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Original Article

Prediction of Development of Neonatal Jaundice by Cord Blood Bilirubin and Albumin

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Abstract:

Background: Neonatal jaundice is a common cause of early postnatal readmission and contributes to both financial and socio-economic burden. In resource-constrained nations, where the patient-to-resource-constrained-bed ratio is very high, early prediction of hyperbilirubinaemia will help in early discharge, prevent re-hospitalization, and reduce the duration of hospital stay. This study aims to estimate the cord blood bilirubin (CBB) and albumin (CBA) levels for future prediction of neonatal jaundice among deliveries at Bhagat Phool Singh Government Medical College for Women (BPS GMC (W)).

Methods: A prospective study was conducted among 384 randomly selected neonates delivered at BPS GMC (W). Socio-demographic data were recorded, and cord blood samples were collected at birth for bilirubin and albumin estimation. Neonates were followed for 10 days to assess the development of clinical jaundice.

Result: Incidence of neonatal jaundice was 21.4% with 10 days of follow-up. 94.8% neonates developed jaundice with CBB level ≥ 2mg/dL, proving it statistically significant. Additionally, 62.7% of neonates with serum albumin < 3 g/dL developed jaundice. Cord blood Bilirubin-to-Albumin ratio proved a good indicator, as area under the curve is 0.933 with sensitivity and specificity of 68.30% and 99.0% respectively at a cut-off level of 0.61.

Conclusion: Cord blood bilirubin and bilirubin-to-albumin ratio may help identify neonates at higher risk of subsequent jaundice and may assist in prioritizing follow-up in resource-limited settings. A bilirubin-to-albumin ratio ≥ 0.61 was found to be a highly specific predictor.

Keywords: cord albumin, cord bilirubin, neonatal jaundice

Introduction

Hyperbilirubinemia is one of the most common causes of readmission during the early neonatal period in developing nations. Hyperbilirubinemia develops on days 2-4 of life in 50% of term and 80% of preterm neonates. Severe hyperbilirubinemia can occur without apparent reason in some healthy neonates and may develop kernicterus.[1, 2] In modern clinical practice, healthy term neonates are allowed to early discharge because of advantages including prevention of nosocomial infections, high patient-to-bed ratio, lower cost, and some social reasons like early naming ceremony. The American Academy of Pediatrics (AAP) recommends that newborns discharged within 48 hours should have a follow-up visit after 48-72 hours.[3] In developing nations, the value of follow-up visits is questionable as mothers do not return due to long travel distances and financial burden.[4] Neonatal jaundice is one of the common reasons for readmission in the early neonatal period, which causes a financial and socio-economic burden on families. In resource-constrained nations, where the patient-to-bed ratio is very high, early prediction of hyperbilirubinaemia will help in early discharge, prevent re-hospitalization, and reduce the duration of hospital stay of babies and mothers.[2] Neonatal jaundice can be treated easily by phototherapy when detected early in the course of illness, which prevents the development of chronic bilirubin encephalopathy (kernicterus) associated with poor outcome, as it may lead to neurological handicap and early death of affected infants even after treatment.[5]

Currently, we don't have a highly reliable and specific investigation to detect jaundice up to 100% at birth, but we can follow neonates with high bilirubin and low albumin values.[6] Also, the bilirubin-to-albumin ratio proved highly useful.[7] Moreover, testing is easy and reports come within hours without delays. So, the concept of predicting the development of jaundice via bilirubin testing is helpful before bilirubin levels reach a critical limit. Cord blood bilirubin (CBB) and cord blood albumin (CBA) are important predictors for neonatal jaundice. Very few studies have been conducted in India, and our study aimed to use cord blood bilirubin and albumin for the prediction of subsequent development of neonatal jaundice so that dreaded complications like kernicterus can be prevented.

Method

Study setting: The present study was conducted among the neonates delivered in the labour room of the Department of Obstetrics and Gynaecology at Bhagat Phool Singh Government Medical College for Women (BPS GMC(W)), Khanpur Kalan, Sonepat, between 30/12/2023 and 30/07/2024.

Type of study: Prospective study.

Sample size: Taking the proportion of neonatal jaundice as 50% in neonates with cord blood bilirubin ≥2mg/dL from a previous study, at 95% confidence interval, 5% absolute precision, the calculated sample size is 384 neonates.[8]

Cut-offs: Cut off for serum bilirubin ≥2mg/dL, serum albumin ≤ 3g/dL, and bilirubin-to-albumin ratio ≥0.61were taken for consideration of hyperbilirubinemia.

Neonatal jaundice was defined as clinically apparent jaundice identified during follow-up and confirmed by serum bilirubin assessment as per departmental paediatric protocol.

Sampling technique: Systematic random sampling was done. Every third delivered neonate was selected for participation in the study.

Study population: Neonates delivered at BPS GMC (W) Khanpur Kalan Sonepat during the study period.

Inclusion criteria:

- Healthy neonates delivered at BPS GMC (W) Khanpur Kalan Sonepat during the study period
- Parents of neonates consenting for participation in the study.

Exclusion criteria:

- Neonates with significant illnesses such as neonatal sepsis, birth asphyxia, respiratory distress syndrome, meconium aspiration syndrome, or any who are critically ill or haemodynamically unstable.
- Neonates with major congenital anomaly.

Data collection: For all 384 neonates, data were collected on a semi-structured proforma after taking informed consent from the parents of the neonates. They were informed that their personal details would not be disclosed and efforts were made to conceal their identities. Detailed history was taken with full emphasis on both antenatal and perinatal history (maternal illness, drugs, fever with rash) and relevant birth history.

For blood sample collection, permission from the Department of Obstetrics and Gynaecology was taken. After delivery of the newborn, the umbilical cord was double clamped and cut at the placental end. As soon as the neonate was removed from the operative field, the cord blood sample was taken after clamping the cord with a sterile cord clamp at the neonatal end by puncturing the cord with a 5 mL syringe at a suitable point after taking proper aseptic measures. During the whole procedure, the umbilical cord was held in a slanting manner for ease of sample collection. The collected blood sample was stored in a red vacutainer away from light to prevent

degradation. The vacutainers were sent to the biochemistry laboratory of the institute for estimation of serum albumin and serum bilirubin by the spectrophotometer technique. Hemolysed samples were excluded from testing.

All the neonates were followed for 10 days for the development of clinical jaundice and the neonates who developed jaundice were treated as per the current protocol in the Department of Paediatrics, BPS GMC (W) Khanpur Kalan Sonepat.

Ethical consideration: The Institutional Ethics Committee, BPS GMC (W) approved the research vide letter number- BPSGMCW/RC993/IEC/23.

Statistical analysis: All the collected data were entered in an Excel spreadsheet and analysed using SPSS version 28. We calculated the mean and standard deviation for quantitative variables, and frequency and percentage for qualitative variables. Chi-square test was applied for determining any association between neonatal jaundice and high cord blood bilirubin, albumin, and other factors associated with it. Sensitivity, specificity, and Area Under Curve (AUC) in the ROC curve were calculated. A p-value less than 0.05 was considered statistically significant.

Result

The present study was conducted among the 384 neonates delivered in the labour room, and they were followed for 10 days. Out of 384 neonates, 82 developed clinical jaundice within 10 days, so the incidence of neonatal jaundice was 21.4%.

Neonatal jaundice was slightly higher in female neonates than in males, but the difference was not statistically significant. The study showed that the mean birth weight of neonates with jaundice was 2.77±0.39 kg, which was less than the mean birth weight of neonates without jaundice, but it was not found to be statistically significant. The study showed that among the breastfed neonates, only 19.6% neonates developed jaundice, whereas 32.1% developed jaundice who were not breastfed timely, which was statistically significant. Nearly half of neonates developed jaundice who were given pre-lacteal feed while less than 1/5th of neonates developed jaundice who were not given pre-lacteal feed which was found statistically significant **(Table 1).**

This study showed that 69.4% neonates born to mothers with urinary tract infections (UTI) developed neonatal jaundice. One-fourth of neonates developed neonatal jaundice whose mother consumed certain drugs during pregnancy. About 15% of neonates developed jaundice whose mothers didn't consume iron and folate tablets during pregnancy. Although it was not significant. Nearly four-fifths of infants of diabetic mothers developed jaundice, which was statistically insignificant. Similarly, two-thirds of neonates of hypertensive mothers develop neonatal jaundice. One -third

of neonates developed jaundice whose mothers had thyroid disorders, which was not significant as compared to only 20.9% neonates of healthy mothers. ABO-Rh incompatibility was present more in neonates with jaundice, which was statistically significant **(Table 2)**.

Table 1. Distribution of neonatal characteristics among the study population

Neonatal Characteristics		Neonatal Jaundice		P value
		Yes (%)	No (%)	
Sex of neonate	Male	40 (20.7)	153 (79.3)	0.762
	Female	42 (22)	149 (78)	
Birth weight of the neonate	<2.5Kg	14 (19.7)	57 (80.3)	0.709
	≥2.5Kg	68 (21.7)	245(78.3)	
	Mean Weight	2.77 ± 0.39	2.8 ± 0.38	0.815
Early initiation breastfeeding	Done	65 (19.6)	266 (80.4)	**0.040**
	Not done	17 (32.1)	36 (67.9)	
Pre- lacteal feed to neonates	Given	18 (47.4)	20 (52.6)	**<0.001**
	Not given	64 (18.5)	282 (81.5)	

Table 2. Association of maternal factors with neonatal jaundice (n=384).

Maternal Factors		Neonatal Jaundice		P value
		Yes (%)	No (%)	
Urinary tract infection	Present	75 (69.5)	33 (30.5)	0.530
	Absent	7 (2.6)	269 (97.4)	
Drugs intake for any disease	Present	11 (24.4)	34 (75.6)	0.590
	Absent	71 (20.9)	268 (79.1)	
IFA tablets course completion in pregnancy	Present	8 (15.4)	258 (77.7)	0.259
	Absent	74 (22.3)	44 (84.6)	
Anemia in pregnancy	Present	59 (40.13)	88 (59.87)	0.847
	Absent	23 (9.7)	214 (90.3)	
Gestational diabetes mellitus	Present	78 (73.5)	28 (26.5)	0.202
	Absent	4 (1.43)	274 (98.57)	
Hypertension	Present	76(67.2)	37 (32.8)	0.209
	Absent	6 (2.2)	265 (97.8)	
Thyroid disorders	Present	6 (30)	14 (70)	0.333
	Absent	76 (20.9)	288 (79.1)	
ABO-Rh incompatibility	Present	20 (87)	3 (13)	**<0.001**
	Absent	62 (17.2)	299 (82.8)	
Gestational age of pregnant mothers	≤37weeks	79 (21.8)	284 (78.2)	0.416
	>37weeks	3 (14.3)	18 (85.7)	

The study showed that 94.8% neonates with jaundice had raised bilirubin levels. Only 5.2% neonates with bilirubin levels > 2 mg/dL had not developed neonatal jaundice. The difference was statistically significant. The data in the table indicated that 62.7% of neonates with cord albumin below 3g/dL developed neonatal jaundice, while only 13.8% of neonates with albumin values higher than 3g/dL developed jaundice, which was statistically significant. In the present study population, the mean cord blood albumin level among neonates who developed jaundice was 3.00 ± 0.99 g/dL, compared to 3.83 ± 0.69 g/dL among those who did not develop jaundice. The study showed that 94.6% of neonates with a bilirubin-to-albumin ratio greater than 0.61 developed jaundice, whereas only 8% neonates with a bilirubin-to albumin ratio below 0.61 developed jaundice. This difference was statistically significant. Similarly, the mean bilirubin-to-albumin ratio in neonates with jaundice was 1.62, whereas levels in neonates without jaundice were 0.24 **(Table 3)**.

Table 3. Association of cord blood bilirubin & albumin levels with neonatal jaundice (n=384).

	Variables	Neonatal Jaundice		P value
		Yes (%)	No (%)	
Cord blood bilirubin	≤ 2 mg/dL	27 (8.3)	299 (91.7)	**<0.001**
	> 2 mg/dL	55 (94.8)	3 (5.2)	
	Mean Total bilirubin (mg/dL) ± SD	4.10 ± 2.71	0.80 ± 0.45	**<0.001**
Albumin levels	≤ 3 g/dL	37 (62.7)	22 (37.3)	**<0.001**
	> 3 g/dL	45(13.8)	280 (86.2)	
	Mean Serum Albumin (g/dL) ± SD	3.00 ± 0.99	3.83 ± 0.69	**<0.001**
Bilirubin-to-Albumin ratio	≤ 0.61	26 (8)	299 (92)	**<0.001**
	> 0.61	56 (94.6)	3 (5.4)	
	Mean Bilirubin-to-albumin ratio ± SD	1.62 ± 0.24	0.24 ± 0.2	**<0.001**

Sensitivity and specificity of cord blood bilirubin at a cutoff level of 2 mg/dL was 67.06% and 99%, respectively. Although the specificity of serum albumin at the cut-off level of 3 mg/dL was 92.72% but sensitivity at the same level was found to be only 45.12% **(Table 4)**.

Figure 1 shows that cord blood Bilirubin-to-Albumin ratio also proves a good indicator as the area under the ROC curve is 0.933 with sensitivity and specificity of 68.30% and 99.0%, respectively, at a cut-off level of 0.61 **(Table 4)**.

Table 4. Sensitivity, specificity, and AUC of cord blood bilirubin and albumin

Variables		Neonatal Jaundice Yes (%)	Neonatal Jaundice No (%)	Sensitivity/ Specificity	AUC	P value
Cord blood bilirubin	> 2 mg/dL	55 (94.8)	3 (5.2)	67.07% / 99.0%	0.911	**<0.001**
	≤ 2 mg/dL	27 (8.3)	299 (91.7)			
Albumin levels	≤ 3 g/dL	37 (62.7)	22 (37.3)	45.12% / 92.72%	0.757	**<0.001**
	> 3 g/dL	45(13.8)	280 (86.2)			
Bilirubin-to-Albumin ratio	> 0.61	56 (94.6)	3 (5.4)	68.30% / 99.0%	0.933	**<0.001**
	≤ 0.61	26 (8)	299 (92)			

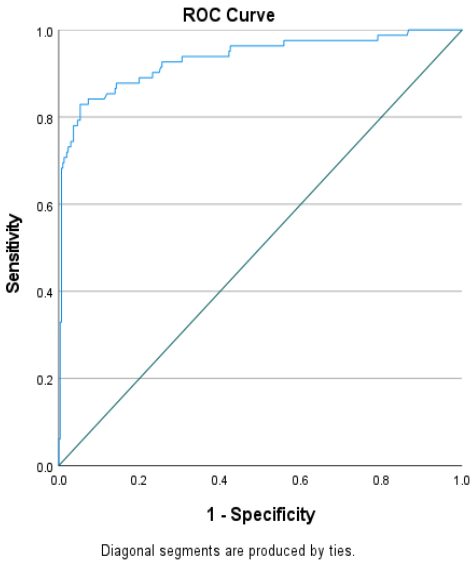

Figure 1. ROC Curve showing cord blood bilirubin-to-albumin ratio sensitivity and specificity in detecting hyperbilirubinemia

Discussion

Neonatal jaundice is the most commonly reported cause for readmission during the early neonatal period. The need for early prediction of hyperbilirubinemia in early-discharged newborns from the hospital is therefore important.

In the present study, cord blood bilirubin and albumin were examined as a tool to predict subsequent neonatal jaundice. In our study, a total of 384 subjects were studied and followed for 10 days; among them, 82 neonates (21.4%) developed jaundice. Incidence was similar to a study done in Nigeria by Chime et al., stating the development of neonatal jaundice in 21% in males and 12% of females.[9] A study done by Rafi et al. in India showed the incidence of neonatal hyperbilirubinaemia 14% (42/300), considering a cut-off of cord bilirubin levels >2mg/dL.[10] Another similar study by Narang et al. showed 14.56% (551/3791) prevalence of neonatal jaundice.[11]

Our study demonstrates that the sex of neonates was not strongly associated with neonatal jaundice, as both sexes were equally affected. The findings were similar to a study done by Rafi et al. in Andhra Pradesh.[10]

Our study revealed that early initiation of breastfeeding is protective for neonates. Among the breastfed neonates, only one-fifth develop jaundice, whereas 1/3rd develop jaundice who were not breastfed timely, which is statistically significant. Similar results were concluded by Bertini et al.[12] The reason behind developing jaundice can be starvation and dehydration in late breastfed neonates, and such practices also put them at high risk of bilirubin encephalopathy.

Pre-lacteal feeding significantly increases the incidence of development of jaundice, while timely breastfeeding reduces the risk of developing jaundice. Nearly half of neonates developed jaundice who were given pre-lacteal feed due to any cause developed jaundice, while less than 1/5th of normal neonates develop jaundice. The reason can be increased infections via pre-lacteal food and utensils. According to Nguyen et al., pre-lacteal feeding and early formula feeding before hospital discharge are associated with higher risks of infection and hospital admission in Vietnamese infants.[13] Support for exclusive breastfeeding should be provided to mothers to avoid the adverse consequences of giving formula milk and pre-lacteal foods.

Our study showed that neonates of mothers with UTI were at high risk of developing jaundice as compared to neonates of healthy mothers. A study by Bilgin et al. found presence of maternal urinary tract infection may contribute to increased infections in the neonatal period.[14] Neonates born to mothers with UTI had a high risk of getting infection while delivering, causing increased hemolysis. It is important to diagnose a UTI in neonates in the perinatal period.

In the present study, 40.13% neonates of anemic mothers developed jaundice. This showed that anemic mothers had a high risk of having anemic neonates. Similar results by Bham et al. state that the overall frequency of newborns with hyperbilirubinemia was 50.6%, and there was a potential connection between the iron supplementation of the mother during pregnancy and the development of neonatal jaundice, suggesting the need to exercise early intervention in pregnant mothers who were at high risk of newborn jaundice.[15]

Our study showed that 67% neonates of hypertensive mothers developed neonatal jaundice. Whereas only 2.2% of neonates of healthy mothers developed subsequent jaundice, which is not statistically significant. However, a study by Boskabadi H et al. states that maternal risk factors for neonatal jaundice with hypertension as most common cause, with 11.85% of prevalence rate.[16] Higher values in our study might be

because of a greater number of referral cases at the only available tertiary care institute in a rural area nearby.

Our study showed that premature birth had 21.8% prevalence of neonatal jaundice, whereas only 14.3% of term neonates developed statistically significant jaundice. Similar results were concluded by Sayed et al. in a study done in Iran.[17] The reason might be a lack of sucking reflex in premature babies, and usually, they are artificially fed for the initial days. Also, there is a replacement of fetal hemoglobin to adult haemoglobin after birth, causing some rise in bilirubin levels, causing stress on the underdeveloped liver to metabolize haemoglobin. But the majority of term neonates (85.7%) remain normal as enzymes for bilirubin metabolism start to function properly. The incidence of ABO Rh incompatibility in our study was 23, out of which 87% neonates developed jaundice, which was statistically significant. ABO-Rh incompatibility causes excessive hemolysis due to the presence of antibodies against neonatal blood cells, causing severe jaundice.

The present study showed that 94.8% neonates with jaundice had raised cord blood bilirubin levels >2 mg/dL, which was statistically significant. A cord blood bilirubin level cut off at 2mg/dL has a good specificity of 99% and sensitivity of about 67%. Nahar et al. showed that cord bilirubin >2.5 mg/dL has a sensitivity 77% and a specificity 98.6% in predicting neonatal hyperbilirubinemia.[18] Pradhan et al. showed that cord bilirubin level >2.5 mg/dL has a sensitivity of 84.1%, specificity of 88.5%.[19] The slight differences may be due to different cut-off levels for cord bilirubin levels.

In the present study, a low albumin value below 3g/dL was found in 62.7% among the neonates who developed jaundice, which was similar to a study done by Assam et al., who stated that 60 out of 100 neonates with cord albumin <2.8g/dL developed significant jaundice within a five-day follow-up.[7] From this study, cord blood albumin level was demonstrated as having good specificity of 92.7%, although it has a low sensitivity of only 45%, which was less than studies conducted by Nahar Z et al. and Pradhan et al.[19]

Bilirubin-to-albumin ratio was calculated for association with the development of jaundice, which turned out to be a good indicator. A ratio higher than 0.61 was among 95% neonates who developed jaundice. Bilirubin-to-albumin ratio proved to be a good indicator with a sensitivity of about 68% along with a specificity of 99% to reduce damage of kernicterus, as detection can be done at an early stage before central nervous system (CNS) complications arise.

Strength:

- Minimally invasive procedure with highly useful results.
- Random sampling greatly removed chances of bias.

- All samples being tested at a single laboratory reduced the chances of variations in results.

Limitations: This study has certain limitations. It was conducted at a single tertiary care center, which may limit generalizability to other healthcare settings. The proportion of preterm neonates in the study population was relatively high due to the referral nature of the institute, which may have influenced the observed incidence of jaundice. Important confounding factors such as oxytocin administration during labor, cephalhematoma, and complications during delivery were not assessed and may have affected the occurrence of neonatal jaundice. In addition, subgroup analyses for maternal conditions such as gestational diabetes and hypertension may have been underpowered due to small sample sizes in those categories.

Recommendation: Frequent outreach sessions should be organized to improve knowledge of the community and make them understand the need for prompt reporting. Community awareness regarding early signs of neonatal jaundice should be improved through counseling during antenatal and postnatal care. Exclusive breastfeeding and timely initiation of feeding should be encouraged. Neonates identified as high-risk based on cord blood parameters may be considered for closer follow-up after discharge. Larger multicenter studies are recommended before establishing standardized risk-based discharge policies. Mothers should be encouraged to breastfeed exclusively, frequently at least 8 times a day, without giving top feeds, glucose, water, etc. Mothers should be informed to consult a doctor if their baby shows yellowing discoloration, excessive cry or irritated behaviour so that dreaded complications can be prevented.

Clinical significance: Neonatal jaundice is a common cause of readmission in the early neonatal period, due to which there is an emotional and socio-economic burden on families. Testing cord blood bilirubin and albumin is a very simple, easy, and non-invasive method to predict the development of subsequent neonatal jaundice. Also, it will help in providing a knowledge source for upcoming clinicians.

Conclusion

The present study suggests that cord blood bilirubin and bilirubin-to-albumin ratio are useful predictors for identifying neonates at increased risk of developing neonatal jaundice. Cord blood albumin alone showed lower sensitivity and therefore may not be suitable as an independent screening test, though it may provide supportive value when combined with bilirubin. Neonates with elevated cord blood bilirubin (>2 mg/dL) and bilirubin-to-albumin ratio (>0.61) may require closer postnatal follow-up for early detection of jaundice. Further multicenter studies with larger and more diverse populations are required before these findings can be applied to broader clinical protocols or discharge policies.

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Conflict of Interest

There is no conflict of interest

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Original Article

From Paper to Precision: A Systematic Review on Digital Technologies for Improving the Quality of Childhood Growth Monitoring

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Abstract:

Background: Childhood growth monitoring is essential for detecting malnutrition and growth disorders. However, traditional paper-based methods are prone to errors, incompleteness, and fragmentation. Digital technologies have emerged as potential tools to enhance efficiency of growth monitoring. This systematic review aims to synthesize evidence on the benefits and challenges of implementing digital technologies for growth monitoring in children.

Methods: A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was conducted across multiple databases. Eligible studies evaluated digital interventions such as mobile health applications with automated anthropometric calculations, computer-based growth monitoring integrated into the electronic health record, and chatbot-based reporting systems. Data were extracted on study design, population, technology features, and outcomes related to data and implementation.

Result: Seven studies were analyzed, representing over 50,000 child growth assessments and involving approximately 400 frontline health workers. Digital technologies improved the completeness, accuracy, and timeliness of data collection. Automation reduced human error, supporting more consistent interpretation of nutritional status, earlier detection and reporting of inadequate growth, along with improved nutritional outcomes. These technologies were highly accepted by frontline health workers for their ability to simplify complex tasks. However, most challenges arose from constraints in digital infrastructure and uneven technology implementation across healthcare facilities.

Conclusion: Digital technologies can transform growth monitoring from a manual, error-prone process into a precise and scalable system for early detection of malnutrition. Addressing challenges is essential for successful implementation and scale-up in health systems.

Keywords: anthropometry, child growth, health information systems, mobile health, pediatric growth assessment

Introduction

Optimal growth monitoring in childhood is a cornerstone of pediatric nutrition and essential for the early detection of malnutrition and weight faltering.[1] In 2024, an estimated 150.2 million (23.2%) children under five globally were stunted and 42.8 million were wasted; in Indonesia, the national stunting prevalence remained high at 19.8%.[2,3] Accurate anthropometric assessment enables timely nutritional interventions and prevents long-term adverse outcomes, including impaired cognitive development, increased morbidity, and mortality.[1]

However, child growth extends beyond nutritional status alone and reflects a complex interplay of biological and environmental factors, including genetic potential, fetal health, endocrine regulation, chronic infection, physical activity, and broader influences such as socioeconomic conditions and family environment.[4-7] The Infant–Childhood–Puberty model further illustrates this complexity by describing growth as overlapping phases, each governed by different biological mechanisms. Growth during infancy is primarily influenced by nutritional factors, whereas growth hormone becomes a major regulator during childhood, followed by the synergistic effects of sex steroids and growth hormone during puberty.[5,8] These concepts highlight that growth is not solely determined by nutrition.

In practice, this complexity requires accurate and consistent growth monitoring across different healthcare settings. In Indonesia, growth monitoring is routinely conducted in primary health care and community-based settings. However, in routine field practice, despite the availability of comprehensive tools such as the Maternal and Child Health (KIA) Handbook, community health workers and healthcare providers frequently encounter difficulties in accurately plotting and interpreting growth charts, particularly in the context of high service workloads. Additionally, caregivers often fail to bring the KIA handbook during health visits, resulting in incomplete documentation and limited accessibility of longitudinal growth data. In parallel with these challenges, digital health technologies for child growth monitoring have rapidly evolved in recent years to support more accurate and continuous growth monitoring.[9-15]

Although evidence on digital growth monitoring is expanding, existing studies differ widely in terms of platforms, settings, and reported outcomes. A comprehensive synthesis of the benefits and challenges relevant to routine child health care, including growth monitoring, is therefore needed. This systematic review aims to summarize the advantages and limitations of digital growth monitoring technologies in early childhood to inform their integration into pediatric growth monitoring programs.

Method

Data Sources and Search Strategy

This systematic review was conducted following PRISMA guidelines. A comprehensive search was independently performed by two reviewers using PubMed, Scopus, and Google Scholar databases, without restrictions on publication year up to 7 August 2025. The search strategy applied to these databases was as follows: ("Electronic Health Records"[MeSH] OR "EHR"[tiab] OR "Digital Record"[tiab] OR "eHealth"[tiab] OR "mHealth"[tiab]) AND ("Manual"[tiab] OR "Paper"[tiab] OR "Paper Based"[tiab]) AND ("Anthropometry"[MeSH] OR "Growth Measurement"[tiab] OR "Stunting"[tiab] OR "Failure to Thrive"[tiab] OR "Malnutrition"[tiab]) AND ("Infant"[MeSH] OR "Child"[tiab] OR "Toddler"[tiab]).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) studies involving children undergoing growth monitoring, (2) studies evaluating digital growth monitoring technologies, and (3) studies reporting outcomes related to growth monitoring. Only original primary studies with full-text articles published in English or Indonesian were included.

The exclusion criteria were: (1) non-original publications, including reviews, editorials, protocols, and conference abstracts without primary data, (2) studies that evaluated nutrition-only interventions, and (3) studies involving digital tools not used for child growth monitoring or describing digital growth monitoring tools without empirical evaluation or outcome data.

Eligibility Criteria

All records were managed in Mendeley, with duplicates removed automatically and manually. Two reviewers independently screened titles, abstracts, and full texts, resolving any discrepancies by consensus.

Data Extraction

Data were extracted using a standardized form and organized in a spreadsheet. Extracted variables included author, publication year, country, study design, population and sample size, clinical setting, type of digital growth monitoring intervention, and comparator where applicable. Outcomes related to data quality (accuracy, completeness, timeliness), usability and acceptability, and operational challenges were also collected.

Quality

Methodological quality was assessed using the cohort version of the Newcastle–Ottawa Scale (NOS). NOS was selected because the primary comparison across studies was based on exposure to digital growth monitoring systems. The NOS is flexible and widely applied to non-randomized observational designs, including

implementation studies, allowing an appropriate assessment of selection, comparability, and outcome domains.

Result

The Study Selection

A total of 147 studies were identified. After removing 37 duplicates, 110 studies were screened, with 65 excluded. Forty full-text articles were assessed, and 33 were excluded for ineligible study types or interventions. Seven studies met the inclusion criteria and were included in the final review **(Figure 1**).

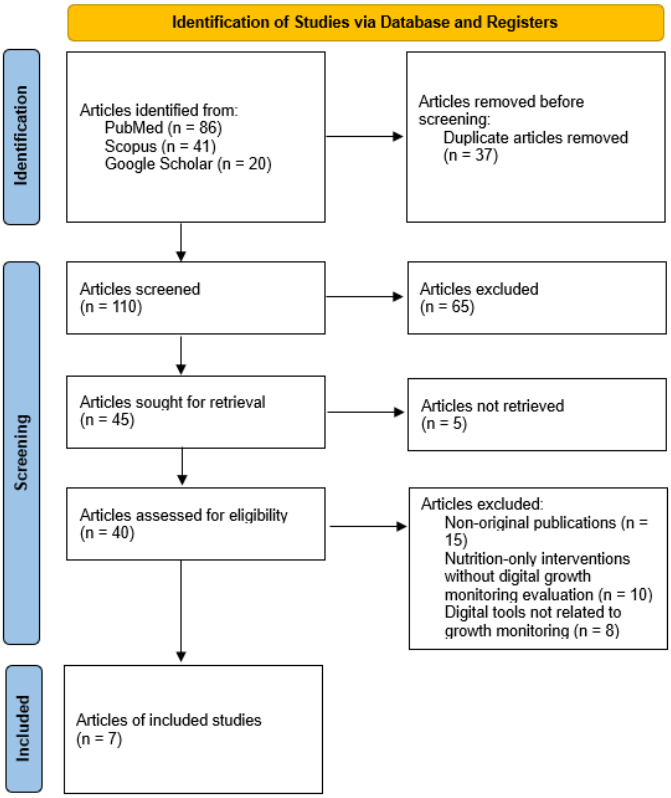

Figure 1. PRISMA flowchart

Quality Assessment

Risk of bias was assessed using NOS, and all included studies demonstrated good methodological quality, with scores ranging from 7 to 9 stars **(Table 1).**

Study Characteristics

The characteristics of the included studies are summarized in **Table 2**. The seven studies were conducted across diverse settings, including community-based, primary care, and hospital contexts in low-, middle-, and high-income countries. Sample sizes varied from small community implementations to large population-based cohorts.

Table 1. Newcastle-Ottawa Scale risk of bias for cross-sectional study

Study	Selection	Comparability	Outcome	Score NOS	Standard AHRQ
Aisyah et al., 2025[9]	★★★	★★	★★	7	Good Quality
Al Rahmad et al., 2024[10]	★★★	★★	★★	7	Good Quality
Nemerimana et al., 2021[11]	★★★★	★★	★★	8	Good Quality
Kana et al., 2020[12]	★★★★	★★	★★	8	Good Quality
Dainty et al., 2018[13]	★★★	★★	★★★	8	Good Quality
Chanani et al., 2016[14]	★★★★	★★	★★★	9	Good Quality
Sankilampi et al., 2013[15]	★★★★	★★	★★★	9	Good Quality

Table 2. Characteristics of included studies

Author, Year	Country – Setting	Study Design	Sample Size	Inter-venion	Control	Result
Aisyah et al., 2025[9]	Indonesia Posyandu—community health posts	Prospective observational descriptive	282 cadres; 4,571 children	WhatsApp-based chatbot for growth data entry	No comparison group	**Completeness:** WhatsApp-based reporting covered 76–90% of children measured at Posyandu, increased over time. **Usability:** Most users reported good usability, with the system perceived as easy to use, variables and data entry flow easy to understand, improved data reporting quality, and adequate user proficiency, including the ability to train peers. **Challenge:** Internet dependence, coverage varied across sites.
Al Rahmad et al., 2024[10]	Indonesia Posyandu	Prospective before–and–after quasi-experimental	123 nutritionists	Mobile-based application for growth monitoring	Month 1 (baseline) measurement with the same digital application	Significant improvements ($p < 0.05$) were observed in completeness (59.8% → 93,8%), timeliness (62.1% →86.6%), accuracy (73.9% → 94.1%), and usefulness (85.0% → 95.9%).

Author, Year	Country – Setting	Study Design	Sample Size	Inter-venion	Control	Result
						Challenge: Implementation required additional training and adaptation for consistent use.
Nemerimana et al., 2021[11]	Rwanda Primary health care	Quasi-experimental	880 infants	Mobile-based application for growth monitoring	Manual growth monitoring is recorded on paper	**Completeness:** Higher completeness of growth monitoring in intervention clinics compared with controls for length-for-age (82% vs 57%), weight-for-age (93% vs 67%), and weight-for-length (90% vs 59%) (all $p \leq 0.001$). **Nutritional outcomes:** Inadequate growth decreased in intervention clinics (59% → 26%) but increased in controls (52% → 56%) ($p < 0.001$); underweight prevalence decreased in intervention clinics (47% → 33%) and increased in controls (30% → 53%) ($p = 0.014$); stunting prevalence decreased in intervention clinics (59% → 44%) and increased in controls (48% → 58%) ($p = 0.041$). **Challenge:** Colour-coded displays without numeric z-scores caused misclassification in borderline cases, resulting in no significant improvement in accuracy.
Kana et al., 2020[12]	Nigeria Tertiary teaching hospital	Prospective observational cohort	3,152 infant records	Computer-based growth monitoring	No comparison group	**Completeness:** Overall data completeness was high (88.5%). **Continuity:** Follow-up attendance declined with age (91.5% at 6 weeks; 77.2% at 10 weeks; 57.8% at 14 weeks; 31.7% at 24 weeks; 22.3% at 36 weeks). Higher maternal education

Author, Year	Country – Setting	Study Design	Sample Size	Inter-venion	Control	Result
						was associated with increased likelihood of follow-up (OR 1.33, 95% CI 1.06–1.51). **Challenge:** Power outages required backup electricity.
Dainty et al., 2018[13]	New Zealand Secondary health care district hospitals	Retrospective observational cohort	8,551 children	Computer-based growth monitoring integrated into the electronic health record	No comparison group	**Completeness:** Entries increased over time (1,962 to 8,407 records); weight was recorded in 98.2%, height in 82.6%, and BMI in 81.5%. **Accuracy:** Very low error rate (0.2%). **Challenge:** Lower uptake in inpatient settings (18.4%) compared with outpatient care (67%), reflecting limited routine inpatient growth measurement.
Chanani et al., 2016[14]	India Community-based home visit	Quasi-experimental crossover	14 frontline health workers; 1,120 child growth assessments	Mobile-based application for growth monitoring	Manual growth monitoring was recorded on paper	**Accuracy:** Error rate reduced from 5.5% (paper-based) to 0.7% (mobile-based) ($p < 0.001$); interrater reliability improved (Cohen's $\varkappa$ 0.79 → 0.97); sensitivity increased (0.79 → 1.00; $p = 0.014$); specificity increased (0.97 → 1.00; $p = 0.002$). **Challenge:** Human errors arising from manual grade selection following automated calculation.
Sankilampi et al., 2013[15]	Finland Primary health care	Quasi-experimental with historical control	32,404 children	Computer-based automated growth monitoring integrated into the electronic health record	Standardized growth monitoring recorded in the electronic health record	**Accuracy:** Higher detection of new growth disorders in the intervention year (0.9 vs 0.1 per 1,000 children; $p < 0.001$); specialist referrals increased (72.7 to 209 annually; $p < 0.001$). **Timeliness:** Reduced diagnostic delay, with earlier

Author, Year	Country – Setting	Study Design	Sample Size	Inter-venion	Control	Result
						identification of abnormal height measurements (median delay 1.79 years). **Challenge:** Increased specialist workload and associated costs due to higher diagnostic yield.

BMI = Body mass index

Discussion

This systematic review summarizes the evidence on digital growth monitoring in childhood and its role in strengthening routine child health care. Digital tools including mobile applications, computer-based records, and WhatsApp-based chatbots were associated with improved growth data recording.[9-15]

In Indonesia, a WhatsApp-based chatbot evaluated by Aisyah et al. simplified data submission by leveraging a platform already familiar to community health cadres, facilitating consistent recording and improving completeness.[9] In Rwanda, Nemerimana et al. demonstrated that mHealth tools with automated growth calculations supported clinical decision-making, which encouraged health workers to complete all required fields so that automated nutritional status interpretations could be generated.[11] Similar patterns were observed in higher-resource settings. In New Zealand, Dainty et al. reported a gradual increase in documentation completeness following the introduction of a digital growth monitoring system that was initially implemented without enforced adoption, allowing health workers to familiarize themselves with its ease of use before routine uptake.[13]

These findings align with broader evidence, a longitudinal German hospital study showing improved documentation completeness across clinical settings after electronic medical record implementation.[16] In line with this, the United Nations Children's Fund and the World Health Organization emphasize the role of digital and mobile health technologies in improving the accuracy, timeliness, and completeness of routine pediatric health data, including growth monitoring.[17]

Beyond data completeness, several studies reported improved measurement accuracy through automated anthropometric calculations and standardized digital plotting. In higher-resource settings, Dainty et al. reported a low error rate in growth assessment using electronic growth charts, supporting more accurate interpretation in routine clinical practice.[13] Sankilampi et al. also reported increased identification of growth disorders and higher referral rates following the implementation of electronic growth charts, highlighting the clinical relevance of improved data precision.[15]

Accurate assessment of child growth requires objective and standardized measures, such as z-scores, which express growth relative to a reference population in standard deviation units.[18] In lower-resource and community-based settings, Chanani et al. demonstrated that mobile-based growth monitoring reduced recording errors during community home visits and minimized variability in performance among community health workers.[14] However, in a low-resource setting, Nemerimana et al. found that nutritional status was initially determined using color-coded visual displays without numeric z-scores, leading to misclassification in borderline cases. Diagnostic accuracy improved only after numeric z-scores were incorporated, underscoring the importance of combining visual aids with precise numerical indicators in digital growth monitoring systems.[11] In addition to underdiagnosis, reliance on imprecise visual tools may also increase the risk of overdiagnosis, as color-coded classifications may not adequately capture individual growth patterns. This is particularly relevant in children older than two years, where normal growth channeling and genetic potential play an important role in growth interpretation, as most children follow a stable growth channel consistent with their genetic potential, termed canalization.[19]

Broader implementation evidence also indicates that mobile applications improve the accuracy of child growth monitoring by automating growth calculations, standardizing chart interpretation, and reducing manual plotting errors. These tools streamline data entry, reduce workload, and enhance the accuracy and reliability of routine growth assessment.[20]

In addition to improvements in completeness and accuracy, several studies reported benefits related to timeliness. Al Rahmad et al. found that digital growth monitoring improved the timeliness of data recording, while Sankilampi et al. showed that electronic growth charts supported earlier detection of growth disorders by reducing diagnostic delays commonly seen with manual systems.[10, 15] Real-time data availability supports faster and more informed clinical decision-making, particularly for time-sensitive conditions.[20, 21] Timely access to growth data enables early detection of weight faltering and timely nutritional intervention during the first 1,000 days of life, which is critical for preventing stunting and supporting optimal growth and cognitive development.[22]

Several studies suggested that ease of use and practicality of digital tools supported their implementation in routine growth monitoring. Digital tools were generally perceived as easier to use than manual growth charts, particularly when calculations and growth interpretation were automated. In community settings, the use of familiar platforms such as WhatsApp-based systems in Indonesia lowered barriers to adoption and supported more consistent data recording.[9] In primary care settings, Al Rahmad et al. described digital growth monitoring as practical for routine anthropometric recording.[10] In community-based settings, where frontline community volunteers with

limited formal health training play a central role in growth monitoring, user-friendly digital tools are essential to support accurate and consistent practice.[23]

Direct nutritional outcomes were assessed by Nemerimana et al., showing that mHealth-supported growth monitoring in rural pediatric clinics was associated with significant reductions in inadequate growth, underweight, and stunting, whereas these indicators increased in control clinics using paper-based monitoring.[11] These findings suggest that digital growth monitoring, when combined with automated growth assessment and decision support, may strengthen the management of weight faltering and contribute to improved nutritional outcomes. Nonetheless, further studies are needed to confirm these effects across settings.

Kana et al. identified limitations in the continuity of growth monitoring despite the use of a digital anthropometric data system, with follow-up attendance declining as children aged. Maternal education was associated with better follow-up, indicating that caregiver-related factors influence continued engagement.[12] Although digital growth monitoring can address practical barriers such as caregivers forgetting to bring paper-based growth records, these findings highlight the need to complement digital systems with caregiver education and supportive strategies to sustain engagement. Qualitative evidence further indicates that caregivers who recognize the importance of growth monitoring and believe it benefits their children are more likely to attend sessions.[24]

Digital records facilitate longitudinal growth assessment through continuous tracking of individual growth trajectories. Long-term evidence links sustained early childhood growth monitoring with improved health, cognitive, and educational outcomes, as well as continued engagement with health services.[25] Beyond individual outcomes, centralized and integrated digital records may strengthen system-level functions by improving data accessibility and supervisory oversight, enabling timely review of data completeness, trend identification, and feedback to health workers.[26]

However, several challenges were identified across studies. Dependence on stable internet connectivity and recurrent power outages disrupted system functionality in some low-resource contexts, requiring additional infrastructure such as backup electricity solutions.[9, 12] Implementation also required training and adaptation, as some health workers needed additional support to use digital systems correctly and consistently.[10, 14] Adoption varied across service settings, reflecting gaps in routine measurement workflows.[9, 13] In addition, higher diagnostic yield in some settings was accompanied by increased specialist workload and additional costs, highlighting the need for adequate system planning to support sustainable scale-up.[15] Taken together, these findings emphasize that successful integration of digital growth monitoring tools requires not only technological readiness but also supportive infrastructure, adequate

workforce capacity, and alignment with existing health system workflows to ensure effective and sustainable use.[27]

Conclusion

Digital growth monitoring shows clear potential to improve the completeness, accuracy, and timeliness of child growth data, thereby strengthening routine child health care. Automated calculations and standardized digital records reduce documentation errors and support more consistent growth assessment across settings. However, implementation challenges related to infrastructure, workforce capacity, workflow integration, and uneven adoption remain. Addressing these system-level constraints is essential to enable effective implementation and sustainable scale-up.

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Conflict of Interest

The authors declare no conflict of interest.

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Case Report

Infantile Liver Failure as the Initial Manifestation of SCYL1-Related CALFAN Syndrome: A Case Report and Literature Review

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Abstract:

Background: CALFAN (Cholestasis, Acute Liver Failure, and Neurodegeneration) syndrome is a rare autosomal recessive disorder caused by biallelic pathogenic variants in SCYL1 (SCY1-like pseudo-kinase 1). It is classically associated with low or normal gamma-glutamyl transpeptidase (GGT) cholestasis, infection-triggered acute liver failure (ALF), and progressive neurodegeneration. Because neurological and skeletal manifestations may be absent during the first hepatic presentation, early diagnosis can be missed unless the hepatic phenotype is recognized.

***Case*:** We describe a 9-month-old female infant born to third-degree consanguineous parents who developed fever-triggered cholestatic jaundice and ALF. Structural biliary disease, viral hepatitis, and common metabolic disorders were excluded. Whole-exome sequencing revealed a homozygous pathogenic nonsense variant in SCYL1 (c.1567C>T; p.Arg523*), consistent with autosomal recessive CALFAN syndrome. No neurological, neuroimaging, or skeletal abnormalities were present at initial presentation. The clinical course was notable for persistent hyperbilirubinemia and a family history of sibling death from infantile liver failure.

***Discussion*:** This case adds to the SCYL1 spectrum by demonstrating isolated infantile ALF without neurological features at presentation, a severe hepatic phenotype with persistent cholestasis, and a novel homozygous null variant in a consanguineous family.

Conclusion: SCYL1 deficiency should be considered in infants with fever-triggered ALF and low/normal-GGT cholestasis, even when neurological and skeletal signs are absent. Early genomic testing, systematic exclusion of low-GGT cholestasis mimics, longitudinal neurological surveillance, timely transplant referral, and recurrence-risk counselling are essential.

Keywords: calfan syndrome, infantile liver failure, SCYL1

Introduction

Cholestasis, Acute Liver Failure, and Neurodegeneration (CALFAN) syndrome is an exceptionally rare autosomal recessive disorder caused by biallelic pathogenic variants in the SCYL1 gene. It is characterized by recurrent episodes of pediatric acute liver failure, low or normal gamma-glutamyl transpeptidase (GGT) cholestasis, and progressive neurodegeneration, with marked phenotypic variability.[1, 2] Acute onset of liver disease without evidence of chronic liver disease with biochemical evidence of severe liver injury, coagulopathy not corrected by vitamin K defined as international normalized ratio (INR) ≥ 1.5 with evidence of hepatic encephalopathy (HE) or INR >2 with or without HE was the defining criteria for ALF.[3]

SCY1-like pseudo-kinase 1 (SCYL1) encodes a protein involved in Golgi-endoplasmic reticulum trafficking. Recent studies have shown that SCYL1 deficiency leads to endoplasmic reticulum stress and increased hepatocellular vulnerability, providing a mechanistic explanation for infection-triggered hepatic decompensation and progressive neurological involvement.[4, 5]

Clinically, SCYL1-related CALFAN syndrome usually presents during infancy or early childhood with episodic cholestatic hepatitis or ALF, often following febrile illnesses or upper respiratory tract infections (URTIs). Liver biochemistry may normalize between episodes, which can delay diagnosis and lead to misclassification as self-limited viral hepatitis. Neurological manifestations-including developmental delay, tremor, peripheral neuropathy, optic atrophy, and cerebellar atrophy-may emerge later in childhood or adolescence.[1, 2, 6]

CALFAN syndrome is exceedingly rare, with fewer than 25 reported cases worldwide to date. Because it overlaps clinically with other causes of low/normal-GGT cholestasis, particularly progressive familial intrahepatic cholestasis (PFIC), bile acid synthesis defects, neuroblastoma amplified sequence (NBAS) related recurrent acute liver failure (ALF), and mitochondrial hepatopathy, so early genetic testing is essential for diagnosis, management, and genetic counselling.[2, 6-8]

Case

A 9-month-old female infant born to parents in a third-degree consanguineous marriage was admitted for evaluation of cholestatic jaundice and liver dysfunction. She was born at term by normal vaginal delivery, with no history of neonatal intensive care unit admission. The mother was hepatitis B surface antigen (HBsAg) positive; however, the infant received hepatitis B immunoglobulin and appropriate hepatitis B vaccination at birth.

At 9 months of age, the child developed an acute febrile illness lasting three days, associated with upper respiratory tract symptoms. Four days after the onset of fever, the child developed jaundice with high-colored urine and pigmented stool (stool color chart 5-6).

There was no history of bleeding manifestations, ecchymotic patches, seizures, or altered sensorium. Mild pruritus developed two days after hospitalization. On examination, the child was icteric and undernourished. Anthropometry revealed severe wasting and stunting, with weight 6 kg (Z-score −3.15), length 66 cm (Z-score −2.72), weight-for-length Z-score −3.09, and preserved head circumference of 45 cm (Z-score −0.15). Developmental milestones were appropriate for age. Abdominal examination revealed hepatomegaly, with the liver palpable 3 cm below the right costal margin, soft in consistency; the spleen was not palpable.

Initial evaluation revealed significant liver dysfunction with total bilirubin of 14 mg/dL (direct 10.6 mg/dL) and markedly elevated aminotransferases (AST 1513 IU/L, ALT 348 IU/L). GGT was within the age-appropriate range (109 IU/L). Serum albumin was preserved (3.94 g/dL). Coagulation studies showed a prolonged INR of 3.56, which was not responsive to parenteral vitamin K. Complete blood count demonstrated anemia with leukocytosis.

Etiological evaluation showed normal thyroid function, negative viral serologies (hepatotropic viruses, Epstein-Barr virus (EBV), cytomegalovirus (CMV), Human herpesvirus 6 (HHV-6), Adenovirus, and human immunodeficiency virus (HIV)), normal immunoglobulin levels, and a negative sepsis screen. Serum bile acids were raised (214umol/L). Serum alpha-fetoprotein, ammonia, lactate, and creatine phosphokinase (CPK) were within normal limits. The lactate/pyruvate ratio was 15:1, which was normal, and the acylcarnitine profile was within normal limits. Ultrasonography of the abdomen showed an altered echotexture and hypoechoic with enlargement of the liver (8.4cm). No dilatation of the intrahepatic biliary tree and common hepatic duct. The gallbladder showed a normal lumen (length 21mm) with a normal wall. The common bile duct (CBD) was normal, 1.8mm. Portal vein diameter was 5.7mm and hepatic veins were normal. The spleen was normal (size 5.5cm). No ascites was seen **(Figure 1)**.

The family history was significant for a sibling who had died in infancy due to liver failure without any identified etiology. Given the combination of normal-GGT cholestasis, fever-triggered hepatic dysfunction, consanguinity, and sibling death from liver disease, a genetic etiology was suspected. Whole-exome sequencing (WES) identified a homozygous pathogenic nonsense variant in the SCYL1 gene (c.1567C>T; p.Arg523*; NM_020680.4), located in exon 11. This variant was classified as

pathogenic according to ACMG criteria and was associated with autosomal recessive CALFAN syndrome.

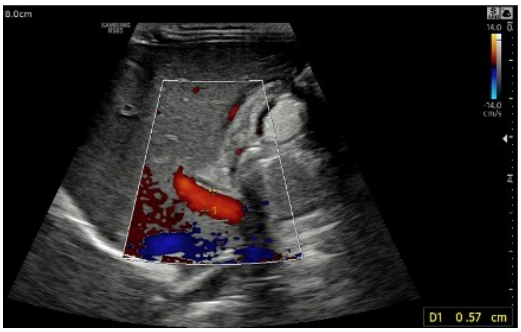

Figure 1. Abdominal ultrasonography showing hepatomegaly with altered liver echotexture. No intrahepatic biliary dilatation, gallbladder abnormality, or ascites is seen.

Imaging evaluation, including skeletal survey and brain magnetic resonance imaging (MRI), revealed no neurological or skeletal abnormalities at presentation. The child was managed conservatively with supportive care, including nutritional rehabilitation with calorie supplementation of 150-180kcal/kg/day, a protein target of 2-3g/kg/day, medium chain triglyceride (MCT)-containing feeds along with night feeds. She also received fat-soluble vitamin supplementation (vitamins A, D, E, and K), parenteral vitamin K for coagulopathy, ursodeoxycholic acid at 20 mg/kg/day, symptomatic treatment for pruritus with antihistamines, and close monitoring with prompt treatment of intercurrent infections. Coagulopathy gradually resolved with supportive management during hospital stay and INR was 1.1 at discharge. However, bilirubin showed an increasing trend, with total/direct bilirubin rising from 14/10.6 mg/dL at presentation to 16/13.5 mg/dL during hospital stay. The family was counselled regarding the risk of recurrent hepatic crises, the need for early liver-transplant evaluation if hepatic dysfunction persisted or recurred, possible future neurological deterioration, and recurrence risk in future pregnancies. Bilirubin trend remained static in follow-up with total/direct bilirubin-13.8/9.6 mg/dL without any further episodes of ALF. The patient remains under close follow-up for growth, liver function, and surveillance for potential neurological manifestations, with a current follow-up duration of 6 months.

Diagnostic Evaluation and Exclusion of Differential Diagnoses

The diagnostic approach was guided by the presence of infantile ALF with cholestasis and normal/low GGT. Structural biliary disease was unlikely because the infant had pigmented stools, a normal-sized gallbladder and CBD, and no sonographic evidence of biliary obstruction. Viral hepatitis and systemic infection were excluded by negative hepatotropic and non-hepatotropic viruses (EBV, CMV, HHV-6, Adenovirus) and sepsis screen. PFIC was considered because of low/normal-GGT cholestasis,

pruritus, raised serum bile acid levels; however, the acute fever-triggered liver failure, consanguinity, sibling death, absence of a typical PFIC phenotype at presentation, and diagnostic SCYL1 variant supported CALFAN syndrome. Bile acid synthesis defects were considered, but were less likely because serum bile acids were raised. Mitochondrial hepatopathy was evaluated by serum lactate, lactate/pyruvate ratio (15:1), ammonia, creatine phosphokinase, and acylcarnitine profile; these did not support a primary mitochondrial or fatty-acid oxidation disorder.[9]. Recurrent ALF associated with mutations like NBAS, Leucyl-tRNA Synthetase 1(LARS 1), tRNA mitochondrial 2-thiouridylase (TRMU) was considered in view of fever-triggered episode and WES identified a pathogenic homozygous SCYL1 variant explaining the phenotype **(Figure 2)**.

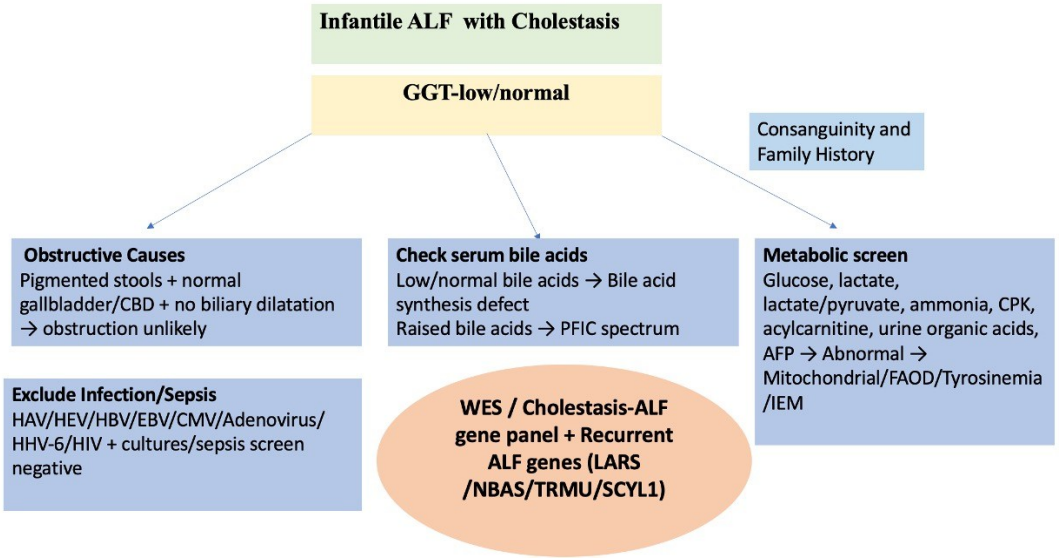

Figure 2. Diagnostic algorithm for infantile acute liver failure with low/normal-GGT cholestasis.

ALF = acute liver failure; GGT = gamma-glutamyl transferase; CBD = common bile duct; HAV = hepatitis A virus; HEV = hepatitis E virus; HBV = hepatitis B virus; EBV = Epstein–Barr virus; CMV = cytomegalovirus; HHV-6 = human herpesvirus 6; HIV = human immunodeficiency virus; PFIC = progressive familial intrahepatic cholestasis; CPK = creatine phosphokinase; AFP = alpha-fetoprotein; FAOD = fatty acid oxidation disorder; IEM = inborn error of metabolism; WES = whole-exome sequencing; LARS = leucyl-tRNA synthetase 1; NBAS = neuroblastoma amplified sequence; TRMU = tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase; SCYL1 = SCY1-like pseudokinase 1.

Discussion

The SCYL1 gene encodes SCY1-like pseudokinase 1, a ubiquitously expressed protein involved in coat protein complex I (COPI)-mediated retrograde trafficking between the Golgi apparatus and endoplasmic reticulum (ER), with a critical role in neuronal

integrity and hepatocellular homeostasis.[4] Loss of SCYL1 impairs COPI-dependent retrograde transport, leading to intracellular accumulation of secretory and membrane proteins, chronic ER stress, and activation of the unfolded protein response. During periods of increased metabolic demand, such as intercurrent infections, this adaptive response may become maladaptive, progressing to hepatocellular apoptosis. A similar vulnerability of cerebellar Purkinje cells likely accounts for progressive neurological involvement in older patients, providing a unifying mechanistic explanation for the combined hepatic-neurological phenotype.[4, 5]

The present case adds clinically useful information to the reported SCYL1 spectrum. First, the disease presented as isolated infantile ALF without neurological, neuroimaging, or skeletal abnormalities. Second, the hepatic phenotype was severe, with persistent cholestasis after the first recognized febrile trigger rather than complete inter-episodic normalization. Third, a homozygous null SCYL1 variant (c.1567C>T; p.Arg523*) in a consanguineous family. Fourth, the family history of sibling death from infantile liver failure suggests that some families carrying null SCYL1 variants may have reduced hepatic reserve and a more aggressive early hepatic course. Therefore, the absence of neurological findings at the first presentation should not delay SCYL1 testing when the hepatic phenotype is compatible.

Pathogenic variants in SCYL1 were initially described in 2015 as the cause of autosomal recessive spinocerebellar ataxia type 21 (SCAR21; OMIM #616719), characterized predominantly by progressive neurodegeneration.[1] Subsequent reports expanded the phenotypic spectrum to include a prominent hepatic presentation, leading to recognition of CALFAN syndrome, defined by low/normal-GGT cholestasis, recurrent acute liver failure, and anticipated neurodegeneration.[2, 6-8] Most reported cases involve homozygous pathogenic variants, frequently in settings of consanguinity, whereas compound heterozygosity has also been documented. Marked inter- and intrafamilial variability has been reported, including differences in the age of hepatic onset—most commonly during infancy—the frequency of hepatic crises, neurological progression, and the need for liver transplantation.[6-8, 10, 11] **(Table 1)**.

The genotype-phenotype correlation remains incomplete. Truncating/null variants, including p.Arg 523*, plausibly result in marked loss of protein function, but published cases show that genotype alone does not fully predict outcome. Kazem et al. reported variable severity of the hepatic phenotype among affected members of the same family carrying the same mutation **(Table 1)**.[6] Environmental triggers such as fever/URTI, diarrhea, nutritional state, age at first decompensation, and modifier genes may influence severity. In the present family, the proband and a deceased sibling with infantile liver failure support a severe familial hepatic phenotype. This observation should be interpreted cautiously because sibling molecular confirmation was not

available; nevertheless, it strengthens the need for genetic counselling and prenatal/preimplantation options in future pregnancies.

Clinically, SCYL1-related liver disease has classically been described as episodic, with normalization of liver biochemistry between episodes of ALF or cholestasis. This pattern, reported in early cohorts, often led to diagnostic delays as transient improvement was misattributed to self-limited viral hepatitis. However, accumulating evidence indicates that hepatic involvement can follow a more aggressive or progressive course in some patients requiring liver transplantation, with no reports of graft failure post liver transplant.[2, 7, 11]

Table 1. Genotypic and phenotypic characteristics of patients with CALFAN syndrome

Study	Gender / No of patients	SCYL1 Variant	Clinical Features - **Hepatic Features (Age of onset).** - **Neurological Features (Age of onset)** - **Skeletal Features (Age of onset)**	Treatment / Outcome
Schmidt et al., 2015[1]	1 Male & 2 Female	Compound heterozygosity family1: gene deletion (Exon 2) family2: frameshift mutation (Exon 8)	- Recurrent low-GGT cholestasis, ALF (early infancy) - Delayed motor milestones, tremors, ataxia (variable) - Scoliosis, joint contractures	Supportive care/ survived
Incecik et al., 2018[12]	1 Female	Homozygous/ Exon 1: C.1420C>T	- Recurrent cholestasis (9 months) - Delayed motor development, mild learning disability, ataxia (infancy) - No skeletal features	Supportive care/ survived
Lenz et al., 2018[8]	7 Patients (5 families)	SCYL1 variants (missense, nonsense, splice-site)	- Recurrent cholestasis, low-GGT, transient liver failure (infancy) - 1/7 Seizures, 6/7 microcephaly, 4/7 motor dysfunction (infancy), 2/7 cerebellar atrophy - 5 out of 7 had skeletal features (short stature, failure to thrive, lumbar lordosis, hip dysplasia, clefting of ribs	Liver transplant in one patient at 23 months of age and satisfactory post-transplant course. Other patients were on supportive care/ all survived
Li et al., 2019[7]	1 Female	Homozygous /Exon 1/ Homozygous SCYL1 exon 1 (NM_020680): c.92_93insGGGC	- Recurrent low-GGT cholestasis, three ALF episodes (14 Months) - Developmental delay, cerebellar ataxia (later childhood)	Supportive care/ survived

Study	Gender / No of patients	SCYL1 Variant	Clinical Features - Hepatic Features (Age of onset). - Neurological Features (Age of onset) - Skeletal Features (Age of onset)	Treatment / Outcome
		CCT, p.(H32Gfs*20)	- Bilateral femoral head necrosis, bilateral hip joint dysplasia	
Shohet et al., 2019[13]	1 Male & 2 Female	homozygous/ exon 4: c.459C>T p. (Gly153Gly)	- Recurrent cholestasis (onset at 5 months) - Pt 1: Developmental delay Pt 2: Motor deterioration - Pt 1: Abnormal thoracic vertebrae Pt 2: Short stature, delayed bone age, small, femoral epiphyses	Supportive care/ survived
Chavany et al., 2020[14]	1 Male	Compound heterozygous: (c.2356_2357insGA p.) (c.1386 + 1G > A	- Recurrent ALF episodes (infancy) - No neurological features - No skeletal features	Supportive care/ survived
Campos et al., 2020[15]	1 Female	Exon 12, homozygosity: c.1636C>T (p.Gln546*)	- ALF (at 13 months) - Tremors and apathy (28 months), severe tremors (6 years), cerebellar ataxia - None	Supportive care/ survived
McNiven V et al., 2021[11]	1 Male and 1 female	pt 1: Exon 3, 7–8, compound heterozygous: (c.399delC; p.Asn133Lysfs*136)	- Pt 1: Recurrent ALF (4 Months). Pt 2: Severe ALF (5 Months) - GDD, cognitive decline, hypotonia, motor weakness, tremors, cerebellar signs Pt 1: 18 months. Pt 2: Age of onset not defined - Short stature, scoliosis, abnormal chest shape, lumbar spine abnormalities	Liver transplant Pt 1:21 months age (diagnosed at 13 years) Pt 2:7 months old (diagnosed at 9 years) Both siblings had satisfactory post-LT courses
Isa et al., 2023[16]	1 Male	Homozygous/ Exon 7: (NM_020680.4):c.895A>T (p.lys299Ter)	- Recurrent cholestasis, three episodes (2 years 8 months) - Intellectual disability, motor delay (toddlerhood) - None	Supportive care/ survived
Youssef et al., 2023[2]	1 Female	Exon 8/ compound heterozygous: c.937delG and c.1509 1510delTG	- Recurrent cholestasis, 3 ALF episodes (9 months) - Mild deficits; progressive ataxia (post-transplant) - None	Liver transplant (at 20 years of age) and satisfactory results

Study	Gender / No of patients	SCYL1 Variant	Clinical Features - **Hepatic Features (Age of onset).** - **Neurological Features (Age of onset)** - **Skeletal Features (Age of onset)**	Treatment / Outcome
Kazem et al., 2025[6]	1 Male and 1 female	Exon11 Homozygous SCYL1 (NM_020680.4):c. 1386+1G > A. (in both siblings)	- Pt 1: Recurrent cholestasis, ALF (16 months) Sibling 2: Asymptomatic - Pt 1: Mild developmental delay; Sibling 2: Normal - None	Supportive care/ survived
Suenera et al., 2025[10]	1 Female	Exon 6/ homozygous: frameshift mutation, c.745_746insG p.lys249ArgisTer58	- Recurrent cholestasis (8 months) - Fine tremors (1 year), developmental delay - None	Supportive care/survived
Present case	Female	Homozygous SCYL1 c.1567C>T (p. Arg523*) nonsense variant	- Fever-triggered infantile ALF (9 Months), sibling death - None at presentation - None at presentation	Supportive care/survived

ALF = acute liver failure; GDD = global developmental delay; GGT = gamma-glutamyl transpeptidase; LT = liver transplant

Low-to-normal GGT cholestasis remains a key diagnostic feature of CALFAN syndrome. Recognition of this biochemical signature is crucial in infants with febrile illness-triggered ALF, especially when associated with consanguinity, family history of unexplained infantile liver failure, pigmented stools, absent biliary obstruction, and negative viral/metabolic evaluation. In such cases, targeted cholestasis with ALF panels or rapid WES should be considered early rather than after repeated hepatic crises.

Liver biopsy findings in SCYL1-related disease are nonspecific and may include variable portal/lobular inflammation, fibrosis, cholestasis, steatosis, and giant-cell hepatitis.[2, 8, 11, 15] In our patient, a liver biopsy could not be performed because of significant coagulopathy. The absence of a biopsy did not preclude diagnosis because the clinical phenotype and homozygous pathogenic SCYL1 variant provided molecular confirmation.

Neurological Evolution and Surveillance

Neurological involvement is a defining but evolutionary component of SCYL1 disease. Progressive cerebellar ataxia, tremor, hypotonia, peripheral neuropathy, optic atrophy, seizures, microcephaly, and variable cognitive impairment have been documented, often emerging after recurrent hepatic decompensations or later in

childhood.[12, 13, 16] Importantly, neurological manifestations may be absent in early infancy, as in our patient, who had normal development and normal brain MRI at presentation. A normal initial neurological examination should therefore be viewed as a baseline, not as evidence against CALFAN syndrome.

After diagnosis, follow-up should include periodic developmental assessment, neurological examination for tremor/ataxia/hypotonia, assessment for peripheral neuropathy when age-appropriate, ophthalmic evaluation for optic nerve involvement, and repeat neuroimaging if symptoms emerge. This counselling is particularly important before liver transplantation because transplantation may stabilize the hepatic disease, but is not expected to prevent later neurological progression.[2]

Beyond the hepatic–neurological axis, extrahepatic manifestations-particularly skeletal abnormalities-further broaden the phenotypic spectrum of CALFAN syndrome. Skeletal findings reported across cohorts include short stature, failure to thrive, scoliosis, vertebral anomalies, hip dysplasia, and delayed bone age.[1, 7, 8, 11] The absence of skeletal involvement in our patient, as well as in several other reported cases, suggests that these features may be age-dependent or influenced by genotype-specific modifiers. Given their reported frequency, routine longitudinal orthopedic assessment is advisable in all affected individuals.

Management of CALFAN syndrome remains largely supportive, focusing on nutritional optimization, fat-soluble vitamin supplementation, cholestasis/pruritus management, prevention and early treatment of intercurrent infection, and close monitoring of bilirubin, INR, transaminases, glucose, ammonia, and encephalopathy.[2, 8]

Referral for liver transplantation should be considered early when there is persistent synthetic dysfunction, recurrent ALF, worsening cholestasis despite supportive care, failure to thrive due to chronic cholestasis, or inability to maintain hepatic stability between infections.[2, 7, 11] In SCYL1 disease, transplantation may reduce hepatic crises and stabilize liver function, but families must be counselled that neurological progression can still occur because the disorder is multisystemic. Therefore, transplant decisions should be individualized and made jointly by hepatology, transplant surgery, neurology, genetics, nutrition, and the family.

This mutation has not been described previously in the literature and only one case has been reported from India till now. Our patient has been under close follow-up for the last 6 months. The family was advised to seek early medical care during febrile illnesses, maintain adequate nutrition and hydration, avoid unnecessary hepatotoxic medications, and continue serial liver and neurological monitoring. Genetic

counselling was provided regarding autosomal recessive inheritance and recurrence risk.

Conclusion

SCYL1-related CALFAN syndrome should be suspected in infants with fever-triggered ALF and low/normal-GGT cholestasis, particularly when there is consanguinity or a family history of unexplained infantile liver failure. The present case emphasizes that neurological and skeletal manifestations may be absent at first presentation, and that a severe hepatic course with persistent cholestasis can occur. Early genomic testing, systematic exclusion of low-GGT cholestasis differentials, proactive nutritional and infection-related supportive care, timely transplant referral for persistent severe hepatic dysfunction or recurrent ALF, and long-term neurological surveillance are the key practical lessons from this case.

Acknowledgement

Written informed consent has been obtained from the patient

Conflict of Interest

None to disclose

Funding Statement

None

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Case Report

Successful Diagnosis and Management in 28-Week Preterm Infant with Gastrointestinal Perforation - A Case Report

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Abstract:

Background: Gastrointestinal perforation (GIP) is a serious cause of neonatal mortality, particularly in very preterm and very low birth weight infants. Despite surgical treatment, mortality remains high. The aim of this study was to report our hospital's intensive care and surgical experience in managing gastrointestinal perforation among very preterm and very low birth weight infants.

***Case*:** A 980-gr female baby was delivered by caesarean section at 28-weeks of gestation due to maternal severe pre-eclampsia and premature rupture of membranes. She developed respiratory distress syndrome and was admitted to the Neonatal Intensive Care Unit (NICU). On the fourth day of life, she developed an acute abdomen and an abdominal X-ray showed pneumoperitoneum. Emergency surgery revealed gastric perforation. Primary repair of the gastric and omental patch was performed. She passed the critical period after surgery and improved. The baby recovered well and was discharged in good condition.

***Discussion*:** In this case, the risk factor of gastrointestinal perforation is associated with asphyxia. Early diagnosis and treatment increase the survival rate in this patient. Postoperative nutrition plays a vital role in the recovery of neonates with gastrointestinal perforation. The transition to enteral feeding must be gradual and individualized, as these infants often face feeding intolerance due to surgical stress, hemodynamic instability, and intestinal inflammation.

Conclusion: Early diagnosis, prompt surgical intervention, and careful postoperative nutritional management are essential to improve survival in preterm infants with gastrointestinal perforation.

Keywords: gastrointestinal perforation, preterm, rupture gastric, surgery

Introduction

Gastrointestinal perforation (GIP), a rare condition in preterm neonates, appears as an important reason for mortality during the neonatal period, with reported high prevalence ranging from 15 - 70%.[1] Risk factors of gastrointestinal perforation may be varied, such as iatrogenic, Necrotizing Enterocolitis (NEC), prematurity, fetal bradycardia, low birth weight, use of nasal Continuous Positive Airway Pressure (CPAP), use of orogastric tube, perinatal hypoxia, who have required resuscitation, hyperpressure in the gastric chamber, and treatment with indomethacin or dexamethasone. Some studies suggested the insertion of a peritoneal drain as a bridging procedure for surgery to gain some health and stability of the newborn, especially in low-birthweight and very low birth weight neonates who cannot tolerate the impact of surgery.[2] Studies have reported no significant difference in mortality between infants treated with laparotomy or peritoneal drain placement when the diagnosis was NEC.[1]

The current standard treatment of neonates with intestinal perforation is surgery. Despite surgical intervention, the mortality rate remains significantly high, with an incidence reached 49%, in very low birth weight and low birth weight neonates with intestinal perforation.[3] Postoperative complications may also cause morbidity and mortality, despite early diagnosis and treatment.[4]

Asphyxia at birth in infants with low Apgar scores is particularly likely to lead to gastrointestinal perforation. Redistribution of blood flow during hypoxia, hypovolemia, or other stress states, with shunting away from mesenteric vascular beds, is thought to result in microvascular injury and subsequent loss of mucosal integrity.[5]

The first signs of spontaneous gastric perforation often occur at 3 to 5 days of life. Abdominal distention is frequently abrupt and rapidly progressive. Signs of hypovolemia and decreased perfusion are usually present, manifested by tachycardia and lethargy. Respiratory difficulty from massive pneumoperitoneum may be the first sign. Infants born of pregnancies complicated by abruptio placentae, placenta previa, and amnionitis (severe fetal distress) and infants delivered by emergency cesarean section are at increased risk and should be carefully observed. Most infants with gastric perforation have evidence of free air on abdominal radiographs.[6]

We present a case of gastrointestinal perforation with pneumoperitoneum in a very preterm neonate, who was successfully treated at our hospital.

Case

A female infant weighing 980 g was delivered by caesarean section at 28 weeks' gestation due to maternal severe pre-eclampsia and prolonged premature rupture of membranes (>12 hours). A complete course of antenatal corticosteroids had been

administered prior to delivery. At birth, the infant exhibited clinical features of respiratory distress syndrome, including tachypnoea and chest retractions. The Apgar scores were 3, 5, and 7 at 1, 5, and 10 min, respectively.

The infant required immediate admission to the Neonatal Intensive Care Unit (NICU), where initial stabilization was performed. Respiratory support was initiated with CPAP at a positive end-expiratory pressure (PEEP) of 7 cmH_2O, fraction of inspired oxygen (FiO_2) of 25%, and flow rate of 8 L/min. The heart rate remained >100 beats/min during stabilization. Exogenous surfactant therapy was not available at the referring hospital. There were no documented pathological cardiotocography findings prior to delivery, and umbilical artery doppler studies were not available. Cord blood gas analysis was not performed; therefore, the degree of perinatal hypoxia could not be definitively quantified. However, clinical signs, including tachycardia and hypotension, suggested possible transient hypoperfusion, a recognized risk factor in very preterm infants. Early minimal nutrition was given within 24 hours of life in the form of oral care using breast milk.

On the fourth day of life, the infant developed a progressive abdominal distention and signs of an acute abdomen **(Figure 1)**. An abdominal radiograph showed free intraperitoneal air consistent with pneumoperitoneum **(Figure 2)**. The infant was transferred to our hospital for further management. Based on the infant's instability and radiographic findings, an immediate surgery was performed with a pediatric surgeon. Intraoperative exploration revealed a single gastric perforation located in the fundus extending from the lesser of curvature to greater curvature, with clean margins **(Figure 3)**. There is no evidence of intestinal necrosis, congenital muscular defect, or distal obstruction. Primary gastric repair with an omental patch was successfully performed. Postoperatively, the baby required mechanical ventilation, broad-spectrum antibiotics, and total parenteral nutrition (TPN). Nutritional management included glucose, amino acids, lipids, electrolytes, and vitamins, with total fluid requirements carefully adjusted according to clinical status. She passed the critical period after surgery and improved; she was extubated on the seventh day after the operation. Parenteral nutrition is necessary during the postoperative period, neonatologist and pediatric surgeon agreed to give adequate parenteral nutrition before the enteral nutrition is given. A trial feed was well tolerated and was slowly increased until full feeds. The baby was discharged and is doing well on follow-up **(Figures 4 and 5)**.

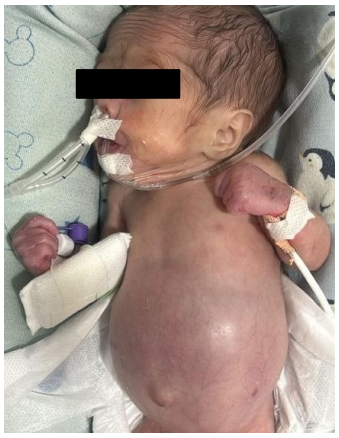

Figure 1. The baby with abdominal distension

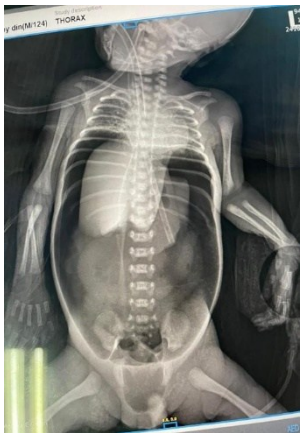

Figure 2. Radiographs revealing a pneumoperitoneum

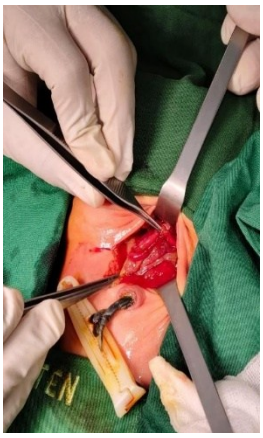

Figure 3. Intraoperative found a gastric rupture

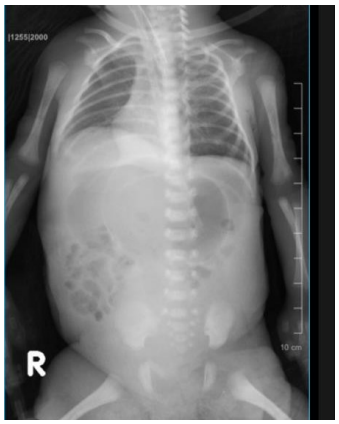

Figure 4. Radiographs 1 day after surgery

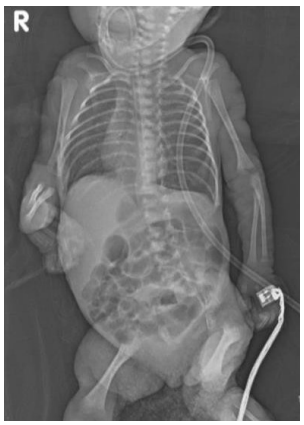

Figure 5. Radiographs 10 day after surgery

Discussion

This case demonstrated a successful diagnosis and management of gastric perforation in a very preterm infant, a condition associated with high mortality despite advances in neonatal care. The major risk factors in this infant included extreme prematurity, very low birth weight, respiratory distress syndrome, and physiological instability during early postnatal adaptation. In this case, the absolute indication for operative intervention was findings a pneumoperitoneum on an abdominal photograph. The indication for surgery is also associated with the best outcome.

Gastrointestinal perforation is a major life-threatening complication in preterm infants, with high morbidity and mortality.[5] It is associated with prematurity, low birth weight, asphyxia at birth or placement of an orogastric tube, ischemia, and exposure to indomethacin or dexamethasone.[1] In our case, the baby was premature, asphyxia at birth, and very low birth weight. The incidence of GIP increases with decreasing gestational age, and the median age of onset is seven days, with a range of 0-15 days.

That implies that GIP usually presents earlier in life, with varying risk factors according to the time of presentation. In comparison, NEC occurs later, usually after the introduction of feeds.

It is important to differentiate neonatal gastric perforation from spontaneous intestinal perforation (SIP) and NEC, as their pathophysiology and risk factors differ significantly. NEC is characterized by intestinal inflammation and necrosis, frequently accompanied by pneumatosis intestinalis and portal venous gas. SIP, in contrast, usually presents within the first week of life as an isolated intestinal perforation, most commonly involving the terminal ileum without surrounding necrosis or significant inflammation. In our patient, intraoperative findings revealed a localized gastric wall perforation without evidence of intestinal necrosis, pneumatosis intestinalis, portal venous gas, or diffuse inflammatory involvement characteristic of NEC. The anatomical location and absence of small intestine involvement also excluded SIP.

The most common cause of neonatal gastric perforation is congenital dysplasia of the muscular layer of the gastric wall, which typically occurs early after birth. The defect is usually localized in the anterior wall of the stomach body. Unlike NEC, gastric rupture is characterized by a large amount of free intraperitoneal air and rapid clinical deterioration due to peritonitis and sepsis.[7] Differences between NEC, SIP, and GIP are presented in **Table 1**.

Diagnosis of gastrointestinal perforation is confirmed by radiographic evidence of pneumoperitoneum. In low-resource settings, differentiation relies heavily on clinical presentation, timing of onset, radiographic findings, and intraoperative evaluation, as advanced imaging and histopathology may not be readily available.[12] A newborn with spontaneous gastrointestinal perforation and peritonitis may initially present with feeding intolerance and physiological instability, including lethargy, temperature instability, recurrent apnea, bradycardia, and delayed capillary refill. Progressive abdominal rigidity, absent bowel sounds, and signs of sepsis strongly suggest intra-abdominal viscus perforation.[13] Operative management remains the accepted treatment for neonates with pneumoperitoneum due to gastrointestinal perforation. Although some infants with medical NEC may initially be managed conservatively, pneumoperitoneum on abdominal radiograph is generally considered an absolute indication for surgical intervention. In some very low birth weight infants who are hemodynamically unstable, primary peritoneal drainage may be considered as a temporizing measure. Early recognition and timely surgical intervention were crucial to achieving a favorable outcome in this high-risk preterm infant.[9] The only absolute indication for operative intervention is pneumoperitoneum on an abdominal radiograph.[14]

Table 1. Differences between NEC, SIP, and GIP [8-11]

	NEC	SIP	GIP
Definition	Inflammatory bowel disease with ischemic and necrosis	Isolated focal intestinal without presentation	Perforation anywhere in the GI tract
Site	Small intestine	Terminal ileum	Gastric, or GI segments
Timing	Later, often after enteral feeding starts	Early, first week of life	Very early, often the first days of life
Population at risk	Preterm infants, especially low birth weight	Extremely preterm, ELBW/VLBW infants	Preterm infants, birth stress, unstable neonates
Main risk	Prematurity, formula feeding, sepsis, dysbiosis	Prematurity, indomethacin, steroids, hypotension	Prematurity, asphyxia, ischemia, positive pressure ventilation, orogastric tube trauma, congenital muscular defect
Pathology	Diffuse intestinal inflammation with necrosis	Small isolated hole with healthy surrounding bowel	Gastric wall rupture/perforation
Necrosis	Yes, common	Yes, common	No
Radiograph	Dilated bowel, pneumatosis, portal venous gas, and free air if perforated	Free intraperitoneal air	Often massive pneumoperitoneum
Clinical presentation	Feeding intolerance, distension, bloody stool, sepsis	Abdominal distension	Sudden distension, tense abdomen, rapid collapse
Operative findings	Necrotic/inflamed bowel	Solitary ileal perforation, viable bowel	Hole in the stomach wall
Management	Medical + surgery if perforation/necrosis	Surgery or drainage, depending on stability	Urgent surgical repair
Prognosis	Significant morbidity and mortality	Variable, often better than NEC	High mortality if delayed

NEC = Necrotizing Enterocolitis; SIP = Spontaneous Intestinal Perforation; GIP = Gastrointestinal Perforation; GI = Gastrointestinal; ELBW = Extremely Low Birth Weight; VLBW = Very Low Birth Weight

Alternative management depends on diagnosis and clinical stability. While laparotomy remains definitive treatment for neonatal gastric perforation, primary neonatal drainage may be considered in extremely preterm or unstable infants as a temporizing measure when immediate surgery is not feasible. In infants with NEC without perforation, conservative management with bowel rest, gastric decompression, intravenous antibiotics, parenteral nutrition, and close monitoring may be appropriate.[15]

The nutrition of the neonate before and after surgery was very crucial. In this case, the pediatric surgeon and the neonatologist consider giving a trial feeding and see how the neonate responds. Both the pediatric surgeon and the neonatologist agreed to start feeding slowly and resting the GI tract after the surgery. Parental nutrition is also very necessary during fasting and recovery from post-operative periods. Nutrition during recovery is exclusively provided by TPN, the same as that for infants being treated for NEC. The most prevalent risk associated with prolonged TPN exposure is cholestasis. The adequate feeding of these infants remains a challenge, as they often cannot tolerate enteral feeding and/or cannot metabolize nutrients properly due to surgical stress. They suffer from hemodynamic instability, preoperative complications, metabolic stress, and inflammation, which can delay nutritional support. An individualized feeding strategy that considers the specific surgical needs and the healing process is, therefore, essential for optimal postoperative recovery.[16]

Conclusion

Neonates with gastrointestinal perforation in very preterm infants remain a life-threatening condition with high mortality. Early recognition, timely surgical intervention, meticulous postoperative care, and individualized nutritional management are essential to improve survival. This case shows that successful outcomes are achievable through a multidisciplinary approach, even in settings with limited diagnostic resources.

Acknowledgement

This case report has received consent for publication from the subject and parents.

Conflict of Interest

This case report has no conflict of interest

Funding Statement

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APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Literature Review

Gut Endocrine Regulation of Pediatric Growth and Weight: Integrating Intestinal Hormones, Inflammation, and the GH–IGF-1 Axis in Health and Disease

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Abstract:

Background: The intestine is increasingly recognized as an endocrine organ through enteroendocrine cells, gut-derived peptides, mucosal trophic factors, and microbiota–host signaling. In children, these pathways influence appetite, nutrient handling, body composition, and growth, including the growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis. This review summarizes how intestinal endocrine function affects linear growth, weight gain, and GH–IGF-1 regulation in children with celiac disease, inflammatory bowel disease, environmental enteric dysfunction, and obesity.

Discussion: Evidence supports a convergent model linking gut function to growth via gut hormone signaling (GLP-1, PYY, CCK, GLP-2, ghrelin), inflammation-driven GH resistance, and microbiota-mediated IGF-1 modulation. Celiac disease can cause growth failure reversible with a gluten-free diet; Crohn's disease impairs growth through inflammation and malabsorption; environmental enteric dysfunction drives population-level stunting; and in obesity, altered incretin responses highlight the intestine as a therapeutic target. Gut-endocrine pathways remain underutilized in pediatric practice. IGF-1 is frequently interpreted without accounting for mucosal inflammation or malabsorption, and cross-specialty fragmentation limits holistic growth assessment. Emerging therapies including GLP-2 analogues and incretin-based agents offer promise, though pediatric data remain limited. Standardizing gut-endocrine biomarkers and integrating intestinal health into growth frameworks are key research priorities.

Conclusion: The intestine is a clinically important endocrine organ in pediatric growth medicine. Integrating gut-endocrine biology into endocrine assessment improves the interpretation of IGF-1 and growth patterns and guides management across undernutrition, chronic intestinal disease, and obesity.

Keywords: GH–IGF-1 axis, gut hormones, intestinal endocrine function, microbiota–host signaling, pediatric growth

Introduction

The intestine is now understood to be an active endocrine organ rather than a passive site of digestion and absorption. Enteroendocrine cells (EECs), although dispersed and relatively sparse, form a highly specialized signaling network that senses luminal nutrients and releases hormones influencing appetite, gastric emptying, motility, insulin secretion, mucosal adaptation, and systemic metabolism.[1-5] This endocrine role is further amplified by neural and paracrine communication with the vagus nerve, pancreas, liver, and central appetite-regulating pathways. As a result, intestinal signaling contributes directly to metabolic homeostasis and indirectly to growth and body composition.

This concept has particular importance in pediatrics, where growth and weight trajectories are dynamic and highly sensitive to nutritional adequacy, inflammation, and hormonal regulation. From an endocrine standpoint, linear growth is primarily mediated by the GH–IGF-1 axis, yet this axis is strongly modified by energy availability, protein intake, absorption, systemic inflammation, and chronic disease burden.[6] Therefore, intestinal pathology can alter growth not only through reduced nutrient absorption but also through endocrine mechanisms that influence appetite, metabolism, and GH/IGF-1 signaling. In clinical practice, this is relevant when a child presents with poor growth velocity, low IGF-1, unexplained weight faltering, or obesity with metabolic dysfunction.

Mechanistic evidence supports a biologically plausible intestine–growth endocrine network extending beyond classical gut hormones. Experimental and translational studies demonstrate that gut microbial composition and colonization states can affect circulating IGF-1 and somatic growth, including skeletal growth and bone remodeling.[7-10] Recent pediatric-focused syntheses further summarize associations between intestinal flora and linear growth across pregnancy, infancy, childhood, and adolescence, and highlight links between dysbiosis and pediatric endocrine disorders.[11, 12] More broadly, the microbiota may function as a "virtual endocrine organ" via microbial metabolites and neuroactive compounds that signal to distal tissue.[13] Together, these observations suggest that the gut microbiota and intestinal environment can modulate endocrine growth pathways through nutrient bioavailability, microbial metabolites, immune signaling, and host anabolic responses.

Among pediatric disorders, celiac disease is one of the clearest human models of intestinal endocrine disruption affecting growth. Children may present with short stature or growth failure even in the absence of classic gastrointestinal symptoms, and treatment with a strict gluten-free diet frequently improves growth parameters and endocrine markers such as IGF-1.[14-17] Similarly, pediatric inflammatory bowel disease (IBD), especially Crohn's disease, is strongly associated with impaired linear growth due to a combination of chronic inflammation, reduced intake, malabsorption, delayed

puberty, and functional GH resistance.[18-21] These disorders highlight that intestinal inflammation may be a primary upstream driver of endocrine growth impairment.

At a population level, environmental enteric dysfunction (EED) has expanded this framework by showing how chronic subclinical intestinal inflammation and barrier dysfunction may contribute to stunting and poor weight gain in early childhood, particularly in low-resource settings.[22-25] Biomarker-based cohort studies suggest that intestinal dysfunction, inflammation, and altered barrier integrity are associated with poor growth and micronutrient abnormalities, helping explain why nutritional supplementation alone may fail in some children.[22-27] EED therefore provides an important bridge between gastroenterology, nutrition, endocrinology, and global child health.

The same intestinal endocrine pathways also influence excess weight gain and pediatric obesity. Gut hormones such as GLP-1 and PYY are central to appetite regulation, while therapeutic manipulation of incretin pathways has demonstrated clinically meaningful weight reduction in adolescents.[1-3, 28-30] Taken together, these observations support the need for a focused pediatric endocrine review that integrates intestinal endocrine physiology, growth failure, weight gain abnormalities, and GH–IGF-1 axis regulation across health and disease. Such a review is important for improving diagnosis, management, and prognosis in children with growth and metabolic disorders.

Objectives of this study are to synthesize how intestinal endocrine function influences pediatric linear growth and weight regulation, and to outline endocrine-oriented diagnostic and management implications across key pediatric disorders.

Methods

We conducted a structured narrative review, prioritizing evidence that links intestinal endocrine pathways (enteroendocrine cell hormones, intestinal integrity/inflammation, and microbiota-related signaling) with pediatric growth and weight outcomes and/or GH–IGF-1 physiology. The evidence base was assembled from PubMed, and Scopus indexed literature, with searches combining terms for intestine/endocrine organ, enteroendocrine cells, gut hormones (GLP-1, PYY, CCK, GLP-2), pediatrics, linear growth/stunting, weight gain/obesity, GH and IGF-1, and major pediatric disease models (celiac disease, inflammatory bowel disease/ Crohn's disease, EDD, and microbiota).

Eligible studies included pediatric clinical studies and high-relevance translational work reporting growth (height/height SDS, growth velocity), anthropometry (weight/BMI), and/or GH–IGF-1-related markers; adult-only studies without pediatric relevance and non-verified/non-indexed reports were excluded.

Given heterogeneity in populations, biomarkers, outcome definitions, and interventions, we used qualitative domain-based synthesis rather than meta-analysis, including direction-of-effect summaries where appropriate.

Given the narrative design of this review, formal risk-of-bias tools were not applied; instead, study quality was considered informally based on study design, sample size, and methodological limitations to contextualize evidence strength. No ethics approval was required because this review used previously published data.

Results

Across the included literature, the intestine consistently emerges as a clinically relevant endocrine organ influencing pediatric growth and weight through three interacting pathways: (i) gut hormone signaling, (ii) mucosal inflammation and barrier dysfunction, and (iii) microbiota-mediated endocrine modulation.[1-13, 22-27] The strongest pediatric disease evidence links intestinal dysfunction to impaired linear growth in celiac disease, pediatric IBD, and EED-associated growth faltering.[14-27] In contrast, obesity literature emphasizes altered gut endocrine responses and treatment opportunities via incretin-targeted therapies, with less direct focus on linear growth outcomes.[1-3, 28-31]

Role of Intestinal Endocrine Function in Growth, Weight, and GH–IGF-1 Regulation

Evidence from physiology and translational studies supports a broad gut-endocrine framework in which EEC hormones regulate appetite, satiation, nutrient transit, and metabolic signaling, while intestinal inflammation and microbiota-derived factors influence anabolic and catabolic balance.[1-13] The GH–IGF-1 axis appears particularly vulnerable to inflammatory intestinal states and chronic nutritional compromise.[6, 18-27]

Clinical pediatric evidence shows reproducible links between intestinal disease and growth impairment. Celiac disease and pediatric IBD are the most clearly established models of intestinally mediated growth failure with endocrine consequences.[14-21] Guidelines emphasize systematic growth monitoring and timely control of intestinal inflammation as core outcomes, particularly in pediatric Crohn's disease and ulcerative colitis.[32-34] EED studies support intestinal dysfunction as a contributor to stunting and poor weight gain in high-burden populations.[22-27] In obesity, incretin-based therapies demonstrate that the intestinal endocrine axis is also a practical therapeutic target in adolescents.[29-31]

Table 1 summarizes the major intestinal endocrine and endocrine-like pathways that can influence pediatric growth and weight. The most direct links to growth failure

arise when intestinal inflammation and malabsorption coexist with endocrine dysregulation.[6, 18-27, 32-34]

Pediatric obesity studies and adolescent incretin trials provide the strongest direct clinical evidence that intestinal endocrine signaling can be therapeutically manipulated to improve weight outcomes **(Table 2)**.[1-3, 28-31]

Celiac disease illustrates a classic, often reversible model of intestinal injury causing impaired growth and altered endocrine signaling, including IGF-1 suppression that may improve with treatment **(Table 3)**.[14-17]

Table 1. Intestinal endocrine pathways relevant to linear growth, weight gain, and the GH–IGF-1 axis in children

Pathway / Hormone	Main Source in GI Tract	Primary Pediatric-Relevant Endocrine Actions	Potential Effect on Linear Growth	Potential Effect on Weight Gain / Body Composition	GH–IGF-1 Axis Relevance	Key Ref. No(s).
GLP-1	Distal ileal/colonic L-cells	Incretin effect, reduced appetite, delayed gastric emptying	Indirect (through improved metabolic milieu and energy regulation)	Reduces energy intake; therapeutic target in obesity	May indirectly improve GH dynamics through adiposity/metabolic improvement	1, 3, 28-31
PYY	L-cells (ileum/colon)	Satiety signaling, slows GI transit	Indirect via energy balance and nutrient handling	Reduces appetite; response may be altered in obesity	Indirect via metabolic effects on GH/IGF-1 regulation	1, 3, 28
CCK	I-cells (duodenum/jejunum)	Satiety, pancreatic enzyme stimulation, gallbladder contraction	Indirect support of digestion/absorption affecting growth	Contributes to meal termination and satiation	Indirect via nutrient assimilation	3-5
GLP-2	L-cells	Intestinal mucosal growth, barrier support, adaptation	May improve growth indirectly by improving absorptive capacity	Improves nutrient absorption and intestinal rehabilitation	Indirect via improved nutrition and reduced inflammatory burden	2, 4

Pathway / Hormone	Main Source in GI Tract	Primary Pediatric-Relevant Endocrine Actions	Potential Effect on Linear Growth	Potential Effect on Weight Gain / Body Composition	GH–IGF-1 Axis Relevance	Key Ref. No(s).
GIP	K-cells (proximal small intestine)	Incretin action and nutrient partitioning	Indirect	May contribute to anabolic storage pathways	Indirect via insulin-mediated nutrient utilization	1, 3, 28
Ghrelin *(primarily gastric, proximal gut axis)*	Stomach > proximal intestine	Orexigenic signal; GH secretagogue	May support growth when intake improves; context-dependent	Increases appetite; altered in obesity/weight loss states	Direct GH stimulation; interacts with nutritional IGF-1 regulation	3, 6
Intestinal inflammatory cytokine milieu *(endocrine-relevant mediator axis)*	Inflamed mucosa / systemic circulation	TNF-α, IL-6 and other cytokines suppress appetite and increase catabolism	Strong negative effect via GH resistance and delayed puberty	Weight faltering and altered body composition	Reduces IGF-1 generation/action, contributes to GH resistance	6, 18-27, 32-34
Microbiota-derived metabolites (SCFAs, bile acid signaling)	Luminal microbiota–host interface	Modulate endocrine signaling, barrier integrity, inflammation	Emerging role in growth via IGF-1-related pathways	Alters energy harvest and metabolic efficiency	Experimental evidence supports IGF-1 modulation	7-13, 22-27

GLP-1 = glucagon-like peptide-1; GH = growth hormone; PYY = peptide YY; GI = gastrointestinal; IGF-1 = insulin-like growth factor 1; CCK = cholecystokinin; GLP-2 = glucagon-like peptide-2; GIP = glucose-dependent insulinotropic polypeptide; TNF-α = tumor necrosis factor alpha; IL-6 = interleukin-6; SCFA = short-chain fatty acids

In pediatric IBD, growth failure is frequently a marker of disease severity and inflammation-driven endocrine disruption rather than reduced intake alone; endocrine and GI monitoring should be integrated **(Table 4)**.[18-21, 32-34]

EED and microbiota literature strongly support the concept that chronic intestinal dysfunction can impair growth through combined absorptive, inflammatory, and endocrine pathways.[7-13, 22-27] **(Table 5)**

Table 2. Pediatric evidence on gut-endocrine signaling and weight regulation in health and obesity

Author, year	Study Design	Population	Gut-Endocrine Focus	Main Outcomes	Endocrine-Growth Interpretation
Suntharesan et al., 2023[30]	Single-blind crossover trial	Children with obesity	Postprandial gut hormone, leptin, glucose, and insulin responses to resistant starch	Demonstrated measurable modulation of postprandial hormonal responses	Supports the intestine as an endocrine intervention target in pediatric obesity
Kelly et al., 2020[31]	Randomized controlled trial	Adolescents with obesity	GLP-1 receptor agonist (liraglutide)	Greater reduction in BMI/BMI-SDS vs placebo plus lifestyle	Confirms the therapeutic relevance of incretin pathways in adolescent obesity
Weghuber et al., 2022[29]	Randomized controlled trial	Adolescents with obesity	Once-weekly GLP-1 receptor agonist (semaglutide)	Significant BMI reduction and metabolic benefits	Reinforces the gut endocrine axis as a clinical treatment pathway
Steinert et al., 2017[3]	Physiologic review	Human physiology	Ghrelin, CCK, GLP-1, PYY physiology	Defined secretion control and functional roles in feeding/glycemia	Foundational physiology for pediatric gut hormone interpretation
Gribble et al., 2019[1]	Mechanistic review	Human/translational	EEC nutrient sensing and hormone release	Clarified cellular nutrient-sensing mechanisms	Mechanistic framework linking diet and disease to gut endocrine output

GLP-1 = glucagon-like peptide-1; BMI SDS = body mass index standard deviation score; CCK = cholecystokinin; PYY = peptide YY; EEC = enteroendocrine cells

Figure 1 summarizes how the pediatric intestine functions as an endocrine organ linking nutrient sensing to linear growth and weight regulation through enteroendocrine hormones (e.g., GLP-1, PYY, CCK/GLP-2), inflammatory/barrier pathways, and microbiota signaling, with downstream effects on the GH–IGF-1 axis.

It highlights key disease models—celiac disease, IBD (especially Crohn disease), and environmental enteric dysfunction/undernutrition—where malabsorption and inflammation can suppress IGF-1 and contribute to growth failure, and it ends with a practical integrated clinical approach (screening, growth/puberty monitoring, contextual interpretation of IGF-1, and obesity therapy using GLP-1 agonists when appropriate).

Table 3. Celiac disease as a model of intestinal endocrine dysfunction affecting linear growth and the GH–IGF-1 axis

Author, year	Study Design	Population	Intestinal Pathology / Intervention	Growth / Endocrine Findings	Clinical Implication
Husby et al., 2020[14]	ESPGHAN guideline	Children/ adolescents	Celiac disease diagnostic guidance	Recognizes growth failure/short stature as a key presentation	Supports celiac screening in endocrine evaluation of poor growth
Mearin et al., 2022[15]	ESPGHAN position paper	Children/ adolescents	Long-term management and follow-up	Emphasizes growth and nutritional monitoring after diagnosis	Growth surveillance is part of standard celiac management
Street et al., 2008[16]	Prospective observational study	Children with celiac disease	Gluten-free diet follow-up	IGF-1 improved after treatment in celiac disease	Supports reversibility of intestinally mediated IGF-1 suppression
Meazza et al., 2014[17]	Clinical review	Pediatric celiac/short stature	Celiac disease in endocrine differential diagnosis	Short stature may be isolated presentation; catch-up growth often occurs	Encourages early GI-endocrine co-management

ESPGHAN = European Society for Paediatric Gastroenterology, Hepatology and Nutrition; IGF-1 = insulin-like growth factor 1; GI = gastrointestinal.

Table 4. Pediatric inflammatory bowel disease (especially Crohn's disease): intestinal inflammation, growth failure, and GH–IGF-1 disruption

Author, year	Study Design	Population	Mechanisms Linked to Growth Failure	Growth / Endocrine Findings	Management Implications
Wong et al., 2010[18]	Clinical observational study	Children/adolescents with IBD and growth retardation	Chronic inflammation, nutrition deficits, altered GH–IGF-1 axis	Demonstrated abnormalities in the GH–IGF–1 axis in growth-retarded pediatric IBD	Endocrine assessment is important in persistent growth failure
Sanderso, 2014[19]	Review	Pediatric IBD	Inflammation, malnutrition, delayed puberty, and GH resistance	Growth problems are common, especially in Crohn's disease	Growth should be a core treatment outcome
Ishige, 2019[20]	Review	Pediatric-onset IBD	Appetite loss, malabsorption, cytokines, and delayed puberty	Growth failure is common and clinically significant	Early disease control and nutrition are central
van Rheenen et al., 2021[32]	ECCO-ESPGHAN guideline	Pediatric Crohn disease	Evidence-based medical treatment and monitoring	Supports timely control of inflammation and systematic monitoring	Better inflammation control may improve growth recovery
Wine et al., 2025[33]	ECCO-ESPGHAN guideline (UC Part 1)	Pediatric UC	Ambulatory care guidance	Standardized care pathways	Structured chronic care supports growth monitoring
Turner et al., 2018[34]	ECCO-ESPGHAN guideline (UC Part 2)	Pediatric acute severe colitis	Acute management guidance	Standardized acute treatment pathways	Rapid disease control reduces catabolic/endocrine burden

IBD = inflammatory bowel disease; GH–IGF-1 = growth hormone–insulin-like growth factor 1; ECCO-ESPGHAN = European Crohn's and Colitis Organisation–European Society for Paediatric Gastroenterology, Hepatology and Nutrition; UC = ulcerative colitis.

Table 5. Environmental enteric dysfunction, undernutrition, and microbiota-linked endocrine effects on growth

Author, year	Study Design	Population	Intestinal/Endocrine Focus	Main Growth-Related Findings	Endocrine Interpretation
Syed et al., 2016[22]	Review	Children in low-	EED pathophysiol	EED linked to stunting and impaired	Supports intestinal pathology as a

Author, year	Study Design	Population	Intestinal/Endocrine Focus	Main Growth-Related Findings	Endocrine Interpretation
		resource settings	ogy and child growth	nutritional recovery	growth-endocrine determinant
Crane et al., 2015[23]	Review	Pediatric/global child health context	Barrier dysfunction, inflammation, malabsorption	EED likely contributes to chronic undernutrition	Integrates GI pathology with endocrine growth failure framework
Harper et al., 2018[24]	Systematic review	Children in LMICs	EED pathways and stunting	Summarized heterogeneous biomarker associations with stunting	Supports multi-pathway rather than single-marker explanation
Tickell et al., 2019[25]	Review	EED mechanisms and management	Permeability, inflammation, microbial and hormonal disruption	Links EED to poor growth and systemic consequences	Reinforces endocrine and immune contributions to growth failure
Iqbal et al., 2018[26]	Prospective cohort	Pakistani children	EED biomarker profiling	Identified promising biomarkers linked to EED burden	May support future endocrine-growth risk stratification
Lauer et al., 2020[27]	Cohort study	Rural Ugandan infants	EED markers, growth and iron status	EED markers associated with poor growth and iron status	Connects intestinal dysfunction with growth and micronutrient-endocrine biology
Yan et al., 2016; Schwarzer et al., 2016; Seely et al., 2021; Hansen et al., 2021[7-10]	Translational studies and mechanistic review	Animal/translational models	Microbiota–IGF-1 signaling and gut–bone axis	Gut microbiota and selected taxa can modulate IGF-1 and growth-related phenotypes; gut hormones are implicated in bone remodeling crosstalk	Provides biologic plausibility for intestine–microbiota–GH/IGF-1 linkage and gut-bone interactions relevant to linear growth
He et al, 2023; Shah et al., 2025; Pires et al., 2024[11-13]	Narrative reviews	Children/adolescents (focused syntheses)	Microbiota and pediatric endocrine phenotypes; linear growth trajectories	Syntheses report associations between microbiota composition and linear growth, and	Supports clinical relevance of dysbiosis and microbiota-targeted strategies alongside nutrition and

Author, year	Study Design	Population	Intestinal/Endocrine Focus	Main Growth-Related Findings	Endocrine Interpretation
				summarize links with pediatric endocrine disorders and metabolic outcomes	inflammation control

EED = environmental enteric dysfunction; GI = gastrointestinal; LMIC = low- and middle-income countries; IGF-1 = insulin-like growth factor 1; GH = growth hormone

Figure 1. The intestine as an endocrine organ in pediatric growth and weight regulation: gut hormones, inflammation, microbiota, and the GH–IGF-1 axis

Discussion

This review supports the intestine as a pivotal endocrine organ in pediatric growth medicine, helping explain why abnormal linear growth or weight trajectories can arise from intestinal dysfunction even when children present through endocrine pathways. A practical framework links pediatric growth and weight to three coupled intestinal domains—gut hormone secretion, intestinal integrity/inflammation, and microbiota-related signaling—through which enteroendocrine cell hormones (e.g., GLP-1, PYY, CCK, GLP-2) translate nutrient sensing into appetite control, motility, absorption, and anabolic potential.[1-5, 28]

The GH–IGF-1 axis appears particularly sensitive to these intestinal domains. Beyond classic GH deficiency, functional suppression of IGF-1 and inflammatory GH resistance can occur in malnutrition or chronic intestinal inflammation.[6, 18-27] Clinically, low IGF-1 in a child with poor growth should therefore be interpreted alongside intestinal symptoms, inflammatory burden, nutritional intake, and growth velocity before attributing findings to primary pituitary pathology; this approach can reduce diagnostic delay and improve targeting of treatment.[14-21, 32-34]

Celiac disease remains a clear human model of intestine-mediated growth impairment, where short stature or poor growth may be a presenting feature and endocrine evaluation may trigger diagnostic consideration. The consistent improvement in growth and IGF-1 following a gluten-free diet underscores partial reversibility when mucosal healing and nutrient restoration occur, supporting low-threshold celiac screening in children with unexplained growth failure or low IGF-1.[14-17]

Pediatric inflammatory bowel disease, especially Crohn's disease, illustrates a more severe multi-mechanistic pathway to growth failure, combining undernutrition with cytokine-driven GH resistance, pubertal delay, and catabolic effects of active disease. Evidence and guidelines emphasize growth as a core outcome of disease control, making serial height velocity and pubertal monitoring clinically meaningful even when gastrointestinal symptoms improve.[18-21, 32-34]

Environmental enteric dysfunction extends the gut–growth endocrine concept to high-burden settings in which chronic intestinal dysfunction may be subclinical yet still contributes to stunting via impaired barrier function, inflammation, and altered nutrient handling.[22-27] Microbiota-related evidence strengthens biologic plausibility by linking microbial states to circulating IGF-1 and growth-related outcomes in experimental and translational work, with pediatric syntheses highlighting dysbiosis-associated endocrine phenotypes and growth trajectories.[7-13] Together, these data support integrated strategies that address gut health and inflammation alongside nutrition.

At the opposite end of the nutritional spectrum, pediatric obesity demonstrates that gut endocrine signaling is also a modifiable pathway in routine care. Incretin and satiety biology has translated into effective adolescent obesity therapy, with GLP-1 receptor agonists producing clinically meaningful reductions in BMI, reinforcing the clinical relevance of gut endocrine pathways beyond malnutrition and inflammatory disease.[1-3, 28-31]

Limitations include heterogeneity across pediatric study designs, biomarker panels, and outcome definitions, which precluded pooled quantitative synthesis, and the fact that some microbiota–IGF-1 concepts are supported more strongly by translational than pediatric interventional data.[7-10] Nonetheless, convergence across physiology, pediatric disease cohorts, and therapeutic trials supports the overall narrative and the informal quality considerations applied to included studies help contextualize the mixed evidence base. Future work should prioritize standardized pediatric gut-endocrine biomarker panels, longitudinal studies linking intestinal markers to height velocity and pubertal timing, and trials that include growth endpoints alongside disease control and weight outcomes.[1-13, 22-31]

Conclusion

The intestine functions as a clinically important endocrine organ in children, influencing linear growth, weight gain, and GH–IGF-1 axis behavior through gut hormone signaling, mucosal integrity, inflammation, and microbiota-related pathways. Fundamentally, enteroendocrine cell-derived hormones—including GLP-1, PYY, CCK, and GLP-2—regulate appetite, nutrient absorption, and anabolic signaling, while intestinal inflammation drives cytokine-mediated GH resistance and IGF-1 suppression; in parallel, microbiota-derived metabolites further modulate systemic endocrine growth pathways. These mechanisms collectively explain why intestinal disease can impair linear growth and alter the GH–IGF-1 axis through routes that are distinct from, yet interacting with, primary pituitary or nutritional deficits. This framework improves pediatric endocrine interpretation of growth faltering, stunting, and obesity, and supports integrated management across celiac disease, IBD, EED-associated growth failure, and obesity. Incorporating intestinal endocrine biology into routine pediatric endocrine assessment can improve diagnostic accuracy, treatment timing, and long-term growth outcomes.

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Conflict of Interest

None declared.

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