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Estimation of Co-Integration of the Relationship between Blood Transfusion and Iron Deposits in Thalassemia Patients and Study of the Effects of Some Physiological Factors

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Abstract

Iron overload is the major cause of morbidity for thalassemia patients. Even non-transfused patients develop secondary iron overload, due to increased intestinal absorption of dietary iron. Iron overload is a leading cause of mortality

and organ failure. It occurs very rapidly in patients who are on chronic transfusion programs. Since humans have no mechanism other than sloughing of the mucosa of their gastrointestinal tracts or menstruation to excrete excess iron, patients who are being transfused every three or four weeks gain 0.5 mg/kg per day of iron in excess of natural losses. Patients who are not on a transfusion regimen are also prone to iron overload due to significantly increased intestinal absorption of iron secondary to ineffective erythropoiesis. Thalassemia is considered one of the diseases that represents a big challenge for Iraqi people because of high morbidity, with an increasing rate every year, therefore, this study focused on the relationship between times of blood transfusion and iron overload in thalassemia patients as well as studying the effect of some physiological factors, such as age, gender, blood type and the type of thalassemia. This study used, a Co-integration (Engle-granger) model and traditional statistical analysis methods to analyse data obtained from the thalassemia centre in- Maysan province, Iraq, for 100 patients over 12 months(year 2015) by recording age group, gender, blood type, type of thalassemia, number of blood transfusions and blood iron levels. Our results demonstrated that there was a positive relationship between both the number of blood transfusions and blood iron levels, the more the number of blood transfusion increased, the more blood iron level and the males was mostly infected than females and children between 1-4 years were the age category with the highest level of infection. The group with blood type O^+ was the most infected group and, finally, thalassemia major beta was the highest registered type. We strongly recommend more precise investigation on this subject, focusing on secondary complications that accompany this disease.

Keywords: Co-integration, Blood, Iron, Thalassemia, physiological factors

1. Introduction

The thalassemia haemoglobin disorder characterised by absent or low installation globin chains manufacture. In most cases, it has been found in malaria zones, tropical and subtropical of the Mediterranean and Middle East countries, the Caucasus, Central Asia, the Indian subcontinent (South Asia) and Southeast Asia [14]. There are two main types of thalassemia are α-thalassemia and β-thalassemia. Blood transfusion is the mainstay of care for people living with thalassemia major and many with Intermedia. The purpose of the move is two-fold: improvement of anemia and suppression of ineffective erythropoiesis. Blood transfusion can prevent the transfer of some of the most serious growth, skeletal and nerve complications of thalassemia major. However, once it has started, complications of blood transfusion become a major source of morbidity. We must set standards and maintain them to ensure a safe and reasonable approach to the use of blood transfusions in the management of these rare disorders [5]. Chronic iron overload is a serious complication of potentially life-saving blood transfusion, which can lead to excess iron deposits in various tissues of the body, especially the liver, heart and endocrine organs [1].

Once storage capacity is exceeded in the body, free iron stimulates the formation

of highly reactive hydroxyl radical roots, which leads to membrane damage and denaturation of proteins. This process leads to tissue damage and, ultimately, to disease and large mortality rates [13].In fact, device failure due to chronic iron overload is the main cause of death in patients with Mrdy- β thalassemia major who receives regular blood transfusions without the proper treatment of chelation. Within 1-2 years from the start of regular blood transfusions, evidence of iron overload is evident as high iron concentration in the liver (LIC) values and high levels of serum ferritin. There is an increased risk of heart disease caused by iron in thalassemia patients with LIC values above 15 mg iron / g dry weight (dry), and patients with ferritin serum values above 2500 mg / L8.Patients with a number of other congenital issues and acquired anaemia, who may receive frequent blood transfusions are also prone to the negative effects of iron [10].

This study aimed determine the causal relationship between the number of blood transfusions for thalassemia patients and the content of high iron, as well as the effects and relationship of some factors on thalassemia (blood type, age, gender, thalassemia type) with the focus on thalassemia patients in Southern Iraq (Maysan), whose data have been obtained from the blood Centre of genetic disease and thalassemia in the province. The Engle Granger method was used to provide a causal analysis of data. The (Engle Granger) and Co-integration are of great importance in the field of applied research and statistical analysis, which many researchers had addressed in various areas of research, but it's used in statistical and medical research was scarce and almost non-existent. As thalassemia poses a threat to the lives of people in general, and the seriousness of iron accumulation, as a result of taking blood doses by people suffering from thalassemia is particularly threatening, this study aimed to determine the long-term causal relationship between high iron levels and a dose of blood given per month for thalassemia patients taking in consideration blood type, gender, age and thalassemia type as important factors that may have an effect on thalassemia morbidity.The study uses common integration (Engle Granger) and other traditional methods of statistical analysis to measure the relationship between variables.

2. Methods and materials

(2-1) causal relationship between giving blood doses and high iron:

Here we investigate the co-integration analysis, the study of Granger causality tests to find the direction of the causal relationship between giving blood doses and high iron levels in thalassemia patients. The purpose was studying the relationship between the number of doses of blood given and the increase in the proportion of iron for thalassemia patients. We used annual data for -100 patients-, from 2015, taken from the - Genetic Disease / Thalassemia centre- in Maysan province. This study provides an overview of an important and relatively recent approach to estimate long-run relationship between blood and iron using 'co-integration', a technique becoming widely used in macroeconomic modelling.

Before estimating the Co- integration and VAR, it is required to examine the stationarity of the variables. Stationarity means that the mean and variance of the

series are constant through time and the auto covariance of the series is not time varying [4]. Therefore, the first step is to test the order of integration (I) of the variables. Integration means that past shocks, remaining undiluted, affects the realizations of the series forever and a series has theoretically infinite variance and a time-dependent mean. For this study, we used tests proposed by Dickey and Fuller [2], Phillips and Perron [9], and Kwiatkowski, Phillips, Schmidt and Shin [6] for testing the properties of unit root for all variables used. If all of the series are non-stationary in levels, it should be stationary in first difference with the same level of lags. For appropriate lag lengths, we use the Akaike. Information Criterion (AIC) and Schwartz Bayesian Criterion (SBC).The Dickey and Fuller test (ADF) takes the following form:

$$\Delta y_t = \alpha_0 + \delta T + \beta y_{t-1} + \sum_{i=1}^{p} \theta_1 \Delta y_{t-1} + \mu_t. \quad (1)$$

And ADF regression tests help to root units in YT, which is the logarithm of the number of the patient's blood, which takes a year of ratios of iron deposited in the body doses. T denotes the deterministic time trend and ΔY_{t-i} is the lagged first differences to accommodate a serial correlation in the error,μ, t, While,α,δ,β, and $\theta$are the parameters to be estimated.
Meanwhile, the Phillips-Peron (PP) test is shown by the equation below:

$$\Delta y_t = \mu + p y_{t-1} + \varepsilon_t. \quad (2)$$

The PP test is used because it will make a correction to the t-statistics of the coefficient from the AR (1) regression to account for the serial correlation. The PP test is a test of the hypothesis P=1 in equation 2. But, unlike the ADF test, there are no lagged difference terms. Instead, the equation is estimated by OLS and then the t-statistics of the P coefficient is corrected for serial correlation inε_t.

The Co- integration allows the analysis to clarify the true relationship between two variables, by searching for co- integration factor and removing its influence when necessary. But the basic time series integrated at the same class variables, which are first class for the purposes of this study. We used a linear regression model to determine the nature of the relationship between Iron and Blood as follows [11]:

$$BLOOD_t = \alpha + \beta . IRON_t + \varepsilon_t. \quad (3)$$

Blood refers to the number of doses given to the patient within one year, and the proportion of iron: is the iron deposited in the patient's body.

Results

Statistical study of the data for our results has shown, it can be divided into several components, listed in the following order:

(1) Results of the statistical analysis of the two series time periods:

The first step in the two time series analysis, is drawing views variables to determine the general direction of the two, where it represents the figure (1) time series for each of the doses of iron and blood given to thalassemia patients within months of 2015. We have observed that there is a growing trend where the more portions given to the patient, the greater the proportion of iron deposits

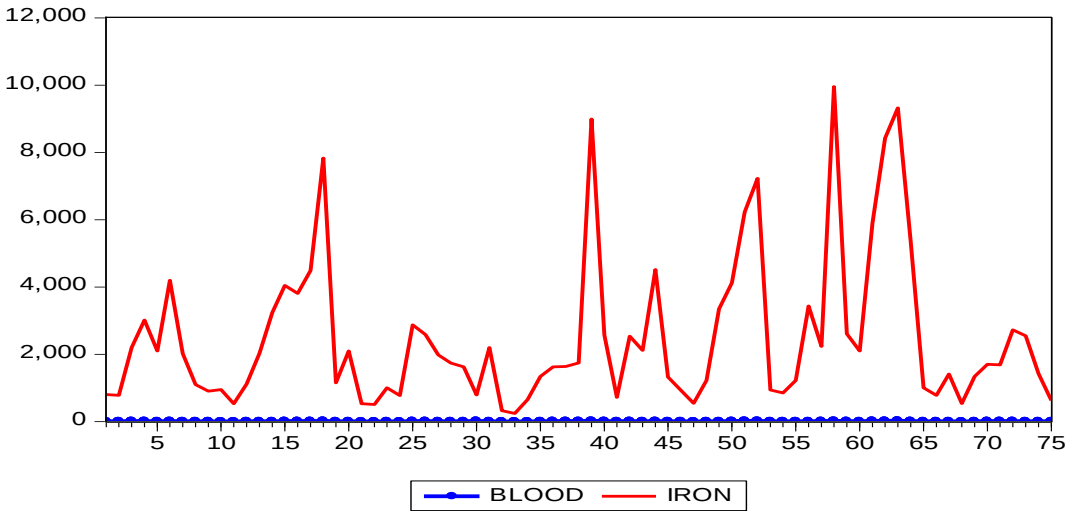

Figure (1) the general trend of a series of blood and iron

(2) Results test Stationarity time series:

Preprocessing testing aims to examine the properties of time series for each of the iron-rate and portions of blood given to thalassemia patients during the year 2015, and to ascertain the extent of stationarity, and determine the rank of the integration of each variable separately. We use (unit root tests). Despite the multiplicity of these tests, however, we have adopted two tests for this study, namely: the test Dickey Fuller expanded testing, and Phillips- Perron to test the null hypothesis theory of the existence of unit root of the instability of the time series, (Phillips-Perron), Dickey Fuller test depends on expanded ADF in the study of the stability series Xt to estimate the following models manner [3].

Least Squares:-

Mod [4] Δx_t=P.X $_{t-1}$-$\sum_{j=2}^{p} \emptyset_j \Delta X_{t-j+1} + \varepsilon_t$, (4)

Mod [4] Δx_t=P.X $_{t-1}$-$\sum_{j=2}^{p} \emptyset_j \Delta X_{t-\ j+1} + c + \varepsilon_t$, (5)

and

Mod [4] Δx_t=P.X $_{t-1}$-$\sum_{j=2}^{p} \emptyset_j \Delta X_{t-j+1} + c + bt + \varepsilon_t$. (6)

The fifth model differs from the fourth; it contains a fixed limit, and the sixth model differs from the fourth and fifth, it contains a fixed and a variable time limit

direction. In order to determine the appropriate length of time lags, it are typically used less than the value of P to a standard ACE, SC After the first differences account

$$(\Delta x_{t-1} = x_{t-1} - x_{t-2}),$$

the second difference

$$(\Delta x_{t-2} = x_{t-2} - x_{t-3}) \quad \text{and} \quad (\Delta x_{t-2} = x_{t-2} - x_{t-3}),$$

Estimation model a way of least squares, is to test hypotheses H_0 =∅=1 Against hypothesis: H1: |∅|<1; If the null hypothesis is accepted, it means having a unitary root, and, thus, the time series is static. For testing Philip- Perron's estimation is based on the same model's Dickey Fuller (DF) that it takes into account the variation is a homogenized error by correcting the non-parametric statistics Dickey Fuller process [12]. Table 1 shows the statistical results that were obtained by the application of two tests at all levels, and also includes the critical values for each test at the moral level of 5%.Through the results of previous tests, it turns out that the two strings are static, not containing a unitary root, as the calculated values are larger than the critical values (Mackinnon), We note that the two strings oscillate around the middle of our constant, with no variation relationship in time. This means that there is a possibility for a joint integration between the blood and increasing doses of iron. To verify this, we will use the method of Engle - Granger co-integration.

Table (1) Results of the unit root stillness time series tests

Augmented Dickey Fuller (ADF)Test						
variable	Constant			Trend		
	Level	Value	Conclusion	level	value	Conclusion
BLOOD	-3.521579	-5.311300	I(1)	-4.086877	-5.317518	I(1)
IRON	-3.524233	-4.340150	I(1)	-4.090602	-4.382865	I(1)
Phillip-Perron (pp)Test						
variable	Constant			Trend		
	Level	Value	Conclusion	level	value	conclusion
BLOOD	-3.521579	-5.369641	I(1)	-4.086877	-5.381007	I(1)
IRON	-3.524233	-5.474117	I(1)	-4.086877	-5.491696	I(1)

(3)The results of the co- integration tests:

Through the root of the previous unit test, it became clear that each variable on an integrated unit of the zero class, The focus of common integration theory on time-series analysis, where each of the Angel and Granger refers to the possibility of generating a linear combination is characterized by stationary of time series and, if possible, to generate this linear mix static, these static time series in this case is the integrated versions of the same rank. Thus, they can be used as variables in the regression level and the gradient is, in this case, false and described the relationship equilibrium in the long run. The formation of a linear combination of the study model is as follows:

$$\varepsilon_t = BLOOD_t - \alpha - \beta.IRON_t \quad (7)$$

(3-1) the results of the co-integration of analysis in a manner Engle – Granger:

The Co- integration that has been developed by Engle Granger's 1983 analysis, Engle Granger. The year 1987 is when many economists recognised this as one of the most important new concepts in the field of econometrics, as well as for the analysis of time series. This method requires two-step, the first estimate concerned the relationship in a way (least squares) where we get the regression equation of the joint integration, then get on the estimated regression residuals (ε), Mix Linear generated from the decline of long-term equilibrium relationship. The second test the stationarity residuum obtained from the first steps in accordance with the following:

$$\Delta\hat{\varepsilon} = \alpha + \delta\hat{\varepsilon}_{t-1} + \Delta\hat{\varepsilon}_{t-1} + \varepsilon_{t-1} \quad (8)$$

$$e_t \sim IN(0)$$

If the statistical (τ) to (ε_{t-1}), is significant, we reject the null hypothesis ($\Delta\varepsilon_{t-1} \sim I(1)$), the existence of the root of the units in the residuum and accept the alternative hypothesis static residuum or($\Delta\hat{\varepsilon}_t \sim I(0)$)[15]

The application of the ordinary least squares method and a gradient between the number of doses of blood and iron we got the estimated relationship table (2) as shown by the following estimation:

$$\hat{BLOOD} = 5.611 + 0.002 * \hat{IRON}$$

After obtaining the leftover regression, several statistical tools where used to test the stationarity residuum, in addition to estimating equation (8) to test the unit root, in order to confirm their findings. We research the possibility of a long-term equilibrium relationship; through the implementation of Co- integration between the studied variables would be so out of leftover appreciation($\hat{\varepsilon}_t$). We have to

make sure that the latter is stable, and for this purpose we examined residuals estimated equation, as well as the autocorrelation of residuals transactions and, in the last test, we used Dickey Fuller expanded and Philip –Perron, in order to enhance the results obtained it. To examine the regression residuals co-integration for this purpose, we have equation Graph values leftover appreciation, see figure (2), which shows that the residuals series regression equation Co-integration was stable. The "string is if stable fluctuated around the middle of our constant; with the variation in time has nothing to do [7]. To be sure, we examined transactions where the residuum series is stable, if the function linked transactions (p_k)not different from zero for($k > 0$)and Table (3) shows the self and the partial series residuum link function and can be seen from this table that the residuum string that represents the process of jamming White, as a function autocorrelation series residuum was found that all the affiliated transactions of gaps (k) generally not different from zero and within the confidence interval [3, 9].

Table (2) Estimate the relationship between blood and iron in a manner least squares

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	5.611229	0.449608	12.48027	0.0000
IRON	0.002038	0.000134	15.19910	0.0000
R-squared	0.759878	Mean dependent var	4.000000	
Adjusted R-squared	0.756589	S.D.dependent var	2.398718	
S.E. of regression	2.603048	Akaike info criterion	3.476488	
Sum squared resid	494.6376	Schwarz criterion	3.520384	
Log likelihood	-177.1580	Hannan-Quinn criter.	3.494325	
F-statistic	231.0127	Durbin-Watson stat	2.408372	
Prob(F-statistic)	0.000000			

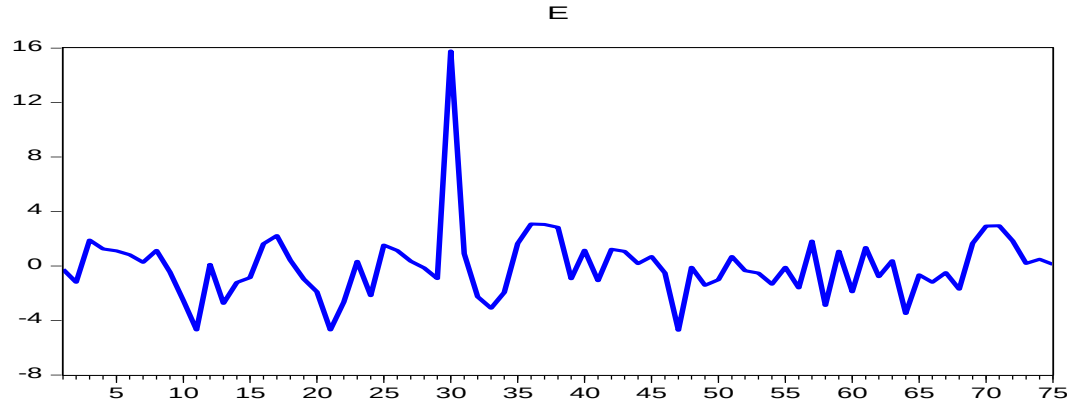

Figure (2) Leftover downhill Co- integration equation

Table (3) Autocorrelation function and partial residuals estimate the slope of the Co-integration equation

	AC	PAC	Q-Stat	Prob		AC	PAC	Q-Stat	Prob
1	0.152	0.152	1.7985	0.180	17	-0.271	-0.199	21.120	0.221
2	0.052	0.029	2.0086	0.366	18	-0.036	0.006	21.248	0.267
3	-0.149	-0.165	3.7906	0.285	19	-0.134	-0.170	23.090	0.233
4	-0.085	-0.042	4.3762	0.357	20	-0.085	-0.167	23.857	0.249
5	-0.015	0.021	4.3948	0.494	21	0.024	0.041	23.919	0.297
6	-0.006	-0.025	4.3982	0.623	22	-0.012	-0.036	23.934	0.351
7	0.033	0.018	4.4895	0.722	23	-0.030	-0.107	24.034	0.402
8	0.053	0.048	4.7355	0.785	24	-0.105	-0.097	25.278	0.391
9	-0.138	-0.169	6.4049	0.699	25	-0.005	-0.033	25.281	0.447
10	0.009	0.058	6.4126	0.779	26	-0.005	-0.113	25.284	0.503
11	0.009	0.041	6.4199	0.844	27	0.078	0.111	26.023	0.517
12	0.064	0.011	6.7986	0.871	28	-0.136	-0.224	28.282	0.450
13	0.152	0.141	8.9483	0.777	29	-0.014	0.020	28.308	0.501
14	0.029	-0.006	9.0256	0.829	30	-0.079	0.036	29.112	0.512
15	-0.055	-0.084	9.3172	0.860	31	0.052	-0.016	29.462	0.545
16	-0.214	-0.156	13.808	0.613	32	0.049	0.018	29.780	0.579

(3-2)Dickey Fuller test results expanded Philip -Perron:

To confirm previous results, we conducted Dickey Fuller expanded testing (ADF) and Philip -Perron (PP). The leftover tests are shown in Table 4, which shows the results of testing the stability leftover downhill Co-integration equation.

Table (4) the results of unit root for residuals export tests

Model type	Model(1) Without constant or trend		Model (2) With constant		Model (3) With constant and trend	
Type of test	ADF	PP	ADF	PP	ADF	PP
Calculated value	-7.332237	-7.350155	-7.281841	-7.300486	-7.235920	-7.255285
The critical value	-2.596586	-2.596586	-3.521579	-3.521579	-4.086877	-4.086877
Probability embarrassment	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000

(4) Results of the study of the causal relationship between blood and iron:

Granger demonstrated that the existence of a Co- integration between two variables means that there is a causal relationship in at least one direction. Therefore we conclude that the lack of a common integration between two variables means there is no causal relationship between them. According to Granger, if we had two time series chains, we can talk about the evolution of two different phenomena over time (t) and two in this study (blood and iron) If the series (blood) containing the information by which they can improve the outlook forecasting series (iron). In this case, we say that the variable (blood) causes the variable (iron). One of the problems that exist in this case is that the time - series data for a variable are often associated, i.e., there is an auto-correlation between one variable's values over time, and, excluding the impact of this auto-correlation, if any, the inclusion of the same variable's values for a number of time gaps as explanatory variables in the causal relationship to be measured. That requires a causality test Granger estimate vector regression model self (VAR), which describes the behaviour of the two variables (blood) and (iron):

$$BLOOD_t = \alpha_0 + \sum_{i=1}^{p} \beta_i \, . \, BLOOD_{t-i} + \sum_{i=1}^{p} \emptyset . IRON_{t-i} + \mu_t \quad (9) \ ,$$

where(μ_t): It represents the model residuals, however before determining the causal relationship between the two variables, we must specify the number of time gaps (p) and the accurate to form VAR (p), because if it is a smaller number of (p) then this leads to an error in the description, and if the number is greater than (p), this leads to a lack of full exploitation of information time series, and it also reduces the degrees of freedom are usually determine the number of time gaps

based on a standard (AIC) (SC) table (5) the steps Granger causality test:

Table (5) Valuable Akaike and Schwarz

Slow	1	2	3	4	5	6
AIC	11,51	11,61	11,83	11,89	11,60	11,52
SC	11,76	12,04	12,43	12,66	12,55	12,67

-Estimate restrictive formula

$$BLOOD_t=\alpha_0+ \sum_{i=1}^{p} \beta_i .IRON_{t-i} +\varepsilon_t. \quad (10)$$

We assume to be$\sum_{i=1}^{p} \emptyset_i$= 0 in equation. Meaning that the variable (blood) does not affect the variable (iron) and then we get the total estimated residuum squares recovered from the restricted equation (10)$(\sum \hat{\mu}_t^2)$.

-Estimation formula is restricted: that the equation (10), and then we can get the total estimated residuum squares recovered from the formula unrestricted equation$(\sum \hat{\mu}_t^2)$.

-Testing the imposition of the following null-hypothesis

$\boldsymbol{H_0}$: $\sum_{i=1}^{p} \emptyset_i$=0, for that, we must calculate statistical Fisher F_C:

$$F = \frac{RSS_1 \ -RSS_2 \ /m}{(RSS_2 \ )/(n-k)} \text{ and } F \sim (m, n-k) \quad (11),$$

where, m is number of lags; k is number of parameters involved in the model; and n is the sample size. The test is to reject the null hypothesis of non-causality between blood and iron, it uses test (f) to decide the existence of a causal relationship or not between the variables in the following form:
If (f) is greater than the calculated tabular it will reject the null hypothesis testing the hypothesis H_0:$(\sum_{i=1}^{p} \emptyset_i = 0)$

$$F_c = \frac{RSS_1 - RSS_2/m}{(RSS_2)/(n-k)} = 4.4 \ \ is\ greater\ than\ F_c = 3.96.$$

And hence reject the null hypothesis and accept the alternative hypothesis that there is a long-term causal relationship between the number of doses of blood given and the high proportion of iron deposited in the organs of the body.

(2-2)Relationships of some factors on the Thalassemia:
Our research included several possible factors that may have effects on thalassemia, among these factors:
(2-2-1)The type of thalassemia:
The two main types of thalassemia are alpha thalassemia and beta thalassemia. (The alpha and beta refer to which haemoglobin gene is affected, and which of the

haemoglobin chains is faulty.) There are some rare types too. Each type of thalassemia (alpha and beta) is then classified into subtypes, according to how severe the condition is. This mainly depends on how many thalassemia genes are involved. The mildest types are called thalassemia trait (or thalassemia minor). The more severe beta types are beta thalassemia major (BTM) and beta thalassemia intermedia (BTI). The more severe alpha forms are Hb Barts (very severe) and HbH disease (moderate). There are also some rare types of thalassemia such as delta beta thalassemia, or combinations of a beta-thalassemia gene with another abnormal haemoglobin gene, such as HbE (Peters M, 2012). Among the data analyzed in our research, results showed that thalassemia beta major was the most common type in the patients table see Table (6)

Table (6) the relationship between age, gender, type of thalassemia

Age	1-4		5-9		10-14		15-24		25-34		35-44		Sum	
Gender	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Great	13	7	9	5	10	11	6	5	1	1	-	-	39	29
middle	9	3	1	3	1	1	1	2	-	-	-	-	12	9
minor	2	1	1	2	1	-	1	1	1	1	-	-	6	5
Sum	24	11	11	10	12	12	8	8	2	2	-	-	57	43
percentage	35%		21%		24%		16%		4%		-			

(2-2-2) blood type:

Patients included in this study were of different blood types and Rh factor (A^+, A^- , B^+, B^- , AB^+, AB^-, O^+, O^-) but our results demonstrated that the blood type O^+ was the most common type affected see Table (7).

Table (7) the relationship between age, gender and type of blood

Age	1-4		5-9		10-14		15-24		25-34		35-44		Sum	
Gender	M	F	M	F	M	F	M	F	M	F	M	F	M	F
A+	3	1	1	1	1	1	1	1	-	1	-	-	6	5
A-	1	1	1	1	1	1	-	1	-	-	-	-	3	4
B+	4	2	2	1	1	1	1	2	1	1	-	-	9	7
B-	1	-	1	1	1	-	1	1	-	-	-	-	4	2
O+	9	4	3	3	5	5	1	1	1	-	-	-	19	13
O-	4	1	1	-	2	1	2	1	-	-	-	-	9	3
AB+	1	1	2	2	1	2	1	1	-	-	-	-	5	6
AB-	1	1	-	1	-	1	1	-	-	-	-	-	2	3
Sum	24	11	11	10	12	12	8	8	2	2	-	-	57	43

2-2-3 the age and gender:

Ages varied among people infected with Thalassemia and ranged between (1- 44) and they were subdivided in to categories (1-4), (5-9), (10-14), (15-24), (25-34) and (35-44) year's. Results showed that the most infected age groups is the

category (1-4). Males were more affected than females. We also noticed that data were absent for patients from category (35-44), which urges us and other researchers to do a more detailed study on that age groups of patients (see Table 7).

Recommendations:
(1) Do more research on this subject focusing on finding other relationships, such as the relationship between age and an increased demand for blood transfusions.
(2) Try to educate patients with Thalassemia to use specific medicines that relive. the symptoms of iron overload and make these medicines available and cheap as much as possible.
(3) Increase awareness of patients and their families to avoid foods that contain high level of iron such as beef, green leaves and beans.
(4) Regular analysis for iron levels will greatly improve the control of iron overload cases.
(5) Patients that need blood transfusion must regulate their intake times as much as possible.
(6) As we noticed from our research, children between 1-4 years were the most affected, and children at that age, as we know, are in a high rate of growth, therefore, multivitamins and growth factors must be given regularly under medical supervision to reduce the effect of thalassemia on their growth as much as possible.

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