A nordic multicenter study on contemporary outcomes of pediatric short bowel syndrome in 208 patients

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SUMMARY
Background & aims: Despite advances in the management of short bowel syndrome related intestinal failure (SBS-IF), large-scale contemporary pediatric studies are scarce. The aim of this multicenter study was to assess key outcomes and clinical prognostic factors in a recent Nordic pediatric SBS-IF population.

Methods: Patients with SBS-IF treated during 2010–2019, whose parenteral support (PS) started at age <1 year and continued >60 consecutive days were included and retrospectively reviewed. All six participating centers followed multidisciplinary SBS-IF management. Risk factors for PS dependency, intestinal failure associated liver disease (IFALD) and mortality were assessed with Cox regression and Kaplan Meier analyses. IFALD was defined with serum liver biochemistry levels.

Results: Among 208 patients, SBS-IF resulted from NEC in 49%, gastroschisis w/wo atresia in 14%, small bowel atresia in 12%, volvulus in 11%, and other diagnoses in 14%. Median age-adjusted small bowel length was 43% (IQR 21–80%). After median follow up of 4.4 years (IQR 2.5–6.9), enteral autonomy was reached by 76%, none had undergone intestinal transplantation, and overall survival was 96%. Half of deaths (4/8) were caused by septic complications. Although biochemical cholestasis occurred only in 3% at latest follow-up and none of deaths were directly caused by IFALD, elevated liver biochemistry (HR 0.136; P = 0.017) and shorter remaining small bowel (HR 0.941; P = 0.040) predicted mortality. Shorter remaining small bowel and colon, and presence of end-ostomy were the main predictors of PS dependency, but not IFALD. Patients with NEC reached enteral autonomy more efficiently and had decreased incidence of IFALD compared to other etiologies.

Conclusions: Although with current multidisciplinary management, prognosis of pediatric SBS is encouraging, septic complications and IFALD still associated with the remaining low mortality rate.

1. Introduction
In short bowel syndrome (SBS) congenital or acquired reduction of gut mass or length leads to intestinal failure (IF) characterized by inadequate absorption, severe malnutrition and need for long-term parenteral support (PS) [1]. Pediatric SBS most often results from necrotizing enterocolitis (NEC) followed by small bowel atresia, midgut volvulus, gastrochisis and Hirschsprung's disease [1,2].
Although intestinal adaptation enables most patients gradually to wean off PS within several years after bowel resection, a significant proportion of patients remain PS-dependent for years or permanently [1,3]. Main goals of SBS-related IF (SBS-IF) treatment include achievement of enteral autonomy by promoting intestinal adaptation, while preserving adequate growth and development and avoiding complications [1,4]. Recent studies suggest that establishment of multidisciplinary care with focus on nutritional management, meticulous central line care and autologous intestinal reconstruction (AIR) surgery has improved outcomes of patients with IF, while rate of intestinal transplantation is decreasing [5–11]. Despite major advances made in the field during the last decades, contemporary multicenter pediatric studies on current outcomes are scarce. The aim of this retrospective cohort study was to assess current management, outcomes, and clinical prognostic factors in a multicentric Nordic pediatric SBS-IF population.

2. Materials & methods

2.1. Ethics

The study was conducted according to the Declaration of Helsinki and the protocol was approved by the ethical committee or institutional review board of each participating center.

2.2. Participating centers

This was a retrospective multicenter study in six Nordic national IF reference centers in Finland (Helsinki), Norway (Oslo) and Sweden (Gothenburg, Lund, Stockholm, Uppsala), each serving populations of 2.5–5.5 million inhabitants (Fig. 1). Before onset of the study inclusion period in 2010, all centers had introduced local multidisciplinary IF management and follow-up programs providing modern fish-oil containing lipid emulsions, cycling of PS, early enteral feeding with breast milk, meticulous central line management, home PS teams, and autologous intestinal reconstruction (AIR) surgery options. The home PS teams oversaw home PS and family education. The home PS was mainly given by the educated family members and if needed by professional care givers. Taurolidine central line locks were routinely used since 2015 in all centers. In addition, Gothenburg and Helsinki possess intestinal transplantation programs established prior to 2010 [12].

2.3. Patients

All consecutive SBS-IF patients born between 1.1.2010 and 31.12.2019 and followed up in the participating centers were included. All included patients had been diagnosed with SBS-IF, had need for PS over 60 consecutive days and had onset of PS during the first year of life [13]. PS included any nutrition and/or fluids given intravenously. Patients without need for long-term PS (<60 days), with onset of PS after one year of age, with primary intestinal dysmotility disorders, such as chronic intestinal pseudo-obstruction, and primary intestinal epithelial diseases were excluded.

2.4. Data collection

Anonymized data from medical records or local SBS-IF registries were recorded using a preformed data collection sheet. Baseline data of interest included gestational age and weight, age at SBS-IF diagnosis and at commencing PS, underlying etiology, remaining bowel anatomy, AIR surgeries and intestinal transplantations. The percentage age-adjusted remaining small bowel and colon length was calculated based on published age-specific normal values [14,15].

At the latest follow up visit, age, gestational age corrected weight-for-age and height-for-age z-scores [16], duration of PS, and weekly number, volume and energy content of PS as well as serum total bilirubin, gamma-glutamyl transferase (GGT) and alanine...
Fig. 2. Underlying etiology of all short bowel syndrome (SBS) patients and according to parenteral support dependency at the latest follow up. NEC; necrotizing enterocolitis, SBA; small bowel atresia, MGV; midgut volvulus, GS; gastroschisis, HD; Hirschsprung disease.
aminotransferase (ALT) levels were recorded. Serum liver biochemistry measurements were performed by local hospital laboratories and were available for 200 (96%) patients. Biochemical cholestasis was defined by increased serum bilirubin >1.5 times above upper normal limit and intestinal failure associated liver disease by > 1.5 elevated bilirubin, GGT and/or ALT [17]. Reaching enteral autonomy was defined as weaning off all PS. Possible time and cause of death was recorded.

2.5. Statistical analysis

Descriptive statistics are presented as frequencies or median (IQR) unless stated otherwise. Mann–Whitney U test or Fisher’s exact test with Bonferroni post hoc test was used for comparison between groups. Predictive value of relevant predetermined patient- and treatment-related factors were analyzed with univariable and multivariable Cox regression models. All significant variables were entered into multivariable models. Kaplan Meier analysis with log rank test was used to evaluate PS dependency. Statistical significance was set at 0.05.

3. Results

3.1. Baseline patient characteristics

Altogether, 208 SBS-IF patients fulfilling the inclusion criteria were included (Fig. 1). The underlying etiology of SBS-IF was NEC in most (49%), followed by small bowel atresia, volvulus, gastrochisis with small bowel atresia, isolated gastrochisis, Hirschsprung’s disease and other diagnosis (Fig. 2). As shown in Table 1, patients had median of 43% (21–80) of age adjusted small bowel and 100% (70–100) of colon remaining, majority (61%) had ileocecal valve preserved and 43% (20%) had ultra short small bowel with less than 20% of age-adjusted small bowel remaining. The median gestational age was 28 weeks, and 83% were born preterm. None of the patients underwent or were listed for intestinal transplantation during the study period.

3.2. Weaning off PS

At the latest follow up at median age 4.4 years, 76% (158/208) of all study participants and 79% (158/200) of survivors had weaned off PS (Fig. 3). The median duration of PS was 10.4 months (Table 2). Of patients older than two years (n = 170), 76% had reached enteral autonomy, including 86% of NEC patients and 67% of patients with other causes of SBS-IF (P = 0.004). Among PS dependent patients, median duration of PS was 49 (27–72) months. At the end of follow up in PS dependent patients, median PS volume was 47 (35–71) ml/kg/day from 7 (range 2–7) PS infusions per week, providing 49 (31–57) kcal/kg/day and corresponding median 60% of recommended daily intake of energy [18] (Table 2). Weaning off PS continued up to 7.4 years of age, which was the longest time to reach enteral autonomy in the present cohort. There was no significant difference in the rate of reaching enteral autonomy between the participating centers (P > 0.05, Fig. 1).

Patients who had weaned off PN had significantly longer remaining age-adjusted bowel length and colon length, more frequently preserved ileocecal valve, had less often enterostomy and were born more often prematurely compared to those who remained PS dependent (Table 1). In Kaplan Meier analyses, cumulative weaning off PS was more frequent in patients with >30% of small bowel remaining compared to those with less than 30% (P = 0.001, Fig. 3), and in patients with NEC compared to other underlying etiologies of SBS-IF (P = 0.008, Fig. 3). In an univariable Cox regression analysis, shorter remaining age-adjusted small bowel and colon length, lack of ileocecal valve, enterostomy and AIR surgery were risk factors for remaining PS dependent (Supplement Table 1). In a multivariable Cox regression, when corrected for the mediating factors, shorter remaining small bowel and colon length as well as presence of enterostomy constituted as significant risk factors for PS dependency (Supplement Table 1).

3.3. Growth

Overall, weight-for-age and height-for-age z-scores were above –2 SD, considered as normal lower limit, in 85% and 86% of patients, respectively (Fig. 4, Table 2). PS dependency had no significant association with weight z-score at the latest follow up. In contrast, height z-scores were more often below –2 SD in patients who remained PS dependent compared to patients who had weaned off PS (Table 2).

3.4. Intestinal failure associated liver disease

At the end of follow up, 18% of patients had any serum liver biochemistry measurement >1.5 times above upper normal limit, including 37% of PS dependent and 13% of weaned off patients (Table 2). As a surrogate for biochemical cholestasis, only five (3%) patients, four of whom were PS dependent, had bilirubin over 1.5 fold above the upper normal limit (Table 2). Patients with SBS-IF

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Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All patients</th>
<th>PS dependent</th>
<th>Weaned off PS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>208</td>
<td>50</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>Age at SBS diagnosis, days</td>
<td>27 (4–61)</td>
<td>14 (1–61)</td>
<td>30 (5–61)</td>
<td>0.049</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>28 (25–35)</td>
<td>34 (27–37)</td>
<td>27 (25–35)</td>
<td>0.014</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>121 (58)</td>
<td>32 (64)</td>
<td>89 (56)</td>
<td>0.411</td>
</tr>
<tr>
<td>Bowel anatomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel, cm</td>
<td>56 (30–92)</td>
<td>26 (15–53)</td>
<td>63 (36–110)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Small bowel, %</td>
<td>43 (21–80)</td>
<td>18 (14–31)</td>
<td>49 (30–87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Small bowel ≤20%, n (%)</td>
<td>43 (20)</td>
<td>27 (54)</td>
<td>16 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ileum preserved, n (%)</td>
<td>149 (72)</td>
<td>22 (44)</td>
<td>127 (80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICV preserved, n (%)</td>
<td>126 (61)</td>
<td>16 (32)</td>
<td>110 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Colon %</td>
<td>100 (70–100)</td>
<td>75 (9–100)</td>
<td>100 (85–100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ostomy at follow up, n (%)</td>
<td>17 (8)</td>
<td>14 (28)</td>
<td>3 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIR surgery, n (%)</td>
<td>16 (8)</td>
<td>9 (18)</td>
<td>7 (4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Repeated AIR, n (%)</td>
<td>8 (4)</td>
<td>4 (8)</td>
<td>4 (3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Intestinal transplantation, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data are median (IQR) or frequencies (percentage). AIR; autologous intestinal reconstruction, ICV; ileocecal valve, PS; parenteral support, SBS; short bowel syndrome, % percentage of remaining age-adjusted bowel length. P-values are for Mann Whitney U-test or Fisher’s exact test between PS dependent and weaned off patients.
Fig. 3. Cumulative risk of PN dependency in A) all SBS-IF patients, B) among Non-NEC and NEC SBS-IF patients, and C) according to remaining age-adjusted small bowel length. IF; intestinal failure, NEC; necrotizing enterocolitis, PS; parenteral support, SBS; short bowel syndrome. Log-rank p-values are shown.
due to NEC had less often elevations in any liver biochemistry values compared to other SBS-IF patients (19% vs 35%, P = 0.016), PS dependency, longer duration of PS, and SBS due to other diagnosis than NEC were significant risk factors for elevated liver biochemistry values in univariable, and current PS dependency and longer duration of PS in multivariable Cox regression model (Supplement Table 2).

3.5. Autologous intestinal reconstruction surgery

Overall, 16 (8%) patients had undergone at least one AIR surgery, which was repeated in eight (50%) patients (Table 1). AIR surgeries included serial transverse enteroplasty (STEP; n = 15) and tapering (n = 1) as primary procedure, and STEP (n = 7) and tapering (n = 1) as secondary ones. Patients who were PS dependent at the latest follow-up had more frequently undergone AIR surgery (18%) compared to patients, who had weaned off PS (4%, P = 0.004). Overall, 44% of AIR surgery patients weaned off PS and maintained their enteral autonomy during follow up. Patients who underwent AIR procedures had markedly shorter absolute and age-adjusted remaining small bowel length [22 cm [12–35] vs 60 (31–100); 17% [10–25] vs 46% [23–82]], shorter age-adjusted colon length [69% (57–80) vs 100% (76–100)] and less often preserved ileocecal valve (13% vs 65%) compared to those who did not undergo AIR surgery (P ≤ 0.001 for all).

3.6. Survival

Overall survival was 96% (200/208). Eight patients died at median age 0.6 (range 0.1–2.2, 0.3–2.1) years. Among patients who died, SBS-IF was secondary to NEC (n = 4), small bowel atresia (n = 2), gastrointestinal atresia (n = 1) and gastrochisis (n = 1). All succumbed patients were born prematurely at median 30 (range 23–36) weeks of gestation and were PS dependent. Cause of death was considered SBS-IF related in four patients who all died of septic complications. Although none of the deaths were directly related to IFALD, elevated liver biochemistry at the last follow-up was a significant risk factor for mortality in addition to shorter remaining small bowel in univariable Cox regression model (Supplement Table 3).

4. Discussion

Our study provides an overview to long-term outcomes of current SBS-IF management in a Nordic multicenter setting. We showed a high overall survival rate of 96% in children with SBS-IF and at least 60 days on PS after median follow up of 4.4 years. Half of the remaining mortality was due to sepsis, and although none of deaths were directly caused by IFALD, only increased serum liver biochemistry, together with a short remaining small bowel, were associated with mortality. Accordingly, recent retrospective single center series on pediatric SBS-IF with including inclusion periods ranging from 2007 to 2018 have reported comparably high survival rates and liver disease as a major risk factor for mortality [19,20]. A recent large multicenter study of 443 patients with median gestational age of 34 weeks reported a survival rate of 89%, also associated with sepsis and IFALD [21–23]. Earlier meta-analysis and multicenter studies have reported clearly lower survival rates with similar risk factors [16,19]. Here, a high survival rate was reached despite a low median gestation age of 28 weeks known to predispose to added mortality, including increased risk of liver disease and sepsis [24,25], although all deaths occurred in severely premature babies during infancy. Rescue intestinal transplantation among these small babies is extremely challenging not only due to shortage of suitable donors, and none of the SBS-IF patients underwent or were listed for intestinal transplantation in the present series. However, intestinal transplantation remains as a valuable rescue strategy for chronic IF when life-threatening complications develop [26]. Previously, relatively high rates of intestinal transplantation, 17–27%, has been reported for pediatric SBS-IF cohorts with comparable follow-up periods [22,23].

Table 2
Survival, growth, nutrition, and liver biochemistry at the latest follow-up.

<table>
<thead>
<tr>
<th>All patients</th>
<th>PS dependent</th>
<th>Weaned off PS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients alive, n (%)</td>
<td>200</td>
<td>42 (21)</td>
<td>158 (79)</td>
</tr>
<tr>
<td>Age, years</td>
<td>4.4 (2.5–6.9)</td>
<td>4.4 (2.7–6.6)</td>
<td>4.5 (2.5–6.9)</td>
</tr>
<tr>
<td>Growth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight z-score, SD</td>
<td>–0.8 (–1.5–0.1)</td>
<td>–0.7 (–2.0–0.1)</td>
<td>–0.8 (–1.5–0.1)</td>
</tr>
<tr>
<td>Weight z-score below –2 SD, n (%)</td>
<td>30 (15)</td>
<td>9 (22)</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Height, z-score</td>
<td>–0.6 (–1.6–0.0)</td>
<td>–1.1 (–2.1–0.1)</td>
<td>–0.6 (–1.5–0.0)</td>
</tr>
<tr>
<td>Height z-score below –2 SD, n (%)</td>
<td>27 (14)</td>
<td>12 (29)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at PS start, days</td>
<td>0.0 (0.0–6.0)</td>
<td>0 (0–3)</td>
<td>0 (0–12)</td>
</tr>
<tr>
<td>Duration of PS, months</td>
<td>10.4 (4.7–29.2)</td>
<td>49 (27–72)</td>
<td>6.8 (4.1–13.2)</td>
</tr>
<tr>
<td>PS volume, ml/kg/day</td>
<td>n/a</td>
<td>47 (35–71)</td>
<td>n/a</td>
</tr>
<tr>
<td>PS energy, kcal/kg/day</td>
<td>n/a</td>
<td>49 (31–57)</td>
<td>n/a</td>
</tr>
<tr>
<td>PS infusions, n per week</td>
<td>n/a</td>
<td>7 (6–7)</td>
<td>n/a</td>
</tr>
<tr>
<td>Serum liver biochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any liver biochemistry &gt; ULN, n (%)</td>
<td>48 (25)</td>
<td>16 (39)</td>
<td>32 (21)</td>
</tr>
<tr>
<td>Bilirubin, μmol/l</td>
<td>13 (11)</td>
<td>5 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>28 (20–39)</td>
<td>38 (26–70)</td>
<td>26 (19–35)</td>
</tr>
<tr>
<td>AST, U/l</td>
<td>31 (16)</td>
<td>12 (29)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>ALT &gt; ULN, n (%)</td>
<td>7 (3)</td>
<td>4 (11)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>ALT &gt; 1.5 ULN, n (%)</td>
<td>26 (13)</td>
<td>11 (27)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>ALT &gt; 1.5 ULN, n (%)</td>
<td>1 (1)</td>
<td>13 (10–21)</td>
<td>13 (10–21)</td>
</tr>
<tr>
<td>GGT, U/l</td>
<td>13 (11–25)</td>
<td>18 (13–41)</td>
<td>n/a</td>
</tr>
<tr>
<td>GGT &gt; ULN, n (%)</td>
<td>22 (11)</td>
<td>9 (23)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>GGT &gt; 1.5 ULN, n (%)</td>
<td>16 (9)</td>
<td>8 (20)</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>

Data are median (IQR) or frequency (percentage). Number of patients with available measurements: ALT for 193, GGT for 174, bilirubin for 172, weight for 195 and height for 175.


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In the present study 75% of all SBS-IF patients weaned off PS mostly before two years of age, while intestinal adaptation and reaching enteral autonomy continued up to 7.4 years of age. In recent studies enteral autonomy rates of 47–85% have been reported with lowest weaning off rates among patients with shortest remaining bowel [19,20,22,23,27,28], while earlier studies have reported weaning off rates between 50% and 63% [21,29,30]. In line with our results, short remaining bowel length, absence of ileocecal valve, delayed stoma closure, and blood stream infections are well-established risk factors for delayed achievement of enteral autonomy in pediatric SBS-IF [19,30]. The present study population had favorable anatomic characteristics with high prevalence of preserved ileocecal valve and relatively low number of cases with ultra-short bowel, which may have affected the favorable outcomes. Our study also confirmed the previously reported finding that premature NEC patients are more likely to achieve enteral autonomy.

Fig. 4. Weight and height Z-scores at the latest follow-up. PS; parenteral support. Horizontal lines highlight –2 SD.
autonomy [31]. As expected, AIR surgery associated with prolonged PS dependency as these patients represented the most severely affected subgroup with more unfavorable intestinal anatomy. In line with our results, a recent systematic review reported that 46% of patients weaned off PS after AIR surgery [32].

Importantly, a great majority of children showed normal growth patterns and although a third of PS dependent patients had lower height z-scores compared to weaned off patients, weaning off PS did not have a negative impact on weight z-scores. In line with our results, previous studies have shown that long-term PS has a negative effect on height in children with SBS-IF [33–35]. In contrast, others have reported that infants with IF have similar growth patterns during the first two years of life regardless of their PS status [36].

In this cohort the overall occurrence of IFALD, defined with a low threshold of 1.5 fold elevation in liver biochemistry, was 18% while no mortality directly related to liver disease occurred. As we addressed the occurrence of IFALD only at the end of follow-up, comparisons to previous studies are difficult [19–21,37]. In children with SBS-IF, Torres and co-authors reported 66% prevalence of biochemical liver disease at enrollment and, in line with our findings, later resolution of hyperbilirubinemia in 95% [20]. In a previous meta-analysis, the overall incidence of IFALD was 44% [21]. When defining IFALD based on liver histopathology, the reported incidence ranges from 16% to 94% [37–41]. Currently, it remains unknown whether modern nutritional therapy, such as fish oil based parenteral lipids, improve liver histopathology, and what is the natural history of liver disease also after weaning off PS. Here, 13% of patients who had weaned off PS showed biochemical evidence of IFALD. We found PS dependency as the main risk factor for IFALD, whereas NEC diagnosis was a protective factor, reinforcing the liver protective effect of achieving enteral autonomy, which was more efficient among NEC patients [31,36].

The retrospective study design and lack of some of the recently published core outcomes [42], including central line-related infections and thrombosis and use of teduglutide treatment are the main limitations of this study. It is plausible that accumulating central line-related complications will affect patient outcomes over time, highlighting the need for future long-term follow up studies addressing these important issues. In addition, effects of parenteral and enteral nutrition composition and emerging use of glucagon like peptide-2 analogues should be addressed in future studies [43]. While liver biopsy remains as the gold standard for assessment of IFALD [38,44], our definition was based on limited biochemical values. Furthermore, in deceased patients, the elevated liver biochemistry at last follow up may reflect acute illness rather than long-term IFALD related problems. Our results are focused mainly on neonatal onset SBS-IF with need for long-term PS as we did not include SBS patients with need for PS less than 60 days and onset of PS after one year of age.

5. Conclusion

In summary, we have demonstrated that modern multidisciplinary treatment enabled high survival and enteral autonomy rates with limited occurrence of biochemical liver disease and need for intestinal transplantation in pediatric SBS-IF. These results may be used for benchmarking of current outcomes and family counseling.

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Author contributions

AM, MP: Conceptualization, study design, and writing the first draft; AM: Data analysis; AM, HEL, TW, HN, HB, SP, KB, CB, LT, PS: Data curation; All authors: Revision for intellectual content and approving the final version of the manuscript.

Conflicts of interest

The authors have no conflicts of interest. This work was generated within the European reference Network for rare inherited and congenital anomalies (ERNICA).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.05.017.

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