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Early 72-Hour Weight Loss and Short-Term Neonatal Outcomes in Very Low Birth Weight Infants: A Prospective Cohort Study

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Research Article

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Abstract

Background: Early postnatal weight loss is an important component of neonatal adaptation and reflects the complex interplay between extracellular fluid contraction, renal maturation, insensible water loss, and fluid management. Although early fluid balance has been associated with neonatal morbidity, the clinical significance of early postnatal weight loss in very low birth weight (VLBW) infants remains incompletely understood, particularly in infants weighing less than 1250 g.

Objective To investigate the association between weight loss during the first 72 hours of life and short-term neonatal outcomes in preterm infants with a birth weight below 1250 g.

Methods: In this prospective cohort study, preterm infants with birth weights below 1250 g admitted to a tertiary neonatal intensive care unit between February 2023 and February 2024 were enrolled. Infants were categorized according to percentage weight loss during the first 72 hours of life as <5%, 5–10%, and >10%. Maternal and neonatal characteristics, early clinical and laboratory findings, respiratory and cardiovascular outcomes, major neonatal morbidities, and mortality were compared among the three groups.

Results: A total of 98 infants were included: 48 (49.0%) had <5% weight loss, 36 (36.7%) had 5–10% weight loss, and 14 (14.3%) had >10% weight loss. Baseline maternal and neonatal characteristics were comparable among the groups. Infants with >10% weight loss received significantly higher cumulative fluid volumes during the first 72 hours ($p<0.001$), had lower serum creatinine concentrations ($p=0.018$), and required fewer surfactant doses ($p=0.042$). No statistically significant differences were observed in respiratory distress syndrome, respiratory support, patent ductus arteriosus, intraventricular hemorrhage, inotropic support, feeding intolerance, early-onset sepsis, or mortality. Nevertheless, infants with >10% weight loss consistently demonstrated numerically lower rates of patent ductus arteriosus, intraventricular hemorrhage, and inotropic support than those with lower degrees of weight loss.

Conclusions: Greater early postnatal weight loss during the first 72 hours of life was associated with reduced surfactant requirements without an increase in mortality or major neonatal morbidities. Although statistically significant differences were not observed for patent ductus arteriosus, intraventricular hemorrhage, or inotropic support, all three outcomes demonstrated consistent numerical reductions among infants with greater weight loss. These findings suggest that early postnatal weight loss may represent a clinically useful marker of successful neonatal adaptation rather than an indicator of adverse short-term outcomes. Larger multicenter studies are warranted to validate these findings and to determine the optimal range of early postnatal weight loss in very low birth weight infants.

Introduction

Preterm birth remains one of the leading causes of neonatal mortality and morbidity worldwide. According to the latest data from the World Health Organization (WHO), approximately 13 million infants are born preterm each year, and prematurity is one of the leading causes of death among children under

five years of age (1). Although survival rates have improved substantially over recent decades, respiratory, cardiovascular, neurological, and gastrointestinal complications continue to represent a major burden of morbidity, particularly among very low birth weight (VLBW) preterm infants (2, 3).

Fluid management during the early postnatal period is one of the most critical components of neonatal intensive care in VLBW preterm infants. During the physiological transition from intrauterine to extrauterine life, a marked contraction of the extracellular fluid compartment occurs, which is clinically reflected by physiological weight loss during the first days after birth (4). While this process is generally well tolerated in term infants, fluid balance in preterm neonates requires considerably more careful management because of immature renal function, a higher total body water content, increased transepidermal water loss, and limited sodium regulatory capacity (3–5).

Early postnatal weight loss reflects not only nutritional status but also the degree of extracellular fluid contraction and cardiovascular adaptation, making it an important clinical indicator (4, 6). Weight loss within physiological limits is considered normal, whereas insufficient weight loss may indicate fluid retention and circulatory overload. Conversely, excessive weight loss may be associated with dehydration, hypernatremia, impaired renal perfusion, and circulatory instability (5, 7). Therefore, the goal of fluid therapy in preterm infants is to achieve an optimal balance that ensures adequate organ perfusion without preventing physiological extracellular fluid contraction (2, 4).

Recent studies have demonstrated that excessive early postnatal fluid administration may be associated with patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and prolonged mechanical ventilation (6, 8, 9). However, there is still no consensus regarding the range of weight loss that should be considered physiological during the first days of life or its impact on short-term neonatal outcomes. In particular, studies evaluating this relationship in preterm infants with a birth weight below 1250 g remain limited (7, 10).

The aim of this prospective cohort study was to evaluate the effect of weight loss during the first 72 hours of life on short-term neonatal morbidity and mortality in preterm infants with a birth weight below 1250 g. In addition, we sought to investigate the relationship between physiological weight loss and major neonatal morbidities, including patent ductus arteriosus, intraventricular hemorrhage, respiratory support requirements, and other significant complications of prematurity.

Materials and Methods

This prospective cohort study was conducted in the Neonatal Intensive Care Unit of Zeynep Kamil Women and Children’s Diseases Training and Research Hospital, University of Health Sciences, Istanbul, Türkiye, between February 2023 and February 2024. This study was approved by the Clinical Research Ethics Committee of Zeynep Kamil Women and Children’s Diseases Training and Research Hospital (Decision No. 34, dated 22 February 2023). The requirement for informed consent was waived due to the retrospective nature of the study.The study aimed to evaluate the association between weight loss during the first 72 hours of life and short-term neonatal morbidity and mortality in preterm infants with a

birth weight below 1250 g. The study was approved by the Institutional Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all enrolled infants before participation.

Preterm infants with a birth weight below 1250 g who were admitted directly to the neonatal intensive care unit during the study period were eligible for inclusion. Infants were included if serial body weight measurements during the first 72 hours of life and complete clinical and laboratory data were available. Infants with major congenital anomalies, chromosomal abnormalities, complex congenital heart disease affecting hemodynamic status, death within the first 72 hours of life, or incomplete medical records were excluded from the study. A total of 98 preterm infants met the eligibility criteria and were included in the final analysis.

Maternal and neonatal demographic and clinical characteristics were prospectively collected from the electronic medical records. Maternal variables included age, gestational age, multiple pregnancy, antenatal corticosteroid administration, preterm premature rupture of membranes (PPROM), preeclampsia, gestational diabetes mellitus, and mode of delivery. Neonatal variables included gestational age, birth weight, sex, Apgar scores, small for gestational age (SGA) status, and the need for delivery room resuscitation.

Birth weight was measured immediately after delivery using a calibrated electronic neonatal scale. Body weight was measured again at 72 hours of life using the same standardized procedure. Percentage weight loss was calculated using the following formula: [(birth weight − weight at 72 hours) / birth weight] × 100. According to the percentage of weight loss, infants were categorized into three groups: Group 1 (< 5% weight loss or weight gain), Group 2 (5–10% weight loss), and Group 3 (> 10% weight loss). This classification was based on previous studies evaluating physiological postnatal fluid adaptation in preterm infants.

Fluid therapy was administered according to the standardized protocol of our neonatal intensive care unit. Daily intravenous fluid intake was individualized according to gestational age, birth weight, urine output, serum electrolyte concentrations, and the infant's clinical condition. During the first 72 hours of life, daily fluid intake, urine output, and body weight changes were recorded. Fluid management was modified when clinically indicated in infants who developed electrolyte disturbances or hemodynamic instability.

The primary outcome of the study was the association between weight loss during the first 72 hours of life and short-term neonatal morbidity. Clinical outcomes included respiratory distress syndrome, surfactant administration, mechanical ventilation, high-frequency oscillatory ventilation (HFOV), patent ductus arteriosus (PDA), medical treatment for PDA, intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), spontaneous intestinal perforation (SIP), early-onset sepsis, late-onset sepsis, retinopathy of prematurity (ROP), and mortality.

Laboratory parameters obtained during the first week of life included serum sodium, serum potassium, blood urea nitrogen, serum creatinine, blood gas pH, base deficit, and lactate concentrations.

Statistical analyses were performed using IBM SPSS Statistics software. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables are presented as mean ± standard deviation, whereas non-normally distributed variables are expressed as median (minimum–maximum). Comparisons among the three study groups were performed using one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. Categorical variables were analyzed using the Pearson chi-square test or Fisher's exact test, as appropriate. A two-sided p value of < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 98 preterm infants with a birth weight below 1250 g were included in the study. Forty-eight infants (49.0%) experienced < 5% weight loss, 36 (36.7%) had 5–10% weight loss, and 14 (14.3%) had > 10% weight loss during the first 72 hours of life.

Baseline maternal and neonatal characteristics were comparable among the three groups. No statistically significant differences were observed regarding gestational age, birth weight, sex, small for gestational age status, mode of delivery, maternal diabetes, preeclampsia, chorioamnionitis, Apgar scores, or delivery room resuscitation, indicating a relatively homogeneous study population (Table 1).

Table 1
Baseline Maternal and Neonatal Characteristics of the Study Population

Gestational age (weeks), mean ± SD	**< 5% Weight Loss (n = 48)**	**5–10% Weight Loss (n = 36)**	**> 10% Weight Loss (n = 14)**	***p* value**
	27.4 ± 2.5	**27.9 ± 2.3**	**27.4 ± 2.3**	**0.727**
Male sex, n (%)	31 (64.6)	22 (61.1)	5 (35.7)	0.148
Birth weight (g), mean ± SD	873.9 ± 239.6	916.4 ± 220.9	947.9 ± 172.9	0.600
Small for gestational age (SGA), n (%)	27 (56.3)	17 (47.2)	4 (28.6)	0.183
Cesarean delivery, n (%)	41 (85.4)	33 (91.7)	11 (78.6)	0.424
Gestational diabetes mellitus, n (%)	4 (8.3)	4 (11.1)	2 (14.3)	0.732
Preeclampsia, n (%)	14 (29.3)	10 (27.8)	8 (57.1)	0.107
Chorioamnionitis, n (%)	2 (4.2)	4 (11.1)	1 (7.1)	0.427
5-minute Apgar score, mean ± SD	6.6 ± 1.5	6.8 ± 1.3	7.0 ± 1.2	0.733
Deliver room resuscitation n (%)	9(18.8)	8(22.2)	1(7.1)	0.464

Early Clinical and Laboratory Findings

The cumulative fluid intake during the first 72 hours increased significantly across the study groups, with infants in the > 10% weight loss group receiving the highest fluid volume (105.8 ± 17.1 mL/kg/day, $p < 0.001$). Serum creatinine concentrations were significantly lower in infants with > 10% weight loss (0.7 ± 0.3 mg/dL, $p = 0.018$). Urine output, serum sodium, potassium, blood urea nitrogen, blood pH, base deficit, and lactate concentrations were similar among the groups (Table 2).

Table 2
Early Laboratory Findings During the First Week of Life

Total fluid intake during the first 72 h (mL/kg/day), mean ± SD	**< 5% Weight Loss (n = 48)**	**5–10% Weight Loss (n = 36)**	**> 10% Weight Loss (n = 14)**	***p***
	83.8 ± 10.3	**95.9 ± 14.1**	**105.8 ± 17.1**	**< 0.001**
İncubator humidty during the first 72 h (mL/kg/h), mean ± SD	75.1 ± 9.6	72.7 ± 7.3	76.8 ± 7.7	0.246
Serum sodium (mEq/L), mean ± SD	145.4 ± 10.1	144.8 ± 5.5	143.9 ± 8.2	0.717
Serum potassium (mEq/L), mean ± SD	5.1 ± 1.4	4.9 ± 1.2	4.9 ± 0.9	0.808
Blood urea nitrogen (mg/dL), mean ± SD	62.2 ± 39.5	60.0 ± 34.6	57.0 ± 40.5	0.639
Serum creatinine (mg/dL), mean ± SD	1.0 ± 0.5	0.8 ± 0.3	0.7 ± 0.3	**0.018**
Blood pH, mean ± SD	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	0.636
Base deficit (mmol/L), mean ± SD	−5.4 ± 5.0	−5.8 ± 3.0	−4.7 ± 3.6	0.444
Blood lactate (mmol/L), mean ± SD	2.6 ± 2.0	2.3 ± 1.3	2.1 ± 0.7	0.816

Respiratory Outcomes

The incidence of respiratory distress syndrome, respiratory support on postnatal day 14, successful weaning during the first 72 hours, peak inspiratory pressure, and the requirement for advanced respiratory support were comparable among the study groups. However, infants with > 10% weight loss required significantly fewer surfactant doses than those with lower degrees of weight loss (0.9 ± 0.3 vs. 1.5 ± 0.9 and 1.2 ± 0.7, p = 0.042) (Table 3).

Table 3
Respiratory Outcomes

Weaning within first 72 h, n (%)	**< 5% Weight Loss (n = 48)**	**5–10% Weight Loss (n = 36)**	**> 10% Weight Loss (n = 14)**	**p**
	8 (16.7)	**5 (13.9)**	**4 (28.6)**	**0.462**
Respiratory support on day 14, n (%)				0.624
• Spontaneous breathing	6 (12.5)	2 (5.6)	2 (14.3)	
• nCPAP	7 (14.6)	8 (22.2)	4 (28.6)	
• NIPPV	15 (31.3)	14 (38.9)	6 (42.9)	
• SIMV	15 (31.3)	10 (27.8)	1 (7.1)	
• HFOV	1 (2.1)	1 (2.8)	-	
Peak inspiratory pressure at 72 h (mmHg)	19.6 ± 3.0	19.3 ± 1.9	19.6 ± 1.7	0.818
Respiratory distress syndrome, n (%)	43 (89.6)	31 (86.1)	13 (92.9)	0.828
Number of surfactant doses	1.5 ± 0.9	1.2 ± 0.7	0.9 ± 0.3	**0.042**

Cardiovascular Outcomes

No statistically significant differences were observed in cardiovascular outcomes among the study groups. Nevertheless, infants with > 10% weight loss showed numerically lower rates of patent ductus arteriosus (28.6% vs. 50.0% and 52.8%) and lower inotropic support requirements (28.6% vs. 41.7% and 38.9%) compared with the other groups (Table 4).

Table 4
Cardiovascular Outcomes

Patent ductus arteriosus, n (%)	**< 5% Weight Loss (n = 48)**	**5–10% Weight Loss (n = 36)**	**> 10% Weight Loss (n = 14)**	**p**
	24 (50.0)	**19 (52.8)**	**4 (28.6)**	**0.283**
Medical treatment for PDA (among PDA patients), n (%)	14 (58.3)	12 (63.2)	3 (75.0)	0.806
Pulmonary hypertension, n (%)	6 (12.5)	4 (11.1)	2 (14.3)	0.951
Systolic blood pressure at 72 h (mmHg)	56.7 ± 5.4	56.9 ± 4.6	**58.3 ± 3.1**	0.490
Diastolic blood pressure at 72 h (mmHg)	28.1 ± 4.2	28.9 ± 2.8	**28.9 ± 3.1**	0.460
Inotropic support, n (%)	20 (41.7)	14 (38.9)	**4 (28.6)**	0.676

Major Neonatal Morbidities

Similarly, the incidence of intraventricular hemorrhage tended to decrease as early weight loss increased (21.4% vs. 37.5% and 30.6%), although this difference did not reach statistical significance. Feeding intolerance, early-onset sepsis, and 7-day mortality were comparable among the three groups (Table 5)

Table 5
Major Neonatal Morbidities and Mortality

Intraventricular hemorrhage	**< 5% Weight Loss (n = 48)**	**5–10% Weight Loss (n = 36)**	**> 10% Weight Loss (n = 14)**	**p**
	18 (37.5)	**11 (30.6)**	**3 (21.4)**	**0.500**
Feeding intolerance	27 (56.3)	18 (50.0)	7 (50.0)	0.825
Early-onset sepsis	3 (6.3)	4 (11.1)	-	0.370
7-day mortality	2 (4.2)	1 (2.8)	1 (7.1)	0.782

Discussion

In this prospective cohort study, we evaluated the association between early postnatal weight loss and short-term neonatal outcomes in preterm infants with a birth weight below 1250 g. The present study extends current knowledge by demonstrating that greater early postnatal weight loss during the first 72 hours of life was not associated with adverse short-term outcomes in this vulnerable population. Instead, infants with > 10% weight loss received higher cumulative fluid volumes, had lower serum creatinine concentrations, and required fewer surfactant doses during the early neonatal period. Although differences in major neonatal morbidities did not reach statistical significance, infants with greater early weight loss consistently demonstrated lower rates of patent ductus arteriosus (PDA),

intraventricular hemorrhage (IVH), and inotropic support. Importantly, greater early postnatal weight loss was not associated with higher mortality or other adverse short-term outcomes. Physiological postnatal weight loss is a normal component of the transition from fetal to neonatal life and primarily reflects contraction of the extracellular fluid compartment. However, in very preterm infants, maintaining an appropriate fluid balance is considerably more challenging because of their high total body water content, immature renal function, increased transepidermal water loss, and limited sodium regulatory capacity. Both inadequate and excessive fluid administration may adversely affect this adaptive process. Consequently, current neonatal practice emphasizes individualized fluid management based on gestational age, urine output, serum electrolyte concentrations, and clinical status rather than targeting a predefined degree of postnatal weight loss (2–5, 7). Our findings support this concept by demonstrating that greater early postnatal weight loss was not associated with worse clinical outcomes despite higher cumulative fluid administration. An interesting finding of our study was that infants with > 10% weight loss received significantly higher cumulative fluid volumes during the first 72 hours of life despite experiencing the greatest degree of weight loss. At first glance, this observation may appear paradoxical. However, postnatal weight change in extremely preterm infants is determined not only by administered fluid volume but also by insensible water loss, transepidermal evaporation, urine output, renal immaturity, and the normal contraction of the extracellular fluid compartment (3, 5, 7). Because extremely preterm infants have an immature skin barrier and a relatively large body surface area, insensible water loss remains substantial during the first postnatal days. Furthermore, fluid therapy in our unit was individualized according to daily weight changes, urine output, electrolyte concentrations, and overall clinical condition. Therefore, the higher cumulative fluid intake observed in infants with greater weight loss most likely represents a clinical response to ongoing fluid losses rather than the cause of the observed weight reduction. These findings emphasize that early postnatal weight loss should not be interpreted solely according to administered fluid volume but rather as the net result of dynamic physiological adaptation and individualized fluid management. Although several studies have investigated the relationship between early fluid administration and neonatal outcomes, relatively few have specifically evaluated early postnatal weight loss as a marker of early adaptation in infants with birth weights below 1250 g. Most previous investigations have focused primarily on cumulative fluid intake or cumulative fluid balance rather than actual postnatal weight change. Therefore, our study provides additional evidence that early postnatal weight loss itself may represent a clinically useful indicator of postnatal adaptation in this particularly vulnerable population.

One of the most interesting observations in our study was the consistent reduction in the incidence of PDA, IVH, and inotropic support among infants with > 10% weight loss. Although these differences did not reach statistical significance, the numerical trend was remarkably consistent across all three outcomes. The frequency of PDA decreased from approximately one-half of infants in the lower weight-loss groups to only 28.6% in the > 10% weight-loss group. Similarly, IVH and inotropic support demonstrated progressive numerical reductions as early weight loss increased. These observations are biologically plausible. Appropriate contraction of extracellular fluid volume may facilitate cardiovascular adaptation by reducing pulmonary overcirculation, improving systemic perfusion, and minimizing

fluctuations in cerebral blood flow during the early transitional period. Previous studies have demonstrated that excessive fluid administration during the first postnatal days is associated with persistent PDA, pulmonary edema, bronchopulmonary dysplasia, and prolonged respiratory support (6, 8, 11). Likewise, optimizing early fluid management has been shown to promote spontaneous ductal closure and reduce the hemodynamic consequences of PDA (8, 11, 12). Although our results do not demonstrate a statistically significant association, the consistent reduction in PDA across increasing weight-loss categories is clinically noteworthy and suggests that greater early postnatal weight loss may represent a marker of more favorable cardiovascular adaptation rather than exerting a direct protective effect. A similar pattern was observed for intraventricular hemorrhage. Germinal matrix hemorrhage is primarily related to the structural fragility of the immature cerebral vasculature and instability of cerebral autoregulation. Hemodynamic fluctuations during the transitional period, particularly those associated with circulatory instability and disturbances in fluid balance, have been implicated in the pathogenesis of IVH (9, 13, 14). Although our study was not sufficiently powered to detect statistically significant differences in IVH, the gradual reduction observed across increasing weight-loss categories supports the hypothesis that successful postnatal adaptation may contribute to more stable cerebral perfusion during the first days of life. Respiratory outcomes were largely similar among the three study groups. Nevertheless, infants with greater early weight loss required significantly fewer surfactant doses. Delayed clearance of fetal lung fluid contributes to respiratory distress syndrome in addition to surfactant deficiency. Previous reports have suggested that excessive fluid administration may increase pulmonary interstitial edema, impair gas exchange, and prolong respiratory support (2, 6, 15–17). Therefore, the lower surfactant requirement observed in our study may reflect more effective pulmonary fluid clearance and improved pulmonary adaptation associated with appropriate extracellular fluid contraction. However, because respiratory support requirements and overall respiratory severity remained comparable among the study groups, this finding should be interpreted with caution. Interestingly, serum creatinine concentrations were significantly lower in infants with greater early weight loss. Neonatal serum creatinine is influenced by several physiological factors, including maternal creatinine transfer, gestational age, muscle mass, renal maturation, and fluid balance. Consequently, lower creatinine concentrations should not be interpreted as evidence of superior renal function (18–20). Rather, they are more likely to reflect differences in postnatal fluid adaptation and physiological maturation. Further studies incorporating additional renal biomarkers are needed to clarify the clinical significance of this finding. Mortality and other major neonatal morbidities were comparable among the three study groups. Mortality in extremely preterm infants is determined by multiple interacting factors, including gestational age, birth weight, severe respiratory disease, sepsis, severe IVH, necrotizing enterocolitis, and multiorgan dysfunction (10, 21, 22). Therefore, early postnatal weight loss alone is unlikely to be an independent determinant of mortality. Our findings instead suggest that early postnatal weight loss may be more informative as a marker of successful postnatal adaptation than as a predictor of survival.

An additional noteworthy finding of our study was the consistent direction of change observed across several clinically important outcomes. Although statistical significance was not reached for PDA, IVH,

and inotropic support, all three outcomes demonstrated progressively lower rates with increasing early weight loss. The concordance of these findings across different organ systems reduces the likelihood that they represent isolated random observations and instead supports the hypothesis that greater early postnatal weight loss may reflect more successful cardiovascular and systemic adaptation. Nevertheless, confirmation in adequately powered multicenter studies remains essential before these findings can influence clinical practice.

The strengths of our study include its prospective design, standardized body-weight measurements, and the relatively homogeneous study population consisting exclusively of infants with birth weights below 1250 g. Furthermore, all infants were managed according to a standardized fluid management protocol within a single tertiary neonatal intensive care unit, minimizing variability in clinical practice. Nevertheless, several limitations should be acknowledged. This was a single-center study with a relatively small sample size, particularly in the > 10% weight-loss group, which may have limited the statistical power to detect significant differences for several clinically important outcomes. In addition, multivariable analyses were not performed, residual confounding cannot be excluded, and long-term neurodevelopmental outcomes were not evaluated.

Conclusion

Rather than defining a specific threshold for acceptable postnatal weight loss, our findings support the concept that early postnatal weight change should be interpreted within the context of individualized fluid management and overall clinical adaptation. Future multicenter prospective studies incorporating echocardiographic assessment, cerebral hemodynamic monitoring, and long-term neurodevelopmental follow-up may help determine whether early postnatal weight loss can serve as a practical bedside marker of successful neonatal adaptation.

Abbreviations

VLBW
Very low birth weight
ELBW
Extremely low birth weight
NEC
Necrotizing enterocolitis
BPD
Bronchopulmonary dysplasia
IVH
Intraventricular hemorrhage
LOS
Late-onset sepsis
PDA

Patent ductus arteriosus.

Declarations

Ethics approval and consent to participate: This study was approved by the Zeynep Kamil Women and Children's Diseases Training and Research Hospital Clinical Research Ethics Committee (Decision No: 34, Date: 22 February 2023). Written informed consent was obtained from the parents or legal guardians of all participants before enrollment. All procedures performed in this study were conducted in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

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Authors' contributions: EY conceived the study, collected the data, performed the statistical analyses, interpreted the results, and drafted the manuscript as part of her residency thesis. EO supervised the study, contributed to the study design, critically revised the manuscript for important intellectual content, interpreted the data, and approved the final version. ST, ED, SS, and GK contributed to the clinical care and follow-up of the study patients, participated in data verification, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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