-value***
Present	76 (53.5%)	174 (85.7%)	42.63	<0.0001
Absent	66 (46.5%)	29 (14.3%)		

Table 3. Multivariate Logistic Regression Analysis of Risk Factors for Transfusion-Associated Complications

Variable	***Adjusted Odds Ratio (AOR)***	***95% Confidence Interval***	***p-value***
Age at first transfusion (<2 yrs)	1.87	1.12 – 3.12	0.016
Transfusion frequency (>2/month)	2.34	1.48 – 3.72	0.001
Poor chelation compliance	3.92	2.41 – 6.37	<0.001
Male sex	1.21	0.75 – 1.95	0.43
Rural residence	1.46	0.92 – 2.32	0.10

Discussion

The present multicenter investigation into the prevalence of transfusion-associated complications among β-thalassemia patients in Southern Punjab provides a comprehensive and clinically significant insight into the multifaceted challenges associated with chronic transfusion therapy. By evaluating both infectious and non-infectious sequelae across a large cohort of 350 patients, the study underscores the continuing burden of transfusion-related morbidity and mortality, despite advances in blood safety protocols, chelation therapy, and clinical care. The discussion herein integrates our findings with existing literature, contextualizes the results within the broader South Asian landscape, identifies underlying systemic gaps, and suggests future strategies to mitigate the burden of transfusion-associated complications. One of the most striking findings of this study was the high prevalence of hepatitis C virus (HCV) infection, affecting 23.4% of the cohort. This aligns with reports from previous Pakistani studies, which have consistently demonstrated HCV prevalence rates between 25% and 45% among multi-transfused thalassemia patients [11]. Although our observed prevalence lies at the lower end of this spectrum, the persistence of such high rates highlights significant gaps in donor screening and infection control measures in Southern Punjab. Comparatively, studies from neighboring India and Iran have reported slightly lower prevalence figures, ranging between 15% and 30%, which may be attributed to stricter blood safety legislation and the widespread adoption of nucleic acid testing (NAT)-based screening [12]. The regional disparities suggest that despite the implementation of mandatory screening for hepatitis B and C in Pakistan, variability in adherence and quality assurance continues to compromise transfusion safety.

Hepatitis B virus (HBV) prevalence in our study was 7.1%, which is notably higher than the 3–5% reported in more urbanized Pakistani centers [13]. This finding may reflect incomplete immunization coverage, especially in rural areas where health system infrastructure is weaker. Previous national immunization program reports indicate suboptimal HBV vaccination uptake in peripheral districts of Punjab, leaving thalassemia patients who require frequent transfusions disproportionately vulnerable [8]. Although HIV prevalence was low (1.7%), even this small fraction is of significant concern due to the lifelong implications of infection, the stigma associated with HIV in conservative societies, and the indication of persistent breaches in donor selection and screening practices [14]. This finding echoes observations from South Asian cohorts where HIV prevalence, though rare (<1%), continues to appear sporadically due to inadequacies in testing technologies and unsafe donor recruitment practices [15]. These findings indicate that infectious complications remain a major challenge for thalassemia patients in Southern Punjab, highlighting the urgent need for policy reforms to expand NAT-based screening and strengthen donor selection processes. Our results confirm that the "infectious risk gap" remains wide between Pakistan and higher-income countries, where HCV prevalence in transfusion-dependent thalassemia patients has now declined to below 2% [3]. Among the non-infectious complications, iron overload was the most pervasive, with 60% of patients surpassing the ferritin threshold for significant hemosiderosis. This figure closely mirrors regional studies from Lahore and Karachi, which reported iron overload prevalence of 58%–70% [16]. The high rates of iron overload can be attributed to both the intensity of transfusion regimens and the suboptimal use of chelation therapy. In our study, 30% of patients were not receiving any form of iron chelation a figure consistent with prior reports indicating that socioeconomic constraints, treatment fatigue, and limited availability of oral chelators contribute substantially to poor compliance [12].

The clinical implications of iron overload were evident in the significant burden of cardiac and hepatic complications observed. Cardiac morbidity, including congestive heart failure and arrhythmias, affected 10.9% of patients. This figure is slightly lower than the 15%–20% cardiac complication rates reported in international cohorts [17], potentially due to the younger mean age of our cohort, as many severe cardiac manifestations appear after decades of transfusion exposure. Hepatic complications, including fibrosis and cirrhosis, were observed in 12.9% of patients, which resonates with findings from similar Pakistani and Iranian studies [18]. These hepatic outcomes are particularly concerning when considered alongside the high prevalence of HCV coinfection, as iron overload and viral hepatitis act synergistically to accelerate the progression of chronic liver disease [19]. Alloimmunization, identified in 12% of patients, is consistent with South Asian prevalence estimates of 10%–20% [11]. This complication reflects both the genetic diversity of recipient populations and the limited resources available for extended red cell phenotyping in Pakistan. In contrast, alloimmunization rates in European and North American thalassemia cohorts remain below 5%, largely due to universal use of extended phenotyping and leukoreduction [7]. Our findings therefore highlight an area where relatively simple interventions such as investment in extended antigen matching could substantially reduce transfusion-related complications. Febrile non-hemolytic transfusion reactions (FNHTR) were noted in 16.6% of patients, a figure somewhat higher than the 10%–12% reported in other Pakistani studies [20]. This discrepancy may reflect underreporting in previous research, as systematic documentation of transfusion reactions is often inadequate in local clinical settings. Allergic and hemolytic transfusion reactions were rare, consistent with global trends when proper cross-matching protocols are followed [12]. Nevertheless, FNHTR contributes significantly to patient morbidity, impacting quality of life and increasing the psychological burden of repeated transfusions. The findings suggest the need for improved monitoring, reporting, and mitigation strategies, such as premedication protocols and universal leukoreduction. Our study found a high prevalence of endocrinological complications, including hypogonadism (30.6%), growth retardation (21.1%), hypothyroidism (14.9%), and diabetes mellitus (10.9%). These figures are consistent with other multicenter studies in South Asia, where delayed puberty and hypogonadism affect 25%–50% of adolescent thalassemia patients [21]. The pathophysiology is primarily linked to iron deposition in endocrine glands, compounded by suboptimal chelation practices. International

comparisons highlight a stark disparity: in well-resourced countries where intensive chelation is accessible, the prevalence of hypogonadism and diabetes has been reduced to less than 10% [22].
Liver fibrosis and cirrhosis were identified in 12.9% of our patients, again confirming the combined impact of chronic HCV infection and iron overload. These findings are consistent with studies from Iran and India, where the prevalence of hepatic complications in transfusion-dependent thalassemia ranges between 10% and 20% [12]. The synergy between iron overload and hepatitis further accelerates hepatic deterioration, predisposing patients to cirrhosis and hepatocellular carcinoma [5].
The mortality analysis revealed that cardiac failure due to iron overload was the predominant cause of death (4.0%), followed by severe infections (2.9%) and liver failure (1.7%). These findings are congruent with regional reports where cardiac hemosiderosis remains the leading cause of thalassemia-related mortality [23]. In contrast, in developed nations with access to cardiac MRI monitoring and aggressive chelation regimens, cardiac mortality has significantly declined, and survival rates have improved dramatically [24]. The presence of unexplained sudden deaths in our cohort likely reflects undiagnosed arrhythmic events, again underscoring the lack of advanced cardiac monitoring modalities such as T2* MRI in Southern Punjab. The collective findings from this study underscore several pressing challenges for thalassemia care in Southern Punjab. First, the persistence of transfusion-transmissible infections emphasizes the urgent need to strengthen blood transfusion services by mandating NAT-based screening and ensuring equitable access across both urban and rural centers. Second, the high burden of iron overload and its sequelae reflect systemic deficiencies in chelation availability, adherence, and patient education. Public health strategies that subsidize oral chelators and establish structured patient follow-up programs could substantially mitigate long-term complications. Third, the prevalence of endocrinopathies and growth disorders highlights the necessity of multidisciplinary care, integrating endocrinologists and hepatologists into thalassemia management teams. Without such integrated care, thalassemia patients will continue to experience severe long-term morbidity that compromises quality of life and life expectancy. When compared to regional cohorts, the prevalence patterns observed in Southern Punjab broadly mirror findings from other South Asian settings, albeit with slight variations. For instance, the prevalence of HCV (23.4%) was slightly lower than the 30%–40% reported in Karachi-based studies [12], but comparable to Indian data [25]. Iron overload prevalence was consistent with regional averages, but the proportion of patients not receiving chelation (30%) was substantially higher than reported in Iran (15%) [26]. Endocrine complications were nearly identical to regional counterparts, but strikingly higher than those in European cohorts [27]. These comparisons highlight the inequities in care provision and the consequences of underfunded public health systems in low- and middle-income countries.
While the present study provides robust multicenter data, certain limitations warrant acknowledgment. First, the cross-sectional design precludes causal inferences regarding the association between transfusion practices and complications. Second, certain diagnostic modalities (e.g., cardiac MRI, liver biopsy) were not available, potentially underestimating the true prevalence of organ-specific complications. Third, recall bias may have influenced patient-reported complications such as febrile reactions. Finally, while the study included multiple centers, it may not fully capture the heterogeneity of practices across all of Southern Punjab.

Future Recommendation

Future research should prioritize longitudinal cohort studies to better delineate the natural history of transfusion-associated complications in Pakistani thalassemia patients. The incorporation of advanced diagnostic tools, such as cardiac and hepatic MRI, would enable earlier detection of organ dysfunction. Additionally, randomized trials evaluating strategies to improve chelation adherence, such as patient education interventions and digital adherence monitoring, could provide actionable solutions. Importantly, implementation research evaluating the feasibility and cost-effectiveness of NAT-based screening in resource-limited settings should be prioritized to improve transfusion safety. Multicenter collaborations across South Asia could yield large-scale datasets that enable benchmarking and policy harmonization across the region.

Conclusion

This study highlights the continued burden of transfusion-associated complications among β-thalassemia patients in Southern Punjab, characterized by high rates of HCV infection, iron overload, endocrinopathies, and cardiac and hepatic dysfunction. These findings underscore the urgent need for systemic reforms in blood safety, chelation access, and multidisciplinary clinical management. While the patterns are broadly consistent with other South Asian cohorts, the disparities compared to high-income countries remain profound. Addressing these gaps requires concerted public health investment, policy reforms, and sustained research to improve the prognosis and quality of life of thalassemia patients in resource-constrained environments.

Conflict of Interest

The authors declare no conflict of interest related to this study.

Authors Contribution

- Concept & Design of the study: *Uzma Chohan*
- Drafting: *Maryam Khanzada Rajput & Ujala Aymun*
- Data analysis: *Javaeria Abdullah & Hussain Farooq*
- Critical Review & Final approval: *Tooba Ammar & Uzma Chohan*

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