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The Role of Consanguinity, Blood group, and Hemoglobin Levels in Beta Thalassemia Vulnerability

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Abstract: The present study project aims to investigate the relationship of β-thalassemia with Consanguinity, Blood group, and Hemoglobin Levels of both gender (male and female), in Saladin Governorate. Variables grouping of (n=100) β-thalassemia patients was performed. The current study is conducted to cover a period of six months. In total 100 patients diagnosed with Beta thalassemia were enrolled. They were divided into two groups, patients in Group I (n = 50) of male and those in Group II (n = 50) of female. The observed consanguinity pattern in both genders was non consanguinity>Cousin, while the observed ABO blood group patterns in male patients were O+>A+>B+>AB+& O-, yet the ABO blood group pattern in the females was $O^+ > A^+ > O^- > AB^+ > B^+$. As well as, Hb levels in the 10-20 age groups were lower than in the other age groups studied.,The study came with conclusion that β-thalassemia patients tend to show a higher frequency of the A+ blood group and the lowest frequency of O- blood group; while consanguinity had no effect on the incidence of beta thalassemia.

Keywords : Beta thalassemia, Consanguinity, Blood group, Hb levels.

1. Introduction

Thalassemia is a hereditary blood disorder that stands out as the most prevalent single-gene inherited condition. It results from a reduction or complete lack of either α- or β-globin chain synthesis, which are essential components of hemoglobin. This condition typically follows an autosomal recessive inheritance pattern, meaning that an individual must inherit the defective genes his/her parents and then continues to develop the disease [1].

Notably, thalassemia occurs with higher frequency in regions where consanguineous marriages (unions between close relatives) are more common. This increased incidence in these areas is the result of a higher probability of both parents' carrying and inheriting from one another the identical genetic mutation to their offspring. [2-4]

The consanguinity-thalassemia link explains how cultural and social practices can contribute to segregating, spreading, and maintaining genetic disorders within populations [1]. Thalassemia and Hemoglobino-pathies Distribution: Different Geographical Locations Beta thalassemia syndromes are a major health problem in the Indian subcontinent where prevalence of beta thalassemia mutations is reported up to 17% with race specific distribution [5]. In India, hemoglobin disorders have been estimated to affect 0.37 per1000 live births [6].

It is especially common in a wide band from the Mediterranean basin, and of course through the Middle East region (including Iran). This occurs leading the situation to reach across India to South China [7]. Beta thalassemia major, also referred to as "Cooley's anemia," typically manifests its symptoms within the period of first twelve months of life in 95% of the patients in total. As a matter of fact, it's estimated that there are approximately 80 million individual who carries the beta thalassemia worldwide [8].

Patients with severe thalassemia require lifelong blood transfusions to provide healthy cells of a red type in blood (RBCs) then suppressing their uninfluential erythropoiesis. However, this repeated exposure to foreign RBCs increases the critical level of risk of red cell allo-immunization - the developing process of antibodies that work opposingly to the transfused RBCs. This can lead to delayed hemolytic transfusion reactions (DHTRs), which are serious complications of transfusion therapy [9].

In a study on thalassemia major patients in Peshawar reveals significant insights into the age and blood group distribution of affected individuals [10]. The age distribution data shows a stark concentration of cases in young children, with the vast majority falling within the 1-10 year age range. This finding aligns with the typical onset of thalassemia major symptoms in early childhood, as noted by [11] in her comprehensive review of beta-thalassemia.

A higher case of B+ blood type was almost followed closely by O+, Etc, among these cases from other patients' Blood group analysis. Such a distribution pattern admittedly is not generally expected in the population, indicating an association of some types with major thalassemia traits at this area. These results corresponded to the study of [12] which also found differences in ABO blood group distribution among thalassemia patients.

The overall focus identified the need for strategies that incorporate awareness, prenatal testing and blood transfusions as cornerstones in managing thalassemia. Some have argued that this testing as identified by [13] may be an instrumental factor for at-risk couples to THINK about their ability plan. Thalassemia major patients, for example, are typically dependent on frequent blood transfusions to preserve quality of life and [14] recently recounted a historical perspective in modern thalassemia therapeutics.

The background information provided on thalassemia, including its types and causes, offers a comprehensive context for understanding this genetic condition. This aligns with the detailed explanations of thalassemia pathophysiology presented by [15] in their chapter on inherited disorders of globin synthesis.

Beta-thalassemia is prevalent in 60 countries, with high incidence in South Asia, including India and Pakistan, as well as Sardinia [16&17]. An estimated 60,000 individuals are affected by thalassemia annually, primarily in developing countries [18].

The ABO blood group system, discovered by Landsteiner in 1900, along with the Rhesus system is fundamental in transfusion medicine and transplantation. Blood type is determined by inherited antigens on red blood cell surfaces, categorized into A, B, AB, and O groups, with Rh positive or negative factors [19 & 20]. These systems play crucial roles in population genetics, forensics, and paternity testing [21& 22]. Research has established connections between blood types and certain diseases. For instance, blood group B has been associated with increased risk of severe periodontitis, while blood type O has been linked to susceptibility to thalassemia [23& 24].

In β-thalassemia, reduced β-globin chain production leads to an excess of α-chains, resulting in the formation of α4 tetramers. These accumulate in red blood cells, causing premature cell destruction [25]. Patients may experience iron overload, a dangerous complication resulting from the disease itself or frequent blood transfusions. Studies have shown that β-thalassemia patients often exhibit elevated liver enzyme levels, indicating

potential liver dysfunction [26]. The liver is typically the first organ affected by iron overload in thalassemia patients. Hepcidin, a hepatic peptide hormone, plays a crucial role in iron homeostasis. Hepcidin deficiency, common in β-thalassemia due to increased erythropoietic activity, is a primary cause of iron excess in iron-loading anemia [27].

Efficient carrier identification is crucial for thalassemia prevention. While genetic testing is highly accurate, its widespread implementation in less developed areas faces limitations. Routine blood testing, being popular and cost-effective, provides numerous parameters for analysis. Since 1970, various formulas using blood routine parameters have been developed to identify β-thalassemia minor [28]. In fact, the patients with critical thalassemia, demanding long-term systematic red blood cell transfusions, are labelled as showing the aspect of transfusion-dependent thalassemia (TDT), necessitating iron chelation therapy and complication monitoring. Common complications in TDT patients include iron overload-related issues such as cardiomyopathy, liver cirrhosis as well as the hormonal deficiencies [29 &30].

Patients with mild to moderate thalassemia not requiring long-term transfusions can obviously be categorized as carrying the aspect of non-transfusion-dependent thalassemia (NTDT). NTDT patients typical experience complications related to chronic hemolysis, including pulmonary artery hypertension, extra-medullary hematopoiesis, cholelithiasis, and iron overload from rise gastrointestinal iron absorb [31]. Additionally, thalassemia patients face a dangerous of infections because immunological disorder associated with both the disease and its clinical treatments [32&33].

Over the past three decades, survival rates for thalassemia patients, particularly those with TDT, have significantly improved due to regular red blood cell transfusions and iron chelation therapy [34]. The most striking difference has been the elimination of iron-overloaded cardiomyopathy and heart failure deaths, attributed to iron chelation therapy and MRI-essential tissue iron overload monitoring [35&36]. While iron overload remains the main factor in TDT patient death, effective management has led to improved outcomes. Other significant contributors to TDT patient mortality include infections, liver diseases, diabetes mellitus, and thromboembolisms [37]. For the patients with NTDT, a large cohort research study has recently shown that in cases of the patients who have a non-transfusion-dependent beta-thalassemia (NTDT) the main reason of early mortality is represented by cardiovascular disease, although hepatic complications remained the main cause of death at increasing ages [38].

2. Materials and Methods

Study contrivance

A structured, self-administered questionnaire was designed after reviewing the relevant literature. Content and face validity were assessed by performing an extensive literature review followed be rigorous screening of the relevant information with consultations from expert in community medicine &hematology. Questions were either multiple choice, dichotomous (yes/no), or open ended and the reported format of questions varied. A pilot study was done in 40 patients from one PHC (primary health center) using convenience sampling prior to starting the data collection, for testing of readability and appropriateness of the tool. Furthermore, the pilot phase also allowed estimating the time each participant

needs for filling out each questionnaire. This led to some changes needing in the questionnaire. Piloted 20 participants were excluded from the study database as.

-Individualistic variables

Individual indicators inclusive age in years, gender of the contributor, marital station, personal and family histories of B thalassemia, Blood group type. Moreover; hemoglobin levels were measured for both gender by used the HemoCue1 Hb 201+ is a photometric device that uses specially designed micro-cuvettes containing three different dried reagents to estimate total blood Hb concentration. The blood sample is wicked into the pretreated cuvette from the fingertip. The Hb value is displayed on the device screen within 30 seconds. No dilution is required, and the device can be used with capillary, arterial, or venous blood. The Pronto1 DCI-mini is designed for use with infants and children weighing 3 to 30 kg. The DCI-mini sensor is a digital clip applied to a small child's finger or on an infant's big toe or thumb and uses a lightweight ribbon cable to connect to the Pronto1 pulse oximetry device. By passing various wavelengths of visible and infrared light through a fingertip or toe, the detector within the sensor can measure changes in light absorption during the blood pulsatile cycle and send the signals to the Pronto1 device. The device then uses a multi-wavelength calibration equation to quantify the percentage of total hemoglobin in blood. The Hb value in g/dl is displayed on a screen within 40 seconds.

Statistical Analysis:

Data management and analysis were conducted using Microsoft Excel and IBM SPSS Statistics version 29 (Armonk, NY: IBM Corp). The analytical process began with normality testing for continuous data. Independent t-tests were then applied to compare means between groups with positive and negative perceptions of consanguineous marriage. For categorical data, chi-square or Fisher's exact tests were used to determine associations. Finally, multiple logistic regression analysis was implemented to identify significant predictors of positive perception towards consanguineous marriage. This comprehensive statistical approach enables the identification of significant relationships and predictive factors related to perceptions of consanguineous marriage within the study population, providing a thorough examination of the collected data.

3. Results

Decrease prevalence of consanguinity among β-thalassemia families. A total of 50 families in male group (parents of β-thalassemia patients) were studied. Consanguinity of parents was observed and reported in following two groups; (i) 22 (11%) were relatives, (ii) 28 (14%) were non relatives (Figure 1).

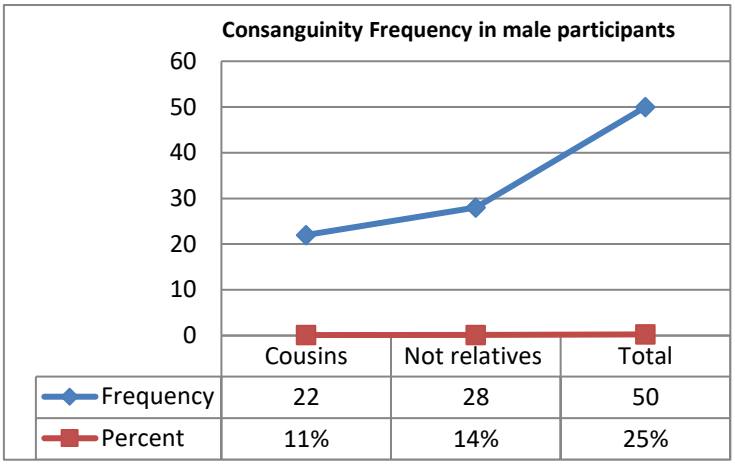

Figure 1: Consanguineous pattern in 50 β-thalassemia studied male families

Decrease prevalence of consanguinity among β-thalassemia families. A total of 50 (25%) families in female group (parents of β-thalassemia patients) were studied. Consanguinity of parents was observed and reported in following two groups; (i) 18 (9%) were relatives, (ii) 32 (16%) were non relatives (Figure 2).

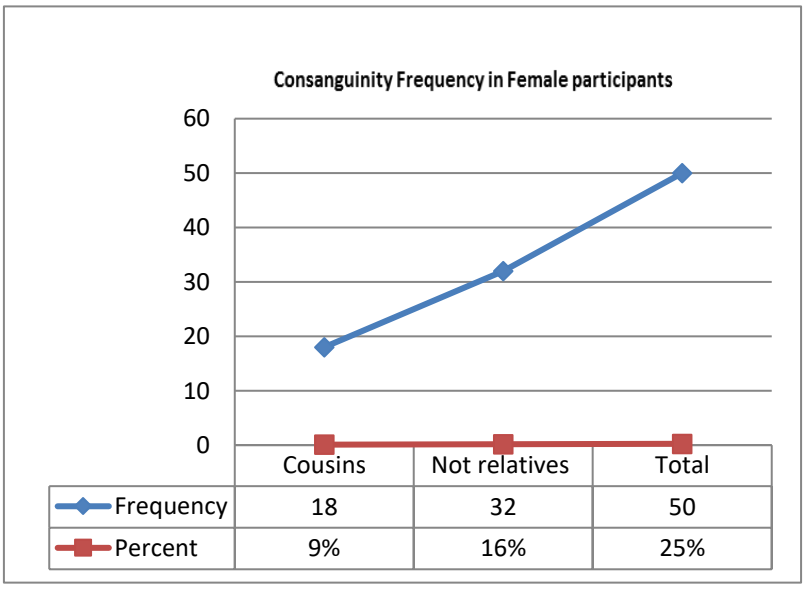

Figure 2: Consanguineous pattern in (50) β-thalassemia studied female families

These 100 families produced a total of 100 children, 50 (25%) males and 50 (25%) females were β-thalassemia.

The data was collected from 50 β- thalassemia male patients including 100 patients, 50 (25%) male patients and 50 (25%) female patients. According to (Figure 3), most of the patients of male β-thalassemia had blood group O^+ (14%, n=28), followed by A^+ (6%, n=12), B^+ (3%, n=3), AB^+ (1%, n=2) and O^- (1%, n=2) blood groups, respectively . According to results, the observed pattern of ABO blood group amongst β- thalassemia patients was $O^+ > A^+ > B^+ > AB^+$ & O^-.

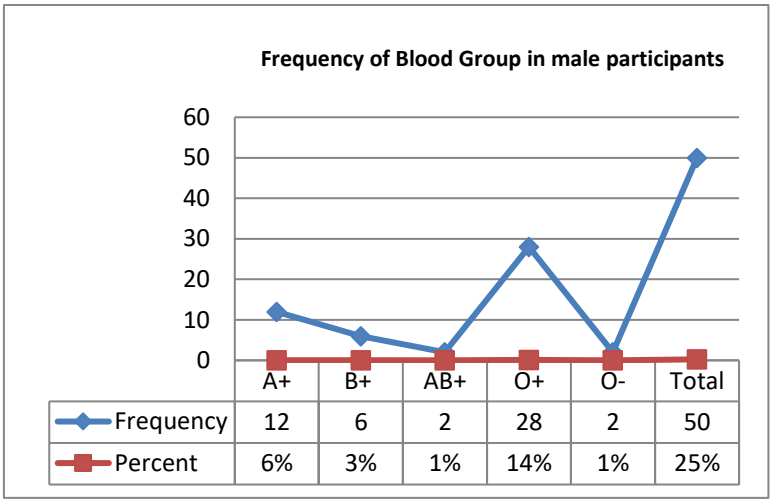

Figure 3: Frequency of Blood Group in (50) β-thalassemia male participants

The data was collected from 50 β- thalassemia male patients including 100 patients, 50 (25%) male patients and 50 (25%) female patients. According to (Figure 4), most of the patients of male β-thalassemia had blood group O^+ (10%, n=20), followed by A^+ (6%, n=12), O^- (4%, n=8), AB^+ (3%, n=6) and B+ (2%, n=4) blood groups, respectively . According to results, the observed pattern of ABO blood group amongst β- thalassemia patients was $O^+ > A^+ > O^- > AB^+ > B^+$.

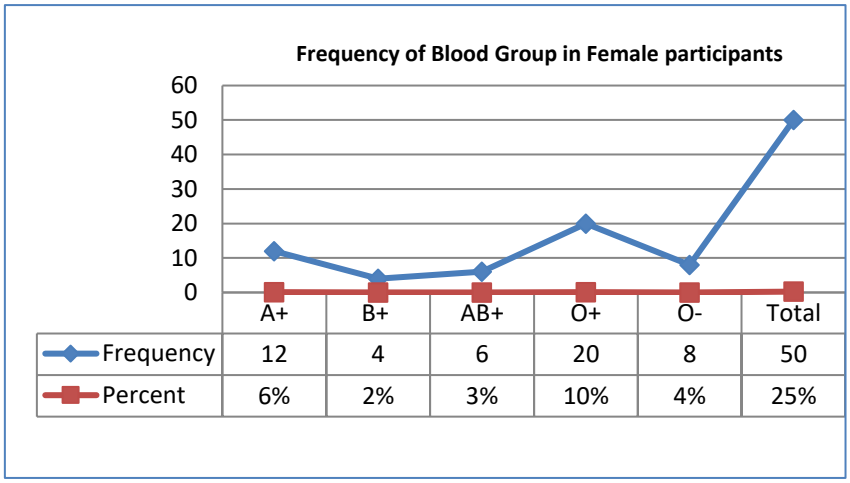

Figure4: Frequency of Blood Group in (50) β-thalassemia female participants

The observed ABO blood group pattern in male was O+>A+>B+>AB+& O-, but ABO blood group pattern in female was $O^+ > A^+ > O^- > AB^+ > B^+$ .The overall frequency of O+ and A+ blood groups was higher in both gender patients.

Hemoglobin level of anemia β-thalassemia traits in male (50) decreased at age (10-20) years more than at age (1-10) and (20-30); as shown in (Figure5).

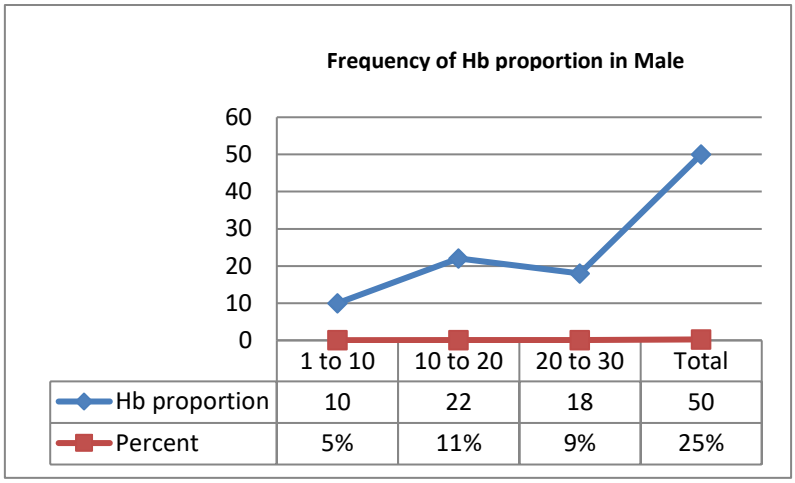

Figure5: Frequency of Hb in (50) β-thalassemia male participants

Hemoglobin level of anemia β-thalassemia traits in female (50) decreased at age (10-20) years more than at age (1-10) and (20-30) as shown in (Figure6)

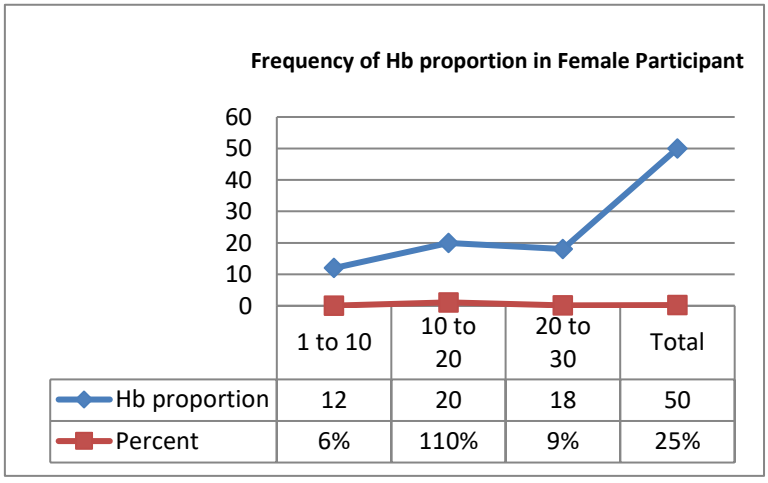

Figure6: Frequency of Hb in (50) β-thalassemia female participants

Hb level in both gender was decreased at same age (10-20) years, but Hb level was decreased less than at (1-10) and (20-30) .The overall frequency of Hb level in (50) male at age (1-10) year was 10 (5%), while the overall frequency of Hb level in (50) male at age (10-20) year was 22 (11%), the overall frequency of Hb level in (50) male at age (20-30) year was 18 (9%).

In female the overall frequency of Hb level in (50) female at age (1-10) year was 12 (6%), while the overall frequency of Hb level in (50) female at age (10-20) year was 20 (10%), the overall frequency of Hb level in (50) female at age (20-30) year was 18 (9%).

4. Discussion

Thalassemia is inherited blood disorders characterized by reduced or absent production of one or more globin chains, essential components of hemoglobin.

This deficiency results in an imbalance in hemoglobin production and leads to ineffective erythropoiesis, where red blood cells fail to mature properly [39]. The severity of thalassemia is determined by which globin chains are affected and the extent of the deficiency. In beta thalassemia, the condition is categorized into three main types based on clinical severity and transfusion requirements: major, intermediate, and minor [40]. Beta thalassemia major is the most severe form, typically necessitating regular blood transfusions from early childhood. Intermediate: Here, beta thalassemia patients usually present with moderate anemia and may require occasional transfusions. Minor: Includes individuals who are mostly asymptomatic in the delta aggregation of clinical symptoms [39]. The impact of consanguinity (especially when it is between first cousins) on the increased incidence genetic disorders such as thalassemia has been well established. In a Moroccan study, Maroczy reported the rates of first cousin consanguinity to be 68.69% while [41] found that out of which about 18.1% had one child with thalassemia major per families and two or more other children affected by TM in their respective families The study showed that 50.25% of the parents responsible for hemoglobinopathies in their children were first cousins (consanguineous mating was significantly associated with increased prevalence of these disorders) [42]. By contrast, the present study found a lower but still significant consanguinity rate: 40.3% of cases had parents who were related and an overall frequency for all patients with respect to consanguineous marriages was 37.3%. These studies highlight the need for genetic counseling and screening programs in consanguineous populations, to offer prevention of adverse outcomes related to hemoglobinopathies such as thalassemia [43]. As the study conducted by Suchitra et al.,[44] 96% of parents in case of β-thalassemia patients were consanguineous including first cousin, distant blood relative and same caste. The high rate of consanguinity in the region contributes much to thalassemia [8], with this study observing that 2.5 times higher risk for a child to be suffered from thalassemia when born by parents who had first cousin marriage compared those non-consanguineous unions [45]. In our study, the highest percentage of consanguinity was observed in synchronization method and first cousin marriages were leaded by maternal lineage among 72% amounting to about three-fourth proportion of total consanguineous unions with thalassemia child showing caste as a significant factor [46]. These results illustrate the intricate relationship between cultural practices and genetic susceptibility in specific populations, emphasizing the importance of offering culturally appropriate and systematic screening for carriers as well as public health programs to tackle high β-thalassemia frequencies among communities with historically increased prevalence due to consanguinity [45]. In another study, it was found a high consanguineous and thalassemia association in the same population. While 38% of the survey respondents were offspring from first cousin marriages, surprisingly only 26% belonged to second-cousin descendants. Of note, 36% of the patients were product of non-consanguineous unions. This very high percentage of consanguinity, especially first cousin marriages, is also in keeping with reports from other studies carried out among populations living where these type of unions are common [47]. Because

during consanguineous marriages breeding of homozygote carriers is more frequent due to the inheritance chances for recessive traits are much increased from common ancestor [48]. This pattern could quite readily be explained by an absence of consanguineous marriages as well reflecting the importance of genetic counseling and screening programmers in areas where thalassemia is common place [49]. The data also supports the observation that consanguinity is important, but other genetic factors and environmental factors must interact in many cases of thalassemia minor because only a third offspring have parental consanguinity for this disorder [48]. In addition, the results also imply that whilst consanguinity is an important risk factor for thalassemia minor other genetic as well as environmental factors are likely to be contributing factors including the fact shown in our study which demonstrated over a third of cases had been born to non - consanguineous parents [50]. Many of studies determined the distribution percentage frequency (prevalence) of ABO blood grouping among thalassemia and normal population in general by traditional methods.

. A study in Kirkuk- Iraq, reported O+ as the most prevalent blood group (48.4%) among thalassemia patients [51]. Similarly, research conducted in Mumbai, India, identified O+ as the predominant blood group in β-thalassemia patients [52]. A subsequent 2014 Kirkuk study corroborated these findings, showing O+ (48.4%) as the most common, followed by B+ (24.2%) and A (18.1%) [53]. In contrast, studies of normal populations have shown some variations. A study in Tikrit city, Iraq, found O+ to be the most common (41.5%) among blood donors. However, in some general population studies, B+ was reported as more prevalent (36%) [54].Notably, AB- and O- blood groups were less frequently associated with thalassemia [55]. A Baghdad study reported O as the most common (59.1%) and AB as the least common blood group among thalassemia patients [56]. In India, blood group distribution shows regional variations, with B being more common in the north and west, while O is more prevalent in the east, south, and central parts [57]. The current study agreed with a study revealed a distinct pattern in blood group distribution among β-thalassemia patients, with blood group O+ being the most prevalent at 34.6%, followed by B (29%), A (25%), and AB (11.4%) [58], this distribution pattern of O > B > A > AB is consistent with findings from previous studies in similar populations [59]. Interestingly, while this overall pattern remains consistent across genders, there are notable gender-specific variations. There was a disparity of ABO blood groups distribution among the study participants based on gender with type O^+ and A more predominant in females while AB^+ (more likely to belong) B were commoner in males This is consistent with previous reports [60]. In The Journal of Medical Virology, a study also notes that there was an empirically large increase in the ratio of Rh-positive relative to Rh-negative blood type among female patients compared with male [61]. These gender-specific disparities in blood group distribution among thalassemia patients may have implications for transfusion management and genetic counseling. The gender-and blood group-specific associations observed here have been consistent with the other studies, suggesting essential parameters

to account for in therapeutic approaches of β-thalassemia patients [62]. B+ seems to be the most common blood group in this study with a frequency of 35.95%, followed by O^{+}:34.82% A^{+}:26.13%, AB:$^{+}$4 and O^{-}1% blood groups [63]. This distribution pattern is strongly in agreement with the study from Ayub Medical College results on similar frequency of ABO blood type among thalassemia major patients [64]. The consistency between these studies strengthens the reliability of the findings and suggests a potential correlation between blood type and thalassemia major susceptibility, particularly for individuals with B+ blood type in the District Peshawar region [65]. This pattern differed from the very common blood type distribution, of many populations this suggest an environmental or genetic background affecting birth rate with thalassemia major within specific Blood groups [66]. The presence of B+ blood type among more thalassemia major patients in this area makes possible–the genetic connections or the predisposing factors with that kind of blood group [67].

The percentage of anemia carriers among Beta-thalassemia studies is consistent with a previous research in Pakistan and globally. In multiple populations, a consistent direction of elevated anemia prevalence among women as compared to men has been noted [68]. The difference in risk of anemia between males and females is even greater during reproductive years, most likely due to the additional requirement for iron related to pregnancy, childbirth and lactation [69]. Moreover, Non-anemic Beta-thalassemia traits had higher mean hemoglobin values as seen in this study [70] this observation argues against an effect mediated directly through the hemoglobin-pathy in anemia, but favor roles for additional contributory factors to this process. These can be some cofactors like nutritional deficiencies, chronic diseases and other genetic differences that also affect hemoglobin production [71]. These results indicate that the etiology of anemia in Beta-thalassemia carriers is considerably complicated and may justify multifaceted treatment strategies. The congruence between our results and those of other studies confirm the reliability of findings, emphasizing that clinical management for Beta-thalassemia carriers will be necessary to take in account both genetic as well environmental factor [72].

5. Conclusions

Discussion according to this systematic review of thalassemia case–control studies, the most important findings were as follows: consanguinity had significant impact on increased prevalence of thalassemia and high proportion of patients' parents in the included studies has -first or second-cousin marriage. This also stresses for mandatory genetic counseling and screening services especially in ethnic communities with high consanguinity. Blood group distribution. Data regarding blood groups among thalassemia patients was reported uniformly in various studies, O+ and A + showed the highest frequency. Such pattern differs from those of) in the general populations, and may be indicative evidence to associate blood type with a risk factor for thalassemia. The distribution of blood group and presence of anemia among thalassemia cases clearly showed sex-

specific variations. Females typically have more common blood group antigens, and a higher prevalence of anemia (that is most frequently seen in reproductive years). Anemia in Beta-thalassemia carriers is a complex issue relatively than the mere presence of hemoglobinopathy; other factors, such as nutritional deficiencies and chronic diseases might contribute to anemia severity. The difference in the distribution of blood group specificity and thalassemia prevalence observed between regions highlights region-specific studies with unique approaches to prevent/manage this complex disease. The consistency of these findings between multiple studies highlights the reliability and calls for an integrated approach including genetic and environmental factors, in clinical management of thalassemia.

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