**How to Cite**:
Kadim, G. A., Ibraheem, S. A. H. A., & Abbas, H. J. (2022). Assessment of growth-related hormones in patients with hereditary hemoglobinopathies. *International Journal of Health Sciences*, *6*(S4), 6753–6764. https://doi.org/10.53730/ijhs.v6nS4.11020

# Assessment of growth-related hormones in patients with hereditary hemoglobinopathies

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***Abstract*---**Background: Hemoglobinopathies are global public health problems affecting developed and non- developed countries with major consequences for human health as well as economic and social development. Patients with hemoglobinopathies often present with endocrine abnormalities due to iron overload, such as pituitary disease which responsible for growth hormone secretion. Therefore, the aim of this study was to assess the effect of iron over on growth in patients with hemoglobinopathies. Methods: A case control study, that included (140) patients with hemoglobinopathies and (50) healthy participants as a control. Growth hormone (GH), insulin like growth factor- 1 (IGF-1) and insulin like growth factor binding protein (IGFBP) were measured by standard mothed. Results: there were significant decrease level of GH, IGF-1and IGFBP; while there were increase level of ferritin, AST, ALT & LDH in hemoglobinopathies patients. Conclusions: There were decreases level of growth-related hormones and IGF-1 is the more sensitive test in assessing growth retardation due iron overload, which needs treatment at an appropriate age.

***Keywords*---**hemoglobinopathies growth hormone, IGFBP, IGF-1.

## Introduction

Hemoglobinopathies appear to be the most prevalent genetic disorders of erythrocyte worldwide. Sickle cell disease (SCD) and thalassemia are two of the

most serious disorders (Lahhob, Mohammed and Abbas, 2021; Leonard *et al.*, 2021). SCD and its subtypes are inherited hemoglobin disorders produced by defective hemoglobin called sickle hemoglobin (HbS). SCA is associated with a significant morbidity and mortality rate (Inusa *et al.*, 2019). Thalassemia is characterized by an imbalance in the alpha/beta globin chain ratio, ineffective erythropoiesis, chronic hemolytic anemia, and compensatory hemopoietic expansion (Haddad *et al.*, 2014).

Multiple blood transfusions and hemolysis can result in iron overload (Origa *et al.*, 2022). Iron overload was significantly associated with GH and IGF-1 status(Al-Naama, Mea'adKadhum Hassan and Karim, 2020). In patients hemoglobinopathy, growth retardation is a common complication and growth hormone deficiency plays an important role. IGF-1 is more sensitive test in assessing growth retardation. Thus, the adverse effects of iron overload, the severity of anemia and a defective secretion of growth hormone GH-IGF-1 axis could explain the short stature and the reduced synthesis low IGF-1 in patients with hemoglobinopathies. Additional factors include hepatic impairment, other associated endocrine complications, and zinc deficiency (De Sanctis *et al.*, 2014; Yassin *et al.*, 2019).

## Materials and methods

A case control study that included (140) patients (50 patients with beta thalassemia major, 40 patients with beta thalassemia intermediate, and 50 patients with sickle cell anemia). The patients' ages were ranged from (5-18) years. All patients were diagnosed by specialist physicians and confirm by clinical examinations and laboratory investigations. The study also, included (50) healthy participants as a control group. Patients with other chronic diseases were excluded. The commercial ELISA kits were used to GH, IGFBP & IGF-1 estimations from FineTest company (China) .

## Statistical analyses

Statistical analyses were performed by using statistical package for social sciences (SPSS), version 26. Data were expressed as mean and standard deviations (SD). $P < 0.05$ was considered statistically significant.

## Results

The demographic characteristics of control subjects and patients with hemoglobinopathies are shown in table 3.1. There was no significant difference in mean age among study groups ($p = 0.239$).

Table 3.1: Demographic characteristics of control subjects and patients with hemoglobinopathies

| Variable | Control<br>*n* = 50<br>Mean ±SD | SCA<br>*n* = 50<br>Mean ±SD | B-TM<br>*n* = 50<br>Mean ±SD | B-TIM<br>*n* = 40<br>Mean ±SD | *P value* |
|---|---|---|---|---|---|
| Age (years) | 10.3 ± 3.5 | 10.9 ± 3.4 | 11.1 ± 3.4 | 9.7 ± 3.7 | 0.239 |
| Gender | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Male, n (%) | 24 (47.5 %) | 23 (46 %) | 27 (54 %) | 21 (52.5 %) | 0.839 |
| Female, n (%) | 26 (52.5 %) | 27 (54 %) | 23 (46 %) | 19 (47.5 %) | |
| | | | | | |
| BMI | 20.8 ± 2.5 | 17.3 ± 6.1 | 18.1 ± 7.6 | 15.8 ± 2.5 | < 0.001 |

n: number of cases; SD: standard deviation; NS: not significant at $p > 0.05$; HS: highly significant at $p \leq 0.01$.

There was significant decrease (p value ≤ 0.05) in the means values of patients for GH, IGFBP, IGF-1; While, there was significant increase in ferritin, ALT, AST, and LDH in comparison with control, table 3.2.

Table 3.2: Comparison of mean values of biochemical markers of control and patients with hemoglobinopathies

| Variabl | Control and SCA | | | Control and B-TM | | | Control and B-TIM | | |
|---|---|---|---|---|---|---|---|---|---|
| | Control *n* = 50 | SCA *n* = 50 | *P value* | Control *n* = 50 | B-TM *n* = 50 | *P value* | Control *n* = 26 | B-TIM *n* = 50 | *P Value* |
| Urea | 20 ± 8.33 | 17 ± 5.44 | 0.275 | 20 ± 8.33 | 17 ± 6.74 | 0.613 | 20 ± 8.33 | 16 ± 5.36 | 0.232 |
| Creatinine | 0.49 ± 0.3 | 0.46 ± 0.9 | 0.994 | 0.49 ± 0.3 | 0.45 ± 0.11 | 0.983 | 0.49 ± 0.3 | 0.45 ± 0.9 | 0.991 |
| GH | 4.19 ± 4.6 | 2.24 ± 2.39 | 0.022 | 4.19 ± 4.6 | 2.09 ± 2.55 | 0.01 | 4.19 ± 4.6 | 2.29 ± 2.09 | 0.042 |
| IGFBP | 5.288 ± 0.402 | 2.48 ± 0.376 | <0.01 | 5.288 ± 0.402 | 2.492 ± 0.297 | <0.01 | 5.288 ± 0.402 | 3.548 ± 0.329 | <0.01 |
| IGF-1 | 386 ± 56.24 | 227 ± 31.49 | <0.01 | 386 ± 56.24 | 226 ± 32.25 | <0.01 | 386 ± 56.24 | 283 ± 47.84 | <0.01 |
| Ferritin | 66.05 ± 80.16 | 3637 ± 1927 | <0.01 | 66.05 ± 80.16 | 3365 ± 1760 | <0.01 | 66.05 ± 80.16 | 3794 ± 2097 | <0.01 |
| Hb | 11.5 ±1.49 | 9.2 ± 1.34 | <0.01 | 11.5 ±1.49 | 11.5 ±1.49 | <0.01 | 11.5 ±1.49 | 9.0 ± 1.68 | <0.01 |
| ALT | 14.4 ± 4.12 | 20.9 ± 7.5 | <0.01 | 14.4 ± 4.12 | 19.06 ± 6.96 | <0.01 | 14.4 ± 4.12 | 20.4 ± 7.45 | <0.01 |
| AST | 15.24 ± 5.13 | 32.8 ± 11.77 | <0.01 | 15.24 ± 5.13 | 32.5 ± 8.78 | <0.01 | 15.24 ± 5.13 | 27.5 ± 6.29 | <0.01 |
| LDH | 95 ± 24 | 115 ± 17 | <0.01 | 95 ± 24 | 120 ± 23 | <0.01 | 95 ± 24 | 119 ± 19 | <0.01 |

B-TM: beta thalassemia major; B-TIM: beta thalassemia intermediate; SCA: sickle cell anemia; n: number of cases; SD: standard deviation; NS: not significant at $p > 0.05$; S: significant at $p \leq 0.05$; HS: highly significant at $p \leq 0.01$. Statistical analysis: one way ANOVA test.

There were highly significant differences (p value ≤ 0.05) in the means values of each of GFBP, IGF-1 and AST between B-TIM and B-TM groups; SCA and B- TIM groups, table 3.3.

Table 3.3: Comparison of mean values of biochemical markers among hemoglobinopathies groups

| Variable | B-TM and SCA | | | B-TM and B-TIM | | | SCA and B-TIM | | |
|---|---|---|---|---|---|---|---|---|---|
| | B-TM *n* = 50 | SCA *n* = 50 | *P value* | B-TM *n* = 50 | B-TIM *n* = 40 | *P value* | SCA *n* = 50 | B-TIM *n* = 40 | *P Value* |
| Urea | 17 ± 6.74 | 17 ± 5.44 | 0.937 | 17 ± 6.74 | 16 ± 5.36 | 0.878 | 17 ± 5.44 | 16 ± 5.36 | 0.997 |
| Creatinine | 0.45 ± 0.11 | 0.46 ± 0.9 | >0.99 | 0.45 ± 0.11 | 0.45 ± 0.9 | >0.99 | 0.46 ± 0.9 | 0.45 ± 0.9 | >0.99 |
| GH | 2.09 ± 2.55 | 2.24 ± 2.39 | >0.99 | 2.09 ± 2.55 | 2.29 ± 2.09 | >0.99 | 2.24 ± 2.39 | 2.29 ± 2.09 | >0.99 |
| IGFBP | 2.492 ± 0.297 | 2.48 ± 0.376 | >0.99 | 2.492 ± 0.297 | 3.548 ± 0.329 | <0.01 | 2.48 ± 0.376 | 3.548 ± 0.329 | <0.01 |
| IGF-1 | 226 ± 32.25 | 227 ± 31.49 | >0.99 | 226 ± 32.25 | 283 ± 47.84 | <0.01 | 227 ± 31.49 | 283 ± 47.84 | <0.01 |
| Ferritin | 3365 ± 1760 | 3637 ± 1927 | 0.835 | 3365 ± 1760 | 3794 ± 2097 | 0.595 | 3637 ± 1927 | 3794 ± 2097 | 0.968 |
| Hb | 9.2 ± 1.15 | 9.2 ± 1.34 | 0.99 | 9.2 ± 1.15 | 9.0 ± 1.68 | 0.892 | 9.2 ± 1.34 | 9.0 ± 1.68 | 0.974 |
| ALT | 19.06 ± 6.96 | 20.9 ± 7.5 | 0.502 | 19.06 ± 6.96 | 20.4 ± 7.45 | 0.782 | 20.9 ± 7.5 | 20.4 ± 7.45 | 0.981 |
| AST | 32.5 ± 8.78 | 32.8 ± 11.77 | >0.99 | 32.5 ± 8.78 | 27.5 ± 6.29 | 0.036 | 32.8 ± 11.77 | 27.5 ± 6.29 | 0.021 |
| LDH | 120 ± 23 | 115 ± 17 | 0.598 | 120 ± 23 | 119 ± 19 | 0.976 | 115 ± 17 | 119 ± 19 | 0.87 |

B-TM: beta thalassemia major; B-TIM: beta thalassemia intermediate; SCA: sickle cell anemia; n: number of cases; SD: standard deviation; NS: not significant at p > 0.05; S: significant at p ≤ 0.05; HS: highly significant at p ≤ 0.01. Statistical analysis: one way ANOVA test.

The regression analysis of clinical and biochemical markers to predict risk in sickle cell anemia was shown in table 3.4. There was a highly significant (p value < 0.01) high odd ratio (1.66) of GFBP in sickle cell anemia.

Table 3.4: Multivariable logistic regression analysis of clinical and biochemical markers to predict risk in sickle cell anemia patients

| Variable | Regression Coefficient | Standard Error | P-value | Odd Ratio | Lower 95% confidence | Upper 95% confidence |
|---|---|---|---|---|---|---|

| | | | | | limits | limits |
|---|---|---|---|---|---|---|
| Gender | 0.08 | 0.401 | 0.841 | 1.084 | 0.494 | 2.377 |
| Age | 0.141 | 0.08 | 0.078 | 1.151 | 0.985 | 1.346 |
| BMI | -0.193 | 0.06 | <0.01 | 0.825 | 0.734 | 0.927 |
| IGFBP | -27.5 | 9934.6 | <0.01 | 1.661 | 1.461 | 1.861 |
| IGF-1 | -0.091 | 0.028 | <0.01 | 0.913 | 0.865 | 0.964 |
| GH | -0.143 | 0.062 | 0.021 | 0.867 | 0.767 | 0.979 |
| Ferritin | 0.082 | 27.791 | <0.01 | 1.085 | 1.045 | 1.125 |
| Hb | -1.477 | 0.328 | <0.01 | 0.228 | 0.12 | 0.434 |
| AST | 0.307 | 0.07 | <0.01 | 1.36 | 1.186 | 1.559 |
| ALT | 0.19 | 0.044 | <0.01 | 1.21 | 1.109 | 1.32 |
| Urea | -0.055 | 0.033 | 0.094 | 0.947 | 0.888 | 1.009 |
| Creatinine | -0.18 | 0.895 | 0.841 | 0.835 | 0.145 | 4.824 |
| LDH | 0.059 | 0.014 | <0.01 | 1.061 | 1.032 | 1.091 |

Statistical analysis: chi-square test; NS: not significant at $p > 0.05$; S: significant at $p \leq 0.05$; HS: highly significant at $p \leq 0.01$.

The regression analysis of clinical and biochemical markers to predict risk in beta thalassemia major was shown in table 3.5. There was a high significant prediction value to predict risk in beta thalassemia major for IGFBP (OR=1.752, p value < 0.01).

Table 3.5: Identification of risk with multivariable logistic regression analysis in beta thalassemia major patients

| Variable | Regression Coefficient | Standard Error | P-value | Odd Ratio | Lower 95% confidence limits | Upper 95% confidence limits |
|---|---|---|---|---|---|---|
| Gender | -0.24 | 0.401 | 0.549 | 0.786 | 0.358 | 1.725 |
| Age | 0.167 | 0.081 | 0.039 | 1.182 | 1.009 | 1.386 |
| BMI | -0.141 | 0.06 | 0.018 | 0.869 | 0.773 | 0.976 |
| IGFBP | -24.951 | 8742.518 | <0.01 | 1.752 | 1.572 | 1.932 |
| IGF-1 | -1.997 | 929.353 | <0.01 | 0.836 | 0.006 | 0.266 |
| GH | -0.151 | 0.061 | 0.014 | 0.86 | 0.763 | 0.97 |
| Ferritin | 0.179 | 72.017 | <0.01 | 1.196 | 1.01 | 1.121 |
| Hb | -1.777 | 0.398 | <0.01 | 0.169 | 0.078 | 0.369 |
| AST | 0.312 | 0.065 | <0.01 | 1.366 | 1.204 | 1.55 |
| ALT | 0.159 | 0.045 | <0.01 | 1.172 | 1.072 | 1.281 |
| Urea | -0.031 | 0.028 | 0.279 | 0.97 | 0.918 | 1.025 |
| Creatinine | -0.249 | 0.876 | 0.776 | 0.779 | 0.14 | 4.34 |
| LDH | 0.06 | 0.014 | <0.01 | 1.062 | 1.033 | 1.091 |

Statistical analysis: chi-square test; NS: not significant at $p > 0.05$; S: significant at $p \leq 0.05$; HS: highly significant at $p \leq 0.01$.

The regression analysis of clinical and biochemical markers to predict risk in beta thalassemia intermediate was shown in table 3.6. There was negative significant prediction value to predict risk in beta thalassemia intermediate for insulin like growth factor binding protein and ferritin.

Table 3.6: Identification of risk with multivariable logistic regression analysis in beta thalassemia intermediate patients

| Variable | Regression Coefficient | Standard Error | P-value | Odd Ratio | Lower 95% confidence limits | Upper 95% confidence limits |
|---|---|---|---|---|---|---|
| Gender | -0.314 | 0.302 | 0.299 | 0.731 | 0.404 | 1.32 |
| Age | -0.024 | 0.021 | 0.253 | 0.976 | 0.937 | 1.017 |
| BMI | -0.785 | 0.16 | <0.01 | 0.456 | 0.333 | 0.624 |
| IGFBP | -65.24 | 27360.14 | <0.01 | 1.236 | 1.006 | 1.406 |
| IGF-1 | -0.093 | 0.032 | <0.01 | 0.912 | 0.856 | 0.971 |
| GH | -0.143 | 0.067 | <0.01 | 0.867 | 0.76 | 0.99 |
| Ferritin | 0.194 | 74.2 | <0.01 | 1.214 | 1.0 | 1.428 |
| Hb | -1.593 | 0.39 | <0.01 | 0.203 | 0.095 | 0.436 |
| AST | 0.353 | 0.076 | <0.01 | 1.423 | 1.226 | 1.651 |
| ALT | 0.181 | 0.047 | <0.01 | 1.198 | 1.093 | 1.314 |
| Urea | -0.059 | 0.035 | 0.087 | 0.942 | 0.88 | 1.009 |
| Creatinine | -0.2 | 0.907 | 0.826 | 0.819 | 0.139 | 4.841 |
| LDH | 0.061 | 0.015 | <0.01 | 1.063 | 1.033 | 1.094 |

Statistical analysis: chi-square test; NS: not significant at $p > 0.05$; S: significant at $p \leq 0.05$; HS: highly significant at $p \leq 0.01$.

In order to evaluate the diagnostic performance of biochemical markers in patients with sickle cell anemia, receiver operator characteristic (ROC) curve analysis was performed and the results were shown in table 3.7 and figure 3.1.

Table 3.7: Characteristics of biochemical markers as predictors of sickle cell anemia diagnosis

| Variable | AUC | 95% CI | Cut-off | Sensitivity % | Specificity % | PPV | NPV | P value |
|---|---|---|---|---|---|---|---|---|
| IGFBP | 1.00 | 0.964 -1.000 | ≤3.234 | 100 | 100 | 100 | 100 | <0.01** |
| IGF-1 | 0.99 | 0.946 - 1.00 | ≤276 | 98 | 100 | 100 | 98 | <0.01** |
| GH | 0.556 | 0.453 -0.656 | <5 | 90 | 34 | 57.7 | 77.3 | 0.348 |
| Ferritin | 1.00 | 0.964 - 1.00 | >75 | 100 | 100 | 100 | 100 | <0.01** |
| Hb | 0.86 | 0.816 -0.90 | ≤10.8 | 99.4 | 60 | 79.9 | 98.4 | <0.01** |
| AST | 0.946 | 0.882 -0.981 | >19.3 | 92 | 96 | 95.8 | 92.3 | <0.01** |
| ALT | 0.773 | 0.679 -0.851 | >17 | 68 | 80 | 77.3 | 71.4 | <0.01** |
| Urea | 0.585 | 0.482 -0.683 | ≤14 | 36 | 84 | 69.2 | 56.8 | 0.139 |
| Creatinine | 0.519 | 0.417 -0.620 | >0.58 | 4 | 58 | 8.7 | 37.7 | 0.778 |
| LDH | 0.887 | 0.808 -0.941 | >99 | 100 | 84 | 86.2 | 100.0 | <0.01** |

AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; *: significant at p ≤ 0.05 **: highly significant at p ≤ 0.01.

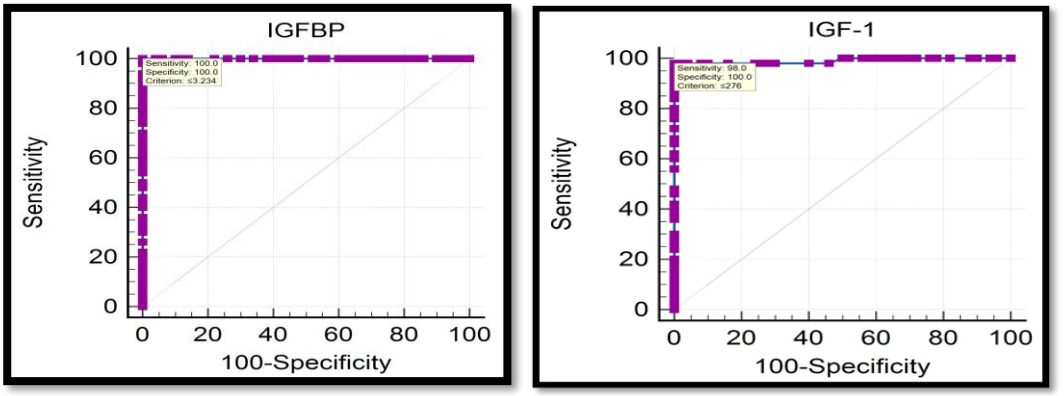


Figure 3.1: Receiver operator characteristic (ROC) curves analyses of some parameters to find the cutoff values that could predict a diagnosis of sickle cell anemia.

Also, the diagnostic performance of biochemical markers in patients with beta thalassemia major, receiver operator characteristic (ROC) curve analysis was performed and the results were shown in table 3.8 and figure 3.2.

Table 3.8: Characteristics of biochemical markers as predictors of beta thalassemia major diagnosis

| Variables | AUC | 95% CI | Cut-off | Sensitivity % | Specificity % | PPV | NPV | P value |
|---|---|---|---|---|---|---|---|---|
| IGFBP | 1.00 | 0.964 - 1.000 | ≤3.065 | 100 | 100 | 100 | 100 | <0.01** |
| IGF-1 | 1.00 | 0.964 - 1.000 | ≤301 | 100 | 100 | 100 | 100 | <0.01** |
| GH | 0.608 | 0.506 - 0.705 | ≤1.2 | 64 | 64 | 64 | 64 | 0.058 |
| Ferritin | 1.00 | 0.964 - 1.000 | >75 | 100 | 100 | 100 | 100 | <0.01** |
| Hb | 0.867 | 0.779 - 0.929 | ≤10.7 | 100 | 60 | 66.7 | 100 | <0.01** |
| AST | 0.947 | 0.883 - 0.982 | >19.3 | 90 | 96 | 95.7 | 90.6 | <0.01** |
| ALT | 0.700 | 0.600 - 0.787 | >19 | 44 | 88 | 78.6 | 61.1 | <0.01** |
| Urea | 0.550 | 0.447 - 0.649 | ≤14 | 38 | 84 | 70.4 | 57.5 | 0.394 |
| Creatinine | 0.510 | 0.408 - 0.611 | >0.22 | 100 | 36 | 61 | 100 | 0.877 |
| LDH | 0.890 | 0.812 - 0.944 | >99 | 100 | 84 | 86.2 | 100 | <0.01** |

AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; *: significant at p ≤ 0.05 **: highly significant at p ≤ *0.01.*

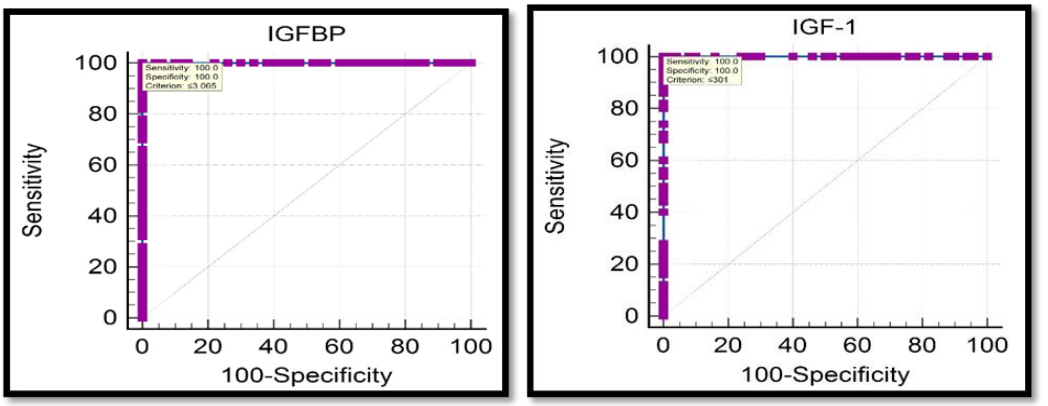


Figure 3.2: Receiver operator characteristic (ROC) curves analyses of some parameters to find cutoff value that could predict a diagnosis of beta thalassemia major

The diagnostic performance of biochemical markers in patients with beta thalassemia intermediate, receiver operator characteristic (ROC) curve analysis was performed and the results were shown in table 3.9 and figure 3.3.

Table 3.9: Characteristics of biochemical markers as predictors beta thalassemia intermediate diagnosis

| Variable | AUC | 95% CI | Cut-off | Sensitivity % | Specificity % | PPV | NPV | P value |
|---|---|---|---|---|---|---|---|---|
| IGFBP | 1.00 | 0.960 - 1.000 | ≤4.092 | 100 | 100 | 100 | 100 | <0.01** |
| IGF-1 | 0.923 | 0.848 - 0.969 | ≤322 | 72.50 | 98 | 96.7 | 81.7 | <0.01** |
| GH | 0.568 | 0.459 - 0.672 | <6.2 | 100 | 28 | 52.6 | 100 | 0.265 |
| Ferritin | 1.00 | 0.960- 1.000 | >75 | 100 | 100 | 100 | 100 | <0.01** |
| Hb | 0.864 | 0.816 - 0.903 | ≤10.8 | 99.4 | 60 | 79.9 | 98.4 | <0.01** |
| AST | 0.936 | 0.864 - 0.977 | >19.3 | 87.5 | 96 | 94.6 | 90.6 | <0.01** |
| ALT | 0.739 | 0.635 - 0.826 | >18 | 60 | 84 | 75.0 | 72.4 | <0.01** |
| Urea | 0.585 | 0.477 - 0.688 | ≤15 | 50 | 68 | 55.6 | 63 | 0.164 |
| Creatinine | 0.514 | 0.406 - 0.620 | >0.3 | 100 | 38 | 56.3 | 100 | 0. 837 |
| LDH | 0.886 | 0.802 - 0.943 | >100 | 100 | 88 | 87.0 | 100 | <0.01** |

AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; *: significant at p ≤ 0.05 **: highly significant at p ≤ 0.01.

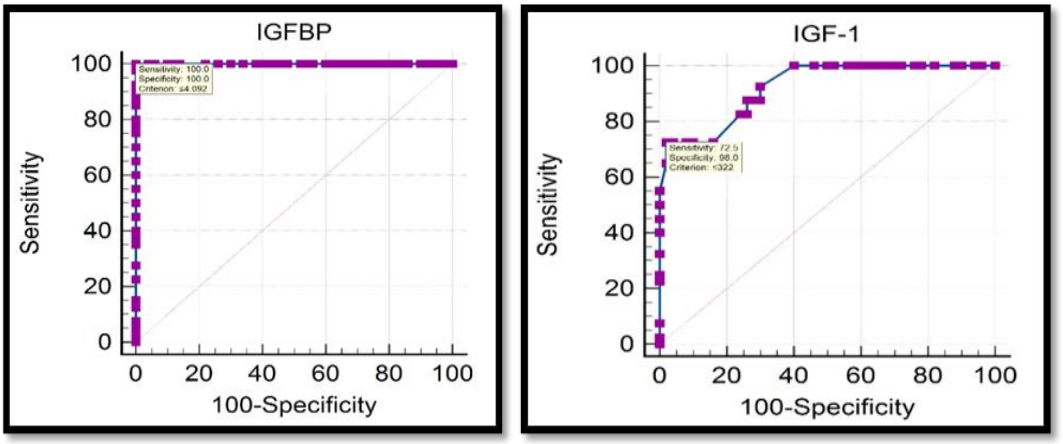


Figure 3.3: Receiver operator characteristic (ROC) curves analyses of some parameters to find the cutoff values that could predict a diagnosis of beta thalassemia intermediate

**Discussion**

**Growth hormone**

Growth retardation is a common problem. Causes include chronic liver disease, iron overload, hormonal changes (abnormalities in growth hormone secretion or, GH-IGF-1 axis dysregulation (Al-Naama, Mea'adKadhum Hassan and Karim, 2020). In B-TM group, the GH was low compared to the control, this result was agreed with previous studies [8]–[10]. Growth hormone impairment is characteristic of thalassemia in which the pituitary gland is significantly intoxicated by iron overload. There are many studies that experienced growth retardation in 53% of beta thalassemia major. The growth retardation is characterized by reduction in growth hormone - insulin like growth factor-1 axis (Faiq, Hamabor and Hama Salih, 2022).

B-TIM is a disease of intermediate severity. It belongs to the non-transfusion dependent thalassemia group, The prevalence of short stature in children and adults with thalassemia is approximately 25% regardless of the type of the thalassemia and serum ferritin concentration(Inati A, Noureldine M, Msndour A, 2014). Also, GH was decrease level compared to the control group, this result was match with previous study(Inati A, Noureldine M, Msndour A, 2014; Karimi *et al.*, 2020).The most frequent endocrine complications reported in B-TIM are growth retardation, delayed puberty, hypogonadism, diabetes, impaired thyroid, parathyroid and adrenal functions, and dyslipidemias. Early recognition and treatment of endocrine complications is important in order to prevent late irreversible sequelae and increase the chances of successful reproduction (Inati *et al.*, 2015). The pathogenesis of growth failure in thalassemia is multifactorial and is mainly due to transfusion iron overload and resulting endocrinopathies (GH deficiency, hypothyroidism, diabetes), nutritional deficiencies, and intensive use of chelating agents particularly deferoxamine. The anterior pituitary is particularly sensitive to iron associated free radical oxidative stress. Even a modest amount of iron deposition in the anterior pituitary by MRI can interfere

with its function. Dysregulation of the GH- IGF-1 axis leads to growth hormone deficiency and growth deceleration (De *et al.*, 2014).

GH was decrease in SCA compared to the control group, the result of this study had similar result with previous studies (Alexandre-Heymann *et al.*, 2019; Mandese *et al.*, 2019). Growth failure in SCD is also believed to be induced by higher energy expenditure and hypermetabolic state resulting from chronic hemolysis. This hypothesis is consistent with the correlation that observed between growth failure, anaemia and haemolysis markers (Alexandre-Heymann *et al.*, 2019).

**Insulin Like Growth Factor Binding Protein (IGFBP) and Insulin Like Growth Factor 1(IGF-1)**

In B-TM group, the IGFBP and IGF-1 were shown decrease levels compared to the control group, that was agreed with previous studies (De Sanctis *et al.*, 2014; Riza1 *et al.*, 2019; Al-Naama, Mea'adKadhum Hassan and Karim, 2020). GH is the most important factor controlling IGF-1 secretion and concentration. A marked IGF-1 deficiency was more common in B-TM patients with associated endocrine complications (De Sanctis *et al.*, 2014). Repeated blood transfusions in thalassemia major patients may cause elevated levels of free iron in blood serum, which then converts hydrogen peroxide into hydroxide ion ($OH^-$), leading to increased reactive oxygen species (ROS) and oxidative stress. Increased ROS decreases mRNA expression of IGF-1, leading to muscle atrophy, sarcomopenia, wasting, and myopathy (Riza1 *et al.*, 2019). The area under the ROC curve for IGF-1 & IGFBP in B-TM was excellent for diagnostic accuracy, whereas sensitivity (100%) and specificity (100%) for both, these markers were highly acceptable for diagnostic test.

In B-TIM, the IGFBP and IGF-1 were shown decrease level compared to the control group, this finding was agreed with previous studies (Dhouib *et al.*, 2018; Yassin *et al.*, 2019). The adverse effects of iron overload, the severity of anemia and a defective secretion of growth hormone GH-IGF-1 axis could explain the short stature and the reduced synthesis low IGF-1 in patients with B-TM and B-TIM(De Sanctis *et al.*, 2014; Soliman and Ahmed, 2014; Yassin *et al.*, 2019).

SCA in this group, the IGFBP and IGF-1 were shown decrease level compared to the control group, this study was agreed with previous study(Mandese *et al.*, 2019). Patients with SCA have significantly decreased IGF-1 concentrations compared to another people with constitutional delay of growth. The poor synthesis of IGF-1 could depend on a defect of the axis(Nunlee-Bland *et al.*, 2004). The area under the ROC curve for IGF-1 & IGFBP in SCA was excellent for diagnostic accuracy, whereas sensitivity (100%) and specificity (100%) for both, these markers were highly acceptable for diagnostic test.

**Conclusions**

There were significant decreases levels of GH, IGFBP & IGF-1; while increases levels of AST, ALT, ferritin & LDH in patients with hemoglobinopathies. Iron overload was significantly associated with growth retardations and liver

disfunctions. IGF-1 is the more sensitive test in assessing growth retardation of these patients. Follow-up of patients to detect and treat endocrine dysfunctions is recommended.

**Conflict of interest**
The authors have no conflict of interest.

**Funding resources**
No external fund was received.

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