



A Prospective Study for the Outcomes of Thalassemia in Kirkuk 2016

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Background: Thalassemia is one of the most globally common chronic hematological disorder. This inherited disorder is characterized by an abnormal production of hemoglobin protein resulting in a life-threatening disease of two main types α and β . In Kirkuk city it was found that, β -thalassemia was the most common disorder and various factors were found to be contributing to the counts of β -thalassemia including ethnic origins and migration that added more burden on the genetic pool of the region and on the inheritance of traits in that area.

Objective: Evaluating the prevalence of thalassemia in Kirkuk city according to a number of parameters that included age, gender and ethnic background of patients along with the assessment of the effect of consanguinity marriage on the incidence of the disease.

Patients & Methods:

Total of (156) clinically diagnosed β -thalassemia patients attending “Thalassemia Unit “ in Azadi Teaching Hospital in Kirkuk City were questioned and data were divided into four cohorts for evaluation; followed by statistical analysis.

Results:

No significant difference was detected in β -thalassemia distribution among males and females in Kirkuk city 2016; β -thalassemia was more prevalent in children born following the years of insecurity in the country generally and Kirkuk city especially. In addition, about (77.56%) of β -thalassemia patients were the outcomes of consanguinity marriage from the first degree cousin whom affected with β -thalassemia minor without their knowledge. Additionally, the distribution of β –



thalassemia patients between different ethnic groups living in Kirkuk and the surrounding areas indicated a significant difference ($p < 0.05$) in the incidence of β – thalassemia in Turkman patients who had recorded the lowest incidence rate of (17.31%) compared to the Kurd patients where they recorded the incidence rate of (37.18%) and Arabs where they recorded the highest incidence rate of (45.52%) among total of (156) β –thalassemia patients where most of them came from rural areas or were internally displaced people.

Conclusions:

β - thalassemia disorder is one of the prevalent inherited diseases in Kirkuk city with increasing frequency among children in the ages of (1-3) years old. Besides, the distribution of β - thalassemia disorder did not vary among males and females in Kirkuk city in the year 2016 and it was concluded that, the frequency of β - thalassemia showed an increase in the years following wars and invasions in Kirkuk city. Moreover, consanguinity marriage increases the frequency of β - thalassemia incidence among both male and female patients. Additionally, individuals with minor β - thalassemia increase the ratio of β - thalassemia incidence among their children and the distribution of β - thalassemia differ according to different ethnic groups.

Key words: Thalassemia, Kirkuk 2016, Prevalence of β -thalassemia, Consanguinity.



دراسة مستقبلية لنتائج التلاسيميا في مدينة كركوك ٢٠١٦

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المقدمة: التلاسيميا هو واحد من أكثر الاضطرابات المزمنة والاكثر شيوعا في العالم. يتميز هذا الاضطراب الوراثي بالانتاج المشوه لبروتين الهيموغلوبين تكون نتيجته مهددة لحياة المريض بنوعه الفا وبيتا. إن التلاسيميا من نوع بيتا هي الاكثر شيوعا في مدينة كركوك وقد وجدت هناك عوامل كثيرة تؤدي الى زيادة أعداد المصابين بالتلاسيميا منها الاختلافات العرقية والهجرة والتي أضافت ضغوطات الى التنوع الوراثي للصفات في تلك المنطقة.

الهدف من الدراسة: لتقييم نسبة انتشار التلاسيميا في مدينة كركوك نسبة الى عدد من العوامل والتي تضمنت العمر، الجنس والاختلافات العرقية إضافة الى تقييم تأثير عامل زواج الاقارب.

المرضى وطرق العمل: مجموع ١٥٦ مريض مشخص سريريا يحضرون الى وحدة التلاسيميا في مستشفى ازادي التعليمي في مدينة كركوك تم استبيانهم وتم تقسيم النتائج الى اربعة مجاميع لغرض التقييم وتم تحليل النتائج احصائيا.

النتائج: لم تكن هناك فروقات احصائية في نسبة الاصابة بين المرضى الاناث والذكور المصابين بالبيتا تلاسيميا في مدينة كركوك في ٢٠١٦. كانت الاصابة بالبيتا تلاسيميا اكثر شيوعا بين الاطفال المولودين في السنوات التي تعقب عدم الاستقرار الامني في البلد عموما وكركوك خصوصا. بالاضافة الى ذلك فقد كانت نسبة (٥٦،٧٧%) من المرضى المصابين هم نتيجة لزواج الاقارب من الدرجة الاولى من ابناء العمومة المصابين بالتلاسيميا الصغرى وبدون علمهم بالاصابة. وكذلك فإن نسبة الاصابة بالبيتا تلاسيميا سجلت النسبة الاقل بين المرضى التركمان بنسبة (١٣،١٧%) يليهم المرضى الكورد بنسبة (١٨،٣٧%) والاعلى بين العرب بنسبة (٥٢،٤٥%) من مجموع ١٥٦ مريض أغلبهم جاؤا من مناطق ريفية أو من النازحين.

الاستنتاجات: البيتا تلاسيميا واحد من الامراض الوراثية الشائعة في مدينة كركوك وإن نسبة هذا المرض تزداد في الاعمار (١-٣) سنة ولم تظهر النتائج فروقات معنوية في نسبة انتشار مرض التلاسيميا بين الاناث والذكور في مدينة كركوك وكذلك فقد وجد ان نسبة انتشار المرض في المدينة تزداد في السنوات التي تلي الحروب والغزو وان زواج الاقارب يزيد من نسبة حدوث المرض وأن الافراد المصابين بالتلاسيميا الصغرى يسببون زيادة في نسبة الاصابة بالتلاسيميا بين اطفالهم بالاضافة الى اختلاف نسبة انتشار التلاسيميا بين الاعراق المختلفة.



الكلمات المفتاحية: الثلاسيميا ، كركوك ٢٠١٦ ، نسبة انتشار البيتا ثلاسيميا ، زواج الاقارب .

Introduction:

Thalassemia is one of the most globally common chronic and genetic hematological disorder [1]. This autosomal single- gene disorder is characterized by an abnormal production of hemoglobin protein and excessive destruction of the red blood cells resulting in a life-threatening disease of two main types α and β [2, 3 &4]. World Health Organization has estimated that, up to 270 million people were affected by thalassemia worldwide and there are 15 to 25 million healthy carriers in the Mediterranean area [5&6]. Thalassemia is also very common in Arab countries with different frequencies where Iraq demonstrated difference in the prevalence of β -thalassemia in different regions from 3.7% to 4.6% [7&8]. Recently, it was found that, severe β -thalassemia accounts for 50,000 to 100,000 deaths per year of all deaths of children under 5 years in low or middle income countries and in Iraq it was found that, there were over 2,000 cases of thalassemia in the Kurdistan Region and Kirkuk with a round 30000 people are carries of β -thalassemia disorder [6&9]. Various factors were found to be contributing to the counts of β -thalassemia in Kirkuk including ethnic origins and migrations that added more burden on the genetic pool of the region and on the inheritance of traits in that area [10]. Still, since the global prevalence of thalassemia is about 2 per 1000 newborns every year; thus, this disorder is considered as a serious public health problem throughout the Mediterranean region and the Middle East [9, 10 &11].

Patients & Methods:

Patients:

Total of (156 patients) clinically diagnosed with β - thalassemia and from both sexes living in Kirkuk city were included in this study. Their ages ranged from (1 to 17) years old. This study was carried out in the “Thalassemia Unit” at Azadi Teaching Hospital in Kirkuk city from January to December 2016 where all of the patients



included in the study met the inclusion criteria of the questionnaire specifically designed for this study.

Methods:

1-Data collection: The data were collected using a questionnaire designed for this investigation according to [3&11] with the following questions:

- Gender
- Date of birth / age
- Type of Thalassemia
- Consanguinity marriage (relationship of patient's parents)
- Ethnic origin (patients with mixed ethnic origin were excluded from the study).
- Patients' residency
- Local or internally displaced individuals.

2- Study protocol: Data were collected after interviewing thalassemia patients and their relatives where all of them filled questionnaires distributed among them and study protocol was divided into four cohorts according to the informations being evaluated in the questionnaires as follows:

- 1- Individual Factors Cohort: Included studying the effect of gender and age of patient on the prevalence of thalassemia.
- 2- Consanguinity Cohort: Included investigating the burden of consanguinity marriage from the first degree relative on the frequency of thalassemia.
- 3- Ethnic origin Cohort: Included the evaluation of the difference in thalassemia incidence between Turkmen, Arab and Kurd living in Kirkuk city.
- 4- Demographical Cohort: included the evaluation of residency and internal displacement on the frequency of thalassemia.

3- Statistical analysis: Data from the study were analyzed using T- test by using SPSS program Ver.10 for Windows.

A P value of <0.05 was considered indicative of a statistically significant difference



Results & Discussion:

This study was carried out during the period between January to December 2016 and total of (156) patients clinically diagnosed with β – thalassemia attending the (Thalassemia Unit) at Azadi Teaching hospital in Kirkuk City for treatment and regular blood transfusion at the age range of (1-17) years old and from both sexes were all approached. All of the considered patients met the inclusion criteria of a questionnaire specifically designed for this study which was distributed among them in order to evaluate the prevalence of thalassemia among certain age group living in Kirkuk city.

The first evaluated factor was the effect of patient's gender on the distribution of β – thalassemia at different age groups and results were shown in figure (1).

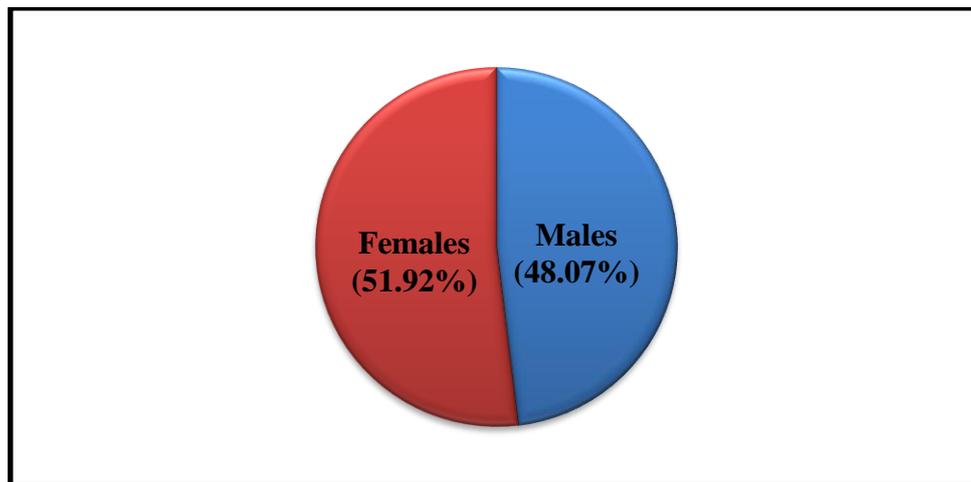


Figure (1): Distribution of β – thalassemia according to patient's gender in different age groups.

Results of this figure showed that, the percentage of affected females (51.92%) with β – thalassemia were not statistically significant ($p > 0.05$) than the affected males (48.07%) among all of the β – thalassemia patients enrolled in this study. This result agree with the results obtained by [3, 12 & 13] where their researches showed that; while, thalassemia affects approximately 4.4 of every 10,000 live births throughout the world, it causes males and females to inherit the relevant gene mutations equally



because it follows an autosomal pattern of inheritance with no preference for gender. Therefore, once parents carry the mutation of thalassemia or are affected by this disorder, they will pass it evenly to their children. In addition, the proportion of β – thalassemia according to age indices was also considered and results were revealed in figure (2).

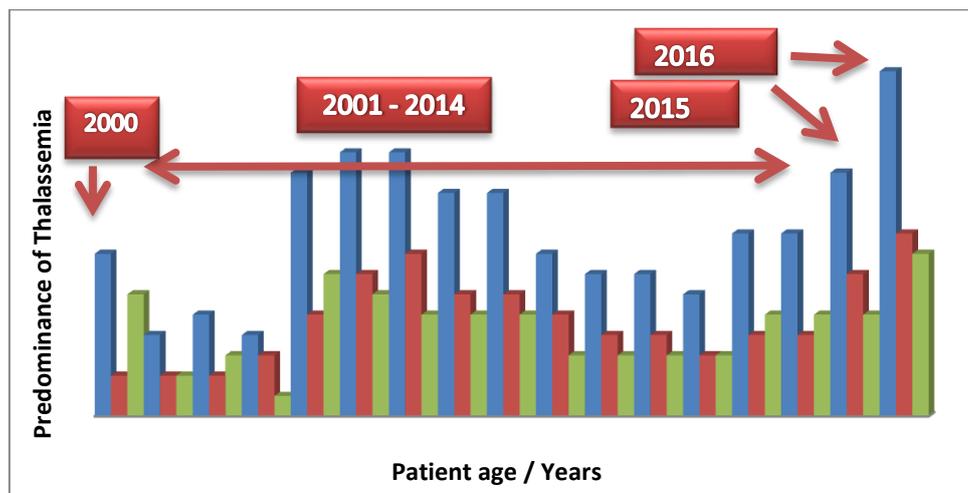


Figure (2): Predominance of β –thalassemia according to patient age among males and females in Kirkuk city during the years from 2000 to 2016; where, Blue columns = total number of β – thalassemia patients, Red columns = β – thalassemia Females, Green columns = β – thalassemia males.

Results of this figure showed a significant increase ($p < 0.05$) in the incidence of β – thalassemia among patients in ages of (17, 13, 12, 11, 2 and 1) years old. Consequently, a comparison was designed in figure (3) between age, gender and date of birth in order to explain the calculated increase in the frequency of β – thalassemia between the patients enrolled in the study.

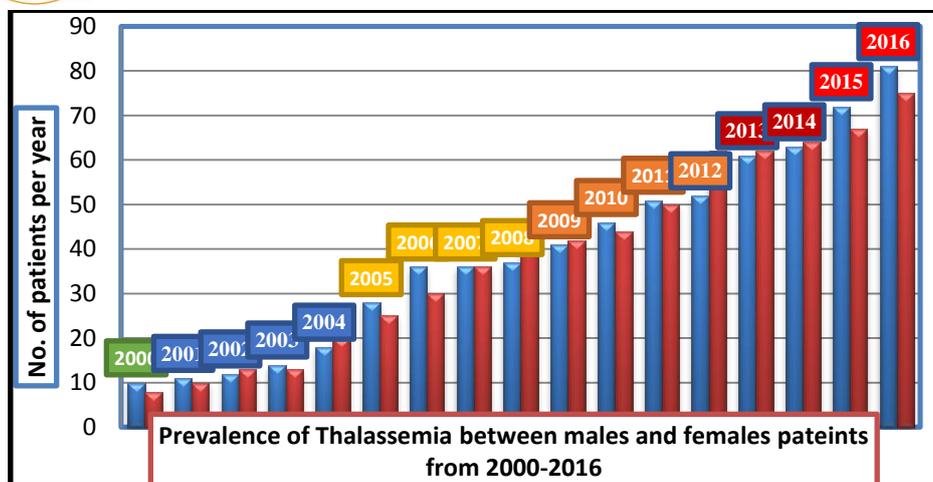


Figure (3):Distribution of β - thalassemia according to patient’s age distributed according to the Year of birth

of the patient from the year 2000 to the year 2016; where, Blue columns = β – thalassemia Female patients, Red columns = β – thalassemia male patients. The results obtained from this figure endorse the results obtained previously where a significant increase ($p < 0.05$) in the incidence of β – thalassemia in both sexes was recorded in the years (2004, 2005 and 2006) than the numbers of patients recorded in the years (2002 and 2003) to about (38 β –thalassemia cases in 2004, 53 cases in 2005 and 66 cases in 2006) respectively. This increase in β - thalassemia cases kept in rising up each year where the incidence of β – thalassemia in both sexes reached its maximum values in Kirkuk city in the year 2016 according to the records of the Thalassemia unit in Azadi Teaching hospital to (156) patients.

However, this is the first time such a comparison is carried out in Kirkuk city where, a study is designed especially for the evaluation of the predominance of β – thalassemia in a city for the last fifteen years.

Though, the obtained results agree with the results obtained by [14-16] where they all revealed an increase in the predominance of β – thalassemia in the city for the last five years. However, the reason behind this increase in the incidence of β – thalassemia in Kirkuk possibly might be due to the effects of insecure conditions of the whole country and especially in Kirkuk city after the year (2003); where “The Iraq war, or sometimes known as the Third Gulf War”, began on March 20, 2003[17]. As a consequence, an increase in the general insecurity in Iraq including (terrorist attacks,



theft, assaults, murder, hostage taking) accompanied with an unstoppable humanitarian crisis in Iraq which increased in terrorist attacks outside of Iraq that eventually ended up with invasion of (The Islamic State of Iraq and the Levant or The Islamic State of Iraq and Syria (ISIS)) in 29 June 2014 and thereafter [18&19].

However, all of these worsening security situation and bad living conditions had increased the rate of consanguinity marriages and inherited diseases in Iraq [19&20] where consanguinity marriages in Iraq range from 40-49% and around 28% are marriages from the first degree cousin [8]. Yet; few published studies described the relationship between increase in β – thalassemia and consanguinity after 2014.

On the other hand, several other studies concerned in consanguinity and prevalence of β – thalassemia had suggested a strong relationship between such conduct and the prevalence of genetic disorders where, a cross-sectional study involved (648 β – thalassemia) patients in Shiraz, Iran in (2004) to determine the demography of β – thalassemia major in Shiraz city and the rate of consanguinity where they declared that, in approximately 49.5% of cases, the patients were outcomes of first-or second-cousin marriages and the significance of pre-marriage counseling in decreasing familial marriages and consequently preventing this autosomal recessive genetic disease [12].

Additionally, in Pakistan, Khan, M.S. *et al.*, had found a very strong relationship between consanguinity ratios in β -thalassemia major patients in the District Bannu in 2015[21]. Recently, a study conducted in Missan Province in 2016 [3] had recorded the highest percentage of β –thalassemia in patients at the ages of (1-3) years old [3]. All of these results agree with the results obtained by Majeed *et al* [22] and Abdul-Karim *et al* [23] that found total of β –thalassemia patients were in the ages < 10 years old probably due to increasing disease load and shortened life expectancy. Moreover, since thalassemia occurs when a person inherits two thalassemia genes, one from each parent where both parents must have the thalassemia minor genes [14-16]. Results of this study had revealed that, approximately (77.56%) of β – thalassemia major patients were the outcomes of the first cousin marriage and this conclusion is more elucidated by the following pedigree analysis figure which was conducted from the

numbers of β –thalassemia affected siblings recognized among the patients enrolled in this study.

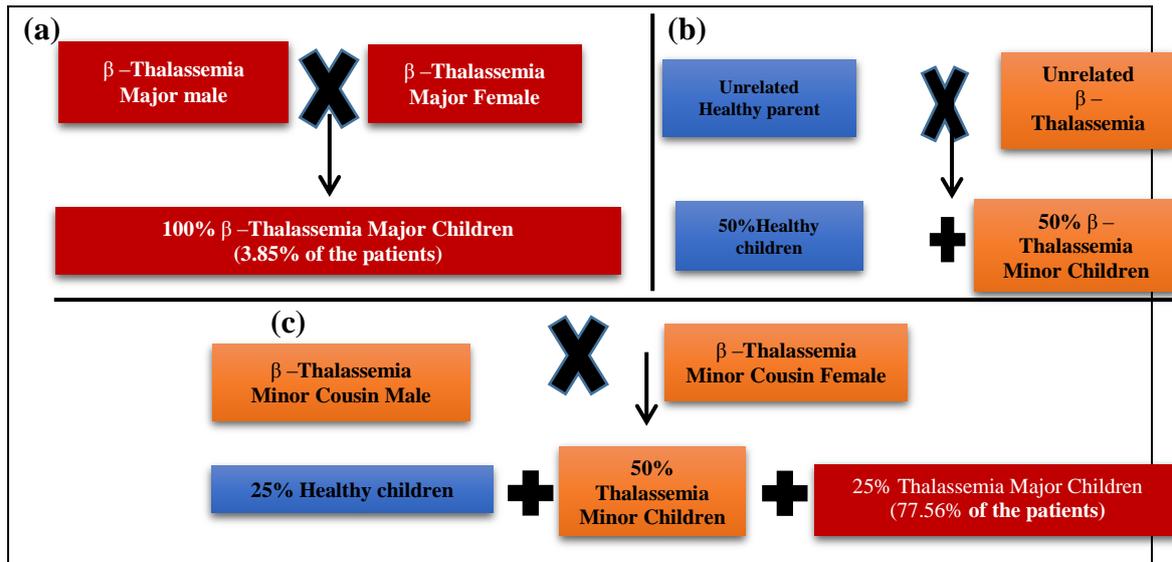


Figure (4): Pedigree analysis of the mode of inheritance of β –thalassemia among sibling patients enrolled in the present study showing the majority of β –thalassemia patients were the outcomes of consanguinity marriages.

Pedigree analysis results revealed in (figure 4) showed that, when two individuals who had β –thalassemia major got married; all of their children had β –thalassemia major (figure 4a) which was the case of (3.85%) of the β –thalassemia major cases enrolled in the study patients where they were the result of (1.28%) of consanguinity and (2.57%) from non- related individuals. Whereas, only (18.59%) of the β –thalassemia minor patients were the outcomes of unrelated β – thalassemia minor parents and healthy ones as shown in (figure 4b).

On the other hand, about (77.56%) of 156 of β –thalassemia major patients were the consequences of consanguinity marriages of the first degree cousin where their parents were β –thalassemia minor individuals as figure (4c). Still, the most interesting finding in this study was that, about (86.15%) of the parents whom had more than one children with unrelated β – thalassemia major did not know that they were β –thalassemia minor individuals.



However, the most acceptable explanation for this result is that, thalassemia major and thalassemia intermedia are inherited in an autosomal recessive pattern, which means, both copies of the HBB gene (which is the gene that provides instructions for making a protein called beta-globin that is a subunit of hemoglobin protein) are mutated [24].

Thus, parents of an individual with major thalassemia should carry one copy of the mutated HBB gene, but they typically do not show any signs or symptoms of the condition (the example in figure 4c) so that, they will not know until they will have a thalassemic child due to the chance of (25%) of giving birth to a normal child too [8, 24 & 25].

Sometimes, however, people with only one HBB gene mutation in each cell develop mild anemia and these mildly affected people are said to have thalassemia minor [24&25] where studies showed that, thalassemia intermedia is less clinically severe than beta-thalassemia major so that people often just use the term “thalassemia” to refer to any person with either thalassemia intermedia or thalassemia major where the distinction between the two cases lies in the need for chronic red blood cell transfusions for “major” and no or intermittent transfusions for intermedia [23-25].

Therefore, results of comparison between thalassemia predominance and the effect of consanguinity had included only β –thalassemia major and minor patients in Kirkuk city. Yet, the distribution of β –thalassemia in Kirkuk city was also evaluated according to different ethnic groups constituting the community in Kirkuk and results were shown in figure (5).

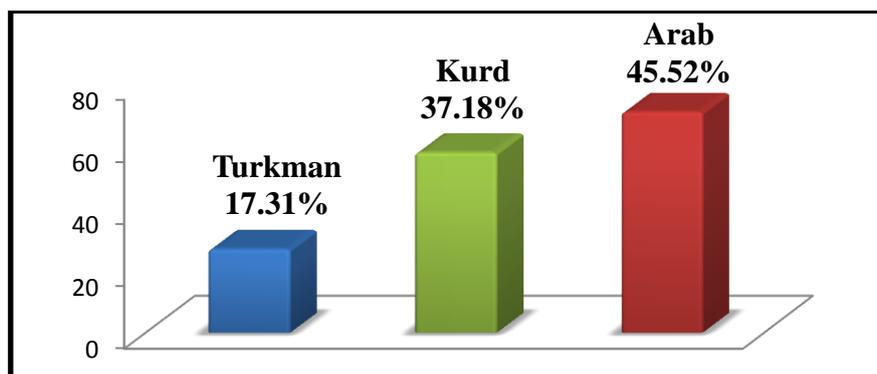




Figure (5): β –thalassemia distribution in Kirkuk 2016 according to different ethnic groups including both males and female patients.

All of the evaluated (156) patients belonged to three ethnic origins (Turkmen, Arab, and Kurd) where results of figure (5) indicated a significant difference ($p < 0.05$) in the distribution of β –thalassemia patients between different ethnic groups living in Kirkuk city and the surrounding areas. It was noticed that, the incidence of β –thalassemia in Turkman patients had recorded the lowest incidence rate of (17.31%) compared to the Kurd patients where they recorded the incidence rate of (37.18%) and Arabs where they recorded the highest incidence rate of (45.52%) among total of (156) β –thalassemia patients where patients from mixed ethnic origins were excluded at the very first beginning of the study. The same results were obtained by Saud, A.M., where she declared in her PhD thesis in 2012 a geographical distribution of thalassaemia in Iraq that reflected a heterogenic background of β -thalassaemia within different Iraqi regions related to different races and ethnic groups [26]. However, results obtained in figure (5) will be more enlightened in table (1).

Table (1): Geographical distribution of β -thalassaemia patients in different districts and sub districts of Kirkuk city.

| Districts &Sub districts in Kirkuk Province 2016 | Frequency Of Turkman thalassaemia patients | Frequency Of Kurd thalassaemia patients | Frequency Of Arab thalassaemia patients |
|--|--|---|---|
| Baghdad Road | 0.64 | 0.21 | 7.69 |
| Al Wasty | 0 | 1.28 | 9.62 |
| Huzairan | 0 | 0.63 | 7.34 |
| Al Hay Al Askari | 0.58 | 8.33 | 5.13 |
| Al Shorja | 0 | 4.52 | 0 |
| Imam Qasim | 0 | 9.11 | 0 |



| | | | |
|--------------|--------|--------|--------|
| Penja Ali | 0 | 7.05 | 7.12 |
| Musalla | 2.56 | 0 | 0.54 |
| Taza | 3.28 | 2.1 | 1.67 |
| Tuz Khurmatu | 4.49 | 1.55 | 0.13 |
| Yayci | 3.11 | 0 | 0.87 |
| Dibis | 0 | 2.28 | 4.86 |
| Daquq | 2.65 | 0.12 | 0.55 |
| Total | 17.31% | 37.18% | 45.52% |

Results of this table ascertained the results obtained from figure (5) where unrelated β –thalassemia was found more predominant between Kurd and Arabs living in the sub districts where a large number of internally displaced people were living near than that percentage of β –thalassemia incidence recorded among people living in the center of the city. These results however, disagree with the results obtained by Jawdat and Norrya in 2010 where they had studied the geographical distribution of β -thalassemia in Kirkuk and showed that, the mutation was more prevalent in Turkman patients, while it was less detected in Arab and Kurds [14]; but agree with the results obtained in [3&8] where studies conducted in Missan and Basrah Provinces respectively showed difference in the distribution of β - thalassemia among people living in the same province . However, the significant increase ($p<0.05$) in the prevalence of β -thalassemia in Kurd and Arab evaluated in this study was probably originating from the consanguinity marriages that increased recently because of the bad living situations and unsecure circumstances that made people resort to their old traditions again. The same results were obtained in [3&8] where no difference was detected between patients from rural or urban areas due to the communality of consanguinity marriages in Iraq.

Conclusion:

From this study the following could be concluded:

- β - thalassemia disorder is one of the prevalent inherited diseases in Kirkuk city with increasing frequency among children in the ages of (1-3) years old.
- Distribution of β - thalassemia disorder did not vary among males and females in Kirkuk city 2016.



- The frequency of β - thalassemia increases in years following wars and invasions in Kirkuk city.
- Consanguinity marriage increases the frequency of β - thalassemia incidence among both male and female patients.
- Individuals with minor β - thalassemia increase the ratio of β - thalassemia incidence among their children.
- Distribution of β - thalassemia differ according to different ethnic groups.

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