International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Longitudinal Hemoglobin Trajectories and Their Association with Growth Response in Short Stature Children (Aged <15 Years) Undergoing Weekly Growth Hormone Therapy: A Real-World Cohort Study

Qingbo Xu[1,2], Yu Yang[1,2], Liling Xie[1,2], Dongguang Zhang[1,2], Haiying Zou[1,2], LanFang Cao[1,2], Li Yang[1,2]

[1]Department of Endocrinology, Genetics and Metabolism, Jiangxi Provincial Children's Hospital, Nanchang, Jiangxi, 330038, People's Republic of China; [2]Department of Endocrinology, The Affiliated Children's Hospital of Nanchang Medical College, Nanchang, Jiangxi, 330038, People's Republic of China

Correspondence: Li Yang, Email yangli05232@163.com

Background: Growth hormone (GH) therapy affects linear growth and may influence hematopoiesis, but dynamic hemoglobin (Hb) changes in children remain unclear.

Objective: To characterize longitudinal Hb trajectories during weekly GH treatment in short stature, including idiopathic short stature (ISS) and growth hormone deficiency (GHD), and to assess their associations with growth response.

Methods: This retrospective cohort study included 165 children with short stature who received once-weekly PEGylated GH therapy for at least 12 months. Hematologic/growth-related parameters were collected at baseline, 6 and 12 months. Group-based trajectory modeling (GBTM) identified Hb trajectory groups. Spearman correlation analysis was performed to evaluate the association between Hb, red blood cell (RBC) count, and insulin-like growth factor 1 (IGF-1). Multivariate logistic regression was used to identify predictors of Hb improvement (≥5 g/L).

Results: Three distinct Hb trajectory groups were identified: ascending (n = 82), ascending-then-descending (n = 51), and stable (n = 32). The ascending group demonstrated the most favorable height SDS improvement at 12 months (mean ΔHtSDS = 1.01), while the ascending-then-descending and stable groups showed more modest gains. IGF-1 levels were moderately correlated with Hb at 12 months (ρ = 0.308, p = 0.001) and RBC counts (ρ = 0.236, p = 0.014). Logistic regression revealed no independent baseline predictor of Hb improvement; however, the inclusion of Hb trajectory group significantly enhanced the predictive model for growth response (adjusted R^2 increased from 0.129 to 0.240; p = 0.018).

Conclusion: Hb trajectories vary significantly among children receiving GH therapy and are moderately associated with height outcomes. Longitudinal monitoring of Hb may serve as a cost-effective dynamic biomarker to guide personalized GH dose titration in pediatric growth disorders. If validated, Hb monitoring may serve as a practical biomarker for personalized GH dosing in pediatric growth disorders.

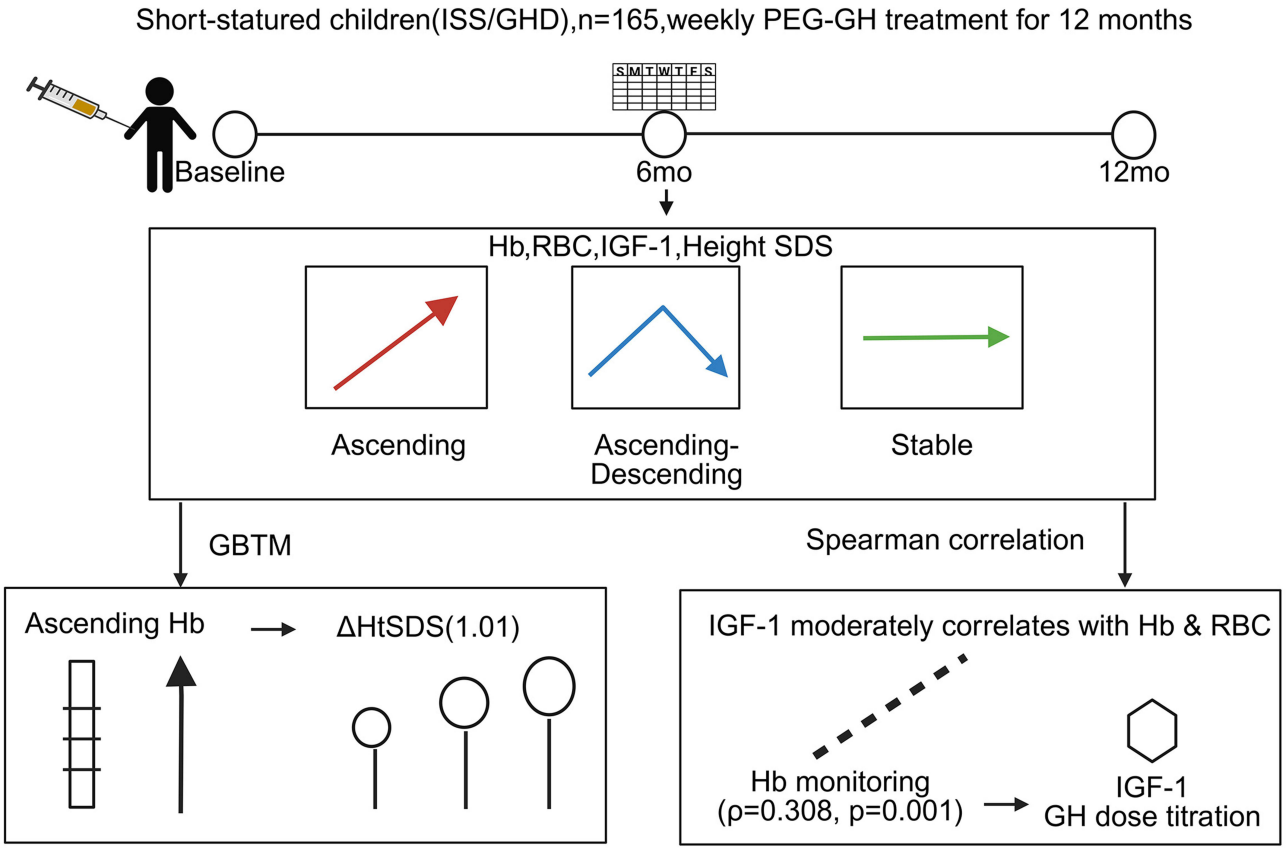
Keywords: trajectory analysis, growth hormone therapy, hemoglobin trajectory, pediatric endocrinology

Introduction

Short stature (defined as height below −2 standard deviations (SD) for age, sex, and ethnicity according to Chinese growth references[1]) remains, one of the most common reasons for referral to pediatric endocrinologists. Its etiology is highly heterogeneous and may stem from genetic, hormonal, environmental, and nutritional influences, as well as prenatal and perinatal factors.[2,3] In clinical practice, recombinant human growth hormone (GH) is administered not only to children with classical growth hormone deficiency (GHD), but also to those with idiopathic short stature (ISS),

Received: 19 May 2025
Accepted: 9 September 2025
Published: 12 September 2025

Graphical Abstract



small for gestational age (SGA) without catch-up growth, Turner syndrome, and other syndromic or chronic conditions.[4–6] While GH therapy primarily aims to promote linear growth and achieve an optimal adult height, its pleiotropic effects on other physiological systems, including the hematopoietic axis Known side effects of GH therapy, such as fluid retention, insulin resistance, and increased hemoglobin levels, have garnered increasing attention.[7]

Recent studies have reported that GH plays a role in erythropoiesis by enhancing the proliferation and differentiation of erythroid progenitor cells, potentially mediated via direct and indirect activation of insulin-like growth factor-1 (IGF-1) signaling.[8–10] In patients with GHD, GH replacement has been associated with increases in hemoglobin concentration and red blood cell counts, even in the absence of anemia at baseline.[11–13] Moreover, hemoglobin expression has been explored as a biomarker for GH exposure, particularly in the context of anti-doping research.[14] These observations underscore the systemic impact of GH beyond somatic growth and highlight a potential link between hematological markers and growth outcomes.

However, the nature and consistency of these hematologic changes across different etiologies of short stature remain poorly defined. GH's influence on erythropoiesis may vary significantly depending on the underlying pathophysiology. For example, children with GHD may exhibit reduced erythropoietic activity due to absolute GH deficiency, while those with ISS or SGA may present with varying degrees of GH insensitivity or resistance, further complicated by differential tissue expression of the GH receptor (GHR).[15,16] In Turner syndrome or other rare syndromic disorders, additional genetic and hormonal abnormalities further confound this relationship. Additionally, children with functional or precocious puberty—unexpectedly included in some mixed cohorts—may demonstrate altered sex steroid levels, which independently modulate erythropoiesis.[17] Therefore, conclusions drawn from mixed cohorts should be interpreted cautiously, as physiological responses may differ fundamentally across subgroups.

Given these complexities, a refined investigation focusing on children with ISS and GHD—two relatively common but pathophysiologically distinct conditions—is necessary to delineate the association between GH therapy and hematopoietic dynamics. Furthermore, since the effect of puberty on erythropoiesis is well-established, the impact of estrogen and testosterone must also be considered, particularly in studies with broad age ranges or those encompassing pubertal transitions.[18]

In this retrospective longitudinal cohort study, we focused on children with GHD and ISS who received weekly GH therapy—a regimen now gaining traction due to its potential for improved adherence and clinical efficacy.[19] We aimed to characterize the trajectories of hemoglobin levels over time using group-based trajectory modeling (GBTM), an advanced statistical approach that identifies latent subgroups with distinct longitudinal patterns. We also evaluated the association between these hemoglobin trajectories and growth outcomes, specifically changes in height standard deviation scores (SDS).[1] Our overarching goal was to determine whether hemoglobin trajectories during GH treatment could serve as early, non-invasive indicators of treatment response. By narrowing the focus to ISS and GHD and accounting for pubertal status, this study aims to provide scientifically robust insights that may improve individualized GH treatment strategies for children with short stature.

Methods

Study Design and Population

This retrospective, single-center study was conducted at the Department of Endocrinology, Genetics and Metabolism, Jiangxi Children's Hospital. Medical records of pediatric patients with short stature who initiated polyethylene glycol recombinant human growth hormone (PEG-rhGH, Jintrolong®) therapy between January 2016 and April 2023 were reviewed. Sample size was determined by power analysis (α=0.05, β=0.2) based on prior Hb effect sizes [16], requiring ≥150 patients. All patients received once-weekly subcutaneous injections of PEG-rhGH. The index date was defined as the initiation of GH treatment.

Inclusion criteria were: (1) age <15 years at treatment initiation, (2) confirmed diagnosis of short stature due to growth hormone deficiency (GHD), idiopathic short stature (ISS), small for gestational age (SGA), Turner syndrome (TS), or other growth disorders, and (3) availability of baseline and 12-month follow-up clinical data. Patients with missing key hematologic or anthropometric values were excluded. The study was approved by the institutional ethics committee of Jiangxi Children's Hospital (Ethics Approval No: JXSETYY-YXKY-20240059) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Prior to the commencement of the study, written informed consent was obtained from the parents or legal guardians of all participating subjects, ensuring their comprehensive understanding of the study's purpose, procedures, potential risks, and benefits.

Diagnostic Criteria

GHD was diagnosed based on growth retardation (height < −2 SDS for age and sex), low serum IGF-1 and IGFBP-3 levels, and a peak GH response <10 ng/mL, this diagnostic cutoff aligns with Chinese guidelines, though international variations exist (eg, <8 ng/mL in some regions), in at least two different GH stimulation tests (eg, clonidine, arginine, insulin). ISS was diagnosed in children with height < −2 SDS, normal birth weight and length, no identifiable systemic, nutritional, or endocrine cause of growth failure, and a normal peak GH response (≥10 ng/mL) during stimulation testing. SGA was defined as birth weight and/or length below –2 SDS for gestational age. For SGA patients, GH prescription followed Chinese guidelines, which recommend treatment when spontaneous catch-up growth fails by age 2 or when height remains below –2 SDS thereafter. Children with Turner syndrome, functional precocious puberty, or rare syndromes were diagnosed according to standard pediatric endocrinology criteria.

Data Collection and Hormonal Assessments

Three time points were established for analysis: Baseline (week 0); 6 months (week 26 ± 30 days); 12 months (week 52 ± 30 days). The following parameters were collected from the electronic medical record: Demographic data: sex, age, diagnosis; Anthropometric data: height, weight, BMI, and their corresponding SDS values; Laboratory tests: hemoglobin,

red blood cell (RBC) count, hematocrit, IGF-1, estradiol (in females), testosterone (in males). Height, weight, and BMI were converted to SDS values based on national Chinese reference standards. IGF-1 levels were measured using the IMMULITE® 2000 immunoassay system (Siemens, Germany), with intra-assay and inter-assay CVs of 2.4–6.3% and 3.0–7.6%, respectively. To assess potential confounding effects of puberty on erythropoiesis, estradiol and testosterone levels were measured. Early puberty was defined as Tanner stage ≥2 or estradiol >20 pg/mL in girls and testosterone >50 ng/dL in boys at baseline.

Group-Based Trajectory Modeling (GBTM)

To characterize patterns of hemoglobin change over time, group-based trajectory modeling was performed using the R package "gbmt" (v0.1.3). Hemoglobin levels at baseline, 6 months, and 12 months were used to model trajectories. A quadratic (second-degree polynomial) function was selected, and three distinct groups were identified based on model fit using Bayesian Information Criterion (BIC) and posterior probability thresholds. To examine the relationship between hemoglobin trajectory and growth response, two linear regression models were developed: Model 1 included sex, baseline age, baseline height SDS, and 12-month IGF-1 change as independent variables; Model 2 added the hemoglobin trajectory group and interaction terms.

Model performance was assessed using R^2, adjusted R^2, and ANOVA to compare model improvement. A simulation analysis was also conducted to visualize how height SDS changes would vary under different hemoglobin trajectory scenarios, based on observed IGF-1 changes.

Statistical Analysis

Statistical analyses were conducted using R version 4.1.2. Continuous variables were reported as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution. Categorical variables were described using frequency and percentage. Between-group comparisons were performed using the Kruskal–Wallis test or Pearson's chi-square test. A two-tailed p-value <0.05 was considered statistically significant. Spearman correlation coefficients were calculated to assess the relationships between Hb, RBC, and IGF-1 levels at baseline and 12 months. The Spearman method was selected due to non-normal distribution and potential outliers. Correlation coefficients (ρ) and corresponding p-values were visualized using a heatmap. To identify independent predictors of hemoglobin improvement, a multivariate logistic regression model was constructed. The dependent variable was defined as an increase in hemoglobin ≥5 g/L from baseline to 12 months. Independent variables included baseline age, IGF-1 level at 12 months, sex, and diagnostic categories. All regression models adjusted for pubertal status (prepubertal vs early puberty). Categorical variables were encoded using one-hot encoding. Odds ratios (ORs), 95% confidence intervals (CIs), and p-values were reported. All modeling and visualization were performed using the stats, ggplot2, and corrplot packages in R.

Results

Baseline Characteristics of the Study Population

A total of 206 pediatric patients with short stature who initiated once-weekly polyethylene glycol recombinant human growth hormone (PEG-rhGH) therapy between January 2016 and April 2023 were screened for eligibility. After excluding those with incomplete hematologic or growth-related data and follow-up less than 12 months, 165 patients were included in the final analysis (Figure 1). The cohort comprised 87 males (52.73%) and 78 females (47.27%), with a mean age of 7.28 ± 2.99 years. The primary diagnoses were idiopathic short stature (ISS, 37.58%) and growth hormone deficiency (GHD, 30.30%), followed by puberty-related short stature (12.12%), small for gestational age (SGA, 5.45%), Silver-Russell syndrome (2.42%), Turner syndrome (1.82%), and other conditions (10.30%).

Puberty-related short stature included both central precocious puberty and early functional puberty. *Early functional puberty* was defined as Tanner stage ≥2 with accelerated growth velocity without central gonadotropin activation Methylmalonic acidemia was grouped into the "Other" category. A comprehensive summary of diagnostic composition, baseline anthropometric indices, and laboratory values across the entire cohort and stratified by hemoglobin trajectory is

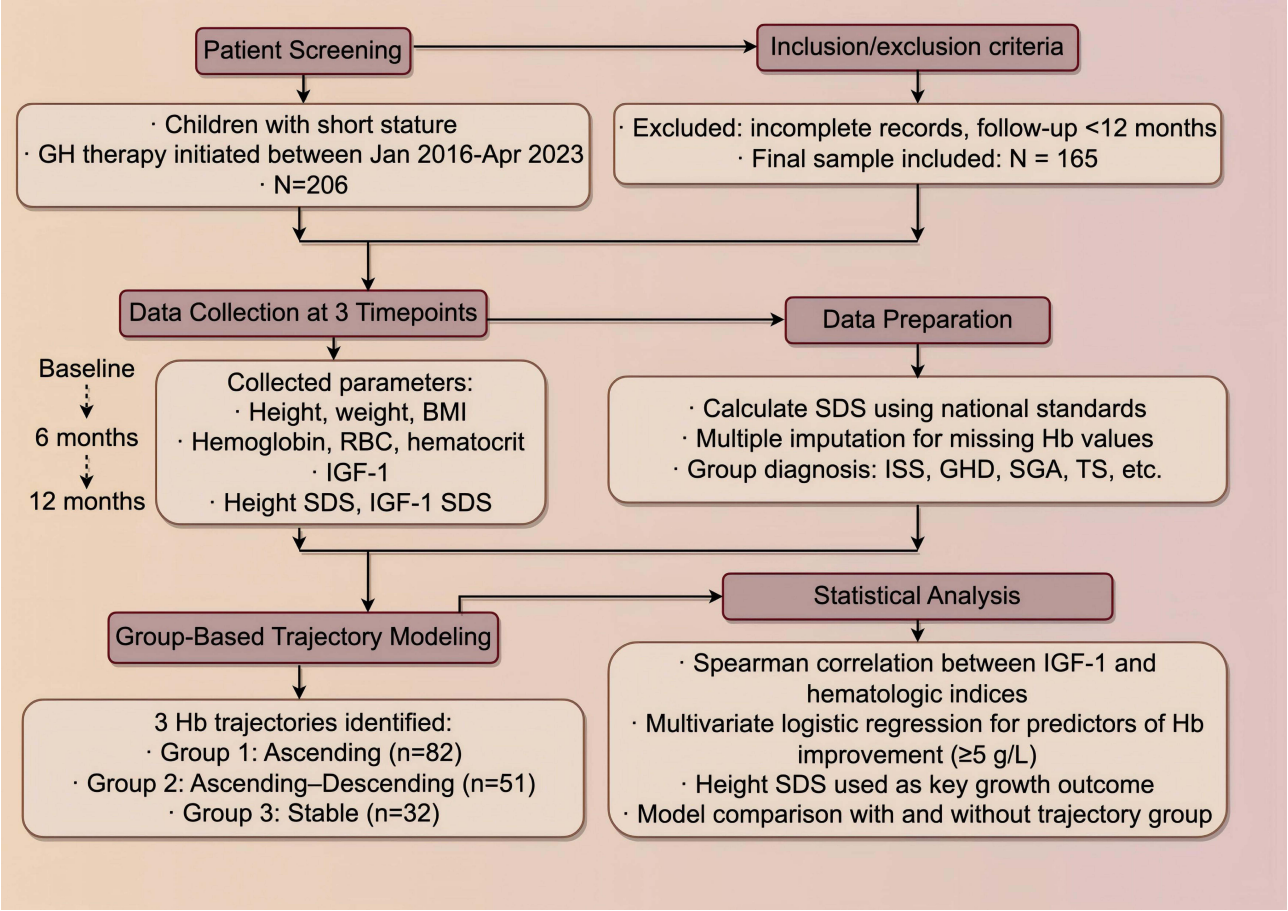


Figure 1 Study flow diagram of patient selection, data collection, and analytic framework.

provided in Table 1. At treatment initiation, the mean height SDS was –1.73 ± 1.30. The mean hemoglobin level was 125.50 ± 8.74 g/L, and the median IGF-1 level was 114.20 ng/mL (interquartile range [IQR]: 67.71–187.00). The cohort was heterogeneous in pubertal status, encompassing both prepubertal and early pubertal children, which may influence erythropoietic and growth responses.

At baseline, anthropometric and erythropoietic indiceswere broadly comparable across the three hemoglobin trajectory groups. However, significant group-wise differences emerged during follow-up. By 6 and 12 months, red blood cell count, hematocrit, and hemoglobin levels showed distinct trends among the groups (all $P < 0.01$). The "Ascending" group exhibited a sustained increase in hemoglobin (from 124.90 ± 9.39 to 133.73 ± 8.64 g/L), as well as higher RBC counts and hematocrit at 12 months, suggesting a more robust erythropoietic response. Growth outcomes and IGF-1 changes also varied among groups but were less pronounced.

Longitudinal Changes in Hematologic and Growth Parameters

He At baseline, anthropometric and erythropoietic indiceswere broadly comparable across the three hemoglobin trajectory groups. However, significant group-wise differences emerged during follow-up. By 6 and 12 months, red blood cell count, hematocrit, and hemoglobin levels showed distinct trends among the groups (all $P < 0.01$). The "Ascending" group exhibited a sustained increase in hemoglobin (from 124.90 ± 9.39 to 133.73 ± 8.64 g/L), as well as higher RBC counts and hematocrit at 12 months, suggesting a more robust erythropoietic response. Growth outcomes and IGF-1 changes also varied among groups but were less pronounced.

Hemoglobin levels increased steadily over the course of GH therapy. The mean hemoglobin rose from 125.50 ± 8.74 g/L at baseline to 130.53 ± 9.30 g/L at 6 months, and to 131.13 ± 8.86 g/L at 12 months. Red blood cell counts, and hematocrit

Table 1 Baseline Demographic, Diagnostic, Anthropometric, and Laboratory Characteristics of the Study Population Stratified by Hemoglobin Trajectory Groups

Characteristic	Overall (N = 165)	Group 1: Ascending (N = 82)	Group 2: Ascending-Descending (N = 51)	Group 3: Stable (N = 32)
Sex, n (%)				
Male	87 (52.73%)	47 (57.32%)	23 (45.10%)	17 (53.13%)
Female	78 (47.27%)	35 (42.68%)	28 (54.90%)	15 (46.88%)
Age (years), mean±SD	7.28 ± 2.99	7.48 ± 2.99	6.97 ± 2.84	7.26 ± 3.27
Diagnosis, n (%)				
ISS	62 (37.58%)	32 (39.02%)	20 (39.22%)	10 (31.25%)
GHD	50 (30.30%)	23 (28.05%)	17 (33.33%)	10 (31.25%)
Puberty-related short stature	20 (12.12%)	11 (13.41%)	7 (13.72%)	3 (9.38%)
SGA	9 (5.45%)	5 (6.10%)	1 (1.96%)	3 (9.38%)
SRS	4 (2.42%)	2 (2.44%)	1 (1.96%)	1 (3.13%)
Turner syndrome	3 (1.82%)	2 (2.44%)	0 (0.00%)	1 (3.13%)
Other	17 (10.30%)	7 (8.54%)	5 (9.80%)	5 (15.63%)
Height (cm), mean±SD	114.02 ± 18.88	115.69 ± 19.61	112.15 ± 16.99	112.70 ± 19.99
Weight (kg), mean±SD	21.69 ± 12.37	22.83 ± 14.55	20.19 ± 9.11	21.18 ± 10.73
BMI (kg/m2), mean±SD	16.02 ± 8.22	16.60 ± 11.38	15.23 ± 2.31	15.77 ± 2.89
Height SDS, mean±SD	−1.73 ± 1.30	−1.64 ± 1.48	−1.77 ± 1.03	−1.92 ± 1.20
Weight SDS, mean±SD	−0.93 ± 4.04	−0.53 ± 5.65	−1.36 ± 0.90	−1.24 ± 1.02
BMI SDS, mean±SD	−0.41 ± 1.57	−0.32 ± 1.68	−0.60 ± 1.67	−0.36 ± 1.06
Hematologic parameters				
Hemoglobin (g/L), Baseline	125.50 ± 8.74	124.90 ± 9.39	124.24 ± 7.78	129.00 ± 7.82
Hemoglobin (g/L), 6 months	-	127.52 ± 8.95	136.13 ± 8.43	129.80 ± 7.59
Hemoglobin (g/L), 12 months	-	133.73 ± 8.64	128.43 ± 8.71	128.64 ± 8.04
RBC ($\times 10^{12}$/L), Baseline	-	4.53 ± 0.36	4.50 ± 0.36	4.59 ± 0.28
RBC, 6 months	-	4.65 ± 0.50	4.82 ± 0.40	4.64 ± 0.31
RBC, 12 months	-	4.80 ± 0.33	4.60 ± 0.41	4.56 ± 0.29
Hematocrit (%), Baseline	-	37.99 ± 2.55	37.86 ± 2.29	38.99 ± 2.20
Hematocrit, 6 months	-	38.47 ± 5.73	40.86 ± 2.49	41.22 ± 10.99
Hematocrit, 12 months	-	40.45 ± 8.44	38.76 ± 10.43	38.73 ± 2.56
Growth parameters				
Height SDS, 6 months	-	−0.98 ± 1.27	−1.30 ± 0.81	−1.66 ± 1.11
Height SDS, 12 months	-	−0.65 ± 1.17	−1.08 ± 3.17	−1.13 ± 0.90
Δ Height SDS at 6 months	-	0.63 ± 1.09	0.46 ± 1.01	0.21 ± 0.94
Δ Height SDS at 12 months	-	1.01 ± 1.10	0.65 ± 3.42	0.68 ± 0.85
IGF-1 (ng/mL), Baseline	114.20 (67.71, 187.00)	119.50 (65.43, 215.00)	110.85 (72.34, 167.68)	110.00 (78.85, 201.00)
IGF-1, 6 months	-	229.00 (165.00, 313.60)	213.00 (136.00, 279.00)	201.65 (159.75, 264.50)
IGF-1, 12 months	-	253.00 (209.70, 337.00)	203.00 (162.00, 314.00)	237.00 (187.50, 305.85)
Δ IGF-1 at 6 months	-	93.70 (48.25, 148.17)	90.35 (40.93, 163.08)	77.40 (56.10, 130.48)
Δ IGF-1 at 12 months	-	118.00 (71.00, 180.43)	109.70 (44.80, 165.10)	102.00 (55.30, 168.45)

Notes: Data are presented as n (%), mean ± SD, or median (interquartile range), as appropriate. Puberty-related short stature includes both central precocious puberty and early functional puberty. Methylmalonic acidemia (MMA) is grouped under the "Other" diagnosis category. Trajectory groups were defined based on longitudinal changes in hemoglobin levels over 12 months: Group 1 (Ascending), Group 2 (Ascending then Descending), and Group 3 (Stable). Δ indicates the change from baseline. *Early functional puberty* was defined as Tanner stage ≥2 with accelerated growth velocity without central gonadotropin activation.

Table 2 Summary of Key Indicators Over Time

Characteristic	Baseline	6 months	12 months
Hemoglobin (g/L)			
Mean±SD Median (IQR) N	125.50±8.74 125.00 (120.00, 130.00) 161	130.53±9.30 130.00 (125.00, 136.00) 160	131.13±8.86 131.00 (126.00, 136.00) 126
Hemoglobin after imputation (g/L)			
Mean±SD Median (IQR) N	125.47±8.69 125.00 (120.00, 130.00) 165	130.48±9.19 130.00 (125.00, 135.00) 165	131.08±8.48 132.00 (126.00, 136.00) 165
Red blood cell (10^{12}/L)			
Mean±SD Median (IQR) Missing	4.53±0.34 4.51 (4.29, 4.72) 161	4.70±0.44 4.65 (4.47, 4.87) 159	4.69±0.36 4.65 (4.47, 4.90) 126
Hematocrit (%)			
Mean±SD Median (IQR) N	38.15±2.43 38.10 (36.40, 39.50) 161	39.70±6.50 39.30 (37.88, 41.33) 160	39.60±8.19 39.30 (37.50, 41.20) 126
IGF-1 (ng/mL)			
Mean±SD Median (IQR) N	140.58±94.99 114.20 (67.71, 187.00) 155	242.43±129.81 213.75 (153.25, 309.25) 162	264.23±125.12 242.50 (175.40, 322.95) 120

Abbreviations: SD, standard deviation; IQR, interquartile range; IGF-1, insulin-like growth factor 1.

followed a similar trend. IGF-1 levels showed a consistent increase, with median values reaching 242.50 ng/mL (IQR: 175.40–322.95) at 12 months. A detailed summary of laboratory values at each time point is presented in Table 2.

These data suggest that GH therapy, even when administered weekly, can influence both linear growth and hematologic indices. While the magnitude of hemoglobin change was modest, the trend was consistent across the cohort.

Identification of Hemoglobin Trajectory Patterns

Group-based trajectory modeling (GBTM) identified three distinct hemoglobin trajectory groups over the 12-month period (Figure 2): Group 1 - Ascending (n = 82): Showed a sustained and gradual increase in hemoglobin; Group 2 - Ascending then Descending (n = 51): Demonstrated a rise at 6 months followed by a decline; Group 3 - Stable (n = 32): Maintained relatively unchanged hemoglobin levels.

These groups differed not only in hemoglobin trends but also in corresponding erythrocyte indices, particularly at 6 and 12 months. The heterogeneity in hemoglobin response suggests interindividual differences in GH-mediated hematopoiesis.

Associations Between Trajectory Patterns and Growth Response

Changes in height SDS also varied. At 6 months, the mean height SDS increase was 0.63 in the Ascending group, compared to 0.46 and 0.21 in the other two groups. By 12 months, the Ascending group maintained the lead, with a mean height SDS gain of 1.01. The ascending Hb group (mean±SD, 1.01 ± 1.10) showed significantly greater than stable group (0.68 ± 0.85) at 12 months in Table 1. While the ascending-then-descending and stable groups showed more modest

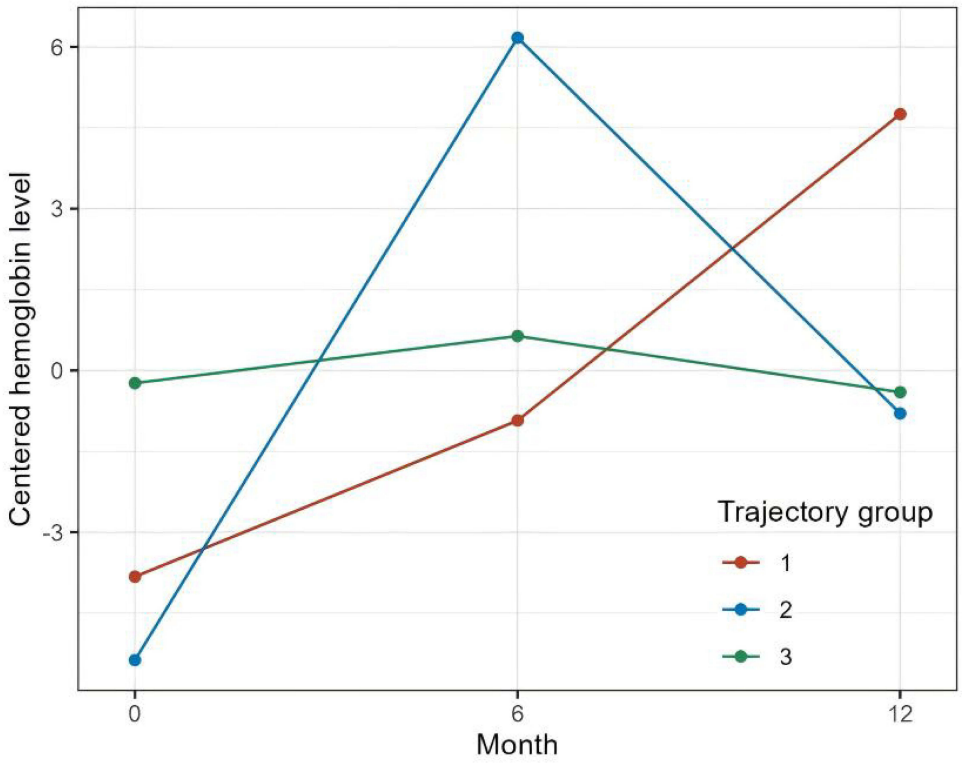


Figure 2 Hemoglobin trajectories over 12 months by trajectory group.

gains (Figure 3). IGF-1 levels increased similarly across all groups, and no significant between-group differences were observed in IGF-1 changes, implying that hemoglobin trends were not simply reflective of systemic IGF-1 exposure.

Hemoglobin Trajectory as an Independent Predictor

To evaluate whether hemoglobin trajectory provided additional predictive value for growth response, two regression models were constructed. In Model 1 (without trajectory group), the adjusted R^2 was 0.1288. Inclusion of the hemoglobin trajectory group (Model 2) increased the adjusted R^2 to 0.2398. ANOVA comparison showed a statistically significant improvement in model fit ($F = 2.33$, $P = 0.018$).

Simulation analysis further demonstrated that patients in the "Ascending" group exhibited more stable and favorable predicted gains in height SDS, particularly in the context of increasing IGF-1 (Figure 4). In contrast, patients in the "Ascending–Descending" group had more variable responses, suggesting that a decline in hemoglobin may reflect suboptimal treatment benefit in some cases.

Correlation Between Hematologic Indices and IGF-1 Levels

To explore the relationships between erythropoietic indices and IGF-1 levels, we conducted Spearman correlation analyses. As shown in Figure 5 and Table 3, IGF-1 levels at 12 months were moderately correlated with hemoglobin levels at both baseline ($\rho = 0.275$, $p = 0.003$) and 12 months ($\rho = 0.308$, $p = 0.001$). A weaker but positive correlation was also observed between IGF-1 and red blood cell counts ($\rho = 0.236$, $p = 0.014$). Baseline hemoglobin levels were strongly correlated with hemoglobin at 12 months ($\rho = 0.687$, $p < 0.001$), indicating a stable hematologic profile over time in most patients. These findings suggest that IGF-1 may contribute to erythropoietic activity during growth hormone therapy.

Predictors of Hemoglobin Improvement

To explore potential clinical predictors of hematologic response to growth hormone therapy, a multivariate logistic regression analysis was performed. The dependent variable was a hemoglobin (Hb) increase of ≥5 g/L at 12 months

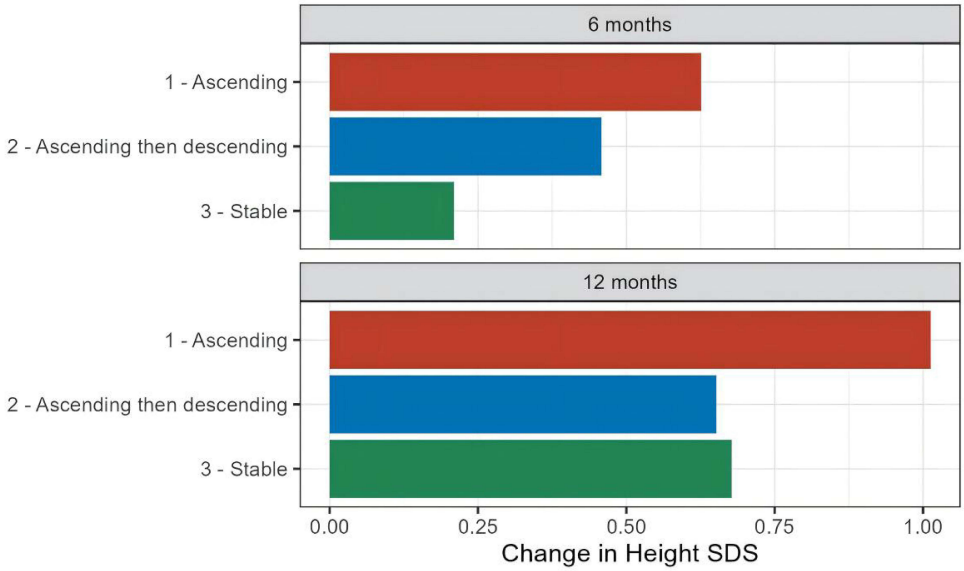


Figure 3 Change in height SDS by trajectory group at 6 and 12 months.

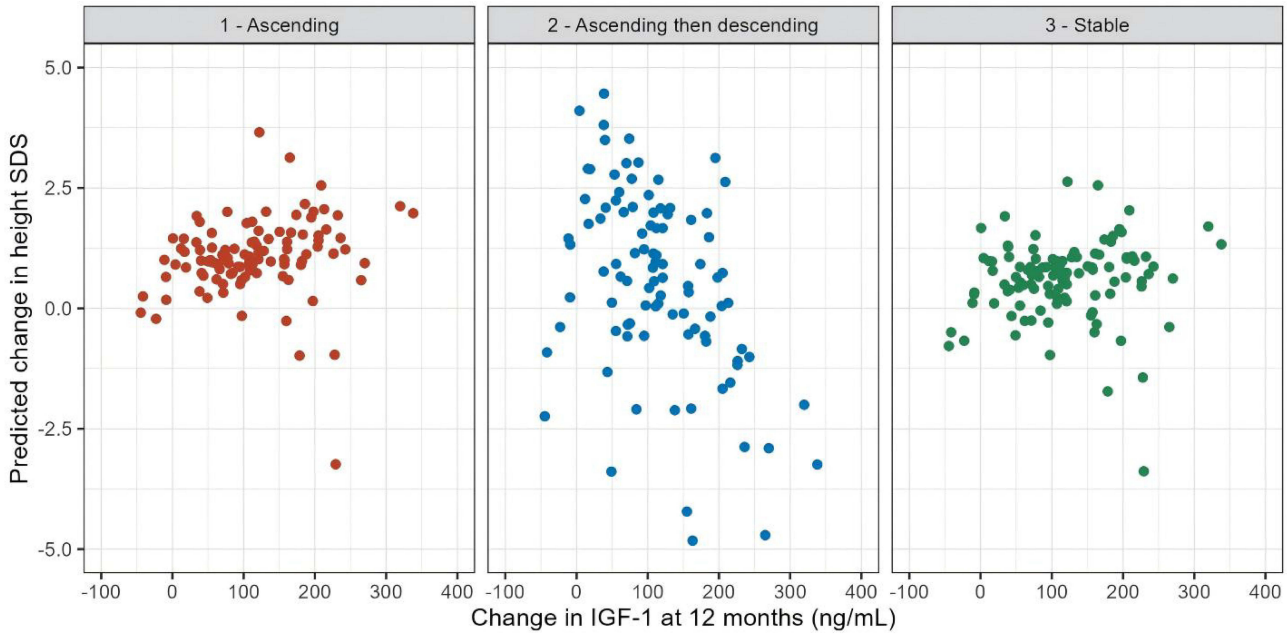


Figure 4 Predicted change in height SDS by trajectory group and change in IGF-1 at 12 months.

compared to baseline. The model included age at baseline, IGF-1 level at 12 months, sex, and diagnostic categories as independent variables.

As shown in Table 4, none of the predictors reached statistical significance. Male sex was associated with a higher odds of hemoglobin improvement (odds ratio [OR] = 3.21, 95% confidence interval [CI]: 0.80–12.95, $p = 0.101$), though this did not achieve significance. IGF-1 level at 12 months showed no independent association with Hb improvement (OR = 0.996, 95% CI: 0.990–1.003, $p = 0.266$). Among diagnostic categories, children with SGA, ISS, GHD, Turner syndrome, and other rare conditions showed varying trends, but all with wide confidence intervals and non-significant p-values (all $p > 0.1$), likely due to limited sample size per subgroup. These findings suggest that while some clinical

https://doi.org/10.2147/IJGM.S541514

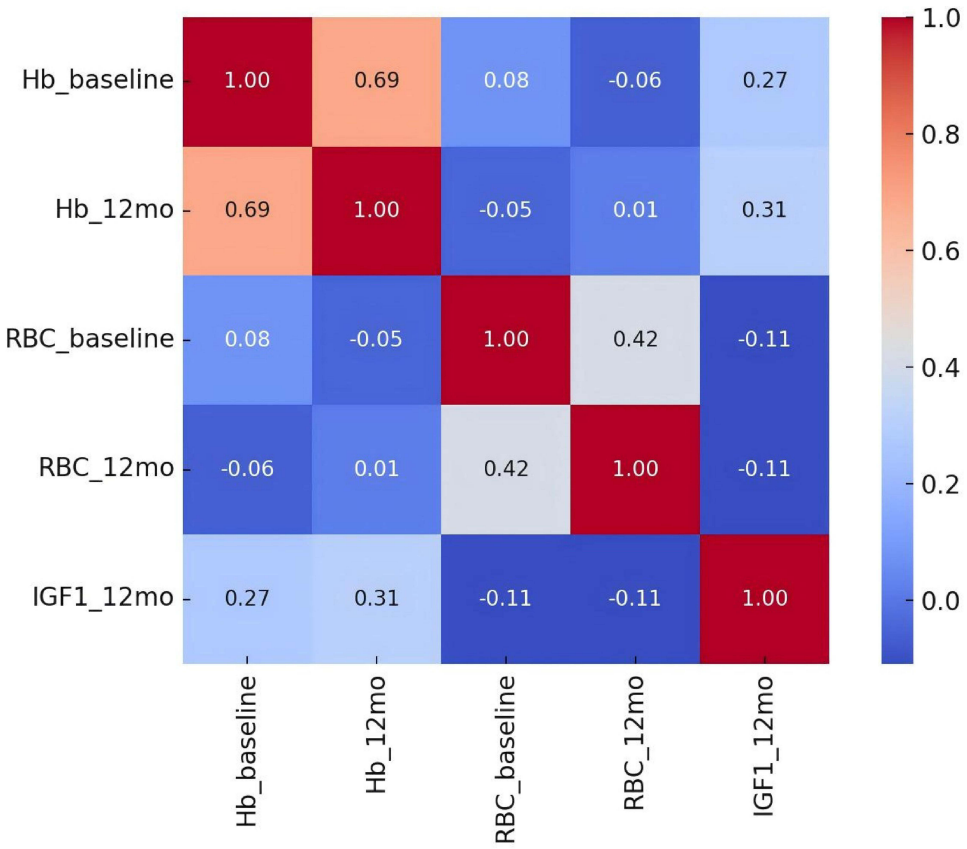


Figure 5 Spearman correlation heatmap of hematologic and IGF-1 variables at baseline and 12 months.

factors may influence erythropoietic response to GH therapy, no single variable was independently predictive of Hb improvement in this cohort. Further studies with larger and more homogeneous populations are warranted.

Discussion

The identification of distinct Hb trajectories and their association with growth response highlights the potential of Hb monitoring as a dynamic biomarker. This finding could have significant implications for GH dose titration and adherence monitoring, enabling more personalized treatment strategies. This study provides novel insights into the hematologic changes observed during growth hormone (GH) therapy in children with short stature, revealing that hemoglobin (Hb) levels do not follow a uniform trajectory but instead cluster into distinct temporal patterns. By applying group-based trajectory modeling (GBTM), we identified three unique Hb trajectories: a steadily ascending pattern, an ascending-then-descending pattern, and a stable pattern. These trajectories were not only reflective of changes in erythropoietic indices

Table 3 Spearman Correlation Coefficients (ρ) and P-values Among Key Hematologic and IGF-1 Variables

	Hb_Baseline	Hb_12mo	RBC_Baseline	RBC_12mo	IGF1_12mo
Hb_baseline	1.0 (p=0.0)	0.687 (p=0.0)	0.078 (p=0.408)	−0.062 (p=0.509)	0.275 (p=0.003)
Hb_12mo	0.687 (p=0.0)	1.0 (p=0.0)	−0.047 (p=0.616)	0.014 (p=0.884)	0.308 (p=0.001)
RBC_baseline	0.078 (p=0.408)	−0.047 (p=0.616)	1.0 (p=0.0)	0.417 (p=0.0)	−0.109 (p=0.247)
RBC_12mo	−0.062 (p=0.509)	0.014 (p=0.884)	0.417 (p=0.0)	1.0 (p=0.0)	−0.109 (p=0.247)
IGF1_12mo	0.275 (p=0.003)	0.308 (p=0.001)	−0.109 (p=0.247)	−0.109 (p=0.247)	1.0 (p=0.0)

Table 4 Logistic Regression Analysis of Predictors for Hemoglobin Improvement (≥5 g/L) at 12 months

Variable	Coefficient	Std Error	OR	95% CI Lower	95% CI Upper	P-value
Intercept	−2.3417	2.0707	0.0962	0.0017	5.5668	0.2581
Age at baseline (years)	0.1477	0.1349	1.1592	0.8898	1.51	0.2736
IGF-1 at 12 months (ng/mL)	−0.0037	0.0033	0.9963	0.9899	1.0028	0.2658
Male sex (vs female)	1.1667	0.7115	3.2115	0.7963	12.9525	0.101
SGA diagnosis (vs others)	1.4609	1.8641	4.3097	0.1116	166.4254	0.4332
	−18.3684	33883.38	0	0	Inf	0.9996
ISS diagnosis (vs others)	0.87	1.3766	2.387	0.1607	35.4531	0.5274
TS diagnosis (vs others)	22.6976	40094.65	7202022520	0	Inf	0.9995
GHD diagnosis (vs others)	1.147	1.3644	3.1488	0.2171	45.6612	0.4005
Growth delay (vs others)	21.3692	37880.39	1907722951	0	Inf	0.9995
MMA diagnosis (vs others)	−20.2466	36864.46	0	0	Inf	0.9996
Other short stature diagnosis	−18.3646	8704.627	0	0	Inf	0.9983
Early puberty (vs others)	2.7894	1.7635	16.2707	0.5132	515.8715	0.1137
Pubertal growth delay (vs others)	1.6284	1.5151	5.0956	0.2615	99.2834	0.2825

Abbreviations: Inf, infinity; IGF-1, insulin-like growth factor 1; ISS, idiopathic short stature; SGA, small for gestational age, GHD, growth hormone deficiency; MMA, Methylmalonic acidemia; TS, Turner syndrome; OR, odds ratio; CI, confidence interval.

such as red blood cell (RBC) counts and hematocrit, but were also moderately associated with longitudinal changes in height standard deviation scores (HtSDS). These findings suggest that dynamic erythropoietic indicesmay serve as early indicators of treatment responsiveness in pediatric GH therapy. Our identification of distinct hemoglobin trajectories and their moderate association with linear growth represents the key finding of this study, highlighting Hb dynamics as a potential early biomarker of treatment responsiveness.

The "Ascending" group, which demonstrated sustained increases in Hb over 12 months, also exhibited the most favorable linear growth, with a mean HtSDS improvement of 1.01. This trend supports the hypothesis that GH therapy may exert erythropoietic effects that synergize with its somatotropic effects. The significantly greater height SDS gain in the ascending groups (mean±SD, 1.01 ± 1.10) showed significantly greater than stable group (0.68 ± 0.85) at 12 months, suggests that sustained Hb elevation may potentiate GH's growth-promoting effects. Several studies in the past five years have substantiated the role of the GH/IGF-1 axis in hematopoiesis. GH receptors are expressed on erythroid progenitor cells, and GH administration has been shown to promote proliferation of hematopoietic stem cells and enhance erythroid colony formation.[20,21] In animal models, GH has also been reported to increase erythropoietin levels and modulate iron metabolism, thus improving hematologic output.

Our use of weekly PEGylated GH therapy may have distinct implications for Hb dynamics compared to daily regimens. Weekly PEGylated GH may yield distinct Hb dynamics versus daily regimens due to sustained IGF-1 exposure.[19] Peak-trough fluctuations in daily GH could attenuate erythropoietic stimulation, whereas weekly formulations provide stable supraphysiological IGF-1 levels. This pharmacokinetic profile might favor sustained erythropoietic activation, potentially explaining the higher proportion of children in the ascending Hb trajectory group (49.7%, 82/165) in our cohort compared to historical reports using daily GH.[14,17]

The findings from our Spearman correlation analysis reinforce this mechanistic link. IGF-1 levels at 12 months showed a statistically significant, moderate correlation with both Hb and RBC levels, indicating that increases in systemic IGF-1 may be accompanied by parallel changes in erythropoietic function. While these correlations do not establish causality, they are consistent with the biological framework in which IGF-1 acts as a mediator of GH-induced hematopoietic activity. Interestingly, however, IGF-1 levels did not differ significantly among the three Hb trajectory groups, suggesting that systemic IGF-1 exposure alone may not fully explain interindividual differences in hematologic response. This was further supported by the logistic regression analysis, which aimed to identify independent predictors of clinically meaningful Hb improvement (defined as ≥5 g/L increase at 12 months). Despite including well-established clinical covariates such as age, sex, diagnosis, and IGF-1 levels, none of these variables reached statistical significance. Male sex showed a non-significant trend toward higher odds of Hb improvement, possibly due to androgen interaction

with GH pathways.[22] However, the lack of statistical significance in our analysis may be attributed to the modest sample size or heterogeneity in pubertal status, which can confound sex-specific effects.

More notably, the inclusion of the Hb trajectory group as an additional predictor significantly improved the explanatory power of the regression model for HtSDS change.[23] This underscores the potential value of longitudinal biomarkers, such as hematologic trends, which capture temporal dynamics and may better reflect the cumulative effects of GH therapy than single-point measurements. From a clinical standpoint, tracking Hb trends during therapy may offer a non-invasive, inexpensive adjunct to standard growth monitoring, potentially identifying children who are responding suboptimally before changes in height become apparent. Hb trajectory monitoring could guide GH dose titration; declining Hb may prompt evaluation for non-adherence or inflammation. While our data reflect Chinese children, Hb trajectories may generalize to other populations given conserved GH-hematopoiesis pathways, though ethnicity-specific validation is needed. GH-related side effects are well documented. Elevations in hemoglobin have been considered part of the pleiotropic actions of GH, but also raise concerns about potential misuse as a performance-enhancing agent. In some jurisdictions, GH use without clear endocrine indications is classified as doping. Nevertheless, large clinical series—including children with organic GHD after oncological treatment—have confirmed that GH therapy is generally safe, even in fragile populations.[24]

The "Ascending then Descending" trajectory group presents an interesting paradox. Although these patients initially demonstrated increased Hb levels, this effect was not sustained, and their height gains were attenuated. This group likely reflects a subset of patients with transient responsiveness or fluctuating adherence, nutritional deficiencies, or unrecognized comorbidities such as subclinical inflammation or iron deficiency. For instance, inflammation-mediated suppression of erythropoiesis via interleukin-6 or hepcidin could blunt Hb gains despite ongoing GH exposure.[25] Unfortunately, inflammatory markers such as CRP or iron indices were not consistently available in our dataset to explore this hypothesis.

The "Stable" group maintained relatively constant Hb levels and achieved modest growth, highlighting that not all patients derive hematologic benefit from GH treatment. This may reflect underlying GH resistance, limited erythropoietic reserve, or a growth-promoting mechanism that is independent of erythropoiesis. These findings emphasize the complex interplay between GH, hematopoiesis, and linear growth and call for more comprehensive phenotyping in future studies, including iron metabolism, erythropoietin levels, and GH receptor polymorphisms.

Methodologically, this study also demonstrates the utility of GBTM as a statistical tool in pediatric endocrinology. Unlike conventional regression or cluster analysis, GBTM identifies latent subgroups within a heterogeneous population based on temporal trajectories, rather than single-point characteristics.[26] This approach is particularly advantageous in the context of GH therapy, which exerts its effects gradually and varies substantially across individuals. By capturing these individualized patterns, GBTM may enhance patient stratification, facilitate early identification of suboptimal responders, and guide adaptive dosing strategies.

Despite these strengths, several limitations should be acknowledged. First, the retrospective design may be prone to residual confounding and information bias. The study was conducted at a single tertiary center, potentially limiting generalizability. Second, pubertal staging was not consistently recorded, yet is a key modulator of both GH sensitivity and erythropoiesis. Third, other factors that influence Hb—such as iron status, dietary intake, menstrual blood loss, or chronic illness—were not systematically controlled. Although our cohort excluded oncology patients, GH-induced Hb elevation may benefit children with organic GHD,[23] particularly those with chemotherapy-related anemia. Fourth, our GHD diagnostic cutoff (<10 ng/mL) follows Chinese guidelines but differs from international standards (eg, <8 ng/mL), potentially limiting cross-population comparability. Finally, the relatively small number of patients in some diagnostic subgroups (eg, TS, MMA) limited our ability to perform stratified analyses. Future multicenter, prospective studies should aim to validate these findings, incorporate more granular clinical and biochemical data, and examine the predictive utility of Hb trajectories in different GH treatment regimens, including daily versus weekly formulations. Integration of multi-omics profiling and machine learning approaches may also help elucidate the molecular mechanisms underlying hematologic response to GH therapy. Our cohort was entirely Chinese, validation in other ethnic and geographic populations is critical, as GH–hematopoiesis interactions may be influenced by genetic background, nutritional status, and healthcare practices.

Conclusion

Integration of Hb trajectory monitoring into GH treatment algorithms should be considered as a future direction once validated prospectively. In conclusion, this study demonstrates that hemoglobin levels follow heterogeneous trajectories during GH therapy in children with short stature, and these trajectories are moderately associated with growth outcomes. Our correlation analysis supports a link between IGF-1 levels and erythropoietic markers, but logistic regression suggests that no single clinical variable can independently predict meaningful Hb improvement. Instead, longitudinal patterns of Hb change—as identified via trajectory modeling—may offer added prognostic value and should be considered as dynamic biomarkers of treatment response. These findings support the integration of hematologic trends alongside traditional growth metrics in the monitoring of GH therapy. Incorporating dynamic modeling approaches such as GBTM into clinical practice could enable more personalized and adaptive GH treatment strategies. Future multicenter, longitudinal studies should confirm these findings and investigate the mechanistic basis of Hb dynamics, including interactions with iron metabolism, inflammation, and pubertal maturation. Integration of Hb trajectory monitoring into GH treatment algorithms should be considered as a future direction once validated prospectively.

Data Sharing Statement

The raw data generated during the current research period can be obtained from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Jiangxi Children's Hospital Ethics Committee (Ethics Approval No: JXSETYY-YXKY-20240059). Prior to the commencement of the study, written informed consent was obtained from the parents or legal guardians of all participating subjects, ensuring their comprehensive understanding of the study's purpose, procedures, potential risks, and benefits.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Key R&D Program Project of Jiangxi Province (No. 20203BBG73041).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Li H, Ji C-Y, Zong X-N, Zhang Y-Q. Height and weight standardized growth charts for Chinese children and adolescents aged 0 to 18 years. *Zhonghua Er Ke Za Zhi*. 2009;47(7):487–492. PMID: 19951507.
2. Polidori N, Castorani V, Mohn A, Chiarelli F. Deciphering short stature in children. *Ann Pediatr Endocrinol Metab*. 2020;25(2):69–79. PMID: 32615685. doi:10.6065/apem.2040064.032
3. Sharma L, Rani D, Kanchan T, Krishan K. Short Stature. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2025. Available from http://www.ncbi.nlm.nih.gov/books/NBK556031/. Accessed August 3, 2025.
4. Sun Y, Ye X, Kennedy H, Smith AGA, Smith RG. Binding domain characterization of growth hormone secretagogue receptor. *J Transl Int Med*. 2022;10(2):146–155. PMID: 35959447. doi:10.2478/jtim-2022-0033

5. Paltoglou G, Dimitropoulos I, Kourlaba G, Charmandari E. The effect of treatment with recombinant human growth hormone (rhGH) on linear growth and adult height in children with idiopathic short stature (ISS): a systematic review and meta-analysis. *J Pediatr Endocrinol Metab*. 2020;33(12):1577–1588. PMID: 33035189. doi:10.1515/jpem-2020-0287
6. Sas T, de Waal W, Mulder P, et al. Growth hormone treatment in children with short stature born small for gestational age: 5-year results of a randomized, double-blind, dose-response trial. *J Clin Endocrinol Metab*. 1999;84(9):3064–3070. PMID: 10487666. doi:10.1210/jcem.84.9.5942
7. Drube J, Wan M, Bonthuis M, et al. Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. *Nat Rev Nephrol*. 2019;15(9):577–589. PMID: 31197263. doi:10.1038/s41581-019-0161-4
8. Drabik M, Lewiński A, Stawerska R. Management of Prader-Labhart-Willi syndrome in children and in adults, with particular emphasis on the treatment with recombinant human growth hormone. *Pediatr Endocrinol Diabetes Metab*. 2022;28(1):64–74. PMID: 35307998. doi:10.5114/pedm.2022.112861
9. Giacomozzi C, Deodati A, Shaikh MG, Ahmed SF, Cianfarani S. The impact of growth hormone therapy on adult height in noonan syndrome: a systematic review. *Horm Res Paediatr*. 2015;83(3):167–176. PMID: 25721697. doi:10.1159/000371635
10. Zhao Q, Li R, Shao Q, Zhang M, Ban B. Recombinant growth hormone improves growth and adult height: a comparison between treated and untreated patients with idiopathic growth hormone deficiency. *Transl Pediatr*. 2025;14(3):442–451. PMID: 40225070. doi:10.21037/tp-2024-576
11. Merchav S, Tatarsky I, Hochberg Z. Enhancement of erythropoiesis in vitro by human growth hormone is mediated by insulin-like growth factor I. *Br J Haematol*. 1988;70(3):267–271. PMID: 2849979. doi:10.1111/j.1365-2141.1988.tb02480.x
12. Merchav S, Tatarsky I, Hochberg Z. Enhancement of human granulopoiesis in vitro by biosynthetic insulin-like growth factor I/somatomedin C and human growth hormone. *J Clin Invest*. 1988;81(3):791–797. PMID: 2963830. doi:10.1172/JCI113385
13. Chaudhry MS, Velardi E, Malard F, van den Brink MRM. Immune reconstitution after allogeneic hematopoietic stem cell transplantation: time to T up the thymus. *J Immunol*. 2017;198(1):40–46. PMID: 27994167. doi:10.4049/jimmunol.1601100
14. Miniero R, Altomare F, Rubino M, et al. Effect of recombinant human growth hormone (rhGH) on hemoglobin concentration in children with idiopathic growth hormone deficiency-related anemia. *J Pediatr Hematol Oncol*. 2012;34(6):407–411. PMID: 22584781. doi:10.1097/MPH.0b013e318253f082
15. Kawa MP, Stecewicz I, Piecyk K, et al. Effects of growth hormone therapeutic supplementation on hematopoietic stem/progenitor cells in children with growth hormone deficiency: focus on proliferation and differentiation capabilities. *Endocrine*. 2015;50(1):162–175. PMID: 25920498. doi:10.1007/s12020-015-0591-0
16. Esposito A, Capalbo D, De Martino L, et al. Long-term effects of growth hormone (GH) replacement therapy on hematopoiesis in a large cohort of children with GH deficiency. *Endocrine*. 2016;53(1):192–198. PMID: 26511947. doi:10.1007/s12020-015-0781-9
17. Ciresi A, Piazza G, Radellini S, Guarnotta V, Mineo MG, Giordano C. Growth hormone and hematopoiesis: a retrospective analysis on a large cohort of children with growth hormone deficiency. *Growth Horm IGF Res*. 2018;42–43:8–13. PMID: 30053742. doi:10.1016/j.ghir.2018.07.005
18. Ding J, Okada S, Jørgensen JOL, Kopchick JJ. Novel serum protein biomarkers indicative of growth hormone doping in healthy human subjects. *Proteomics*. 2011;11(17):3565–3571. PMID: 21751372. doi:10.1002/pmic.201100077
19. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Stat Methods Med Res*. 2018;27(7):2015–2023. PMID: 29846144. doi:10.1177/0962280216673085
20. Zhang S, Wang G, Lyu Y, et al. Human growth hormone supplement promotes human lymphohematopoietic cell reconstitution in immunodeficient mice. *Immunotherapy*. 2022;14(17):1383–1392. PMID: 36468406. doi:10.2217/imt-2021-0278
21. Wang S, Wang G, Zhang M, et al. The dipeptide Pro-Asp promotes IGF-1 secretion and expression in hepatocytes by enhancing JAK2/STAT5 signaling pathway. *Mol Cell Endocrinol*. 2016;436:204–210. PMID: 27473671. doi:10.1016/j.mce.2016.07.028
22. Gharahdaghi N, Phillips BE, Szewczyk NJ, Smith K, Wilkinson DJ, Atherton PJ. Links between testosterone, oestrogen, and the growth hormone/insulin-like growth factor axis and resistance exercise muscle adaptations. *Front Physiol*. 2020;11:621226. PMID: 33519525. doi:10.3389/fphys.2020.621226
23. Al Shaikh A, Daftardar H, Alghamdi AA, et al. Effect of growth hormone treatment on children with idiopathic short stature (ISS), idiopathic growth hormone deficiency (IGHD), small for gestational age (SGA) and Turner syndrome (TS) in a tertiary care center. *Acta Biomed*. 2020;91(1):29–40. PMID: 32191651. doi:10.23750/abm.v91i1.9182
24. Sodero G, Agresti P, Triarico S, et al. Growth hormone replacement therapy in pediatric brain tumor survivors. *Minerva Pediatr*. 2022;74(3):340–348. PMID: 35142454. doi:10.23736/S2724-5276.22.06799-4
25. Abboud E, Chrayteh D, Boussetta N, et al. Skin hepcidin initiates psoriasiform skin inflammation via Fe-driven hyperproliferation and neutrophil recruitment. *Nat Commun*. 2024;15(1):6718. PMID: 39112467. doi:10.1038/s41467-024-50993-8
26. Nagin DS, Jones BL, Elmer J. Recent advances in group-based trajectory modeling for clinical research. *Annu Rev Clin Psychol*. 2024;20(1):285–305. PMID: 38382118. doi:10.1146/annurev-clinpsy-081122-012416