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Serum IGF-1 and Associations with Hepatic Biochemistry and Height for Age in Children with Chronic Liver Disease: A Mixed-Aetiology Cross-Sectional Study

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Highlights

What are the main findings?

- IGF-1 was below the platform-specific lower reference limit in 4 of 74 children with chronic liver disease, all of whom had severe underlying disease.
- In children without liver transplantation, IGF-1 was associated with serum albumin, cholinesterase, direct bilirubin, and height-for-age, and these associations persisted after adjustment for age and sex.

What are the implications of the main findings?

- IGF-1 in children with chronic liver disease should be interpreted against age-, sex- and platform-specific reference intervals, which remain largely unverified below six years of age.
- IGF-1 is a candidate correlate of hepatic biochemistry and attained height in paediatric chronic liver disease; longitudinal studies are needed before any diagnostic, prognostic or monitoring role can be considered.

Abstract

Background: Serum insulin-like growth factor 1 (IGF-1) is a hepatically synthesised marker of growth hormone action and is associated with hepatic function and growth. Its interpretation in paediatric chronic liver disease (CLD) has been limited by the absence of platform-specific paediatric reference intervals. The CALIPER programme has recently verified sex- and age-specific IGF-1 reference intervals on the DiaSorin Liaison XL immunoassay for children aged 6 to <19 years, and these intervals were applied descriptively in this cohort. **Methods**: Cross-sectional study of 74 children (median age 8.5 years; range 0.2 to 17.9) with CLD of mixed aetiology, followed at a single national reference centre between 28 July 2023 and 6 August 2026. IGF-1 was measured on the DiaSorin Liaison XL and classified using platform-specific manufacturer intervals, verified by CALIPER in most age and sex partitions from 6 to <19 years and in two partitions below six years. A reference-interval-derived pseudo-SDS was used in the correlation analyses; it is not a validated SDS and does not establish control of age and sex confounding. Correlations with hepatic biochemistry, transient elastography, and anthropometric z-scores were tested by Spearman

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rank; between-group differences by Kruskal-Wallis. Log-transformed IGF-1 was additionally modelled with adjustment for age and sex. Post-transplant recipients were analysed separately. **Results**: IGF-1 below the platform-specific lower reference limit was uncommon (4/74, 5.4%). In the primary analysis (non-transplant, $n = 61$), IGF-1 pseudo-SDS correlated positively with serum albumin ($\rho = +0.49$, $p < 0.001$), cholinesterase ($\rho = +0.33$, $p = 0.009$), and height-for-age z-score ($\rho = +0.42$, $p < 0.001$, $n = 60$), and inversely with direct bilirubin ($\rho = -0.35$, $p = 0.006$) and recorded fibrosis stage ($\rho = -0.31$, $p = 0.014$), but not with liver stiffness ($\rho = -0.18$, $p = 0.17$, $n = 57$). Associations with albumin, cholinesterase, direct bilirubin and height-for-age persisted in log(IGF-1) models adjusted for age and sex. Unadjusted IGF-1 differed markedly across aetiological groups ($p < 0.001$); the pseudo-SDS comparison was not statistically significant ($p = 0.334$), without establishing that age confounding was removed. Post-transplant recipients had the numerically highest pseudo-SDS values ($n = 13$, not formally compared). **Conclusions**: This selected single-centre cohort showed exploratory cross-sectional associations of a reference-interval-derived IGF-1 index with hepatic biochemistry and height-for-age. The findings do not establish independent associations, incremental clinical value, diagnostic performance or a monitoring role.

Keywords: insulin-like growth factor 1; chronic liver disease; children; CALIPER reference intervals; hepatic synthetic function; height-for-age; cholestasis; liver fibrosis

1. Introduction

Insulin-like growth factor-1 (IGF-1) is a polypeptide structurally related to insulin, synthesised predominantly by hepatocytes under growth hormone (GH) stimulation [1,2]. Because of this hepatic dependence, the GH/IGF-1 axis is particularly vulnerable to liver disease, and in chronic hepatic conditions, impairment of the axis correlates with the degree of hepatocellular dysfunction [2,3]. In children, IGF-1 mediates the GH effect at the growth plate, drives linear growth, and is required for bone mass accrual [4,5]. In paediatric chronic liver disease (CLD), disruption of the axis has consequences beyond hepatic function.

Two principal mechanisms have been proposed for the IGF-1 reduction observed in affected children. The first reflects the loss of functional hepatocyte mass and synthetic capacity in advanced disease [1,2]. The second is acquired GH resistance: affected children frequently present with normal or elevated serum GH levels alongside low IGF-1, a pattern attributed to reduced hepatic responsiveness to GH [1,6]. In a small cohort of children with inherited liver disorders, Maghnie et al. found that even when caloric and protein intake were adequate for age, IGF-1 synthesis failed to rise appropriately in response to GH administration and correlated with height SDS, consistent with an endocrine contribution to growth failure that is not fully explained by nutritional status [7]. Holt et al. reported that GH resistance is present early in paediatric liver disease and worsens with its progression, particularly in the presence of portal hypertension, whereas children with short stature after successful portoenterostomy responded to GH [6].

Malnutrition complicates interpretation, because undernutrition suppresses IGF-1 synthesis [8] and is itself a consequence of CLD. Intensive enteral feeding improved nutritional status in ten children with advanced cirrhosis [9]. However, Holt et al. showed that nasogastric feeding improved nutritional status without normalising circulating IGF-1 or its binding proteins [10]. This study did not use multivariable analysis to separate hepatic and nutritional contributions.

Paediatric studies report reduced serum IGF-1 levels compared with healthy controls, with lower concentrations in more advanced disease. Dehghani et al. reported significantly lower IGF-1 and IGFBP-3 in cirrhotic children awaiting liver transplantation, with a negative

correlation to Child-Pugh class [11]. El Koofy et al., in a cross-sectional study of 69 Egyptian children with CLD of mixed aetiology, found serum IGF-1 significantly lower than in healthy controls and lowest in children classified as Child-Pugh C [12]. Growth failure is one of the most visible correlates of this deficiency: growth failure or malnutrition complicates chronic liver disease in approximately half of affected children [6], and abnormalities of the IGF-1/IGFBP axis have been proposed to explain, at least in part, the growth failure of end-stage liver disease [13].

Beyond its role in growth, IGF-1 has been proposed as a non-invasive marker of hepatic fibrosis. In adults, low serum IGF-1 is associated with cirrhosis in chronic hepatitis C [14] and with both hepatic dysfunction and fibrogenesis in advanced CLD of mixed aetiology (cholestatic disease excluded), where it also predicts liver-related mortality [15]. Circulating IGF-I and IGF-II levels have been associated with histological features in children with obesity and biopsy-proven non-alcoholic fatty liver disease [16]. In adolescents with obesity and biopsy-proven metabolic-associated fatty liver disease, lower GH and IGF-1 were associated with fibrosis [17].

Despite the accumulating evidence, most paediatric studies of the GH/IGF-1 axis in CLD are limited by small sample size, aetiologically heterogeneous cohorts and, importantly, by the lack of platform-specific paediatric reference intervals. Prior series have relied either on manufacturer-declared ranges without independent verification or on reference intervals derived from different immunoassay platforms, which may not be interchangeable [18]. The CALIPER programme has now verified the paediatric reference intervals provided in the DiaSorin Liaison XL package insert for children aged 6 to <19 years; corresponding intervals for children aged 0 to <6 years did not verify, with results exceeding the manufacturer's upper limits [18]. The present study applies these platform-specific reference intervals to a paediatric CLD cohort; their verification does not validate the derived pseudo-SDS.

The aims of the present study were: (i) to characterise IGF-1 status in a paediatric cohort with CLD of mixed aetiology; (ii) to examine correlations between IGF-1 and biochemical markers of hepatic synthetic function and cholestatic severity; (iii) to examine correlations between IGF-1 and hepatic fibrosis assessed by transient elastography; (iv) to examine correlations between IGF-1 and nutritional status; and (v) to compare IGF-1 across principal aetiological groups. Because absolute IGF-1 concentrations depend on age and sex, the analyses used a reference-interval-derived index. This transformation does not substitute for statistical adjustment.

2. Materials and Methods

2.1. Study Design and Population

This was an observational cross-sectional study conducted at the 2nd Paediatric Clinic, Emergency Clinical Hospital for Children, Cluj-Napoca, Romania, between 28 July 2023 and 6 August 2026. Children aged 2 months to 18 years with established CLD of any aetiology followed at the centre during the study period were eligible. Eligibility required contemporaneous serum IGF-1 measurement and complete demographic and clinical data at the study visit. IGF-1 was not part of the study protocol and was measured during routine care, not for a specific clinical indication; the reasons why it was not measured in some children were not recorded. All children with an available IGF-1 measurement during the study period were included, and none were excluded on clinical grounds. For children with more than one recorded assessment during the study period, the first complete assessment was retained for cross-sectional analysis. Of 129 children with chronic liver disease followed at the 2nd Paediatric Clinic, Cluj-Napoca, between 28 July 2023 and 6 August 2026, 55 were excluded because no IGF-1 measurement was available, yielding an analytic cohort of 74 (Figure 1). Clinical grouping was aetiology-based; post-transplant recipients (n = 13) were

analysed separately from the primary hepatic function and fibrosis correlations. IGF-1 and recorded F0–F4 stage were available in all 74 children; quantitative liver stiffness (kPa) was available in 68/74 (91.9%).

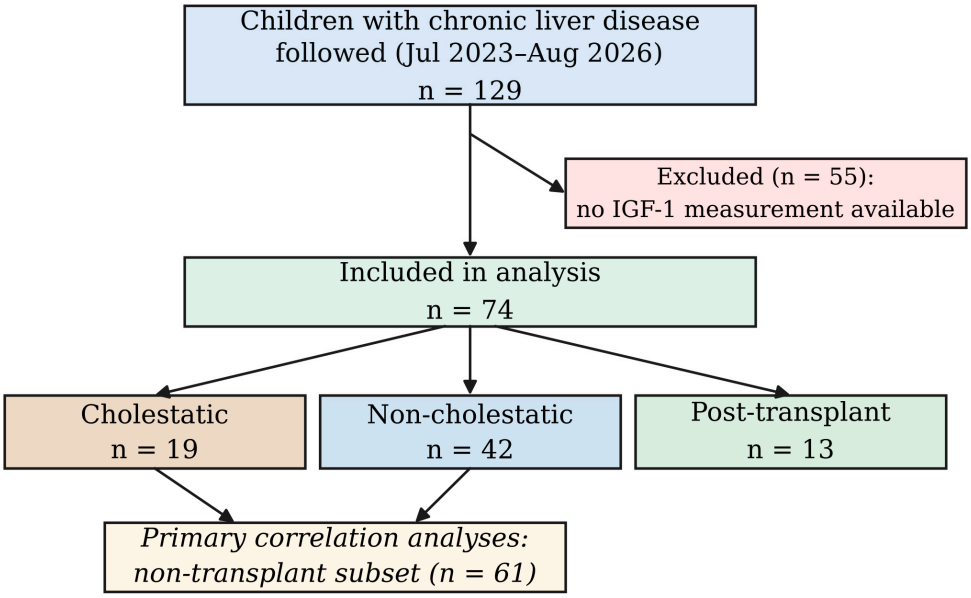

Figure 1. Patient flow diagram. Sensitivity analyses: full cohort ($n = 74$); non-transplant children in CALIPER-verified partitions ($n = 40$); non-transplant children aged ≥ 3 years with transient elastography ($n = 45$).

Aetiological categories, as recorded at enrolment, were: chronic cholestatic disorders (biliary atresia post-Kasai portoenterostomy, Alagille syndrome, progressive familial intrahepatic cholestasis, and other cholestatic disorders); autoimmune hepatitis, including autoimmune sclerosing cholangitis; chronic hepatitis B; Wilson disease; inherited metabolic disease (including glycogen storage disorders, hereditary fructose intolerance, and lysosomal acid lipase deficiency); vascular hepatic disease (Abernethy malformation); and children who had undergone liver transplantation prior to the study visit. For inferential comparisons across aetiologies, four analytic groups were defined: (1) cholestatic; (2) autoimmune; (3) chronic hepatitis B; and (4) metabolic-mixed, combining Wilson disease, inherited metabolic disease and vascular disease to preserve statistical power in the Kruskal-Wallis test. Post-transplant recipients were reported separately because their hepatic synthetic function is derived from a functioning graft rather than from the native diseased liver, and their IGF-1 physiology is expected to differ accordingly; one child originally enrolled with biliary atresia underwent liver transplant before the study visit and is counted under the post-transplant group throughout all tabulations and analyses.

This cohort includes 40 of the 66 children previously reported in the vitamin A and E study conducted at the same centre [19]; the remaining 34 children in the present analysis had IGF-1 measured outside the enrolment window of the vitamin A/E study, and 26 children from the vitamin A/E cohort are not included here because IGF-1 was not measured. The present analysis addresses a distinct research question (cross-sectional associations of IGF-1 with hepatic biochemistry and height-for-age) in an extended cohort with a longer enrolment window.

The study was approved by the Ethics Committee of the Emergency Clinical Hospital for Children, Cluj-Napoca (approval number 94/28.07.2023) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from parents or legal guardians and assent from children aged seven years or older.

2.2. Clinical and Biochemical Assessment

Patients were assessed at a single study visit. Anthropometric measurements included weight, height (or supine length in children under two years), body mass index, mid-upper-arm circumference and triceps skinfold, performed by trained personnel using calibrated equipment. Age- and sex-standardised z-scores for weight-for-age (WAZ), height-for-age (HAZ) and BMI-for-age (BMIz) were computed using WHO Anthro 3.2.2 and AnthroPlus 1.0.4 reference software within the age ranges of validity of each index. MUAC-for-age z-scores (MUACz) were computed against the WHO Anthro reference for children below five years of age and against the reference of Mramba and colleagues [20] via the Peditools implementation for children aged 60 to 228 months. Stunting and severe stunting were defined as HAZ below −2 and below −3, respectively. Measurement position (recumbent length or standing height) was entered as recorded for each child. Bilateral pitting oedema was not systematically recorded and was entered as absent; weight-based indices may therefore be overestimated in children with ascites or organomegaly. WHO Anthro software: https://www.who.int/tools/child-growth-standards/software (accessed on 23 November 2026); WHO AnthroPlus: https://www.who.int/tools/growth-reference-data-for-5to19-years/application-tools (accessed on 23 November 2026); PediTools implementation: https://mail.peditools.org/growth/?calc=mramba_muac (accessed on 23 November 2026).

Venous blood was drawn in the fasting state. Aspartate and alanine aminotransferases, gamma-glutamyltransferase, total and direct bilirubin, total protein, albumin, cholinesterase, total cholesterol and triglycerides were measured by standardised automated methods on a Mindray BS-2800 M biochemistry analyser (Mindray Bio-Medical Electronics, Shenzhen, China). Prothrombin time, expressed as international normalised ratio (INR), was measured on an automated coagulometer at the same visit. All laboratory determinations were performed at the certified laboratory of the Emergency Clinical Hospital for Children, Cluj-Napoca.

Transient elastography was performed using a FibroScan device (Echosens, Paris, France). Measurements were performed according to the manufacturer's recommendations; probe type and measurement-quality parameters were not systematically documented. Liver stiffness (kPa) was available for 68 children and was analysed as a continuous variable. Fibrosis stage (F0–F4) was recorded on the transient elastography report by the examining physician, based on liver stiffness interpreted against published paediatric cut-off values [21,22]. Stage was not histologically confirmed and cannot be equated with histological METAVIR stages; it is therefore reported descriptively and used only in secondary analyses. For the six children without retrievable stiffness values, the stage was taken from the transient elastography report, which documented the examiner's F0–F4 classification without the stiffness value in kPa. Cirrhosis was recorded when established by imaging and/or elastography.

2.3. IGF-1 Measurement

Serum IGF-1 was measured on a Liaison XL automated chemiluminescent immunoassay analyser (DiaSorin, Vercelli, Italy) at the certified hospital laboratory. Assays were performed according to the manufacturer's package insert, with successful calibration and quality control verified prior to each analytical run. Results were reported in ng/mL and converted to SI units (nmol/L) by dividing by 7.649, based on the molecular weight of IGF-1 [18]. Both units are reported.

2.4. Classification of IGF-1 Status

IGF-1 status was classified using sex- and age-specific reference intervals provided in the DiaSorin Liaison XL package insert, which were independently verified by the CALIPER

program for children aged 6 to <19 years using serum from a healthy paediatric reference cohort [18]. For children aged 0 to <6 years, CALIPER verification was not established in the source study; the manufacturer intervals were nonetheless applied to this age band and analyses restricted to CALIPER-verified partitions were performed as sensitivity checks. A parallel classification using the current local-laboratory version of the package insert (expressed in ng/mL) was applied for comparison of categorical classifications. Verification status was assigned per age and sex partition, as reported in the source study; the applied limits and the verification results are listed in Supplementary Table S5.

For each patient, the lower and upper reference limits (LL and UL) corresponding to their sex and age partition were obtained. Three categorical classifications were derived: (i) IGF-1 below LL ("below the platform-specific lower reference limit"); (ii) IGF-1 within the reference interval; (iii) IGF-1 above UL. Using only the applied lower and upper reference limits, a pseudo-SDS was computed under the assumption of a log-normal distribution as $(\ln[\text{IGF-1}] - \mu)/\sigma$, where $\mu = (\ln[\text{LL}] + \ln[\text{UL}])/2$ and $\sigma = (\ln[\text{UL}] - \ln[\text{LL}])/3.92$. This pseudo-SDS is not a validated z-score; it is a reference-interval-derived continuous index. Its construction does not establish removal of confounding by age or sex, and zero is the log-midpoint of the applied reference limits, not a verified healthy-population mean. The lower and upper limits map to −1.96 and +1.96 under this formula.

2.5. Statistical Analysis

Statistical analyses were performed using jamovi 2.7.30 (jamovi project; jamovi.org), which runs on R 4.5. Continuous variables are reported as median and interquartile range (IQR); categorical variables as counts and percentages. Because all IGF-1 measures were non-normal (Shapiro-Wilk $p < 0.001$), non-parametric tests were used throughout: Spearman rank correlation for continuous-continuous and continuous-ordinal associations, and Kruskal-Wallis analysis for multi-group comparisons. A two-sided p-value below 0.05 was considered statistically significant. Denominators for each analysis reflect available measurements; no imputation was performed. 95% confidence intervals for Spearman coefficients were obtained by Fisher z-transformation with the Fieller standard error. To address confounding by age and sex, each principal marker was additionally examined in a separate linear model with natural-log-transformed IGF-1 (nmol/L) as the outcome and sex, age, and age^2 as covariates; effects are reported as percentage differences in IGF-1 with 95% CI. These models were added at revision and are exploratory. A natural cubic spline for age (4 df) and heteroscedasticity-robust (HC3) standard errors were used as sensitivity analyses (Python 3, statsmodels 0.15). Children included in the analysis and the 55 children excluded because no IGF-1 measurement was available were compared descriptively using standardised mean differences (SMD), with growth indices for excluded children computed using the same WHO algorithms. Correlations were not adjusted for multiple comparisons; they are reported with 95% confidence intervals as exploratory associations, and the family-wise significance should be interpreted with caution. The pseudo-SDS is a continuous index derived from platform-specific reference limits within each partition (see Section 2.4); readers should note that the partition-specific transform introduces between-partition heterogeneity in the standardised score, and the analysis restricted to the CALIPER-verified subset is reported alongside as a sensitivity check. jamovi: https://www.jamovi.org/features.html (accessed on 23 November 2026); R: https://www.r-project.org/ (accessed on 23 November 2026).

The primary analysis of correlations between IGF-1 and markers of hepatic function, cholestasis, fibrosis and nutrition excluded post-transplant recipients ($n = 13$), in whom hepatic synthetic function is derived from a functioning graft, and IGF-1 may be influenced by graft function, treatment, and time since transplantation. The same correlations in

the full cohort ($n = 74$) and in the subset restricted to CALIPER-verified age and sex partitions are reported as sensitivity analyses. IGF-1 pseudo-SDS was the primary IGF-1 measure because absolute serum IGF-1 varies markedly with age and sex; unadjusted IGF-1 concentrations are reported in parallel for descriptive comparison. The comparison of IGF-1 across aetiological groups (Kruskal-Wallis) was performed on the four groups defined above; post-transplant patients were reported descriptively but excluded from the omnibus test for the reason stated in Section 2.1. Liver stiffness (kPa) was the primary fibrosis variable; the elastography-derived stage (F0–F4) was analysed as a secondary variable.

During the preparation of this manuscript, the authors used Claude (Opus 5 and Opus 5.5; Anthropic) to assist with synthesising published literature and with improving the language and structure of the text. During revision, it was also used to assist with data verification and with the statistical reanalysis, which was independently replicated by the authors in jamovi. The tool was not used for study design, patient screening, data collection, or the generation of conclusions. The authors reviewed and edited all output and take full responsibility for the content.

3. Results

3.1. Cohort Characteristics

The analytic cohort comprised 74 children with a median age of 8.5 years (IQR 3.0 to 11.8; range 0.2 to 17.9 years). Girls slightly outnumbered boys (40 [54.1%] vs. 34 [45.9%]). Cholestatic disease was the commonest aetiology (19 children, 25.7%), followed by autoimmune hepatitis (16, 21.6%), post-transplant recipients (13, 17.6%), metabolic disease (11, 14.9%), chronic hepatitis B (7, 9.5%), Wilson disease (6, 8.1%) and vascular disease (2, 2.7%). For the planned three-way clinical grouping, 19 children (25.7%) had cholestatic disease, 42 (56.8%) had non-cholestatic CLD, and 13 (17.6%) were post-transplant. The recorded stages were predominantly F0 or F1: 55 children (74.3%) were staged F0 to F1, 19 (25.7%) had significant fibrosis ($F \geq 2$), and 8 (10.8%) had recorded F4 stage. Quantitative liver stiffness was available in 68 children (median 5.0 kPa, IQR 4.0 to 7.2). Baseline biochemistry indicated preserved hepatic synthetic function in most patients (median albumin 4.60 g/dL, IQR 4.21 to 4.80; median cholinesterase 8244 U/L, IQR 6424 to 9512; median INR 0.95, IQR 0.90 to 1.01). Nutritional status was, on aggregate, close to reference: median HAZ +0.11 (IQR −1.07 to +0.69); stunting ($HAZ < -2$) was documented in 7 of 72 assessed children (9.7%) and severe stunting ($HAZ < -3$) in 3 (4.2%). Full baseline characteristics are summarised in Table 1. Included children were similar to the 55 children without a valid IGF-1 measurement in age, liver stiffness, hepatic biochemistry and growth indices (all absolute SMD < 0.25), with comparable sex and aetiology distributions (Supplementary Table S1).

Table 1. Demographic, clinical and biochemical characteristics of the study cohort ($n = 74$).

Characteristic	Value
Demographics	
Age, years, median (IQR)	8.5 (3.0 to 11.8)
Age range, years	0.2 to 17.9
Age < 12 mo, *n* (%)	5 (6.8)
Age 1 to 11 y, *n* (%)	45 (60.8)
Age 11 to 16 y, *n* (%)	20 (27.0)
Age 16 to 18 y, *n* (%)	4 (5.4)
Sex (male), *n* (%)	34 (45.9)
Sex (female), *n* (%)	40 (54.1)

Table 1. *Cont.*

Characteristic	Value
Aetiology (7 categories)	
Cholestatic, *n* (%)	19 (25.7)
Autoimmune, *n* (%)	16 (21.6)
HBV, *n* (%)	7 (9.5)
Wilson, *n* (%)	6 (8.1)
Metabolic, *n* (%)	11 (14.9)
Vascular, *n* (%)	2 (2.7)
Post-transplant, *n* (%)	13 (17.6)
Clinical group (aetiology-based)	
Cholestatic, *n* (%)	19 (25.7)
Non-cholestatic, *n* (%)	42 (56.8)
Post-transplant, *n* (%)	13 (17.6)
Recorded F0–F4 category	
F0, *n* (%)	38 (51.4)
F1, *n* (%)	17 (23.0)
F2, *n* (%)	4 (5.4)
F3, *n* (%)	7 (9.5)
F4, *n* (%)	8 (10.8)
Liver stiffness (kPa), median (IQR), $n = 68$	5.0 (4.0 to 7.2)
Cirrhosis (clinician-diagnosed), *n* (%)	9 (12.2)
Hepatic biochemistry, median (IQR)	
AST, U/L	44 (29 to 87)
ALT, U/L	42 (22 to 95)
GGT, U/L	28 (17 to 71)
Total bilirubin, mg/dL ($n = 72$)	0.56 (0.43 to 0.90)
Direct bilirubin, mg/dL ($n = 73$)	0.18 (0.14 to 0.31)
Albumin, g/dL	4.60 (4.21 to 4.80)
Cholinesterase, U/L	8244 (6424 to 9512)
INR	0.95 (0.90 to 1.01)
Anthropometry, median (IQR)	
Weight, kg	29.5 (14.0 to 44.0)
Height, cm ($n = 72$)	132.5 (97.5 to 151.5)
BMI, kg/m^2 ($n = 71$)	17.3 (15.2 to 19.7)
Weight-for-age z (WAZ) ($n = 42$)	0.00 (−1.42 to +0.85)
Height-for-age z (HAZ) ($n = 72$)	+0.11 (−1.07 to +0.69)
BMI-for-age z (BMIz) ($n = 72$)	+0.25 (−0.46 to +1.12)
MUAC-for-age z (MUACz) ($n = 63$)	+0.13 (−1.04 to +0.68)
Stunting (HAZ < −2), n/assessed (%)	7/72 (9.7)
Severe stunting (HAZ < −3), n/assessed (%)	3/72 (4.2)
Serum IGF-1	
IGF-1, ng/mL, median (IQR)	162.4 (73.6 to 292.9)
IGF-1, nmol/L, median (IQR)	21.23 (9.62 to 38.30)
IGF-1 pseudo-SDS, median (IQR) †	+0.74 (+0.09 to +1.30)
IGF-1 range, ng/mL	12.0 to 572.0
IGF-1 below lower reference limit, n (%) *	4 (5.4)
IGF-1 within reference interval, *n* (%)	65 (87.8)
IGF-1 above upper reference limit, *n* (%) *	5 (6.8)
CALIPER-verified age and sex partition, *n* (%) ‡	48 (64.9)

† IGF-1 pseudo-SDS is an approximation computed as $(\ln[\text{IGF-1}] - \mu)/\sigma$, with $\mu = (\ln[\text{LL}] + \ln[\text{UL}])/2$ and $\sigma = (\ln[\text{UL}] - \ln[\text{LL}])/3.92$, using sex- and age-specific manufacturer reference

limits, verified by CALIPER in most age and sex partitions from 6 to <19 years and in two partitions below six years. It is not a validated standard deviation score. The implied lower and upper index values are −1.96 and +1.96; this is not a diagnostic scale. * Reference intervals from the DiaSorin Liaison XL package insert, verified by the CALIPER program for children aged 6 to <19 years [18]. ‡ Partition-specific CALIPER verification. Non-verified partitions are predominantly in children aged 0 to <6 years. HBV, chronic hepatitis B; HAZ/WAZ/BMIz/MUACz, height-/weight-/BMI-/mid-upper-arm-circumference-for-age z-scores (WHO/Mramba reference); IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase; IGF-1, insulin-like growth factor 1; INR, international normalised ratio; LL/UL, lower/upper reference limit; MUAC, mid-upper arm circumference; SDS, standard deviation score.

Analytic 4-group scheme used for inferential comparisons across aetiologies (Section 3.6): (1) Cholestatic (n = 19); (2) Autoimmune (n = 16); (3) Chronic hepatitis B (n = 7); (4) Metabolic-mixed = inherited metabolic disease + Wilson disease + vascular disease (n = 19). Post-transplant recipients (n = 13) reported separately.

3.2. Serum IGF-1: Distribution and Reference-Based Classification

Serum IGF-1 was measurable in all 74 children (median 162.4 ng/mL, IQR 73.6 to 292.9; equivalent to 21.23 nmol/L, IQR 9.62 to 38.30; range 12.0 to 572.0 ng/mL). The wide observed range reflects the strong age dependence of circulating IGF-1 across the paediatric age spectrum. Applying sex- and age-specific DiaSorin Liaison XL manufacturer reference intervals, verified by CALIPER in most age and sex partitions from 6 to <19 years and in two partitions below six years [18], four children (5.4%) had IGF-1 below the lower reference limit; five (6.8%) had IGF-1 above the upper reference limit; and the remaining 65 (87.8%) were within the reference interval (Figure 2). Of the four children below the applied lower reference limit, all had severe underlying disease at the study visit—two with cholestatic cirrhosis (Alagille syndrome and biliary atresia with recorded F4 stage, aged 20 and 28 months respectively), one with an Abernethy vascular malformation and cirrhosis (aged 12.9 years), and one adolescent with glycogen storage disease and marked stunting (HAZ = −3.76; aged 17.9 years). Forty-eight children (64.9%) fell within CALIPER-verified age and sex partitions; the remaining 26 (35.1%) were in partitions not verified in the source study (25 children younger than 6 years and one boy aged 14 years; Supplementary Table S5) [18]. A parallel classification using the current local-laboratory version of the package insert (in ng/mL) agreed with the CALIPER-based classification in 73 of 74 children (98.6%); one post-transplant female aged 2 years was reclassified as elevated by the local intervals due to a version difference at the (F, 2 to <3 y) upper reference limit.

The pseudo-SDS distribution had a median of +0.74 (IQR +0.09 to +1.30; Section 2.4). The reference-limit construction does not establish that zero is the centre of a healthy population. CALIPER verification of the manufacturer intervals was not established in most partitions below six years [18]. Reference-limit choices and partition-specific transformations may change between-participant ranks and the resulting correlations. The positive index distribution cannot establish preserved hepatic function relative to healthy children.

3.3. IGF-1 and Hepatic Synthetic Function

Correlations between IGF-1 pseudo-SDS and markers of hepatic synthetic function and cholestasis are shown in Table 2 and Figure 3. In the primary analysis restricted to non-transplant children (n = 61), IGF-1 pseudo-SDS correlated positively with serum albumin (Spearman ρ = +0.490, $p < 0.001$), positively with cholinesterase (ρ = +0.334, p = 0.009), inversely with direct bilirubin (ρ = −0.349, p = 0.006), and was not significantly associated with INR (ρ = +0.042, p = 0.749). In log (IGF-1) models adjusted for age and sex, IGF-1

was 57.7% higher per 0.5 g/dL albumin (95% CI 31.1 to 89.8), 9.9% higher per 1000 U/L cholinesterase (95% CI 2.6 to 17.7) and 18.4% lower per doubling of direct bilirubin (95% CI 8.9 to 27.0), whereas INR was not associated ($p = 0.78$; Supplementary Table S2). These are unadjusted cross-sectional correlations of the transformed index. Associations with albumin and cholinesterase may reflect shared hepatic influences, nutritional status, inflammation, or other unmeasured factors. Full-cohort correlations including post-transplant recipients are shown separately in Table 2.

Table 2. Spearman rank correlations between the reference-interval-derived IGF-1 pseudo-SDS and hepatic and nutritional markers, in the non-transplant analysis and sensitivity analyses.

Variable Pair	Primary (Non-tx, $n = 61$)	Full Cohort ($n = 74$)	Sensitivity (Verified × Non-tx, $n = 40$)
Hepatic synthesis			
IGF-1 vs. albumin	+0.490 (95% CI +0.26 to +0.66; $p < 0.001$, $n = 61$)	+0.409 ($p < 0.001$, $n = 74$)	+0.518 ($p < 0.001$, $n = 40$)
IGF-1 vs. cholinesterase	+0.334 (95% CI +0.08 to +0.55; $p = 0.009$, $n = 61$)	+0.282 ($p = 0.015$, n = 74)	+0.470 ($p = 0.002$, $n = 40$)
IGF-1 vs. INR	+0.042 (95% CI −0.22 to +0.30; $p = 0.749$, $n = 61$)	+0.014 ($p = 0.906$, $n = 74$)	−0.009 ($p = 0.954$, $n = 40$)
Cholestasis			
IGF-1 vs. direct bilirubin	−0.349 (95% CI −0.56 to −0.10; $p = 0.006$, $n = 61$)	−0.367 ($p = 0.001$, $n = 73$)	−0.240 ($p = 0.136$, $n = 40$)
Fibrosis			
IGF-1 vs. recorded stage (F0–F4)	−0.313 (95% CI −0.53 to −0.06; $p = 0.014$, $n = 61$)	−0.370 ($p = 0.001$, $n = 74$)	−0.298 ($p = 0.061$, $n = 40$)
IGF-1 vs. liver stiffness (kPa), non-tx	−0.183 (95% CI −0.43 to +0.09; $p = 0.173$, $n = 57$)	−0.240 ($p = 0.049$, $n = 68$)	−0.121 ($p = 0.464$, $n = 39$)
IGF-1 vs. liver stiffness (kPa), non-tx, ≥ 3y (validity-restricted)	−0.101 (95% CI −0.39 to +0.21; $p = 0.509$, $n = 45$)	-	-
Nutrition			
IGF-1 vs. HAZ	+0.418 (95% CI +0.18 to +0.61; $p < 0.001$, $n = 60$)	+0.352 ($p = 0.002$, $n = 72$)	+0.366 ($p = 0.020$, $n = 40$)
IGF-1 vs. WAZ	+0.117 (95% CI −0.24 to +0.45; $p = 0.511$, $n = 34$)	+0.099 ($p = 0.532$, n = 42)	−0.110 ($p = 0.708$, $n = 14$)
IGF-1 vs. BMIz	+0.144 (95% CI −0.12 to +0.39; $p = 0.274$, $n = 60$)	+0.170 ($p = 0.153$, $n = 72$)	+0.214 ($p = 0.186$, $n = 40$)
IGF-1 vs. MUACz	+0.274 (95% CI −0.01 to +0.51; $p = 0.049$, $n = 52$)	+0.288 ($p = 0.022$, $n = 63$)	+0.317 ($p = 0.068$, $n = 34$)

Values are Spearman rho (p-value, n). Sensitivity analysis restricted to non-transplant children in CALIPER-verified age and sex partitions (Supplementary Table S5). IGF-1 pseudo-SDS is the reference-interval-derived index used in the analyses (see Section 2.4). The additional kPa sensitivity row (non-transplant, age ≥ 3 years) is an additional age-restricted analysis; its inclusion does not establish universal validity of transient elastography above this age.

3.4. IGF-1 and Hepatic Fibrosis

IGF-1 pseudo-SDS correlated inversely with the recorded fibrosis stage (F0 to F4) in the non-transplant subset (Spearman $\rho = -0.313$, $p = 0.014$, $n = 61$). Quantitative liver stiffness was available in 68 children; in the non-transplant subset ($n = 57$), the correlation was $\rho = -0.183$ ($p = 0.173$). In non-transplant children aged three years or older ($n = 45$), it was $\rho = -0.101$ ($p = 0.509$). Restricted to the 57 non-transplant children with both measures, IGF-1 correlated with recorded stage ($\rho = -0.291$, $p = 0.028$) but not with liver stiffness, although stage and stiffness were strongly correlated ($\rho = +0.860$; Supplementary Table S4). In the adjusted model, the association with liver stiffness was imprecise (−19.0% per doubling of kPa, 95% CI −34.0 to −0.5; $p = 0.045$) and was not retained with robust standard

errors ($p = 0.19$). The discrepant results do not establish an association between IGF-1 and fibrosis measured by transient elastography. Because the recorded stage is the examiner's categorical interpretation of the same elastographic examination (Section 2.2), liver stiffness, as the underlying continuous measurement, was considered the primary fibrosis measure.

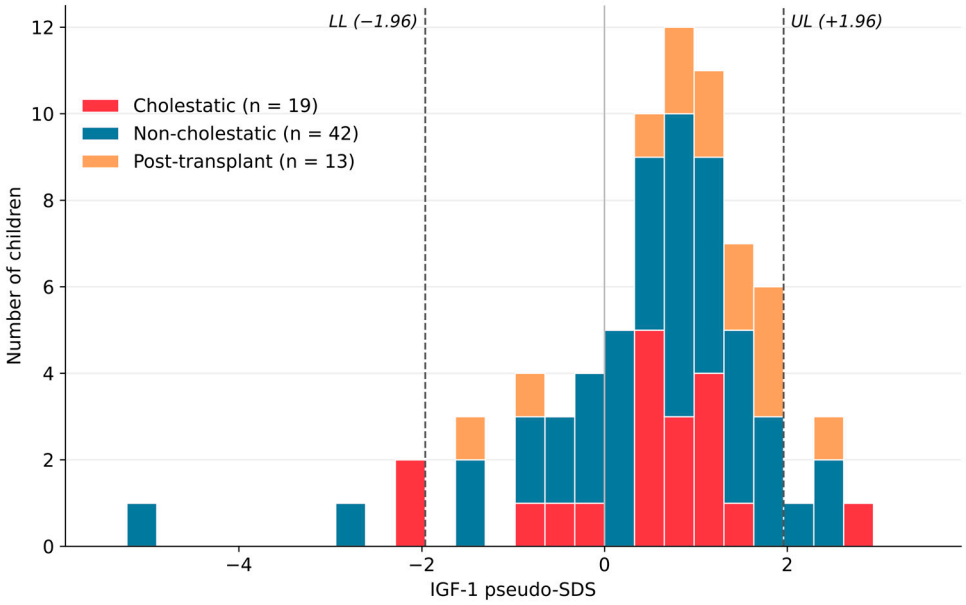

Figure 2. Distribution of the reference-interval-derived IGF-1 pseudo-SDS ($n = 74$), stacked by clinical group. The displayed dashed lines at −1.96 and +1.96 mark the applied lower (LL) and upper (UL) reference limits (Section 2.4), and the solid line at 0 marks their log-midpoint; these guides do not represent validated diagnostic thresholds or an observed healthy-population mean.

3.5. IGF-1 and Nutritional Status

Among nutritional indices, IGF-1 pseudo-SDS correlated most strongly with height-for-age z-score (HAZ; Spearman $\rho = +0.418$, $p < 0.001$, $n = 60$), with a weaker positive correlation with MUAC-for-age z-score ($\rho = +0.274$, $p = 0.049$, $n = 52$); weight-for-age z (WAZ; $\rho = +0.117$, $p = 0.511$, $n = 34$) and BMI-for-age z (BMIz; $\rho = +0.144$, $p = 0.274$, $n = 60$) did not reach significance. After adjustment for age and sex, IGF-1 was 22.3% higher per one-unit increase in HAZ (95% CI 8.9 to 37.5; Supplementary Table S2). HAZ describes attained stature relative to age and sex; a single visit does not measure linear growth velocity. WAZ and BMIz are anthropometric indices and do not establish the timing or cause of nutritional changes. The smaller WAZ sample reflects the age limits of the applied reference.

3.6. IGF-1 Across Aetiological and Clinical Groups

The comparison of IGF-1 across four aetiological groups (cholestatic, autoimmune, chronic hepatitis B, and metabolic-mixed [metabolic + Wilson + vascular]) compares raw concentrations with the reference-interval-derived index. When compared as unadjusted concentrations (ng/mL or nmol/L), IGF-1 differed significantly across groups (Kruskal-Wallis $H = 20.60$, $p < 0.001$, $n = 61$). When the same comparison was performed on the primary IGF-1 measure (pseudo-SDS, reference-interval-derived), the difference was not statistically significant ($H = 3.40$, $p = 0.334$; Table 3). Raw and reference-interval-derived analyses use different transformations; their different p-values do not establish that age or sex confounding has been removed. The post-transplant subgroup is described separately in Table 3.

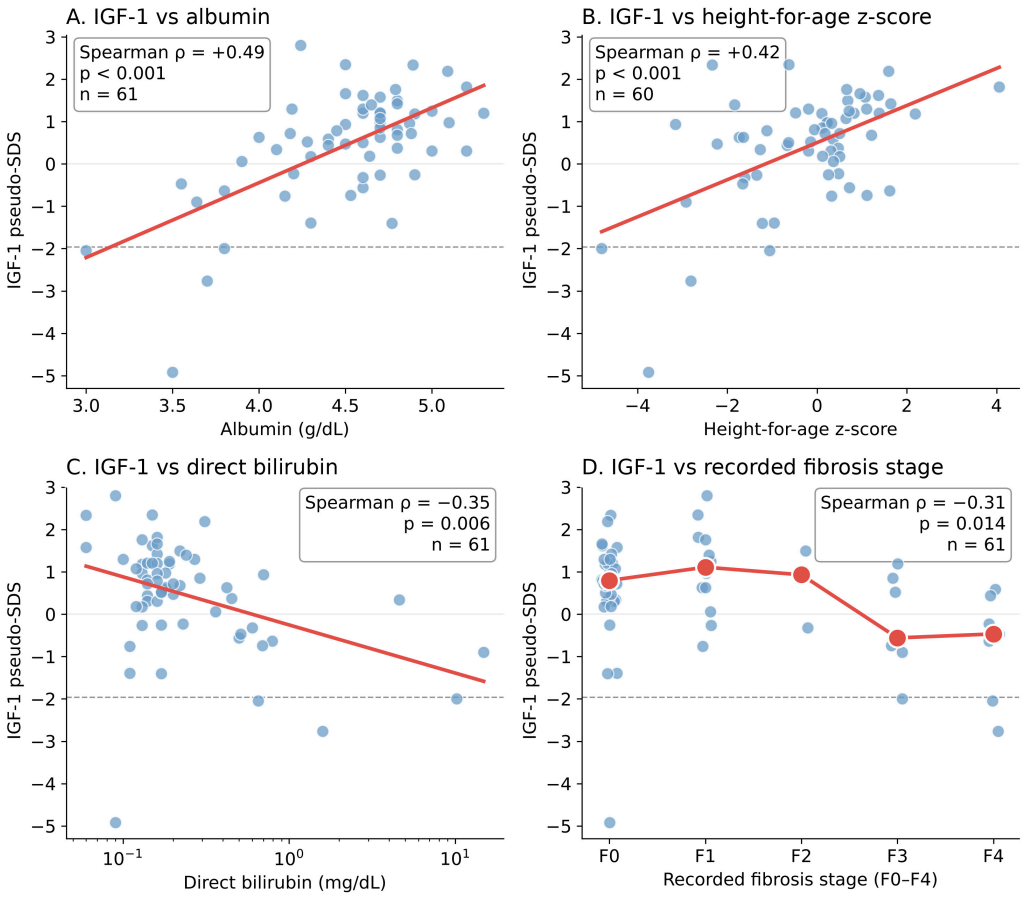

Figure 3. Reference-interval-derived IGF-1 pseudo-SDS and principal correlates in the non-transplant cohort. Panel (**A**): albumin. Panel (**B**): height-for-age z-score. Panel (**C**): direct bilirubin, displayed on a logarithmic horizontal axis. Panel (**D**): recorded fibrosis stage, with jitter and a line connecting group medians. The plotted dashed line at −1.96 marks the applied lower reference limit (LL) and the 0 guide its log-midpoint; these guides are not validated diagnostic thresholds or a healthy-population mean. Lines are visual aids and do not establish independent or causal relationships.

Table 3. IGF-1 across four aetiological groups (Kruskal-Wallis); post-transplant recipients reported separately.

IGF-1 Measure	Cholestatic	Autoimmune	HBV	Metabolic-Mixed	*p* (Kruskal-Wallis)	Post-Transplant (Separate)
IGF-1 pseudo-SDS †	+0.63 (+0.01 to +1.20); *n* = 19	+0.58 (−0.24 to +1.14); *n* = 16	+1.18 (+0.96 to +1.34); *n* = 7	+0.30 (−0.45 to +1.25); *n* = 19	H = 3.40; *p* = 0.334	+1.16 (+0.72 to +1.71); *n* = 13
IGF-1, nmol/L	9.24 (6.28 to 15.32); *n* = 19	33.35 (25.08 to 45.86); *n* = 16	43.74 (27.63 to 48.01); *n* = 7	15.31 (8.85 to 25.02); *n* = 19	H = 20.60; *p* < 0.001	25.66 (12.16 to 41.31); *n* = 13
IGF-1, ng/mL	70.7 (48.0 to 117.2); *n* = 19	255.1 (191.8 to 350.8); *n* = 16	334.6 (211.3 to 367.2); *n* = 7	117.1 (67.7 to 191.4); *n* = 19	H = 20.60; *p* < 0.001	196.3 (93.0 to 316.0); *n* = 13

Median (IQR); *n* = observations per group. Metabolic-Mixed = Metabolic + Wilson + Vascular (collapsed for statistical power). † The pseudo-SDS is a reference-interval-derived index. The contrast between raw and transformed comparisons does not establish independent aetiological effects or control for age and sex confounding. HBV, chronic hepatitis B.

The three clinical groups are described in Table 4 without a formal omnibus comparison. Post-transplant recipients are excluded from inferential group comparisons, as specified in Section 2.5. Post-transplant values are identical to those in Table 3.

Table 4. Descriptive IGF-1 summaries across the three clinical groups.

IGF-1 Measure	Cholestatic (n = 19)	Non-Cholestatic (n = 42)	Post-Transplant (n = 13)
IGF-1 pseudo-SDS †	+0.63 (+0.01 to +1.20)	+0.70 (−0.16 to +1.27)	+1.16 (+0.72 to +1.71)
IGF-1, nmol/L	9.24 (6.28 to 15.32)	25.48 (15.40 to 43.67)	25.66 (12.16 to 41.31)
IGF-1, ng/mL	70.7 (48.0 to 117.2)	194.9 (117.8 to 334.0)	196.3 (93.0 to 316.0)

Median (IQR). † The pseudo-SDS is a reference-interval-derived index. Post-transplant recipients are described separately and are not included in an omnibus test.

3.7. Sensitivity Analyses

Three sensitivity analyses were performed. First, correlations were recomputed in the subset with CALIPER-verified age partitions (predominantly ages 6 to <19 years; Supplementary Table S5) and non-transplant status (n = 40). The direction and magnitude of the primary correlations were preserved for albumin, cholinesterase, and HAZ. Three associations remained directionally consistent but fell below the $\alpha = 0.05$ threshold in this smaller subset: direct bilirubin, fibrosis stage ($\rho = -0.298$, $p = 0.061$) and MUACz ($\rho = +0.317$, $p = 0.068$), with uncertainty that cannot be attributed to sample size alone (Table 2). Second, IGF-1 status classification using the current local-laboratory package-insert intervals (in ng/mL) yielded concordant classifications in 73 of 74 patients (98.6%); the single discordant case was a post-transplant female aged 2 years reclassified as elevated by the local intervals due to a package-insert version difference at the (F, 2 to <3 y) upper reference limit. This concordance applies to the three-way IGF-1 categorical classification only; because pseudo-SDS is computed from the numerical values of reference limits, any shift in these limits would move the continuous scores; when the pseudo-SDS was recomputed from the local-laboratory limits, the primary correlations were materially unchanged (e.g., albumin $\rho = +0.490$, HAZ $\rho = +0.420$; Supplementary Table S3). Finally, the adjusted models were robust to modelling age with a natural cubic spline, and the associations with albumin, cholinesterase, direct bilirubin and HAZ were retained with robust standard errors (Supplementary Table S2).

4. Discussion

In this selected single-centre cohort, the reference-interval-derived IGF-1 pseudo-SDS was associated with albumin, cholinesterase, direct bilirubin and HAZ in the non-transplant analysis (Table 2). These associations persisted in models adjusted for age and sex. The index was also associated with recorded fibrosis stage, while the continuous stiffness analyses did not show clear evidence of an association. Raw concentrations and the transformed index produced different aetiological comparisons. These cross-sectional results do not establish independent associations or clinical utility.

The association with albumin is compatible with shared hepatic influences on the two proteins. Nutritional status and inflammation are alternative explanations that were not separated in these analyses. Cholinesterase showed a positive association, whereas INR did not. The limited INR range may contribute to uncertainty, but these cross-sectional analyses do not identify its cause.

Studies in adults and in specific paediatric liver conditions have examined relationships between the IGF system and hepatic disease [14–17]. In the present cohort, the recorded stage association was not reproduced clearly with continuous liver stiffness. Because the stage is a categorical interpretation of the same elastographic examination, this discrepancy more likely reflects the limited precision of both estimates than a true divergence between the two measures. The stage result does not support a claim that IGF-1 measures fibrosis.

The analyses showed an association with HAZ and a weaker association with MUACz; WAZ and BMIz did not show clear evidence of an association (Table 2). HAZ measures attained stature, and the study did not measure longitudinal growth velocity. The observed pattern does not separate hepatic, endocrine, and nutritional influences. Small nutritional-intervention studies provide related context [9,10], but they do not establish the mechanism underlying the present associations.

The different findings from raw concentrations and the reference-interval-derived index illustrate sensitivity to the analytical scale. The index uses age and sex partitions but does not demonstrate control of age and sex confounding. A nonsignificant transformed comparison does not exclude aetiological differences. Post-transplant recipients were assessed at a single post-transplant visit; the data do not establish changes caused by transplantation.

CALIPER verified the manufacturer IGF-1 reference intervals for children aged 6 to <19 years; verification was not established below six years [18]. This verification concerns the intervals and does not itself validate the derived pseudo-SDS. Restriction to the verified age partitions preserved some associations, but the direct bilirubin, fibrosis stage, and MUACz results remained uncertain (Table 2). Categorical agreement between package-insert versions does not establish equivalence of continuous scores or correlations; when recomputed under the local-laboratory limits, the correlations were materially unchanged (Supplementary Table S3).

4.1. Limitations

This study has several limitations. It is single-centre, cross-sectional and observational, so causal inference is precluded, and longitudinal changes in IGF-1 in response to disease progression or therapy cannot be assessed. A valid IGF-1 measurement was available in 74 of 129 children followed during the study period, and the 55 without a measurement were excluded on that basis alone; included and excluded children were similar in measured characteristics (Supplementary Table S1), which does not exclude selection on unmeasured factors. IGF-1 was not requested for a specific clinical indication; however, because it was measured during routine care rather than by study protocol, selection related to whether IGF-1 was measured cannot be excluded and could affect both the observed proportion below the applied lower reference limits and the strength of the IGF-1-growth associations; the direction and magnitude of any such bias cannot be determined from these data. The cohort is aetiologically heterogeneous, which limits inference within individual disease categories and does not establish generalisability. Post-transplant recipients ($n = 13$) were reported separately rather than included in aetiological analyses; while this is methodologically appropriate, it reduces the statistical power of aetiology comparisons. The WHO reference software for WAZ is validated only up to age 10, limiting the sample size for this analysis in older children. Circulating IGF-1 rises steeply through puberty; the pseudo-SDS uses age and sex reference partitions but does not establish confounding control or account for pubertal stage. Because the aetiological groups differed in age composition, they are likely to have differed in pubertal distribution, so residual confounding by pubertal stage cannot be excluded in the reported comparisons. Concurrent medication was not accounted for: glucocorticoids and other immunosuppressants act on the GH/IGF-1 axis and were plausibly used in the autoimmune and post-transplant groups, which, respectively, showed the highest unadjusted IGF-1 and the highest pseudo-SDS. Drug exposure may therefore confound the between-group comparisons and the graft-associated IGF-1 observed after transplantation. IGFBP-3 was not measured; the molar IGF-1/IGFBP-3 ratio, which provides additional information on bioavailable IGF-1 in liver disease, is a natural extension of this work. GH resistance was not directly assessed. Fibrosis stage was derived from transient elastography and not histologically confirmed, and oedema was not recorded.

4.2. Clinical and Research Implications

The present study supports further investigation of IGF-1 as an exploratory correlate of hepatic biochemistry and attained height in children with CLD. It does not establish screening accuracy, additional value beyond routine markers, a monitoring role or a treatment indication. Longitudinal data and appropriately adjusted analyses are needed to assess these questions.

5. Conclusions

In this selected mixed-aetiology cohort, a reference-interval-derived IGF-1 index showed cross-sectional associations with hepatic biochemistry and height-for-age. The index is not a validated SDS and does not establish independent associations. Discordant recorded-stage and continuous-stiffness findings limit fibrosis interpretation. Clinical diagnostic, prognostic, and monitoring roles remain unestablished.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/children13121660/s1, Table S1: Characteristics of included assessments and of children excluded for lack of a valid IGF-1 measurement; Table S2: Associations of hepatic and growth markers with log-transformed IGF-1, adjusted for age and sex; Table S3: Spearman correlations of IGF-1 pseudo-SDS computed from the CALIPER-verified package-insert limits versus the current local-laboratory limits (non-transplant children); Table S4: Correlations of IGF-1 pseudo-SDS with recorded fibrosis stage and with liver stiffness in identical patients (non-transplant children with both measures); Table S5: Applied IGF-1 reference limits by age and sex: DiaSorin Liaison XL package insert with CALIPER verification, and current local-laboratory version of the package insert.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Emergency Clinical Hospital for Children, Cluj-Napoca (approval number 94/28.07.2023).

Informed Consent Statement: Written informed consent was obtained from all parents or legal guardians, and assent from children aged seven years and older.

Data Availability Statement: The de-identified dataset used for this analysis is available from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AIH	Autoimmune hepatitis
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BMIz	Body mass index-for-age z-score
CALIPER	Canadian Laboratory Initiative on Pediatric Reference Intervals
CI	Confidence interval
CLD	Chronic liver disease
GH	Growth hormone
GGT	Gamma-glutamyltransferase
HAZ	Height-for-age z-score
HBV	Hepatitis B virus
IGF-1	Insulin-like growth factor 1
IGFBP-3	Insulin-like growth factor-binding protein 3
INR	International normalized ratio
IQR	Interquartile range
LL	Lower reference limit
MUAC	Mid-upper arm circumference
MUACz	Mid-upper arm circumference-for-age z-score
SDS	Standard deviation score
UL	Upper reference limit
WAZ	Weight-for-age z-score
WHO	World Health Organization

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