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Original Article

Serum IGF-1 and IGFBP-3 Levels Before and After Induction Chemotherapy in Children with Acute Lymphoblastic Leukemia

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Abstract

Background: The growth hormone–insulin-like growth factor (GH–IGF) axis is suppressed by systemic inflammation and catabolism. We assessed the dynamics of Insulin-like Growth Factor-1 (IGF-1) and Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) in children with acute lymphoblastic leukemia (ALL) at presentation and after induction chemotherapy, and we examined their relationships with disease metrics and nutritional status.

Materials and Methods: In a prospective cohort with a healthy control group, we enrolled 27 pediatric ALL patients and 95 healthy children. After 2 deaths and 2 withdrawals, paired pre/post-induction analyses were performed in 23 patients. IGF-1 and IGFBP-3 were measured using a chemiluminescent immunoassay on the Immulite 2000 system at baseline and on day 33. Anthropometrics and routine disease indices (WBC, cytogenetics, DNA index, measurable residual disease (MRD) were recorded. Data were analyzed using SPSS version 26 using chi-square, Fisher's exact test, T-test, Wilcoxon signed-rank, and Mann–Whitney U. P-value<0.05 was considered significant.

Results: At diagnosis, patients had significantly lower IGF-1 (53 [34–111] vs. 168 [107.5–288] ng/mL; $p < 0.001$) and IGFBP-3 (1650 [1325–2890] vs. 3306 [2476–4149.5] ng/mL; $p < 0.001$) than controls. Following induction, IGF-1 increased from 53 [34–111] to 98 [79–138] ng/mL ($p < 0.001$), and IGFBP-3 from 1650 [1325–2890] to 2190 [1764–3799] ng/mL ($p = 0.001$). MRD status was not associated with IGF-1 (pre-induction: $p = 0.459$; post-induction: $p = 1.000$) or IGFBP-3 (pre-induction: $p = 0.312$; post-induction: $p = 0.825$) levels, or with their changes during induction (IGF-1: $p = 1.000$; IGFBP-3: $p = 0.923$).

Conclusion: IGF-1 and IGFBP-3 are suppressed at diagnosis and rebound after induction in pediatric ALL. These findings demonstrate dynamic changes in IGF-1 and IGFBP-3 during induction therapy. Further longitudinal studies are needed to determine whether these biomarkers have clinical utility.

Keywords: Insulin-Like Growth Factor I; Insulin-Like Growth Factor Binding Protein 3; Leukemia

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Introduction

Acute lymphoblastic leukemia (ALL) represents the most frequent malignancy in children. Recent genomic and bioinformatic studies have provided deeper insights into the complex molecular landscape of ALL, revealing distinct gene expression profiles and dysregulated molecular pathways that differentiate newly diagnosed from relapsed disease (1). Modern risk-adapted treatment protocols, primarily guided by measurable residual disease (MRD), have substantially improved survival outcomes. However, while MRD provides a precise measurement of the leukemic response, it offers limited insight into the child's systemic recovery during induction therapy. This critical phase is often marked by complex physiological stressors, including systemic inflammation, acute catabolism, frequent infections, and the metabolic side effects of corticosteroid exposure (2). Consequently, there is an unmet clinical need for simple, biologically grounded biomarkers that can complement MRD by dynamically reflecting the patient's overall physiological or "host" status (3). The growth hormone–insulin-like growth factor (GH–IGF) axis emerges as a promising candidate for monitoring this systemic status. In pediatric populations, the hepatic production of IGF-1 and its principal binding protein, IGF-binding protein-3 (IGFBP-3), is highly responsive to the host's physiological and inflammatory status. During systemic inflammation, cytokine-mediated hepatic growth hormone resistance suppresses the GH–IGF-1 axis, resulting in reduced circulating levels of IGF-1 and IGFBP-3 (4).This suppression is further exacerbated by malnutrition and the acute catabolic state often seen at the onset of malignancy. Conversely, as the inflammatory burden declines and nutritional status improves during successful treatment, the GH-IGF axis typically begins to recover (5).

In pediatric ALL, previous studies have described a characteristic temporal pattern, with low circulating concentrations of IGF-1 and IGFBP-3 at diagnosis followed by a progressive increase during the induction phase of treatment. This recovery is thought to reflect restoration of GH–IGF-1 axis activity as systemic inflammation resolves and nutritional status improves with effective therapy (6). Understanding these dynamics may provide clinicians with a more holistic view of the child's response to both the disease and the treatment.

Given the importance of these metabolic and physiological indicators, the present study aimed to: (1) compare circulating IGF-1 and IGFBP-3 levels between newly diagnosed children with ALL and control children; (2) assess longitudinal within-patient changes from baseline to the end of induction (day 33); and (3) examine the associations of these biomarkers with clinical predictors, including age, sex, BMI/BMI-Z, WBC count, cytogenetics, DNA index, and MRD.

Material and Methods

Study design and settings

We conducted a prospective cohort study with a healthy control group at 17 Shahrivar Hospital, Iran. Recruitment and data collection were performed from September 2023 to February 2025.

Children 1–18 years with newly diagnosed ALL who had not yet started chemotherapy were eligible. Written and/or verbal informed consent was obtained from parents/guardians before any study procedures. Exclusion criteria were prior initiation of Chemotherapy, known metabolic disorders, or hepatic/renal diseases that could alter the GH–IGF axis. To ensure data integrity and minimize potential confounding, children with a history of endocrine or metabolic disorders, previous malignancies, hepatic or renal dysfunction, or chronic inflammatory diseases were excluded. Patients who failed to achieve remission following first-line induction therapy and required salvage treatment, as well as those who withdrew consent, were classified as study withdrawals.

We enrolled children attending the pediatric clinic who required venous blood sampling for non-metabolic reasons and whose parents/guardians provided consent.

Sample size

Sample size was calculated based on the study

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by Zakhary et al (7). The sample size was calculated to provide 80% power at a two-sided α of 0.05 to detect a minimum clinically relevant difference of 0.5 standard deviations in IGF-1 concentrations, based on findings from previous studies. This yielded a target of 27 ALL patients. All 27 enrolled ALL patients were included in baseline comparisons with the control group. After two deaths and two withdrawals, 23 patients had paired baseline and post-induction samples and were included in longitudinal analyses.

Data gathering

For all participants, we recorded age, sex, height, weight, and calculated BMI and BMI-Z using standard pediatric algorithms. Height was measured to the nearest 1 cm and weight to the nearest 100 g. For ALL patients, disease-related variables included immunophenotypic subtype, cytogenetic translocations, DNA index, WBC at diagnosis, and MRD status (negative if <0.01%). For ALL patients, venous blood was collected at two time points: baseline (pre-chemotherapy) and end of induction (day 33). Controls provided a single serum sample. Both IGF-1 and IGFBP-3 measurements were performed using a chemiluminescence (CL) assay with the Immulite 2000 system (Siemens, Germany).

For methodological accuracy, the assay was described as a chemiluminescent immunoassay rather than an enzyme-linked immunosorbent assay (ELISA). Blood samples were collected in the morning after a 12-hour overnight fast, promptly centrifuged, and stored at −80°C until analysis. Samples were thawed only once immediately before testing to minimize potential degradation associated with repeated freeze–thaw cycles.

Ethical considerations

Potentially eligible participants were approached consecutively during routine visits. Study aims, procedures, and risks/benefits were explained to parents/guardians; written informed consent was obtained before enrollment. The study was conducted in accordance with institutional and national ethical standards (ethical code: IR.GUMS.REC.1402.314).

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) for normally distributed data and as median (interquartile range [IQR]) for non-normally distributed data. Categorical variables were presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. The normality of continuous variables was assessed using the Shapiro–Wilk test. For within-participant pre–post comparisons, paired-samples t-tests were used for normally distributed data, whereas the Wilcoxon signed-rank test was applied when the normality assumption was not met.

Between-group comparisons of patients with ALL and controls were performed using independent-samples t-tests; Welch's correction was applied when homogeneity of variance was violated, and the Mann–Whitney U test was used for non-normally distributed data. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. No adjustment for multiple comparisons was applied because subgroup and correlation analyses were prespecified as exploratory. All analyses were conducted using SPSS version 26. Paired analyses were restricted to participants with measurements available at both time points, and no imputation was performed for missing data.

Results

A total of 27 children with newly diagnosed ALL were enrolled in the study. Paired pre- and post-induction measurements were available for 23 patients. Accordingly, baseline analyses were performed using the full ALL cohort (n = 27), whereas longitudinal pre–post induction analyses were restricted to participants with complete measurements at both time points (n = 23).

Among the 27 enrolled patients, two patients died during induction therapy, and two patients were withdrawn due to loss of follow-up/withdrawal of consent. None of the enrolled patients failed to achieve remission following induction therapy or required salvage treatment. The healthy control group comprised 95 children. Among the patients, 59.3% were female, and 40.7% were male. The mean age of the participants

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was 7.59 years with a standard deviation of 3.42 years. Participants ranged in age from 1 to 15 years, corresponding to an overall age range of 14 years. This age distribution is consistent with the typical age of onset for acute lymphoblastic leukemia (ALL). B-cell acute lymphoblastic leukemia (B-ALL) was more prevalent than T-cell ALL (T-ALL), with 92.6% of patients diagnosed with B-ALL and only 7.4% (two patients) with T-ALL. The mean body mass index (BMI) of the patients was 18.03 ± 5.01. The lowest recorded BMI was 12.1, while the highest was 33.1. To provide a more precise assessment of body weight, BMI Z-scores were calculated, yielding a mean of 0.26 ± 2.12, indicating that most participants fell within the normal weight range. At diagnosis, the white blood cell (WBC) count, an important prognostic marker in ALL, had a mean of approximately 18,000/mm³, with values ranging from 900 to 46,600/mm³. Another important prognostic indicator, the DNA index, showed a mean of 0.999 ± 0.014.

It is noteworthy that out of 27 enrolled patients, two patients unfortunately died during the induction phase, and two others were withdrawn from the study. Therefore, while all 27 patients were included in comparisons between the patient and control groups, only 23 patients were considered for pre- and post-treatment comparisons and for analyses of hormonal changes across different variables. Chromosomal translocations were detected in 18.5% of patients, while 81.5% showed no evidence of chromosomal abnormalities. Following the induction phase, 40.7% of 23 patients were MRD-positive, whereas 59.3% were MRD-negative.

The control group consisted of 95 healthy children, of whom 57.9% were female. The mean age of this group was 8.84 years with a standard deviation of 4.14 years. Statistical analysis showed no significant difference in age between the two groups (p = 0.187), confirming that the groups were well-matched for age. There was also no significant difference in sex distribution between the ALL and control groups (female: 59.3% vs. 57.9%; male: 40.7% vs. 42.1%; χ^2 test, p = 1.000).

Sex and IGF-1/IGFBP-3 levels

Among patients with ALL, 9 were males and 14 females. Pre-induction IGF-1 in males was median 43, IQR 29–67 versus median 50, IQR 36–100.5 in females (p = 0.549, Mann–Whitney U test). Post-induction levels were median 110, IQR 82–131 in males and median 94, IQR 82.5–140.5 in females (p = 0.950). Pre-induction IGFBP-3 was median 1560, IQR 1110–2400 in males and median 1499, IQR 1365–2475 in females (p = 0.592), while post-induction IGFBP-3 was median 3201, IQR 2109–3451 in males versus median 2057, IQR 1710–4173 in females (p = 0.729). The changes in IGF-1 (median 75, IQR 34–81; females: median 50, IQR 15.5–62.6; p = 0.344) and IGFBP-3 (males: median 1451, IQR 220–1891; females: median 398, IQR 109–1230; p = 0.329) were not significant, indicating no association between sex and hormone levels or changes during induction.

Age and IGF-1/IGFBP-3 levels

Spearman correlation revealed strong positive associations between age and hormone levels. Pre-induction IGF-1 correlated with age ($\rho = 0.68$, $p < 0.001$) and pre-induction IGFBP-3 ($\rho = 0.62$, $p < 0.001$). Post-induction IGF-1 ($\rho = 0.65$, $p < 0.001$) and IGFBP-3 ($\rho = 0.71$, $p < 0.001$) also correlated positively with age. However, changes in IGF-1 ($\rho = 0.18$, p = 0.403) and IGFBP-3 ($\rho = 0.22$, p = 0.303) were not associated with age. These results indicate that older children had higher baseline and post-induction GH–IGF axis activity, while the magnitude of induction-related changes was independent of age.

BMI/Z-score and IGF-1/IGFBP-3 levels

IGF-1 was inversely associated with BMI Z-score both pre-induction ($\rho = -0.39$, p = 0.045) and post-induction ($\rho = -0.74$, $p < 0.001$), and IGFBP-3 post-induction also showed a negative correlation ($\rho = -0.51$, p = 0.014). Changes in IGF-1 during induction were negatively correlated with BMI ($\rho = -0.49$, p = 0.017) and Z-score ($\rho = -0.43$, p = 0.039), while IGFBP-3 changes were not significant.

ALL subtype and IGF-1/IGFBP-3 levels

Comparison between B-cell (n = 21) and T-cell

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(n = 2) ALL patients revealed significantly higher IGF-1 in T-cell patients pre-induction (229.00 ± 12.73 ng/mL vs. 68.35 ± 56.72 ng/mL; p = 0.023) and post-induction (254.50 ± 50.20 ng/mL vs. 109.10 ± 63.99 ng/mL; p = 0.043). Pre-induction IGFBP-3 showed a trend toward significance (3654.50 ± 333.05 ng/mL vs. 1951.32 ± 974.58 ng/mL; p = 0.051). Hormonal changes during induction were not significantly associated with ALL subtype. Due to the small T-cell sample, these results should be interpreted with caution.

Given that only two patients had T-cell ALL, this subgroup analysis should be considered exploratory, and no definitive conclusions regarding differences between B-cell and T-cell ALL can be drawn.

Baseline WBC count and IGF-1/IGFBP-3 levels

No significant correlations were observed between WBC at diagnosis and IGF-1 or IGFBP-3 pre- or post-induction (ρ = –0.37 to 0.15, all p > 0.05) or with changes during therapy.

Cytogenetic status and IGF-1/IGFBP-3 levels

Comparing patients with (n = 4) and without (n = 19) chromosomal translocations revealed no significant differences in IGF-1 or IGFBP-3 at pre- or post-induction, nor in changes during therapy (all p > 0.05), suggesting that cytogenetic abnormalities did not impact hormonal dynamics.

DNA index and IGF-1/IGFBP-3 levels

Spearman correlation showed a weak positive association between pre-induction IGFBP-3 and DNA index (ρ = 0.40, p = 0.037). Other correlations with IGF-1, post-induction IGFBP-3, and hormonal changes were non-significant (p > 0.05), indicating minimal overall association between DNA index and GH–IGF axis activity.

MRD status and IGF-1/IGFBP-3 levels

Comparison of MRD-negative (n = 15) and MRD-positive (n = 8) patients revealed no significant differences in IGF-1 or IGFBP-3 at pre-induction (IGF-1: 76.30 ± 73.37 vs. 86.00 ± 66.20 ng/mL, p = 0.459; IGFBP-3: 1950.13 ± 1130.74 vs. 2262.73 ± 919.94 ng/mL, p = 0.312) or post-induction (IGF-1: 119.80 ± 66.45 vs. 125.38 ± 93.40 ng/mL, p = 1.000; IGFBP-3: 2725.47 ± 1297.79 vs. 3053.62 ± 1801.64 ng/mL, p = 0.825), and changes during induction were also non-significant (IGF-1: 43.50 ± 68.94 vs. 39.38 ± 68.90, p = 1.000; IGFBP-3: 775.34 ± 819.30 vs. 790.89 ± 993.60, p = 0.923). Thus, MRD status was not associated with GH–IGF axis activity.

Table I: Comparison of IGF-1 and IGFBP-3 Levels Between the Control and ALL Patient Groups (Before Chemotherapy)

Variable	Control Group (n=95)	ALL Patients (n=27)	P-value*
IGF-1 (ng/ml)	168 (107.5–288)	53 (34–111)	<0.001
IGFBP-3 (ng/ml)	3306 (2476–4149.5)	1650 (1325–2890)	<0.001

Data are presented as median (interquartile range). *Based on the Mann–Whitney U test.

Table 1 presents the comparison of serum hormone levels between healthy controls and children with ALL before initiation of Chemotherapy. The median serum concentrations of both IGF-1 and IGFBP-3 were significantly higher in the control group than in patients with ALL at baseline (both p < 0.001).

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Table II: Comparison of IGF-1 and IGFBP-3 Levels in ALL Patients Before and After Induction Therapy

Variable	**Before chemotherapy (n=23)**	**After induction therapy (n=23)**	**Δ Change**	**P-value***
IGF-1 (ng/ml)	53 (34–111)	98 (79–138)	54 (19–77)	<0.001
IGFBP-3 (ng/ml)	1650 (1325–2890)	2190 (1764–3799)	662 (109–1500)	0.001

Data are presented as median (interquartile range).
***Based on the paired Wilcoxon test. Δ values represent the paired within-patient changes from baseline to the end of induction therapy.**

Table II shows serum levels of IGF-1 and IGFBP-3 in ALL patients at two time points: before the start of chemotherapy and one month after initiation of induction therapy. The results indicate that the median levels of IGF-1 and IGFBP-3 increased significantly after induction therapy (IGF-1: $p < 0.001$; IGFBP-3: $p = 0.001$). The changes in IGF-1 and IGFBP-3 also demonstrate a significant upward trend following treatment. It should be noted that out of 27 enrolled patients, two patients unfortunately died during the induction phase, and two others were withdrawn from the study, resulting in a total of 23 patients included in this analysis.

Discussion

In this observational cohort study, serum levels of IGF-1 and IGFBP-3 in children with ALL at diagnosis were significantly lower compared with age-matched healthy controls. These findings align with numerous previous studies; for example, Zhao et al. reported that both IGF-1 and IGFBP-3 levels were reduced at diagnosis and significantly increased after complete treatment, indicating that initiation of chemotherapy rapidly elevates these hormones (8). Similarly, in the present study, IGF-1 and IGFBP-3 levels significantly increased after induction chemotherapy ($p < 0.001$), although they may remain below the levels observed in healthy children. Such post-treatment increases have also been reported in other studies; for instance, Kochadag et al. observed a pronounced rise in IGF-1 from day 8 of treatment in children with ALL (9).

In the present study, sex was not significantly associated with serum IGF-1 or IGFBP-3 concentrations, with no significant differences observed between male and female patients. Similarly, the WBC count at diagnosis was not significantly associated with either hormone concentration ($p > 0.05$). No significant differences in IGF-1 or IGFBP-3 concentrations were observed according to cytogenetic status, including the presence or absence of chromosomal translocations, or MRD status. In contrast, hormone concentrations differed significantly according to ALL immunophenotype; however, this finding should be interpreted with considerable caution because the T-ALL subgroup included only two patients ($n = 2$), compared with 25 patients with B-ALL ($n = 25$). A weak but statistically significant positive correlation was observed between pretreatment IGFBP-3 concentration and DNA index ($\rho = 0.40$, $p = 0.037$), suggesting a modest association between IGFBP-3 and this baseline disease characteristic.

These findings are broadly consistent with previous international studies. Previous research has reported markedly reduced IGF-1 and IGFBP-3 concentrations at the time of ALL diagnosis (8). Although IGF-1 elevations have been described in some pediatric malignancies (10), studies specifically investigating childhood ALL have more commonly reported reduced concentrations of IGF-1 and IGFBP-3. During treatment and subsequent disease recovery, these hormone concentrations generally tend to increase toward normal values (8). Consistent with this pattern, Kochadag et al. demonstrated that induction chemotherapy was associated with a rapid increase in IGF-1 concentrations, with changes correlating with inflammatory markers (9). This finding is concordant with the longitudinal changes observed in the present study and supports the potential relationship between recovery of the GH–IGF-1 axis and resolution of the systemic inflammatory state

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during induction therapy.

In an exploratory subgroup analysis, patients with T-cell ALL had higher IGF-1 concentrations than those with B-cell ALL; however, this finding should be interpreted cautiously given the very small number of T-cell cases. This aligns with limited prior data, as T-ALL cells in adolescents and adults often display more aggressive growth profiles. Genetic studies indicate that B-ALL cells are more likely to express IGFBP-3, whereas T-ALL cells predominantly express IGFBP-2 (11). Recent evidence indicates that the IGF-1 receptor (IGF-1R) is an important regulator of leukemic cell proliferation and survival, supporting the IGF signaling pathway as a potential therapeutic target in acute lymphoblastic leukemia. (12).

Serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) measurements are mainly used in pediatric endocrinology for evaluating growth hormone–related disorders; therefore, their interpretation in childhood cancer should be cautious and context-dependent (13), whereas others, including Brahmkhatri et al., demonstrate the critical role of IGF-1/IGFBP-3 in tumorigenesis through apoptosis inhibition, proliferation, and angiogenesis (14).

Given the significant differences in IGF-1 and IGFBP-3 levels between ALL patients and healthy controls, these hormones may reflect alterations in the physiological, inflammatory, and metabolic status of children with ALL. However, their clinical utility as biomarkers for treatment monitoring remains to be established and requires validation in larger, prospective studies. Previous research has suggested that measuring these factors at diagnosis and during treatment can provide biologically informative data (8). Although IGF-1 and IGFBP-3 are not currently standard diagnostic or prognostic tests for ALL, their decline at diagnosis and subsequent rise during treatment may reflect treatment-related physiological recovery rather than established clinical utility. Kochadag et al. also suggested that IGF-1 elevation post-Chemotherapy reflects treatment effects (9). Therefore, the observed dynamic changes in these hormones should be regarded as hypothesis-generating indicators of systemic recovery and require validation in larger, prospective studies before their potential clinical application can be established.

In the current study, there were no significant associations between IGF-1/IGFBP-3 and classical prognostic parameters, such as cytogenetics, MRD, or DNA index, limiting their use as independent prognostic markers. Some earlier studies reported that low IGFBP-3 levels were associated with poorer survival, although evidence after 2005 remains limited. Evidence regarding the prognostic value of IGFBP-3 in childhood ALL remains limited and inconsistent. Current risk stratification relies primarily on validated markers, including measurable residual disease (MRD), cytogenetic abnormalities, and molecular features, rather than circulating IGFBP-3 concentrations (15). Although some studies have suggested potential associations between IGFBP-3 and disease characteristics, these findings have not been consistently replicated. Nevertheless, observations such as the positive correlation between IGFBP-3 and DNA index warrant further investigation in larger, prospective, and longitudinal studies.

The IGF system plays a key role in cell growth and survival, making IGF-1R an attractive therapeutic target in leukemia and other malignancies (12). Several anti-IGF-1R monoclonal antibodies have entered clinical trials, though results to date have been limited, with many early studies failing to achieve clinical benefit (16). IGFBPs may represent an alternative therapeutic strategy for modulating IGF signaling, potentially offering a more targeted approach with fewer adverse effects (14). Future therapeutic strategies may include IGF antagonists alone or in combination with conventional ALL treatments.

The inverse correlations observed between IGF-1 and both BMI and BMI-Z warrant cautious interpretation, as early-treatment BMI may be influenced by corticosteroid-induced fluid shifts, changes in adiposity, and the timing

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of assessment relative to the transition from a catabolic to an anabolic state. Concurrent assessment of inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), may help clarify the relationships between IGF-1, nutritional status, and systemic inflammation (17–19). The absence of significant associations between pre- and post-treatment IGF-1/IGFBP-3 levels and treatment changes emphasizes that these hormones primarily reflect patient physiological status rather than ALL prognosis (15, 20–21).

Potential mechanisms underlying the alterations in IGF-1 and IGFBP-3 include systemic inflammation–induced hepatic growth hormone resistance, which may impair JAK2/STAT5 signaling and consequently suppress hepatic IGF-1 synthesis. Systemic inflammation can suppress the growth hormone–insulin-like growth factor (GH–IGF) axis through cytokine-mediated hepatic growth hormone resistance, while improvement in inflammatory and nutritional status during therapy may contribute to recovery of IGF-1 and IGFBP-3 levels (9, 22-24). Recent studies indicate that alterations in the IGF axis, including reduced IGF-1 and dysregulated IGF-binding proteins, reflect the systemic metabolic and inflammatory status of patients with acute lymphoblastic leukemia rather than disease-specific tumor burden (25,26).

Despite its prospective design and standardized methodology, this study has certain limitations, including a relatively small sample size for specific subgroups—particularly T-cell ALL—which restricts the generalizability of findings regarding diverse biological subsets.

Additionally, multiple subgroup comparisons and correlation analyses were performed without adjustment for multiple testing. Therefore, these findings should be considered exploratory and require confirmation in larger independent cohorts.

Furthermore, while the study identified a significant hormonal rebound on Day 33, the absence of concurrent pro-inflammatory cytokine measurements (e.g., IL-6, TNF-α) limits our ability to provide a definitive mechanistic link between systemic inflammation and hepatic GH resistance. Additionally, the potential confounding impact of high-dose corticosteroids during induction therapy on the GH–IGF axis remains a factor that is difficult to isolate. Future multi-center studies with larger cohorts and longitudinal monitoring beyond the induction phase are warranted to determine if early recovery of IGF-1 and IGFBP-3 serves as a reliable predictor of long-term event-free survival. Moreover, incorporating age- and sex-adjusted Standard Deviation Scores (SDS) in future research would enhance the precision of growth factor interpretation relative to healthy developmental trajectories.

In the univariate analysis, CD66c and CD123 co-expression was associated with decreased OS and DFS and a higher risk of relapse. However, this association did not remain significant in the multivariate model, indicating that it is not an independent prognostic factor. In contrast, isolated CD123 expression was linked to positive MRD and an increased risk of relapse. These observations provide clinically relevant preliminary insights, particularly in settings with survival disparities, but they require confirmation in larger cohorts with extended follow-up and integrated molecular data.

Conclusion

This study demonstrates that serum IGF-1 and IGFBP-3 are significantly reduced at ALL diagnosis and substantially increase following induction chemotherapy, consistent with international findings. Importantly, no significant associations were observed with baseline risk factors, including WBC count or genetic status. These results indicate that changes in IGF-1 and IGFBP-3 reflect disease course and treatment rather than initial diagnostic features, underscoring the role of the IGF system in ALL pathophysiology and its potential role to reflect treatment-related physiological changes, which requires further validation before clinical application. Future studies may benefit from reporting age- and sex-adjusted SDS values for improved

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interpretability.

Availability of Data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare no conflicts of interest.

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Ethical Considerations

The ethics committee approved this study of Guilan University of Medical Sciences (NO: IR.GUMS.REC.1402.314).

Authors' Contributions

Setila Dalili contributed to the study conceptualization, methodology, supervision, and critical revision of the manuscript. Shahin Koohmanaee participated in data collection, investigation, and manuscript drafting. Mercedeh Enshaei contributed to data collection, investigation, and literature review. Mohadeseh Safari Ghasabsaraii participated in data collection and manuscript preparation. Mohammad Ali Esfandiari participated in data collection and manuscript preparation. Ehsan Kazemnejad Leili performed the statistical analysis and contributed to data interpretation. Afagh Hassanzadeh Rad contributed to the data interpretation, manuscript writing, and critical revision. Adel Baghersalimi conceived and supervised the study, contributed to methodology, reviewed and revised the manuscript critically for important intellectual content, and approved the final version as the corresponding author. Bahram Darbandi conceived and supervised the study, contributed to methodology, reviewed and revised the manuscript critically for important intellectual content, and approved the final version as the corresponding author. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Artificial Intelligence Use Disclosure Statement

The authors used ChatGPT (OpenAI) solely for language editing and improvement of the clarity and readability of portions of the manuscript. The AI tool was not used for data collection, data analysis, interpretation of results, or generation of scientific conclusions. All AI-assisted text was critically reviewed, verified, and approved by the authors, who take full responsibility for the accuracy and integrity of the final manuscript.

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