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Estimation of Coagulation FXlll and FXIII A1 Serum Levels in Iraqi Individuals Affected with FXIII Deficiency

Murtadha A. Alshami[1,2], Asmaa Mohammed[1]

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ABSTRACT

Background: The uncommon bleeding condition known as factor XIII (FXIII) deficiency can cause symptoms that range from cerebral hemorrhage to delayed umbilical cord separation. When activated, FXIII is essential for maintaining clot stability and promoting fibrin polymer cross-linking, which guarantees efficient hemostasis. A genetic or acquired FXIII deficiency can cause aberrant bleeding tendencies and decreased clot stability. In Iraq, FXIIID is a common rare bleeding disorder.

Methods: Samples included in this study were families that have some affected individuals with coagulation factor XIII deficiency and healthy persons that are unaffected by any bleeding disorder, with different ages and from different areas of Baghdad- Iraq, to determine FXIII and FXIII-A1 serum levels by Elisa among different genotype individual affected with FXIII deficiency with hime families in addition to recounting some of the coagulation tests (PT, PTT, INR and platelete account).

Result: The results revealed a statistically significant difference in platelet counts between the two groups (P<0.01), with affected individuals exhibiting a significantly higher mean platelet count (240.20 *10^9/L±70.21) compared to the control group (201.05*10^9/L ±27.64). Affected individuals exhibited a significantly shorter PTT (31.60 s±4.36) compared to the control group (33.88 s±2.74) with a P-value (P=0.04), while their INR values were significantly higher (1.12±0.20) compared to controls (0.99±0.12) (P=0.02). No significant difference was observed in PT values between the two groups. The mean of FXIII-A1 was (2.38, 2.86 and 7.54) ng/ml and the mean of FXIII in total was (212.51, 222.81 and 230.38) ng/ml, respectively; homozygote, heterozygote and control group. In a comparison of the difference in the level of FXIII and FXIII A1 between the affected and the control, the rate decrease in the level of FXIII as a whole is approximately 36% below the normal level, while the rate decrease in FXIII A1 is approximately 69% below the normal level.

Key words: Coagulation factors, ELISA, FXIII A, FXIII deficiency, FXIII.

INTRODUCTION

Coagulation Factor XIII (FXIII) is essential to the blood coagulation process's later phases (Zhang *et al.,* 2024; Yahya *et al.,* 2024). The process of halting bleeding, known as hemostasis, depends on the coordinated activity of many clotting factors and platelets. A sequence of events called the coagulation cascade is triggered when a blood artery is injured, resulting in the formation of a stable blood clot (Dull *et al.,* 2021; Al-Khuzaay *et al.,* 2024).

Congenital factor XIII deficiency and acquired factor XIII Deficiency (Pelcovits *et al.,* 2021; Hameed *et al.,* 2024). The inherited genetic abnormalities causing congenital factor XIII deficiency led to the condition existing from birth. Moreover, it is divided into moderate and severe versions according to the blood's remaining Factor XIII activity (Yan *et al.,* 2018; Abd El-Rahmana *et al.,* 2024). While moderate deficit partially reduces Factor XIII activity, severe deficiency is defined by limited or nonexistent Factor XIII activity. Conversely, acquired factor XIII is acquired later in life due to various illnesses, including liver disease (Strilchuk *et al.,* 2020; Alyasiri *et al.,* 2024). Some types of cancer, inflammatory diseases and some drugs. Usually temporary, acquired factor XIII insufficiency goes away once the underlying cause is addressed (Alshehri *et al.,* 2021; Al-Maliki *et al.,* 2025). All the coagulation factors are produced by the hepatocytes in the liver. The only notable exception is FVIII, which is mostly produced by tissue and liver sinusoidal endothelial cells (Hmeed *et al.,* 2025; Abass *et al.,* 2025). These components are usually present in blood plasma in a latent or inactive form. Since most of the factors are proteases, one way to think of them in their latent stage is as zymogens (Butenas *et al.,* 2002; Elsamie *et al.,* 2021). FXIII-B is present in plasma in higher concentrations than FXIII-A, with around half of the former being free. Following the cleavage of AP-FXIII in the presence of Ca_2^+, the FXIII-B subunit dissociates during FXIII activation and at last, FXIII-A is fully active (Byrnes *et al.,* 2024). There is limited information available regarding the exact mechanism of

[1]Department of Biotechnology, College of Science/University of Baghdad, Baghdad, Iraq.

[2]College of Biotechnology, Al-Nahrain University, Baghdad, Iraq.

Corresponding Author: Murtadha A. Alshami, Department of Biotechnology, College of Science/University of Baghdad, Baghdad, Iraq. Email: alshami.mortadha@yahoo.com

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interaction between FXIII-A and FXIII-B. Sushi number 1 appears to be involved in the creation of FXIII-A_2B_2 heterotetramers, whereas sushi numbers 4 and 9 appear to be critical in the dimerization of FXIII-B (Hurják *et al.,* 2020; Byrnes *et al.,* 2024; Ghiath *et al.,* 2025). The present study aims to After the previously mentioned essential roles of FXIII-A, some objectives must be achieved, the connection between FXIII-A activity levels.

MATERIALS AND METHODS

Study group

This study was conducted in the Hemophilia Ward, Children Welfare Teaching Hospital, Medical City, Baghdad, Iraq and private medical Laboratories. The duration of the study was extended from November 2021 until August 2023. Samples included in this study were families that have some affected individuals with coagulation factor XIII deficiency and healthy persons that are unaffected by any bleeding disorder, with different ages and from different areas of Baghdad- Iraq. under the supervision of the consultant and after obtaining approval for the sampling of patients and control.

Blood collection

5 milliliters of blood (venous blood) were collected by a 5 ml plastic disposable syringe. The collected blood was divided into three groups: The first group of blood was preserved in EDTA tubes (for routine coagulation tests), whereas the second group was in a gel tube for serum collection to determine FXIII and FXIII-A1 serum level by Elisa. The last group transferred to a sodium citrate tube. Gently mixed to prevent clotting of blood and temporarily stored in an ice box pending transfer to the laboratory.

Coagulation routing test

Clinical routine tests for bleeding disorders include platelet count, prothrombin time test and partial prothrombin time test. These tests assess platelets, coagulation and INR using electrical impedance, flow cytometry and automated methods (Mindary). Blood is then centrifuged and clotting time is quantified manually.

Determination of coagulation factor XIII serum level

The double antibody sandwich ELISA technique is used for *in vitro* quantitative detection of human serum coagulation Factor XIII. Two types of kits were used: FXIII and FXIII A1 kites. The composition of each kit, the assay procedure and the calculations are presented together due to the fact that all kits are produced by the same company (MyBiosource/USA) and are based on similar principles. The process involves transferring standards and samples into wells, attaching the target protein to the immobilized antibody, introducing a biotin-conjugated protein-specific antibody, washing with avidin-conjugated Horseradish Peroxidase and then introducing a substrate solution. The color intensity increases in direct correlation with the bound protein, the development is halted and the color's magnitude is quantified. Fig 1 and 2 explain the stander curve of the mention kits FXIII and FXIII A1 (Karpati *et al.,* 2000).

Statistical analysis

Analysis of data was carried out using the available statistical package of SPSS-26 (Statistical Packages for Social Sciences-version 26). Data were presented in simple measures of frequency, percentage, mean, standard deviation and median (minimum-maximum values).

RESULTS AND DISCUSSION

Platelet count

This study investigated the platelet counts of all members of affected families with FXIIID that were studied and compared to a control group. The results revealed a statistically significant difference in platelet counts between the two groups ($P<0.01$), with affected individuals exhibiting a significantly higher mean platelet count (240.20 $*10^9$/L) compared to the control group (201.05$*10^9$/L) as shown in Table 1. Despite the difference between the two groups, the results of both groups are within the normal range of 150-450 $\times$ 10^9/L (Hoffman *et al.,* 2022). However, the number of platelets in those affected by factor XIII deficiency

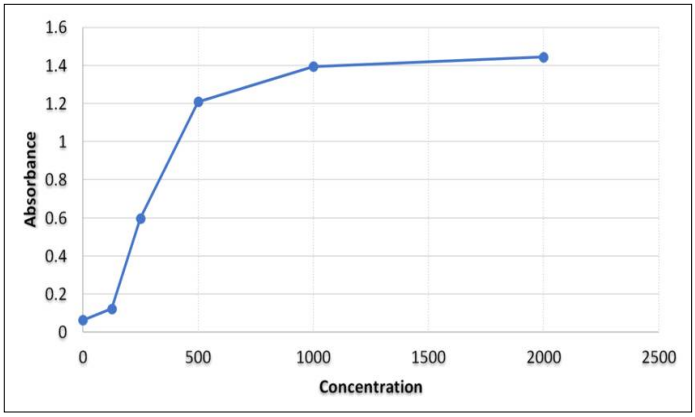


Fig 1: Stander curve of coagulation FXIII eliza kite.

is higher than in normal groups. This finding contrasts with some previous studies on Factor XIII deficiency, which have reported normal platelet counts in affected individuals (Nurden *et al.,* 2021; MObaid *et al.,* 2025). However, other research has shown that a subset of patients with Factor XIII deficiency may present with thrombocytosis, likely due to compensatory mechanisms triggered by impaired clot formation and wound healing (Badulescu *et al.,* 2024; Kareem *et al.,* 2023).

The elevated platelet counts observed in our study could be a result of increased platelet production stimulated by chronic low-grade fibrinolytic activity or a compensatory response to impaired platelet function due to the absence of Factor XIII A cross-linking (Patalakh *et al.,* 2024; Altemeemi *et al.,* 2021). while Factor XIII deficiency is primarily associated with impaired fibrin cross-linking, a subset of patients may present with elevated platelet counts, possibly as a compensatory mechanism. Fig 3 shows a little comparison between the two groups and is involved within the normal range.

Coagulation tests: PT, PTT and INR analysis

These coagulation parameters, prothrombin time, partial Thromboplastin time and International Normalized Ratio (PT, PTT, INR), were measured in affected individuals with FXIIID and a control group. Table 2 describes the result of these parameters for the affected and control groups.

The obtained results made it possible to state that there was a statistical difference between the values of PTT and INR in the two groups. Affected individuals exhibited a significantly shorter PTT (31.60 s) compared to the control group (33.88 s) with a P-value (P=0.04), while their INR values were significantly higher (1.12) compared to controls (0.99) (P=0.02). No significant difference was

Table 1: The mean of platelet count to patients compared with controls.

	Group	N	Mean *10^9/L± S.D.	P-value
PLT	Patients	33	240.20±70.21	>0.01**
	Controls	20	201.05±27.64	

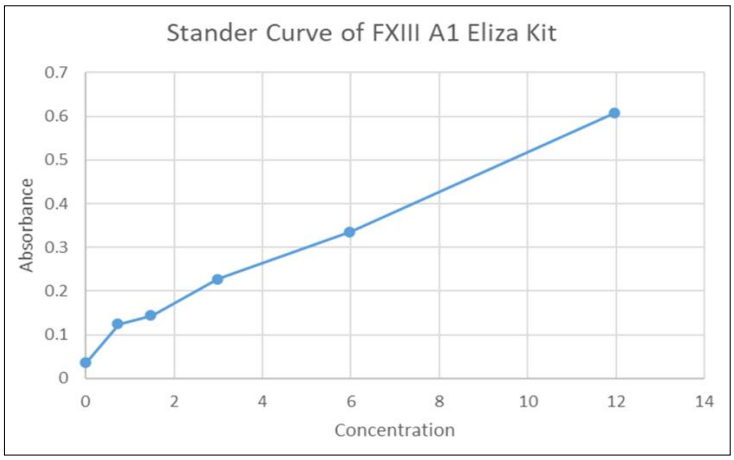


Fig 2: Stander curve of FXIII A1 elisa kite.

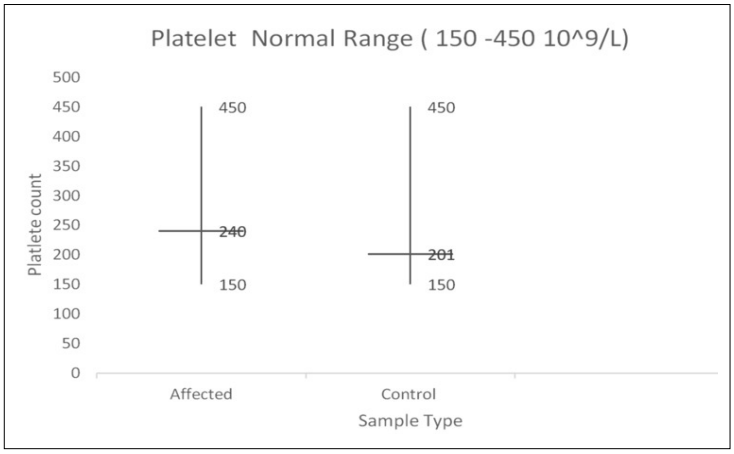


Fig 3: The mean of platelet count to patients compared with controls.

observed in PT values between the two groups. These findings are partially consistent with previous research examining the impact of affected with blood disorders. This pattern of normal PT with prolonged PTT and elevated INR aligns with the typical coagulation profile observed in Factor XIII deficiency (Batsuli and Kouides, 2021; Zedan *et al.,* 2022). This pattern arises because Factor XIII plays a crucial role in stabilizing fibrin clots, while having minimal impact on the initial stages of coagulation measured by PT (Wolberg and Sang, 2022; Al-Maliki *et al.,* 2024). The slightly prolonged PTT and elevated INR in patients reflect the delayed and weaker clot formation due to the absence of FXIII A-mediated fibrin cross-linking, even though the intrinsic and common coagulation pathways measured by PT remain unaffected (Favaloro *et al.,* 2019; Saleh *et al.,* 2024).

FXIII and FXIII A1 srum level

In this work, the serum level of factor XIII in the blood was quantitatively estimated as a whole, in addition to the estimation of factor XIII A1 in affected candidates (in the three groups that involve homozygote, heterozygote and Suspected genotype) with those of non-affected healthy control group by immunological method (ELISA). More specifically, the mean of FXIII-A1 was (2.38, 2.86 and 7.54) ng/ml and the mean of FXIII in total was (212.51, 222.81 and 230.38) ng/ml respectively, homozygote, heterozygote and control group. Just like the above-mentioned results that can shown in Table 3, the results were significantly decreased in the affected group in comparison to the control group (P<0.01).

In a comparison of the difference in the level of FXIII and FXIII A1 between the affected and the control, as shown

Table 2: The mean of PT, PTT and INR to patients compared with controls.

	Group	No.	Mean (s)± S.D.	P-value
PT	Affected	33	14.37±1.81	0.2 NS
	Controls	20	13.76±0.50	
PTT	Affected	33	31.60±4.36	0.04*
	Controls	20	33.88±2.74	
INR	Affected	33	1.12±0.20	0.02*
	Controls	20	0.99±0.12	

Table 3: Serum level of FXIII and FXIII A1 detected by immunological method (ELISA).

Group	Homozygosity	N	XIII a1 Mean (ng/ml) ± S.D	XIII total Mean (ng/ml) ± S.D
Affected	Homozygote	16	2.38±0.56	212.51±41.01
	Heterozygote	14	2.86±1.08	222.81±62.19
	suspected	3	2.31±0.65	230.38±30.20
Controls	Controls	20	7.54±1.54	327.20±30.88
p-value		a	>0.01**	>0.01**
		b	>0.01**	>0.01**
		c	>0.01**	>0.01**
		d	0.29	0.78

a. Homozygote vs. Controls; b. Heterozygote vs. Controls; c. suspected vs. Controls; d. Homozygote vs. Heterozygote vs. Unknown.

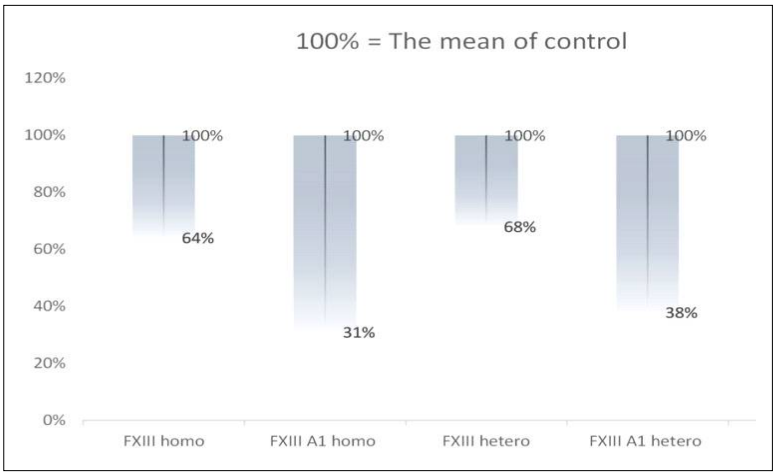
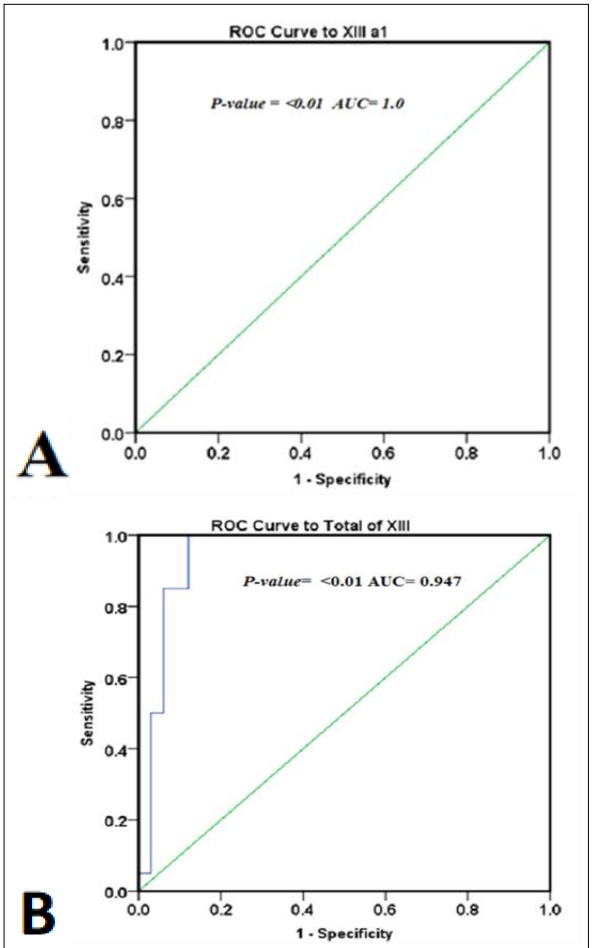


Fig 4: Percentage decrease of serum level of FXIII and FXIII A1 in homozygote and heterozygote groups.

Table 4: Area under the curve to serum level.

Parameter	Area	Std. error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
FXIII serum level	0.947	0.033	>0.01**	0.882	1.000
FXIII A1 serum level	1.000	0.0001	>0.01**	1.000	1.000

a. Under the nonparametric assumption; b. Null hypothesis: true area = 0.5



A: ROC curve to FXIII serum level and B: ROC curve to FXIII A1 serum level.

Fig 5: ROC curve.

in (Fig 4), the rate decrease in the level of FXIII as a whole is approximately 36% below the normal level, while the rate decrease in FXIII A1 is approximately 69% below the normal level. This confirms the coagulation FXIII effect in this study due to deficiency in subunit A of coagulation FXIII. This is consistent with Ichinose (2001) discuss an increase or decrease in total FXIII levels usually correlates with the amount of available FXIII-A1, but in certain physiological or pathological conditions, FXIII-A1 can exist in free form and may not directly correlate with total FXIII levels, but (Katona *et al.,* 2000; Al-Dulimi *et al.,* 2023) that explain There is not always a relationship between the plasma FXIII concentration and the various subunits. In the case of FXIII-B deficiency, for example, FXIII-A is detectable, albeit at low concentration and no A_2B_2 complex is present.

As shown in the previous data, the difference between the homozygote group (affected with symptoms) and the heterozygote group (carrier/ affected without symptoms) of FXIII or FXIII A1 been little difference, Approximately equivalent 3% in FXIII and about 9% in FXIII A1, (Karimi *et al.,* 2018) explain in homozygous individuals with mutations that produce a non-functional or partially functional FXIII-A1 protein, ELISA may still detect some level of the protein, despite it being enzymatically inactive. This could result in similar readings between heterozygous and homozygous individuals. Thomas (2018) mentioned that FXIII-A1 can exist in different forms, such as the cellular form produced by platelets, monocytes and macrophages. In homozygous people, the FXIII-A1 levels may be overestimated if the ELISA detects both cellular and plasma FXIII-A1. Given that homozygous individuals may still make cellular FXIII-A1 that is detected by the ELISA and heterozygous persons may have decreased plasma FXIII-A1, this could account for the convergence in results. Mangla *et al.* (2024) mentioned that Immunological assays identify FXIII-A, FXIII-B and FXIIIA_2B_2 complex deficiency types but cannot detect rare types, such as type II defects, where the FXIII-A subunit is present but functionally inactive.

Statistical applications

Receiver operating characteristic (ROC) curve

This study employed a Receiver Operating Characteristic (ROC) curve analysis to assess the diagnostic accuracy of coagulation FXIII A1, FXIII as total, which discriminates between affected with Factor XIII deficiency and healthy controls. The significance of the Receiver Operation Characteristic (ROC) curve is that it discriminates the ideal cut-off value with the optimum diagnostic performance and classifies a patient's illness as positive or negative based on test findings. The ROC curve can also be used to compare the results of two or more tests and assess a test's overall diagnostic performance (Nahm, 2022). AUC values vary from 0 to 1 and they are divided into five classes: According to (Sachs, 2017), AUC values of 0.5 indicate no discrimination, 0.5-0.7 indicate poor discrimination, 0.7-0.8 indicate good discrimination, 0.8-0.9 indicate very good discrimination and >0.9 indicate excellent discrimination. Table 4 shows the area under the Curve FXIII serum level as total and FXIII A1 serum level in affected compared with control and describes the ROC.

AUC is 0.94 with FXIII serum level and 1 with FXIII A serum level indicates excellent discrimination indication with

FXIIID disorder; Fig 5 explains the ROC curve of FXIII and FXIII A1 serum levels in distinguished with healthy control.

Several studies have shown that quantitative estimation of FXIII A1 by immunological method (ELISA) is considered highly accurate compared to other detection methods like measuring FXIII activity by 5 molar urea, as mentioned in Muszbek *et al.* (2017) and Karimi *et al.* (2018).

CONCLUSION

Our conclusion is that Enzyme ELISA is a promising and good technology for accurately detecting FXIII activity. It is anticipated to increase sensitivity at low levels, which are the most clinically relevant. To fine-tune the assay's dynamic range and, thus, its upper limit of linearity, more tests are required. The ELISA technique might offer a better diagnostic test with additional refinement and verification.

Conflict of interest

All authors declare that they have no conflict of interest.

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