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RESEARCH ARTICLE

The Phosphatidylinositol 3-Kinase as a Potential Diagnostic Marker for Beta-Thalassemia and Its Correlation with Hemoglobin Profiles

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ABSTRACT

The erythropoietic dysfunction and iron insufficiency associated with β-Thalassemia (β-TH) underscore the importance of augmenting traditional diagnostic techniques with independent biomarkers, beyond standard panels. This single-center case–control study (n = 120 β-TH major, 55; β-TH intermedia, 25; control, 40) examined whether circulating phosphatidylinositol-3-kinase (PI3K) distinguishes patients from controls and correlates with hemoglobin fractions. The serum PI3K was significantly higher in β-TH ($p < 0.001$), with excellent discrimination tested in serum (AUC = 0.934; optimal cut-off > 1301 pg/mL; sensitivity 100%, specificity 80%). In a multivariable model, HbA_2% and HbF% were both positively and independently associated with PI3K. These results are biologically consistent with the interaction of erythroid stress, iron homeostasis, and PI3K–AKT signaling, and suggest that PI3K provides unique and complementary diagnostic value in parallel with traditional markers. While human serum circulating PI3K in β-TH data with formal diagnostic parameters are quite scarce. These results suggest that PI3K may serve as a non-invasive complementary biomarker and support multi-center, longitudinal validation with cut-offs confirmation, temporal responsiveness around transfusion/chelation, and supplemental clinical utility in prediction models. Any therapeutic implications targeting the PI3K pathway remain exploratory and require disease-specific studies.

Keywords: Beta-thalassemia, Biomarker, Hemoglobin, Iron overload, Phosphatidylinositol 3-kinase, Thalassemia intermedia, Thalassemia major

Introduction

The β-TH is a hereditary hemoglobin disorder characterized by impaired beta-globin synthesis, ineffective erythropoiesis, hepcidin suppression, and chronic iron overload with adverse consequences on organs including liver, heart, and endocrine glands.[1,2] Clinical severity ranges from asymptomatic carriers to transfusion-dependent severe forms, significantly affecting prognosis and quality of life.[3,4] Traditional diagnosis uses hemoglobin fractionation (HbA, HbA_2, HbF) and hematology and biochemistry tests.[5] While useful to diagnose and classify, these parameters only partly reflect disease dynamics and may not detect early organ involvement.[6] In transfusion-dependent β-TH, iron overload and chelation remain the core aspects of clinical practice.[7] MRI continues to serve as the reference standard for quantifying liver iron concentration for assessing iron burden and the management of thalassemia through chelation therapy. High cost and limited availability, particularly in low-resource settings, limit it to be a routine test.[8] Therefore, complementary biomarkers are required to refine risk assessment without replacing conventional diagnostic methods.[2] Within this context, phosphatidylinositol 3-kinases (PI3K) represent a biologically plausible candidate for investigation.[9,10] PI3K is a membrane-associated

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lipid kinase that phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate (PIP_3), thereby recruiting PH-domain proteins such as AKT and activating downstream pathways regulating cell survival, metabolism, and growth in hematopoietic and other cells.[11] Contemporary models of β-TH position the PI3K–AKT axis at the interface of erythroid stress and iron homeostasis, with emerging evidence also linking oxidative stress, ferroptosis, and marrow stress responses to disease severity.[12] Cross-disease literature underscores the breadth and druggability of PI3K–AKT signaling, including cancer,[13,14] immunodeficiency,[6] and diabetes.[15] These observations highlight biological reach rather than disease-specific utility in β-TH. Cross-context reports also modulate immune-metabolic signaling intersecting with PI3K, illustrating pathway breadth, while disease-specific relevance must be established within β-TH. Pharmacognosy literature also discusses anti-inflammatory modulators intersecting with PI3K-related signaling, underscoring pathway breadth beyond hematology while remaining outside the present study's scope.[16]

Despite this biological plausibility, human data on circulating PI3K in β-TH remain limited, and prior studies have not characterized its diagnostic performance against healthy controls or its independence from hemoglobin fractions. Accordingly, this study aimed to determine whether serum PI3K is elevated in β-TH compared with healthy individuals and to quantify its performance using ROC analysis, and to examine whether PI3K shows independent associations with hemoglobin fractions (HbA, HbA_2, HbF) in multivariable models.

Methods and materials

Study design

This case–control study, involving patients with β-TH and healthy controls, was conducted from January to March 2025 at Al-Karamah Specialized Center for Genetic Blood Disorders in Baghdad, Iraq. The study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the institutional ethics committee.

Study participants

A total of 120 individuals were recruited for the study using a consecutive sampling method. The cohort included 55 patients with β-TH major (28 females, 27 males), 25 individuals with β-TH intermedia (14 females, 11 males), and 40 healthy individuals (19 females, 21 males) with no prior medical history. All patients with thalassemia were seeking routine blood transfusions at the center.

Inclusion criteria included individuals with a confirmed diagnosis of β-T major or β-T intermedia, verified according to recent clinical definitions and hemoglobin fraction patterns as per international guidelines.[17]

Participants who had undergone splenectomy, cholecystectomy, or had a history of hepatitis B, hepatitis C, or malignancy were excluded from the study. Furthermore, individuals who refused to provide informed consent were excluded. Demographic variables (age and sex) and clinical parameters (including history and duration of thalassemia) were collected from each participant.

Sample collection and laboratory analysis

Between 8:00 and 11:00 a.m., ten milliliters of venous blood were obtained from each participant. The blood was immediately divided into two portions. The first portion was placed in an EDTA tube for direct analysis of whole blood assays, including platelet count (PLT), white blood cell count (WBC), packed cell volume (PCV), and hemoglobin electrophoresis. The second portion was collected in a gel tube, allowed to coagulate at room temperature for 30 minutes, and then centrifuged at 3,000 revolutions per minute for ten minutes to isolate the serum. The serum was then divided into small aliquots in 2 mL Eppendorf containers. One aliquot was immediately used for analysis of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Serum Ferritin (S.Ferr), Blood Urea (BU), and serum creatinine (SC). The remaining aliquots were stored at –20°C for later quantification of serum PI3K.

Biomarker quantification and reference ranges

PI3K biomarker levels were quantified utilizing a commercially available ELISA kit from SUNLONG BIOTECH, China, following the manufacturer's guidelines. The established reference ranges for other assessed biomarkers were: ALT (0–41 U/L), PLT ($150–400\times10^9$/L), WBC ($3.5–11.0\times10^9$/L), PCV (35–55%), AST (0–40 U/L), S.Ferr (Female: 20–250 ng/mL, Male: 30–50 ng/mL), BU (2.7–8.1 mmol/L), and SC (40–106 μmol/L).

Anthropometric assessments

The weight and height of each participant were measured, and Body Mass Index (BMI) was calculated as weight (kg) divided by the square of height (m^2).[18]

Statistical analysis

Analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 25 (IBM Corporation, New York, USA), and MedCalc (version 20.027). The statistical significance level was set at $P < 0.05$.

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Given the non-normal distribution of our data, constant variables are presented as median with interquartile range (IQR). To compare differences among the study groups for these skewed distributions, the Kruskal–Wallis test was employed, as it is the appropriate non-parametric equivalent to one-way ANOVA.

To investigate the independent association between PI3K levels and thalassemia, a multivariate linear regression analysis was conducted. This method was chosen to control for potential confounding variables. This analysis was also used to determine the specific relationship between PI3K levels and key hemoglobin electrophoresis variables (HbA, HbA_2, and HbF).

The diagnostic utility of serum PI3K was evaluated by generating Receiver Operating Characteristic (ROC) curves.[19] The Youden index was used to determine the optimal cut-off value that maximizes the balance between sensitivity and specificity.[20] To further assess the diagnostic contribution of PI3K, we used DeLong's test to compare the combined predictive ability of PI3K with hemoglobin electrophoresis profiles (HbA, HbA_2, and HbF).[21]

Results

As shown in Table 1, there were no significant differences in median age, sex, AST, PLT, WBC, or PCV among the three study groups. However, BMI, ALT, S.Ferr, BU, and SC all exhibited statistically significant variations between the groups. These observations highlight the unique clinical phenotypes of the patient populations. Biochemical analysis indicated that serum levels of PI3K were significantly greater in the β-TH-major and intermedia groups than in the healthy control group ($P < 0.001$). In the same line, hemoglobin electrophoresis had significant differences between the groups ($P < 0.001$), with a marked decrease in HbA and significant increase in HbF in the patient groups confirming the expected diagnostic profile of thalassemia.

A multivariate linear regression analysis was employed to determine independent connections between PI3K and hemoglobin electrophoresis variables. As shown in Table 2, HbA_2 and HbF were found to be significant and independent predictors of PI3K, indicating a strong relationship between the new biomarker and the core pathophysiology of hemoglobin synthesis.

Table 1. The demographic, clinical, and laboratory characteristics of the study groups.

Parameters	β-TH-major (n = 55)	β-TH-intermedia (n = 25)	Healthy (n = 40)	*P*-value
Age (years)	23 (20–26)	23 (21–29)	25 (21–27)	0.292
Sex [number (%)]				
Male	27 (49.10)	11 (44)	21 (52.5)	0.120
Female	28 (50.90)	14 (56)	19 (47.5)	
Duration	19 (18–22)	15 (10–17.5)	–	–
BMI (Kg/m2)	24.77 (22.31–27.01)	21.78 (19.53–24.49)	25.03 (24.14–25.93)	0.012*
ALT (U/l)	25.70 (17.82–46.30)	14.80 (11.08–26.76)	18.00 (13.75–21.70)	0.009*
AST (U/l)	28.27 (22.60–39.14)	26.63 (18.50–38.80)	17.15 (14.00–21.00)	0.260
PLT (10^9/l)	313.00 (247.00–445.00)	271.00 (202.00–403.50)	233.50 (200.00–255.50)	0.116
WBC (10^9/l)	6.90 (5.80–9.10)	7.10 (5.70–9.95)	6.65 (5.72–7.07)	0.884
PCV %	24.80 (22.70–27.70)	27.30 (24.10–30.15)	40.90 (38.57–43.40)	0.087
S. Ferr (ng/ml)	2271.60 (1116.20–5118.50)	1195.90 (746.00–2492.35)	140.50 (61.17–171.97)	0.000*
BU (mmol/l)	4.57 (4.10–5.37)	3.68 (3.04–5.05)	4.29 (3.67–4.99)	0.006*
SC (μmol/l)	48.44 (40.50–58.00)	43.12 (36.62–46.60)	53.82 (53.04–70.72)	0.015*
HB A%	5.50 (4.20–12.70)	52.70 (32.65–75.00)	91.80 (89.95–93.60)	0.000*
HB A_2%	3.40 (2.80–5.40)	4.80 (3.55–6.55)	3.05 (2.80–3.20)	0.000*
HB F%	90.10 (80.40–92.60)	30.50 (19.15–64.15)	0.80 (0.80–0.80)	0.000*
PI3K (pg/ml)	1748 (1497–1894)	1430 (1175–1498)	865 (814–1012)	0.000*

*Data are presented as median (IQR).
Comparisons were performed using the Kruskal–Wallis test.
**P*-value < 0.05 is significant.
β-TH-major: β-Thalassemia major patients, β-TH-intermedia: β-Thalassemia intermedia patients, Healthy: Healthy individuals.
BMI: Body Mass Index, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, PLT: Platelet Count, WBC: White Blood Cell Count, PCV: Packed Cell Volume, S.Ferr: Serum Ferritin, BU: Blood Urea, (SC): serum creatinine, HBA: Hemoglobin adult, HBA_2: Hemoglobin adult2, HBF: Hemoglobin fetal, PI3K: Phosphatidylinositol 3-kinases.

Table 2. Multivariate linear regression analysis of the relationship between PI3K and HB-electrophoresis variables.

	Unstandardized	Coefficients	Standardized Coefficients		
Variables	B	Std. Error	Beta	T	*P*-value
HB A%	10.637	7.009	0.956	1.518	0.132
HB A_2%	48.172	13.139	0.246	3.666	0.000**
HB F%	18.031	6.689	1.696	2.695	0.008**

B: Unstandardized Beta Coefficients.
HBA: Hemoglobin adult, HBA_2: Hemoglobin adult2, HBF: Hemoglobin fetal.

Table 3. Area under the ROC curve, Accuracy, and cut-off of PI3K in differentiating healthy individuals from those with Thalassemia.

AUC	*P*-value	Cutoff value	Sensitivity	Specificity	Accuracy	PPV	NPV
0.934	< 0.001	>1301.42	100.00	80.00	0.80	90.90	100.00

AUC (Area under the curve). PPV (Positive predictive value). NPV (Negative predictive value).

The ROC curve analysis in Table 3 and Fig. 1 confirmed PI3K's excellent diagnostic potential. The biomarker demonstrated an AUC of 0.934 ($P<0.001$), with a high sensitivity of 100.00% and a specificity of 80.00% at an optimal cut-off value of >1301.42 pg/ml.

To further assess PI3K's unique contribution, DeLong's test was used to compare its predictive ability with that of the standard hemoglobin profiles. As presented in Table 4 and Fig. 2, the results indicated a significant difference between the ROC curves of PI3K and those of HbA ($P = 0.0238$), HbA_2 ($P<0.001$), and HbF ($P = 0.0137$). These findings are crucial because they suggest that PI3K does not simply replicate the diagnostic information provided by conventional markers, but instead offers a distinct and complementary diagnostic value.

Discussion

Serum PI3K concentrations were significantly higher in β-TH than in healthy controls ($_p<0.001$), with a numerical trend toward higher values in β-TH-major relative to β-TH-intermedia. To our knowledge, this is the first human evaluation of circulating PI3K in β-TH, and the pattern is biologically plausible given the links among ineffective erythropoiesis, iron dysregulation, and PI3K–AKT signaling.[15,22,23] At the optimal cut-off > 1301 pg/mL, PI3K showed excellent discrimination (AUC = 0.934; sensitivity 100%; specificity 80%). In multivariable models, HbA_2% and HbF% were independently and positively associated with PI3K (both $_p \leq 0.008$), whereas HbA% was not significant, and DeLong comparisons indicated that PI3K's AUC differed significantly from that of conventional Hb fractions, underscoring its complementary diagnostic value rather than

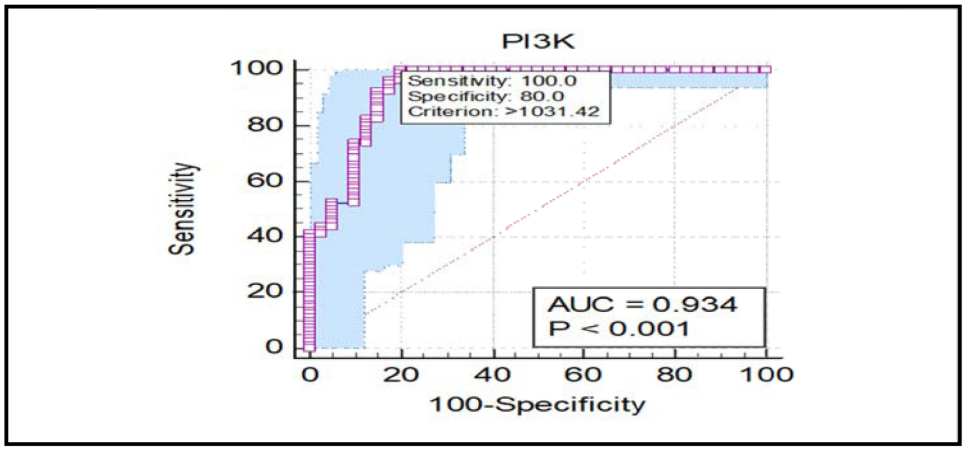

Fig. 1. The ROC curve evaluation regarding the predictive value of serum PI3K concentration in Thalassemia patients versus healthy individuals.

Table 4. Comparison of PI3K and HB-Electrophoresis tests of thalassemia patients using DeLong's test for correlated ROC curves*.

Difference Between Areas	Standard Error	95% CI	z Statistic	*P*-value
PI3K - HbA_% 0.061	0.027	0.00818 to 0.115	2.260	0.0238
PI3K - HbA_2_% 0.216	0.053	0.112 to 0.320	4.083	< 0.0001
PI3K - HbF_% 0.066	0.026	0.0136 to 0.119	2.464	0.0137

PI3K: Phosphatidylinositol 3-kinase, HBA: Hemoglobin adult, HBA_2: Hemoglobin adult2, HBF: Hemoglobin fetal, SE: Standard error, CI: Confidence interval.

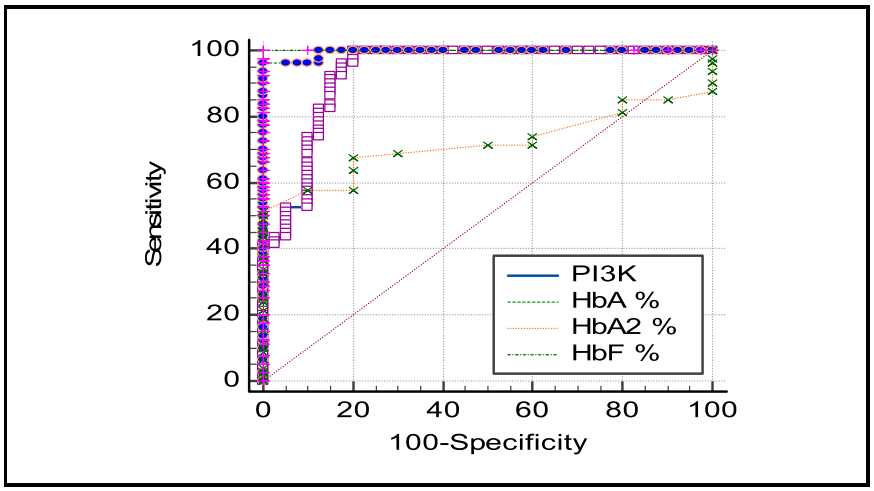

Fig. 2. Comparing the ROC curve between PI3K and hemoglobin electrophoresis of patients and healthy individuals.

as a replacement for standard assessments. Beyond hematology, dysregulated PI3K–AKT signaling is also implicated in neurodegeneration, highlighting the pathway's translational breadth without implying disease-specific therapy in thalassemia.[16,17] Clinically, PI3K may help flag early organ involvement, such as subclinical cardiac injury that routine panels may miss, supporting more proactive surveillance alongside LIC-MRI-based iron monitoring.[8,9] External validation in multi-center, longitudinal cohorts, ideally with standardized peri-transfusion sampling, remains necessary to confirm cut-offs and test responsiveness.

Notably, intercurrent infections or inflammatory states were not systematically ascertained and could influence circulating signaling markers.

Conclusion

Expanding on previous evidence associating the PI3K-AKT biology in erythroid stress and iron dysregulation, we demonstrate that serum PI3K is elevated in β-TH (intermedia and major) and discriminates cases from healthy participants (AUC = 0.934; optimal cut-off >1301 pg/mL; sensitivity 100%; specificity 80%). In multivariable models, HbA_2% and HbF% were independently and positively associated with PI3K, and DeLong comparisons indicated incremental diagnostic value relative to conventional hemoglobin fractions. Taken together, these findings support PI3K as a complementary biomarker that may help flag early organ involvement beyond routine panels; it should be interpreted alongside standard assessments such as LIC-MRI, not as a replacement.

External validation of cut-offs in multi-center, longitudinal cohorts with standardized peri-transfusion sampling is warranted to test temporal responsiveness and confirm generalizability. It is essential to verify that PI3K contributes incremental clinical value within existing prediction models or any therapeutic implications related to the PI3K pathway.

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Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images that are not ours have been

included with the necessary permission for republication, which is attached to the manuscript.
- No animal studies are present in the manuscript.
- Author(s) signed on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Baghdad.

Authors' contributions statement

D.K.M. and L.O.F. contributed equally to the study's conceptualization and design. D.K.M. conducted the experimental work and collected the data. L.O.F. supervised the study and guided the research process throughout. D.K.M. and L.O.F. contributed to data interpretation and manuscript writing. All authors reviewed and approved the final version of the manuscript before submission.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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فوسفاتيديلينوسيتول 3-كيناز كمؤشر تشخيصي محتمل لمرض بيتا ثلاسيميا وارتباطه بمستويات الهيموغلوبين

دعاء قحطان محمد، ليلى عثمان فرحان

قسم الكيمياء، كلية العلوم للبنات، جامعة بغداد، بغداد، العراق

الخلاصة

يبرز الخلل في تكوين خلايا الدم الحمراء ونقص الحديد المرتبط بمرض الثلاسيميا بيتا (β-TH) أهمية تعزيز أساليب التشخيص التقليدية بعلامات حيوية مستقلة، تتجاوز الفحوصات القياسية. فحصت هذه الدراسة أحادية المركز، التي اعتمدت على تصميم الحالات والشواهد (n=120؛ β-TH كبرى 55؛ β-TH متوسطة 25؛ اصحاء 40)، ما إذا كان تركيز إنزيم فوسفاتيديل إينوسيتول-3-كيناز (PI3K) في الدورة الدموية يميز المرضى عن المجموعة الضابطة، وما إذا كان يرتبط بمستويات الهيموجلوبين. كان مستوى PI3K في مصل الدم أعلى بشكل ملحوظ لدى مرضى الثلاسيميا بيتا ($p < 0.001$)، مع تمييز ممتاز تم اختباره في المصل (مساحة تحت المنحنى = 0.934؛ نقطة القطع > 1301 بيكوغرام/مل؛ الحساسية 100%، والنوعية 80%). في نموذج الانحدار المتعدد، ارتبط كل من HbA_2% وHbF% بشكل إيجابي ومستقل مع PI3K. تتوافق هذه النتائج بيولوجياً مع تفاعل اجهاد الكريات الحمراء، توازن الحديد، وإشارات PI3K-AKT، وتشير إلى أن PI3K يوفر قيمة تشخيصية فريدة ومكملة بالتوازي مع المؤشرات التقليدية. في حين أن بيانات PI3K في مصل الدم البشري لدى مرضى الثلاسيميا بيتا (β-TH) مع المعايير التشخيصية الرسمية نادرة جدًا، فإن هذه النتائج تشير إلى أن PI3K قد يكون بمثابة مؤشر حيوي تكميلي غير جراحي، ويدعم التحقق الطولي متعدد المراكز مع تأكيد نقاط القطع، الاستجابة الزمنية حول عمليات نقل الدم/العلاج بالاستخلاب، والفائدة السريرية الإضافية في نماذج التنبؤ. وتبقى أي آثار علاجية تستهدف مسار PI3K استكشافية وتتطلب دراسات خاصة بكل مرض.

الكلمات المفتاحية: الثلاسيميا بيتا، المؤشر الحيوي، الهيموجلوبين، فرط الحديد، فوسفاتيديل إينوزيتول 3-كيناز، الثلاسيميا المتوسطة، الثلاسيميا الكبرى.