RESEARCH ARTICLE

Molecular and Hematological Characterization of Alpha Thalassemia in Nineveh Province

Ghaleb Satea Ghaleb Noaman*[1], Zainab Issam Ali Al-Hatem[2]
[1]Hematology Laboratory, Ibn-sina Teaching Hospital, Mosul, Iraq.
[2]Hematology Laboratory, Al-Hadba Specialized Hospital, Mosul, Iraq.

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***Corresponding author: Ghaleb Satea Ghaleb Noaman , ghalibsatea@gmail.com**
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ABSTRACT

Background: Iraq reports high occurrence of Alpha (α) thalassemia. However, limited data exist on the epidemiology of causative α-globin mutations in Nineveh.

Aims: To analyze the α- thalassemia alleles mutational spectrum in Nineveh and to establish the mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) cut-off value for α^0- thalassemia trait.

Methods: Retrospective study was conducted at Ibn-Al-Atheer and Ibn-Sina Teaching Hospitals between the years 2021 to 2025. Records of a total of 320 persons attending the Premarital Screening Unit were examined. 159 persons had normal α- globin gene (normal control group), and 161 had mutated α-globin gene (of which 7 persons have α^0 mutations while the other 154 were α^+ mutations). All individuals underwent complete blood count, serum ferritin, hemoglobin variant, polymerase chain reaction study. Data were analyzed using IBM-SPSS 26.

Results: Detection of 15 α-gene mutations were confirmed, with $-\alpha^{3.7}$ was the most frequent (42.8%). The mean of MCV (70.81±3.14 fL) was statistically lower within α^0-trait than normal α-gene. The optimum cut-off of MCH level in claiming and predicting α^0-thalaessemia trait is 25 pg, for MCV the best cut-off level is 74 fL.

Conclusion: The study defines prevalent mutant α-gene variants in Nineveh, with -alpha$^{3.7}$ predominant. MCV and MCH are useful data to select individuals for molecular tests to determine the α-thalassemia carrier status. Both the MCV & MCH cut-off point most probably will decrease the number of the persons requirements for further α-thalassemia DNA study. Our findings will provide baseline for genetic counselling, public health planning and premarital screening programs in the region.

Keywords: Alpha thalassemia, mutations, molecular characterization, Nineveh.

INTRODUCTION

Thalassemias constitute a spectrum of inherited blood disorders characterized by a defect in the genes that code for the synthesis of hemoglobin (Hb) subunits. These genetic mutations lead to an imbalance in Hb formation and the accumulation of unpaired chains inside red blood cells (RBCs). As a result, the cells are more brittle and undergo premature destruction, forming a state of hemolytic anemia and ineffective erythropoiesis [1]. The transmission of Alpha-thalassemia (α-thalassemia) follow an inherited, autosomal recessive pattern [2]. Across the Indian subcontinent, Mediterranean, Southeast Asian and African regions α-thalassemia has Historically manifested as the most dominant hemoglobinopathy [3]. Almost more than 120 α-thalassemia mutations have been reported [4]. It can be broadly categorized into deletional and non-deletional thalassemias. The scope of deletion mutation may ablate either single or dual gene cluster on the affected chromosome [4] resulting in one of three carrier states (heterozygous or homozygous for alpha zero and alpha plus (α^+)-thalassemia) and two clinical states (Hb Barts hydrops fetalis syndrome and HbH disease) [5]. The two most common relevant kinds of α^+ thalassemia (decrease in the expression of one or two of the alpha-globin genes) are $-\alpha^{3.7}$ and $-\alpha^{4.2}$. Faulty production (deleted or mutated) of one or two α-globin loci leads to mild to moderate alterations in the red cell indicies. α^0-thalassemia is primarily involved by the total absence of biallelic α-globin genes and the variants designated according to the region of discovery. For clarification, labeled as $--^{SEA}$ (South East Asia), and $--^{MED}$ (Mediterranean) reflects the regional origins of these genomic deletions [6]. Moreover, thalassemia can occur with completely normal α genes where a deletion of the locus control region alpha (LCRA); essential for normal expression of the α globin genomic cluster; is widely reported [7]. The sum of functional alpha-globin genes directly impacts the imbalance between α- and non–α-globin chains, which sequentially control the extent of clinical severity of thalassemia α. [8]. Since α2

gene provides approximately two-thirds of α-globin production, disruption or mutations impacting the α2 gene are bonded with a more profound diminish of α-globin production. When fetal α-globin chains diminished (below 70% of normal), an overproduction of gamma (γ)-globin chains result in formation of insoluble γ tetramers (Hb Barts). In the adult's state, overproduction beta (β)-globin chains causes accumulate and assembling insoluble β-globin tetramer called HbH [8]. The current study aimed to determine the frequency and types of alpha gene mutations in persons who attending Premarital Screening Unit in Nineveh, Iraq, find the correlation between Complete Blood Count (CBC) parameters and α gene mutations and to determine cut-off value for MCV and the MCH to facilitate differentiation between α^0 and α^+ thalassemia cases.

MATERIAL/PATIENTS AND METHODS

Ethical Consideration

The study was approved by The Council of Iraqi Board of Medical Specializations (Order No.8413; Date: 24/October/2024) and also (Order No. path80; Date: 31st Oct, 2024). Approval and agreement from Premarital screening unit of Ibn -Sina teaching hospital, Ibn Al-Atheer teaching hospital and Ministry of Health/Nineveh Health Directorate (Order No. 53917; Date: 11th Nov. 2024).

Study Design

A retrospective study, 2021–2025

Selection and description of participants

The study included 320 persons attending premarital screening unit in Ibn Al-Atheer and Ibn Sina Teaching Hospitals. All age groups and both sexes were recruited. Each individual underwent a CBC and those presenting with hypochromic RBC indices (defined as MCV below 80 fL and MCH below 27 pg) were referred for further evaluation through serum ferritin testing [9]. If Serum ferritin was (>12ng/ml), for both sexes) iron deficiency anemia will not considered [9] We proceed to the third test which is High-performance liquid chromatography (HPLC) to consider the diagnosis of the α thalassemia trait (normal or low HbA_2 and HbF <1%) and exclude the β -thalassemia (trait, major, intermedia). Structural hemoglobin variants were identified based on their retention times by HPLC [9]. The DNA analysis by PCR (polymerase chain reaction, Vienna lab strip assay) was adopted to confirm the diagnosis of alpha thalassemia trait (either α^+ or α^0 mutations). [9]

Technical information

Complete Blood Count (CBC)

A five mL blood sample was collected from each subject by venipuncture in ethylenediaminetetraacetic acid (EDTA) anticoagulated tube, and red cell parameters were estimated by an automated hematological analyzer (Nihon Kohden, Japan) and (Swelab, Sweden) is utilized to conduct a CBC for all persons, for measuring RBC, Hb, MCH, MCV, Red cell distribution width (RDW) indices.

Serum Ferritin

2–3 mL of venous blood sample was collected in gel tube and get 1ml of serum from it, investigation was done by (Mini-Vidus, France).

Hb Variants

to measure the percents of HbA_0, A_2 and HbF, at least 1-2 ml of blood sample was obtained from each subject by venipuncture in (EDTA) anticoagulated tube. This investigation was done by (Bio-Rad Variant II device, VARIANT™; Bio-Rad Laboratories, Hercules, CA, USA) at Ibn al-Atheer teaching hospital & (Bio-Rad D-10, VARIANT™; Bio-Rad Laboratories, Hercules, CA, USA) at Ibn-Sina teaching hospital.

Polymerase Chain Reaction (PCR)

To detect common α-globin alterations, including single- and double-gene deletions, small deletions, point mutations, and even gene triplications, DNA was extracted from whole blood using a phenol-chloroform method, amplification, then a combination of (PCR), and reverse hybridization was performed according to manufacturer protocol (Vienna Lab α-Globin StripAssay®, Vienna lab Diagnostics, Vienna, Austria). The assay covers 21 mutations of alpha genes. [10]

Statistical analysis

Initial data management were conducted in sheets of Microsoft Excel 2010. Followed by statistical analysis using IBM-SPSS 26 (IBM Company, Armonk, New York). The normality of these data verified via Shapiro-Wilk test, which supported the selection of the parametric tests. The categorical data were expressed in frequencies and proportions while the numerical data were expressed through their minimum & maximum limits, means and standard deviations were calculated. Bar, Pie and Box plot was used. The numerical data were compared by unpaired t-tests to To evaluate the disparities between the two means. Non-parametric test, Mann-Whitney U test was used for only one parameter between two independent groups. Receiver operating characteristic (ROC) curve also used to qualify sensitivity and specificity. An area under the curve (AUC) of: 0.5 to < 7 suggest no discrimination (ability to diagnose patients with and without disease or condition based on the test), 0.7 to < 0.8 considered acceptable discrimination, while 0.8 to 0.9 classified as excellent discrimination > 0.9 considered outstanding discrimination. $P \leq 0.05$ considered as significant.

Note: In some tables we use both parametric and non-parametric tests as serum ferritin test have a wide normal range in both females 13-150 ng/ml, and in

males 30-400 ng/ml so it is better to use non-parametric test as Mann-Whitney U in this situation for s.ferritin.

RESULTS

This study included 320 persons with either normal α-globin gene (159 persons, considered as control group, diagnosed by PCR), and mutated α- globin gene carriers (161 persons, of which 7 persons have α^0 mutations while the other 154 were α^+ mutations diagnosed by PCR). The distribution of the studied sample according to age group showed that 34.8% out of the studied sample had age 20-24 years. The distribution of the studied sample according to sex manifests that males were 59.7%, and 40.3% were female with a male-to-female ratio of 1.5:1. Different α gene mutations are detected with their hematological indices and are showed in Table 3. The comparison of hematological parameters between α^0-thalassemia trait and normal α gene individuals was revealed in Table **1**. Which show that the mean of MCV was statistically lower in α^0 thalassemia trait than those with normal α gene individuals (p value = 0.016). HbA_0 (was statistically higher in α^0 thalassemia trait than those with normal α gene individuals p value = 0.027). No statistically significant differences were found between α^0-thalassemia trait and normal α gene individuals in regard to RBC count, Hb, MCH, RDW, HbA_2 and HbF. The comparison of hematological indices between α^+-thalassemia and α^0-thalassemia traits was revealed in Table 2. No statistically significant differences were found except for Hb F (p value = 0.045) which is significantly higher in α^+ than α^0.

Table 1
Comparison of hematological parameters between α^0 thalassemia trait and normal α gene individuals.

Hematological Indices	α^0 thalassemia trait (n=7)	Normal α gene (n=159)	P*
	Mean ± SD	Mean ± SD	
RBC (*10^{12}/L)	5.60±0.88	5.34±0.60	0.263
Hemoglobin (g/dl)	13.40±1.32	13.68±1.80	0.690
MCV (fL)	70.81±3.14	74.97±4.44	0.016
MCH (pg)	24.26±1.87	25.63±2.18	0.103
RDW (cv)	11.34±0.82	12.92±2.27	0.070
S. Ferritin (ng/ml) Median (min – max)	42.0 (14.8 – 380.0)	44.10 (3.0 – 384.1)	0.422**
HbA0 %	87.47±1.69	86.42±1.19	0.027
HbA2 %	2.63±0.28	2.61±0.44	0.921
Hb F %	0.24±0.05	0.42±0.26	0.079

* Independent t-test, ** Mann-Whitney U test, SD (Standard deviation)

Table 2
Comparison of hematological parameters between α^+ and α^0 thalassemia traits individuals.

Hematological Indices	α+ thalassemia trait (n=154)	α0 thalassemia trait (n=7)	P*
	Mean ± SD	Mean ± SD	
RBC (*10^{12}/L)	5.57±0.56	5.60±0.88	0.899
Hemoglobin (g/dl)	13.95±1.68	13.40±1.32	0.399
MCV (fL)	73.78±5.07	70.81±3.14	0.127
MCH (pg)	25.12±2.08	24.26±1.87	0.284
RDW (cv)	12.59±1.67	11.34±0.82	0.051
S. Ferritin (ng/ml) Median (min - max)	46.50 (4.2 - 387.1)	42.0 (14.8 - 380.0)	0.697**
HbA0 %	86.42±1.52	87.47±1.69	0.075
HbA2 %	2.66±0.31	2.63±0.28	0.770
Hb F %	0.42±0.23	0.24±0.05	0.045

[*] Independent t-test, [**] Mann-Whitney U test, SD (Standard deviation).

Table 3
Variation (mean ± SD) in Hematological Features of α^0 and α^+ Thalassemia Mutations

α^0 Gene Mutations

Mutation	n	RBC (×10¹²/L)	Hb (g/dL)	MCV (fL)	MCH (pg)	RDW (cv)	HbA0 (%)	HbA2 (%)	HbF (%)	%
--MED	2	6.05 ± 1.70	13.56 ± 2.05	68.20 ± 4.24	23.35 ± 3.75	10.90 ± 1.13	89.05 ± 2.76	2.55 ± 0.07	0.25 ± 0.07	0.6
$\alpha\alpha^{PA1}$	1	6.27	15.20	69.90	24.30	11.40	86.10	2.50	0.20	0.3
$\alpha\alpha^{PA2}$	3	5.09 ± 0.21	12.53 ± 0.50	71.30 ± 1.39	24.63 ± 1.48	11.50 ± 1.04	86.67 ± 0.46	2.83 ± 0.32	0.27 ± 0.06	0.9
$-\alpha^{3.7}/\alpha\alpha^{PA2}$	1	5.59	13.90	75.50	24.90	11.70	88.10	2.30	0.20	0.3
Total	7	5.60 ± 0.88	13.40 ± 1.33	70.81 ± 3.14	24.26 ± 1.87	11.34 ± 0.83	87.47 ± 1.69	2.63 ± 0.28	0.24 ± 0.05	2.1

α^+ Gene Mutations

Mutation	n	RBC (×10¹²/L)	Hb (g/dL)	MCV (fL)	MCH (pg)	RDW (%)	HbA0 (%)	HbA2 (%)	HbF (%)	%
$\alpha^{3.7}$	119	5.53 ± 0.55	14.03 ± 1.68	74.65 ± 4.54	25.40 ± 1.86	12.65 ± 1.73	86.44 ± 1.59	2.67 ± 0.31	0.42 ± 0.23	37.2
$-\alpha^{4.2}$	5	5.35 ± 0.47	13.20 ± 2.25	72.16 ± 8.89	24.80 ± 4.02	12.66 ± 2.40	86.52 ± 0.61	2.56 ± 0.26	0.34 ± 0.27	1.4
$-\alpha^{4.2}/\alpha\alpha^{-5nt}$	1	5.64	12.50	72.20	26.00	13.10	87.50	2.40	0.30	0.3
$-\alpha^{3.7}/\alpha^{3.7}$	13	5.90 ± 0.65	13.73 ± 1.89	68.03 ± 3.68	23.07 ± 1.68	12.07 ± 1.15	86.62 ± 1.21	2.69 ± 0.36	0.46 ± 0.28	4.1
$\alpha\alpha^{5NT}$	6	5.61 ± 0.30	14.37 ± 0.97	75.83 ± 1.22	25.62 ± 0.50	13.47 ± 1.53	85.67 ± 1.55	2.62 ± 0.21	0.58 ± 0.26	1.9
$-\alpha^{3.7}/\alpha\alpha^{5nt}$	3	6.24 ± 0.71	13.67 ± 1.34	64.50 ± 3.24	22.03 ± 1.79	12.13 ± 0.51	86.53 ± 1.46	2.80 ± 0.17	0.23 ± 0.06	0.9
$-\alpha^{3.7}/-\alpha^{4.2}$	1	5.94	13.00	69.40	21.90	12.40	85.80	2.10	0.20	0.3
Cd19	1	6.00	15.30	73.20	25.50	11.00	85.80	2.90	0.30	0.3
Cd14/Cd59	1	5.62	14.70	77.60	26.20	12.10	86.80	2.90	0.50	0.3
$(\alpha^{tc}\alpha)$	1	4.85	12.60	72.90	25.90	10.80	86.40	2.70	0.40	0.3
$(\alpha\alpha\alpha/\alpha\alpha)$	3	5.39 ± 0.50	12.80 ± 2.62	73.60 ± 8.72	23.53 ± 3.69	12.37 ± 1.88	85.60 ± 2.17	2.53 ± 0.40	0.43 ± 0.32	0.9

HbA (Haemoglobin of adult), HbF (Haemoglobin of fetus), SD (Standard deviation), S. Ferritin (Serum ferritin).

The comparison of both sensitivity and specificity of MCH cut-off point at 25.9 pg and 25 pg for α^0 thalassemia trait (when MCH less than 25.9 pg , this cut-off value has been shown not to be differential between those with α^0 and α^+-thalassemia(low specificity), however, if we used MCH cut-off value of 25 pg to recognize α^0 thalassemia trait we found that the specificity was higher (66%) compared to the specificity when MCH cut-off value at 25.9 pg (47%) with good sensitivity). The difference between the sensitivity and specificity of MCV cut-off value at 74 fL and at 75 fL for α^0-thalassemia traits (when use MCV cut-off value of 74 fL to identify α^0 thalassemia trait we found that the specificity was higher (70%) compared to the specificity when MCV cut-off value at 75 fL (60%) with good sensitivity) are shown in Table 4 and Table 5 respectively. According to the ROC curve analysis in (Fig 1), the best cut-off of MCH level in predicting α^0 - thalassemia trait is 25 pg with the sensitivity of 71% and a specificity of 66% (95% CI: 0.588-0.868) with the (AUC) area under the ROC curve of 0.728 and (p value 0.040) , while for MCV the best cut-off of MCV level in predicting α^0- thalassemia trait is 74 fL with the sensitivity of 86% and a specificity of 70 % (95% CI: 0.716-0.924) with the area under the ROC curve (AUC) of 0.820 and (p value 0.003).

When established MCH cut-off value 25 pg was applied to the validation people (α^0 and α^+ trait), the positive predictive value (PPV) was 90% and the negative predictive value (NPV) was 98% with 71% sensitivity and 66% specificity as shown in table (6). While when MCV cut-off point of 74 fL was applied to the validation people (α^0 and α^+ trait), the PPV was 90% and NPV was 98% with 86% sensitivity and 70% specificity respectively. The findings are summarized in Table 6.

Table 4
Comparison of MCH cut-off point for α^0 thalassemia trait.

MCH Cut-off (pg)	Sen (%)	Spec (%)	AUC*	95% CI**	p-value
≤ 25.9 (high cut-off)	86	47	0.728	0.588–0.868	0.040
≤ 25.0 (low cut-off)	71	66	0.728	0.588–0.868	0.040

* Area under curve, ** Confidence interval

Table 5
Comparison of MCV cut-off point for α0 thalassemia trait.

MCV	Sen (%)	Spec (%)	AUC*	95% CI **	p
≤ 74 fL (low cut-off value)	86%	70%	0.820	0.716-0.924	0.003
>75 fL (high cut-off value)	85%	60%	0.820	0.716-0.924	0.003

* Area under curve, ** Confidence interval

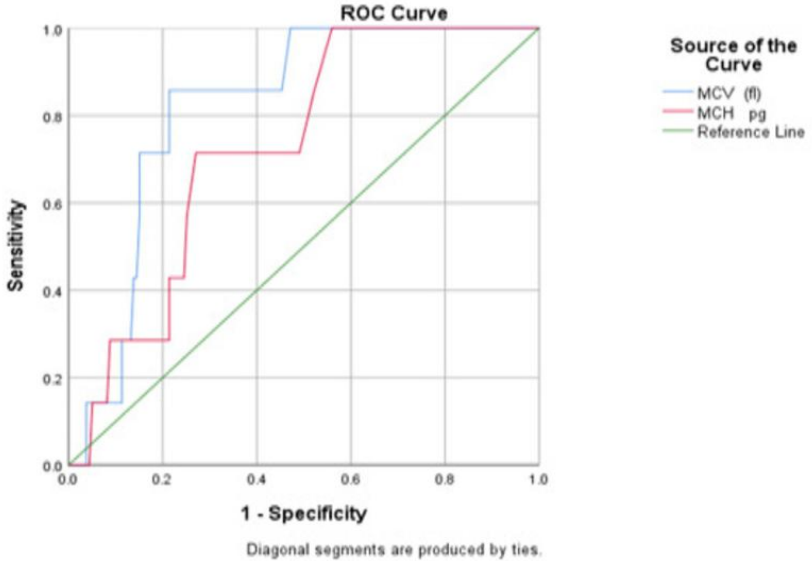

Fig 1. ROC curve of MCH and MCV in identifying α^0 thalassemia

Table 6
Positive predictive value and negative predictive value of MCH and MCV after applying different cut-off points in the validation group.

parameter	α^0 thalassemia	α^+ thalassemia
MCH ≤ 25.0 pg	90 % (PPV)	10%
MCH >25.0 pg	2%	98% (NPV)
MCV ≤ 74.0 fL	90 % (PPV)	10%
MCV >74.0 fL	2%	98% (NPV)

PPV (Positive predictive value), NPV (Negative predictive value).

DISCUSSION

The α -thalassemia trait is often seen in several regions, like the Asian countries, Middle East [11]. Saudi Arabia is most nation in world frequently high with thalassemia [12]. It is feasible to have patients with HbH disease or Hydrops fetalis from a husband and wife with α -thalassemia trait this will be according to the type of α- thalassemia mutations (for i.e α α^{PA2} mutation can give rise to HbH disease instead of α^0 thalassemia) [13]. The current study determined the usual mutant α gene variants and their relative dispersion in Nineveh province. Such inclusive perception of population-specific mutations is vital to shape screening recommendations, counseling programs, and prenatal diagnosis policies for thalassemia prevention. The majority of the 320 recruited individuals fell into the 20–24 and 15–19 age groups, comprising 34.8% and 29.2% of the cohort, respectively. Conversely, only a small fraction of the participants was in the 10–14 (0.6%) and over 40 (3.1%) age categories. This is consistent with Shamoon PR [14] and Jameel FA studies [15]. Fifteen different α -gene mutations were detected. The most frequently encountered α genotype mutation is -$\alpha^{3.7}$ which agrees with studies of Al-Allawi NA et al. [16] and Saboor M et al. [17], While not consistent with study done by Adekile A et al which reported that The commonest genotype was homozygosity for the polyadenylation-1 mutation ($\alpha^{PA-1}\alpha/\alpha^{PA-1}\alpha$) in 33.3% of the samples in kuwait (and reveal these mutations also $\alpha^{CS}\alpha/\alpha^{CD142}\alpha$, $--^{SEA}/-\alpha^{3.7}$ ….etc which are not found in my study) [18]. This mean that the frequency of α gene allele is different in keeping with the diverse ethnic groups of community and geographical spread and so this is significant in deciding the strategy in the screening program of thalassemia in a nations or provinces. The current study realized that individuals with α^0 thalassemia trait manifested a significantly lower mean MCV level in contrasted with those possessing normal α gene and this is consistant with studies done by Keikhaei B et al. [19] and Ahmad R et al. [20]. The results of this study show that individuals with the α^0-thalassemia trait revealed a significantly higher mean HbA_0 level compared with those having a normal α gene, this consistent with study of Ahmad R et al. [20]. In the current study , both α^0 and α^+ thalassemia trait have MCH less than 25.9 pg and this cut-off value has been shown not to be differential between those with α^0 and α^+-thalassemia, however, if we used MCH cut-off value of 25 pg to recognize α^0 thalassemia trait we found that the specificity was higher (66%) compared to the specificity when MCH cut-off value at 25.9 pg (47%) with good sensitivity . Our findings are comparable with a study Keikhaei B et al. [19] But not consistent with study done by Idris F et al which established that the best cut-off level of MCH level in predicting α^0 thalassemia carriers is 23.5pg with the sensitivity of 98% and a specificity of 85% (95% CI: 0.956 – 0.983) with the area under the ROC curve (AUC) of 0.969 ,the discrepancy between their results and the current study arises because the majority of α^0-thalassemia subjects in our cohort presented with higher MCH values. This variation in diagnostic thresholds is expected and can be attributed to the different population genetics and ethnic backgrounds of the studied cohorts. [21]. If we used MCV cut-off value of 74 fL to identify α^0 thalassemia trait we found that the specificity was higher (70%) compared to the specificity when MCV cut-off value at 75 fL (60%) with good sensitivity, our findings are comparable with a study Keikhaei B et al. [19]. In the validation group, when MCH cut-off point less than 25 pg and MCV cut- off value less than 74 fL were applied separately, majority (90%) of subjects were correctly classified into the α^0-thalassemia trait .While when MCH cut-off value >25 pg and MCV cut- off value >74 fL were applied separately, the 98% of subjects were correctly classified into the α^+- thalassemia trait, the very high negative predictive Value (98%) means that an MCH >25 pg and MCV >74 fL almost certainly excludes α^0 in this population, these results are comparable with study done by Idris F et al. [21]. With these encouraging figures, it is most likely to reduce the number of individuals needed referral for further α-thalassemia DNA analysis leading to a more targeted screening program and subsequently alleviate the laboratory workload and budgetary requirements. When comparing the current study with similar researches conducted in

other Iraqi provinces (such as Erbil and Duhok), our findings extend and confirm the regional data on α-thalassemia. However, none of the previous studies established specific MCV or MCH cut-off values for predicting α^0-thalassemia trait. This represents a key additional contribution of the present study.

Limitations of the study include small number of α^0-thalassemia cases and its retrospective nature in addition to limited mutation panel (only we investigate the 21 most common mutations of alpha genes in our country).

CONCLUSIONS

The $\alpha^{3.7}$ and $-\alpha^{4.2}$ deletions, along with $\alpha\alpha^{IVS1(-5nt)}$ alleles constitute the most prevalent encountered α globin genotype mutations in Nineveh indigenous cases. The most sensitive and specific MCH cut-off point at 25 pg and MCV cut-off point at 74 fL for predicting α^0-thalassemia trait. This most likely limits the necessity for further expensive α thalassemia DNA analysis leading to substantial cost saving. MCH provides the most reliable diagnostic performance as a single-parameter test for predicting the α^0-thalassemia trait.

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Conflict of interest

No Conflict of interest

Ethical consideration

The study was approved by Ministry of Health / Nineveh Health Department, Ethical Committee No. of paper approval (53917/November/2024).

Participants Consent: not applicable (A written consent form was not obtained from participants before the study was conducted because it is retrospective study and depends on hospital records).

Author's contribution

The first author shared in the Design, Definition of intellectual content, Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation and writing, Manuscript editing, Guarantor.

Second author: Concepts, Manuscript review and comments and Supervision

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