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Clinical Relevancy Statement. Predicting the weaning off long-term parenteral nutrition in children with intestinal failure due to neonatal short bowel syndrome is important to adapt the management. The residual short bowel length and the underlying cause, as known prognostic factors, are not sufficient to assess the timing towards enteral autonomy. Predictive factors should help the clinician to reduce the volume of parenteral nutrition and finally wean off the patient, or on the contrary consider early other treatments such as GLP-2 analogs or intestinal transplantation. In our study, the increasing variation of plasma citrulline concentrations over time seems to represent a reliable predictor of weaning off PN in children with neonatal SBS.

Abbreviations:

AA: Amino acid

CVC: Central venous catheter

EN: Enteral nutrition

ETF: Enteral tube feeding

HPN: Home parenteral nutrition

ICV: Ileo-caecal valve

IF: Intestinal failure

IRC: Intestinal rehabilitation center

ITx: Intestinal transplantation

LILT: Longitudinal intestinal lengthening and tapering

LSHD: Long segment Hirschsprung's disease

NEC: Necrotizing enterocolitis

NPEI: Non-protein energy intake

NPEI/REE: Non-protein energy intake divided by the resting energy expenditure

PN: Parenteral nutrition

PNDI: Parenteral nutrition dependency index

REE: Resting energy expenditure

SBS: Short bowel syndrome

What is known

- The most commonly used predictors for long-term outcome in neonatal short bowel syndrome (SBS) patients include the remnant small bowel length, the presence of the ileo-caecal valve (ICV) and the colon.
- Citrulline is a non-protein alpha-amino acid produced nearly exclusively by the enterocytes in the small bowel. Its plasma concentration reflects functional small intestine mass.
- In adults and children, plasma citrulline has been correlated with enterocyte mass and the length of small bowel.

What is new

- The small bowel anatomical ESPEN SBS classification in 3 types for predicting potential for parenteral nutrition weaning in neonatal SBS.
- The decrease of parenteral caloric intake to assess intestinal adaptation instead of the increase of enteral calories.
- Repeated measurements of plasma citrulline levels, which are negatively correlated with the PN intake, to predict the probability of weaning off PN in addition to the residual bowel length and the anatomical type.

ABSTRACT

Background: Long-term parenteral nutrition (PN) is the mainstay of the therapeutic strategy in intestinal failure (IF) due to neonatal short bowel syndrome (SBS). Our aim was to identify prognostic factors for PN weaning and to assess if measuring plasma citrulline concentrations over time could account for the intestinal adaptation in progress.

Methods: This retrospective study included children with neonatal SBS with surgical measurement of the residual bowel length and repeated plasma citrulline assessments during a 4-year follow-up. The degree of IF was assessed by the PN dependency index (PN caloric intake/Resting energy expenditure). The analysis was carried out according to SBS anatomical groups: end-jejunostomy (type 1), jejuno-colic (type 2) and jejuno-ileal anastomosis (type 3).

Results: Fifty-five patients (8 type 1, 27 type 2, 20 type 3) were included. None of the patients with SBS type 1, 11 (41%) with type 2 and 11 (55%) with type 3 were weaned off during the follow-up period. Plasma citrulline levels significantly increased with time in patients who were finally weaned off PN; conversely, the levels did not consistently increase in patients who were still on PN at the end of the study period. There was an inverse relationship between plasma citrulline levels and the PN dependency index. The increasing citrulline levels had a positive effect on the probability of weaning, 2.7 times higher for each point increase in citrulline. No significant effect of age and residual bowel length at baseline was found.

Conclusion: The increased plasma citrulline level over time in addition to the SBS anatomical type is a reliable marker for subsequent PN weaning. The prediction of PN weaning assessed solely by the residual bowel length or a single measurement of citrulline is insufficient and should also take into account the anatomical type of SBS and repeated measurements of plasma citrulline levels.

Key words: intestinal failure, short bowel syndrome, parenteral nutrition, parenteral nutrition dependency index, plasma citrulline

INTRODUCTION

Neonatal short bowel syndrome (SBS) is the leading cause of intestinal failure (IF) in children (1,2). It is characterized by a state of malabsorption resulting from massive reduction of the absorptive surface after extensive small bowel resection (1,2). Long-term parenteral nutrition (PN) and home-PN are the mainstay of the therapeutic strategy to achieve normal growth, physical development and quality of life in children with SBS-IF (3-12).

There is a growing interest in finding biomarkers that can reliably predict a child's intestinal autonomy potential. The most commonly used predictors for long-term outcome in neonatal SBS patients include the remnant small bowel length, the presence of the ileo-caecal valve (ICV) and the colon (13-20). However, technical difficulties for achieving precise measurements during surgery, the potential intestinal growth in length during the third trimester of gestation for premature infants and the intestinal changes related to small bowel adaptation may limit the use of small bowel length as a completely reliable predictive marker. We need to find reliable biomarkers able to predict the potential for achieving intestinal autonomy at an early stage. It is paramount to identify those children likely to have the ability to be weaned off PN and those children likely to have an irreversible IF who may benefit from an early treatment with GLP-2 analogs (21-24) or ultimately intestinal transplantation (ITx) (25-27).

Citrulline is a non-protein alpha-amino acid produced nearly exclusively by the enterocytes in the small intestine (28-30). Its plasma concentration reflects functional small intestine mass. In adults and children, plasma citrulline has been correlated with enterocyte mass and the length of small bowel (31-33). Although citrulline appears to be a strong biomarker of enterocyte mass, its correlation with intestinal absorption is weaker (30,34) probably due to other mechanisms playing a role in intestinal absorption such as the part of intestine resected (jejunum or ileum), intestinal dysmotility, small intestinal bacterial overgrowth and energy

salvage through the colon (34). It is also questioned whether a single plasma citrulline sample can be considered as an accurate indicator of nutrient absorption in SBS patients as well as a potential marker for weaning off PN.

Our aim was to identify the value of repeated plasma citrulline measurements for predicting PN weaning in children with neonatal SBS according to the anatomical classification of SBS (35). As a consequence, it might help the clinician in quantifying intestinal adaptation in progress and identify early the patients that will be able to be weaned off PN and the ones that will require very long term PN and adapt the management accordingly.

PATIENTS AND METHODS

Patients

This retrospective longitudinal single-center cohort study was performed at the Division of Pediatric Gastroenterology, Hepatology and Nutrition, National Reference Center for Rare Intestinal Disease and intestinal rehabilitation center (IRC) at Necker-Enfants Malades University Hospital, Paris, France.

Children with neonatal SBS on long-term PN were recruited. Criteria for inclusion were: patients with neonatal SBS exclusively followed at our IRC during the years 2009 to 2019; measurement of the length of residual small intestine during surgery; repeated plasma citrulline assessment (>2); and a minimum of 4 years follow-up period.

Exclusion criteria were as follows: late referral to our institution, infants with multiple birth defects, renal failure defined as GFR < 15 ml/min/1.73m^2 or severe comorbidities (autoimmune disease, neoplasia).

SBS patients were divided into three groups according to the European Society for Clinical Nutrition and Metabolism (ESPEN) anatomical classification system (35): type 1 with end-

jejunostomy and no colon in continuity; type 2 with jejuno-colic anastomosis with no ICV and a part of the colon in continuity; and type 3 with jejuno-ileal anastomosis with preservation of both the ICV and the entire colon in continuity.

Methods

All children received PN from birth and were discharged on home-PN (HPN) with a central venous catheter (CVC). PN supply was provided in accordance with the clinical requirements and the ESPGHAN guidelines to allow optimal growth (36). Such PN support includes the use of 1.5-2.5 g/kg/day amino acids through a pediatric solution, Vaminolact® Fresenius Kabi (Bad Homburg, Germany). The non-protein caloric intake consisted of 70-80% of energy as glucose and 20-30% energy provided by a 20% intravenous lipid emulsion (SMOF lipid® Fresenius Kabi, Bad Homburg, Germany). Basal amounts of vitamins (Cernevit Clintec Parenteral®) and trace elements (Aguettant®) are added to the PN solution. Calcium, phosphate and magnesium are calculated according to the patient needs and their stability in the PN solution (37). Enteral feeding was always associated with PN. Oral feeding was preferred to enteral tube feeding (ETF) to enhance intestinal adaptation (38). However, ETF was an option for a few children with severe eating disorders in order to progress towards enteral autonomy (38).

The degree of IF was assessed by using the PN dependency index (PNDI). The PNDI is established from the ratio between: the non protein energy intake supplied by PN for achieving normal growth and the resting energy expenditure (REE) calculated by using Schofield formula for age, gender, body weight and size (37, 39, 40).

In order to adapt PN intake for achieving normal growth and to calculate the PNDI, growth was assessed during outpatient clinics, 3 to 4 times a year. Children were weighed using a digital scale accurate to 0.1kg. The height was measured in a recumbent (under 2 years old) or

standing position, with an accuracy to the nearest 0.1cm. All body weight and height values were reported to *Sempé and Pedron* French growth charts (41).

Plasma citrulline concentrations were regularly performed during follow-up, outside any inflammatory or infectious state. Plasma samples were maintained at -70°C until analysis. Amino acids (AA) were extracted from the plasma by protein precipitation, then separated by ion exchange chromatography, leading to the measurement of plasma citrulline concentration. We studied the trend of plasma citrulline concentration, measured in µmol/l, on the basis of a maximum of 4 time points with an interval of one year between two measurements. The observation period started at the first plasma citrulline concentration measurement, regardless of post-natal age or post-surgical time, measured in stable clinical conditions.

Residual small bowel length had been measured along the anti-mesenteric side starting from the ligament of Treitz, either during resection or at the time of closure of stomas.

Baseline demographics data included birth date and gender. Clinical variables included patient's primary diagnosis, age at the time of first recorded citrulline, body weight and size and the mode of feeding, oral and/or ETF.

Ethics

This retrospective cohort study was approved by the local ethical committee. All data were made anonymous for the analysis. No international registration was needed because of the design of the study, which did not meet the criteria of a clinical trial.

Statistics

Patients included in this study were followed during a period of 4 years. A descriptive analysis of the main characteristics of subjects was performed according to the three types of SBS (35). Given that the quantitative variables were not normally distributed, we reported the

median value and the interquartile range as summary statistics and applied the non-parametric Kruskal Wallis test to evaluate differences between groups at baseline. Absolute and percentage frequencies were used to summarize qualitative variables and Chi-square exact test was performed to evaluate between-groups differences at baseline. To evaluate the probability of being weaned off PN in a period of 4 years we analyzed the Kaplan Meier survival curves. Since we observed PNDI and plasma citrulline concentration over different periods for each patient we applied the multiple mixed effects Cox regression model (42) for repeated measures to understand the association between citrulline and probability of being weaned off. Thus, PNDI was categorized as a binary variable, where 1 indicated values of PNDI = 0 (Weaned off PN) and 0 for values > 0 (Undergoing PN). Plasma citrulline concentration entered in the model as variation over two consecutive time points to understand whether changes through periods of such quantity significantly affected the probability of PN weaning. The use of this specification allowed us to consider heterogeneity between patients by applying a random intercept and a random slope for citrulline variation. Age at baseline, type of SBS and residual small bowel length measured at initial surgery, were used as control variables. The results of the multiple mixed effect Cox model estimation were summarized through Hazard Ratios (HR) and their confidence interval. For all analyses, the significance level was established at alpha = 0.05. Statistical analysis was performed using R statistical software version 3.6.0.

RESULTS

One hundred and four patients with neonatal SBS were followed in our center during the observational period (12 with type 1, 58 with type 2 and 34 with type 3). Forty-eight did not meet the inclusion criteria because of late referral, lack of repeated plasma citrulline assessments or because of a follow-up period < 4 years; one child with SBS type 1 was

excluded as the patient underwent intestine-liver transplantation at 18 months of age. A total of 55 patients were included in the study; 8 had SBS type 1, 27 type 2 and 20 type 3. Five different underlying conditions caused SBS: necrotizing enterocolitis (NEC) (n=17), gastroschisis (n=15), midgut volvulus (n=11), long segment Hirschsprung disease (LSHD) (n=8) and intestinal atresia (n=4) (table 1). Five SBS type 2 patients underwent longitudinal intestinal lengthening and tapering (LILT) according to Bianchi's procedure (43,44).

Table 2 shows the main characteristics of subjects stratified by the three anatomical types of SBS. At baseline, the three groups did not differ significantly for age, gender, body weight and length, plasma citrulline levels or PNDI. The excluded patients had similar characteristics than the included ones: 6 had SBS type 1, 27 type 2 and 16 type 3. No statistical differences were found in age, citrulline levels at baseline and the residual bowel length compared to the included patients in each SBS type group.

At the end of the study period, none of the patients with SBS type 1 had been weaned off PN, while 11 children (41%) with SBS type 2 and 11 (55%) with SBS type 3 were weaned off PN. In Figure 1, the Kaplan Meier curve reports the cumulative probability to be weaned off PN during the follow-up period for SBS type 2 and 3. Patients with SBS type 3 showed higher probability to achieved enteral autonomy at the end of the follow-up period compared to patients with SBS type 2 ($p = 0.035$). None of the patients in group 1 was weaned off PN after 4 years, thus the related survival curve was not included in the figure 1. The median time for weaning off PN was 2.14 years (IQR: 1.83; 3.09) for patients with SBS type 2 and 1.7 years (IQR: 1.34; 2.16) for patients with SBS type 3.

Figure 2 shows the plasma citrulline concentration distribution over time in patients undergoing PN and patients weaned off PN for SBS type 2 and 3 during the study period. Plasma citrulline had increased with time in patients weaned off PN, but not in patients who remained dependent on PN exhibiting a relative plateau. No significant difference in terms of

citrulline concentration was found at the first time point between patients weaned off PN and patients still undergoing PN (p=0.84 for type 2, p=0.65 for type 3), statistically higher concentration were instead reported in patients weaned off PN from time point 2 to time point 4 in both types of SBS ($p < 0.001$). For patients undergoing PN the median PNDI value at the end of the follow-up period were respectively 109% (IQR: 91; 112.5), 102% (IQR: 72.5; 116) and 94% (IQR: 79.5; 130) in SBS type 1, type 2 and type 3 groups.

Figure 3 shows the negative relationship between plasma citrulline and PNDI for all SBS types. Spearman correlation coefficients were respectively -0.36 in type 1 SBS group, -0.69 in type 2 and -0.65 in type 3.

The multiple mixed effect Cox regression results were reported in Table 3. Patients with SBS type 1 were excluded from the estimation because none of them was weaned off PN during the study period. With the introduction of the variation of plasma citrulline concentration, the probability of being weaned off PN after 4 years was not significantly associated with the SBS type, differently from the univariate Kaplan Meier model. Patients who reported a unit increase in the variation of plasma citrulline concentration across two time points were nearly 3 times (HR 2.707) more likely to be weaned off parenteral nutrition. None of the others baseline characteristics (age at baseline and SB length at initial surgery) affected the probability of weaning off PN after 4 years in the cox regression analysis.

DISCUSSION

This study showed that SBS anatomical type, better than residual bowel length, influences the time for achieving intestinal autonomy and that progressive increase of plasma citrulline concentrations over time seemed to be a reliable predictor for subsequent weaning off PN with a negative correlation between plasma citrulline concentrations and the PN dependency

index. To our knowledge, this is the first study involving sequential measurements of plasma citrulline concentrations and the level of PN intake over time in children with SBS.

All children had a SBS following a neonatal event and were on long-term PN from birth, providing adequate nutritional supply for optimal growth (36, 37). As the anatomical characteristics differed, the results were shown according to each SBS type. The three groups did not differ for all baseline clinical characteristics. The results showed the different probabilities to wean off PN according to the three anatomical SBS types. None of the patients with SBS type 1 could be weaned off PN during the study period, while the patients with SBS type 3 showed a higher probability of achieving enteral autonomy than the patients with type 2. Data reported in the literature suggest that the prediction of PN weaning is mostly provided by the length of residual bowel measured at the time of surgery (13-20) and small bowel length is a well accepted predictive indicator of enteral autonomy. However, the precise determination of intestinal residual length is sometimes difficult. This is often the case if the bowel is inflamed (ie, NEC) or extensively adhesing (i.e., gastroschisis) (46). Thus, surgeons do not always measure easily/accurately the length of the remaining small intestine; these measurements can also be unreliable because of the requirement for multiple anastomosis and because the smooth muscle tone of the bowel can vary. Furthermore, the pediatric population has a great potential for longitudinal bowel growth and the rapid bowel adaptation would not be reflected in the static measure obtained during a single operation. As the age at the time of surgical resection influences the expected following rate of the intestine longitudinal growth and hence the post-resection bowel adaptation, we selected only patients on long-term PN for neonatal SBS. Indeed, the elongation of the intestine is known to be rapid in the first 4 years of post-natal life, especially the third trimester of gestation and the first year of life, and it seems to remain constant in the following years until adolescence (47). This reinforces the idea that both the surgical measurement of residual intestine and the

variable potential of bowel adaptation after surgery might make small bowel length alone not as relevant as recognized.

Plasma citrulline concentration is a simple and reliable marker of reduced enterocyte mass (28). Its concentration seems to be correlated to the absorption rate in some intestinal diseases (30) but should be used with caution to evaluate intestinal function in children with SBS. Actually, the correlation is particularly valuable for short lengths but tends to disappear for higher values (29, 30). Rhoads et al (31) showed that there might be a relative plateau in plasma citrulline in children with bowel length >100 cm and evaluated the correlation between single plasma citrulline concentrations and PN dependency (measured as percentage of enteral calories tolerated) in the SBS population. They identified a serum cut-off level of 19 µmol/l associated with the development of enteral tolerance, defined by less than 8 stools per day in patients with normal growth and serum electrolytes, and concluded that higher plasma citrulline concentrations might predict the development of enteral autonomy. It was also clear that sequential determination (tested only in 5 patients) might be more helpful than cross-sectional determination to ascertain if bowel adaptation was taking place. Other studies continued to investigate the question about how quickly to advance the enteral feeds in relation to citrulline plasma levels: Bailly-Botuha et al. (32) showed that no patient with a plasma citrulline concentration < 11 µmol/l was able to be weaned off PN and considered residual bowel length as the main marker predicting whether patients with SBS would be weaned off PN. Fitzgibbons et al. (33) proposed that a cut-off of 15 µmol/l might serve as a prognostic measure regarding the probability of future PN weaning. A recent meta-analysis (30) concluded that citrulline is moderately correlated with enteral absorption in various conditions and 20 µmol/l seemed to be the most prevalent cut-off level. No study correlated the course of plasma citrulline changes to the possibility of weaning off PN in the future. We hypothesized that serial assessment of plasma citrulline along the course of SBS management

might reflect the intestinal adaptation process. In our study we showed that plasma citrulline concentrations and the PN dependency index were negatively correlated. In our experience, the reduction of PN intake while maintaining normal growth better reflects intestinal adaptation than the increase of enteral feeds. Indeed, quantifying enteral intake without measuring malabsorption inherent to SBS does not accurately reflects intestinal function. PN requirements for achieving normal growth remain, therefore, the best measure of the degree of intestinal sufficiency in this setting. Thus, expressing PN dependency in non-protein calories divided by REE (calculated using Schofield equation) allows us to have an indirect marker of intestinal adaptation according to the age, the gender, the weight and the height of the child (39): if the ratio decreases, the PN dependency diminishes reflecting the increase of intestinal absorption capacity, independently of enteral intake.

In our study, a single assessment of citrulline plasma level was not sufficient to measure outcome. The improvement towards enteral autonomy corresponded to the significant increasing trend of plasma citrulline over time. In this regard, an increasing level in plasma citrulline concentrations looked like a reliable marker for assessing whether the patients would be weaned off or not, at least for SBS type 2 and type 3. The length of residual small bowel, measured at the time of surgery, was not sufficient for predicting the probability to wean off PN. Patients weaned off during the 4-year follow up showed higher citrulline levels as early as two years from baseline, showing that an increasing variation of plasma citrulline concentration over two years might already predict the possibility of achieving intestinal autonomy and it should encourage clinicians to keep reducing PN. Conversely, plasma citrulline levels that do not increase regularly may be an indication to an early use of GLP-2 analogs for enhancing the trophicity of the intestinal mucosa and stimulate intestinal adaptation.

Repeated plasma citrulline assessment should be considered as an index for predicting intestinal autonomy only if interpreted according to the type of SBS. In our study, the cumulative probability of weaning off PN depended on the anatomical type. In the setting of SBS, the colon, whenever preserved, plays a crucial role in the salvage of energy, production of trophic factors, and absorption of water and electrolytes (34, 45, 48). Our study confirms the crucial role of the colon in SBS explaining the low probability for achieving enteral autonomy for patients with SBS type 1 (mainly children with LSHD), even if the residual intestinal length and the citrulline at baseline could be twice as much as in children with SBS type 3 (34).

This study has some limitations: the first one being the small number of patients that we could include, especially regarding patients with SBS type 1 which did not allow us to conduct the statistical analysis on this group. Despite this, the included patients were cohort representative: the patients who could not be included because of a lack of data were not significantly different to the included patients regarding the type of SBS, the diagnosis, the age and the citrulline levels at baseline. Another limitation was that we could not perform stool balance analysis to evaluate accurately the absorptive capacity of the remnant bowel. As previously reported (34, 49) the comparison between the consumed calories and the fecal energy loss directly reflects the net intestinal absorption of macronutrients and is the best index to evaluate the intestinal absorption capacity and the potential for autonomy. Nevertheless, the positive variation of plasma citrulline according to the PN dependency index may represent an easier measure of PN dependency in clinical practice.

CONCLUSION

In conclusion, this study showed that the variations of plasma citrulline levels, which were negatively correlated with the PN dependency index, may help to predict the probability of PN weaning, in addition to the residual bowel length and to the type of SBS. Repeated measures of plasma citrulline concentration during SBS patients' follow-up should be performed. A single citrulline assessment is not sufficient to know which patient will remain on very long-term PN (candidate for other treatments) or will be weaned off PN without the need for GLP-2 analogs/transplantation. In clinical practice, using the ESPEN anatomical classification for SBS, quantifying bowel adaptation with the reduction of PN intake and repeated assessment of plasma citrulline levels should be encouraged. Further studies should contribute to elaborate a PN weaning score including the residual bowel length, the anatomical type, the PN dependency index and plasma citrulline longitudinal variations.

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Table 1. Causes of SBS.

n = 55	**Type 1 (n= 8)**	**Type 2 (n=27)**	**Type 3 (n=20)**
Diagnosis – [n]			
- NEC	-	11	6
- Intestinal atresia	-	1	3
- Gastroschisis	-	11	4
- Mid gut volvulus	-	4	7
- LSHD	8	-	-

NEC: necrotizing enterocolitis; LSHD: Long segment Hirschsprung disease

Table 2. Characteristics of subjects according to type of short bowel syndrome.

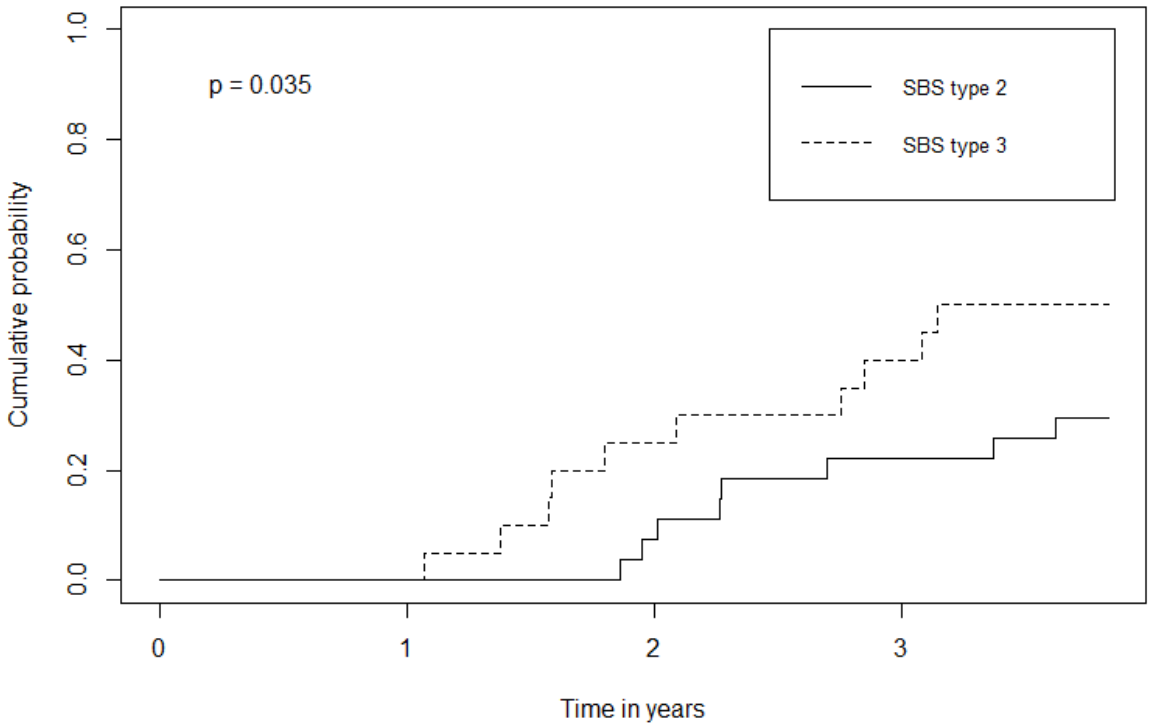
n = 55	**Type 1 (n= 8)**	**Type2 (n=27)**	**Type 3 (n=20)**	**p**
Gender [M (%)]	7(87.5)	17(63)	15(75)	0.284[b]
Age at baseline [years, median (IQR)]	1.57(0.94;2.07)	0.81(0.65;1.27)	0.97(0.46;1.33)	0.422[a]
Body weight [kg, median (IQR)]	8.8 (7.5;10.5)	8.6 (7.5;10.4)	8.9(7.5;10.5)	0.899[a]
Length [cm, median (IQR)]	71(67; 77.5)	70(66.6; 77.4)	70.5(66.9;77.6)	0.826[a]
Residual SB length at baseline [cm, median (IQR)]	65(47.75;71.50)	50(39;67.5)	37(26.75;56.5)	0.151[a]
Citrulline at baseline µmol/l [median (IQR)]	10.5(3.75;13.5)	10(6.5;14)	7.5(5;9.5)	0.570[a]
PNDI at baseline % [median(IQR)]	120(108.5;128.5)	130(107;149)	123.5(90;145.5)	0.650[a]
Patients weaned off PN [n(%)]	0(0)	11(41)	11(55)	0.023[c]
ETF [yes,n(%)] (n=4)	2(25)	5(18.5)	3(15)	0.800[c]
OF [yes,n(%)] (n=38)	6(75)	24(88.9)	17(85)	0.675[c]

[a]Kruskal Wallis test, [b]Chisquare test, [c]Fisher exact test. *Abbreviations: M male, ETF enteral tube feeding, OF oral feeding*

Table 3. Hazard Ratio (HR) of the Mixed effect Cox regression.

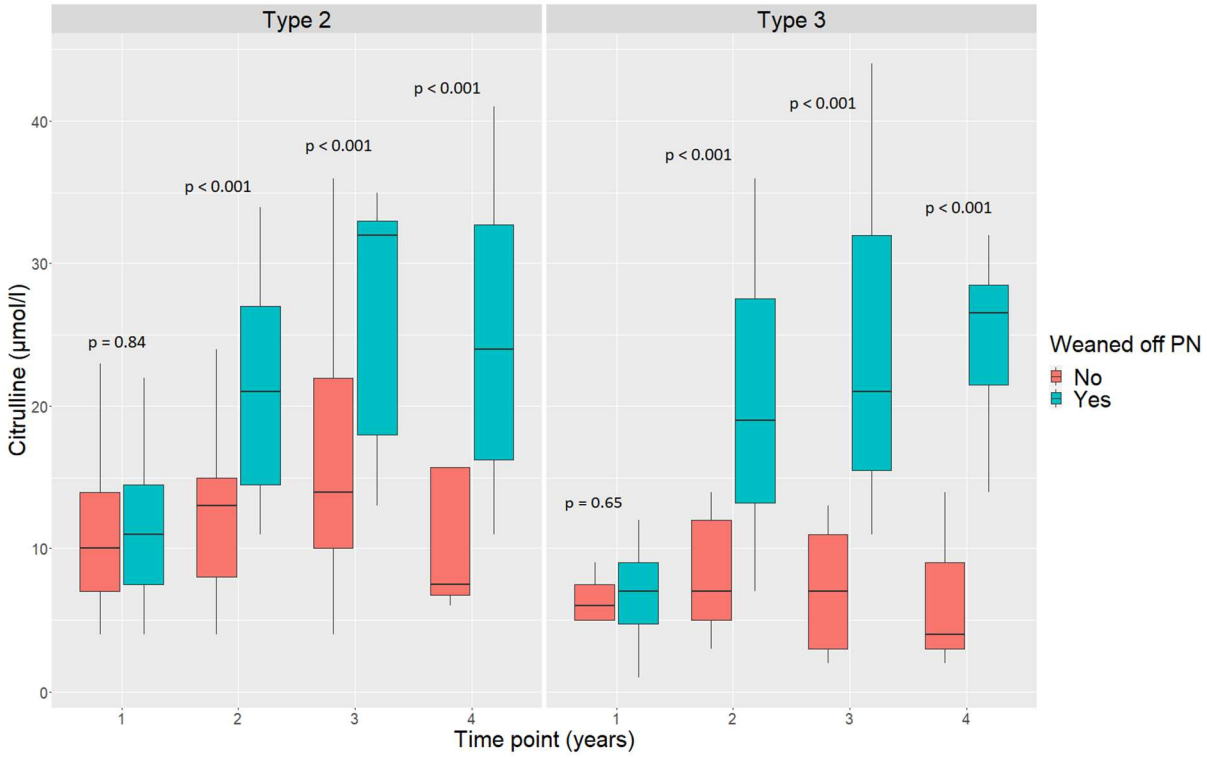
Variables	**HR (CI 95%)**	**p-value**
Age at baseline	0.501 (0.225; 1.113)	0.09
Residual bowel length	1.011 (0.976; 1.029)	0.230
Plasma citrulline variation over time	2.707 (1.442; 5.085)	0.002
SBS Type 3 (SBS Type 2 as reference)	1.585 (0.504; 4.983)	0.240

Figure 1. Cumulative probability to be weaned off PN in a 4 year period according to the type of SBS.



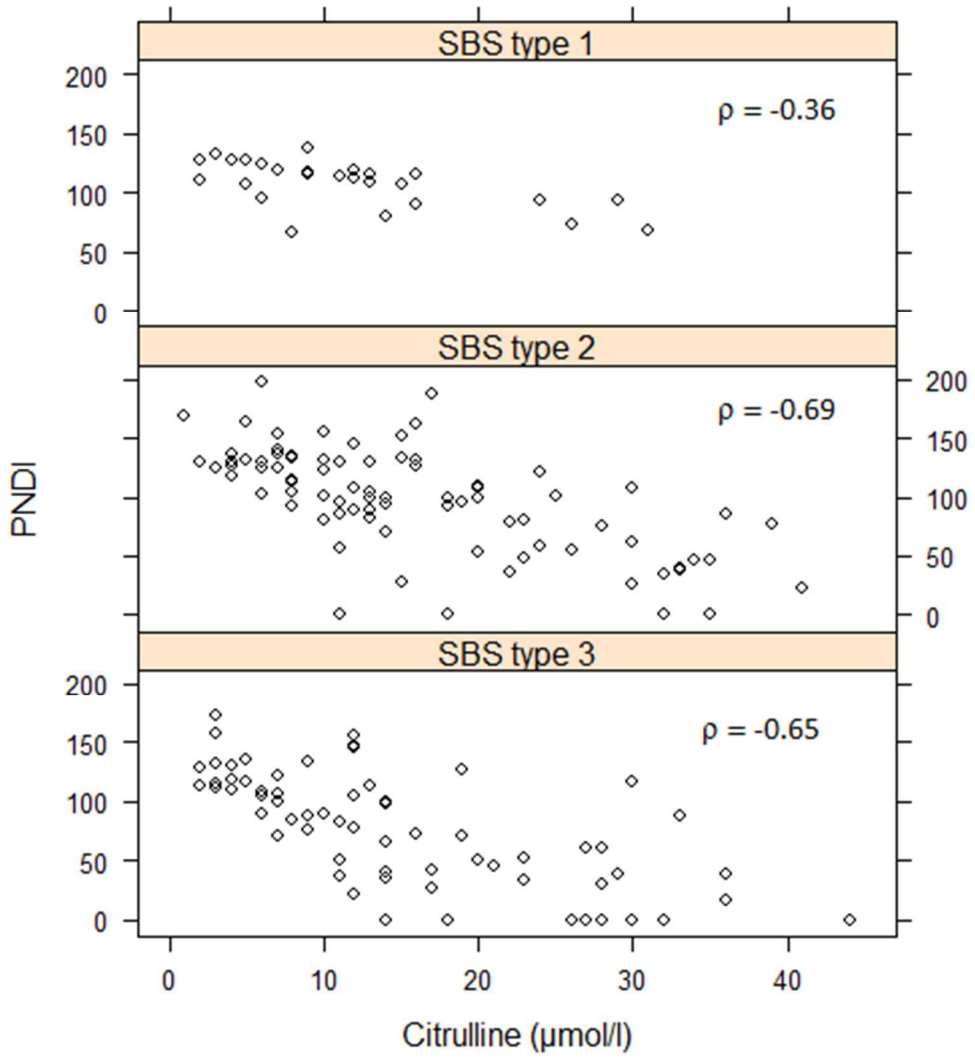
p refers to the log-rank test

Figure 2. Evolution of citrulline plasma levels (µmol/l) over time in patients with SBS type 2 and type 3.



p refers to the Wilcoxon test

Figure 3. Relationship between PNDI (%) and citrulline plasma levels (µmol/l) according to SBS type.



ρ refers to the Spearman rho correlation