Mortality and parenteral nutrition weaning in patients with chronic intestinal failure on home parenteral nutrition: A 30-year retrospective cohort study

Mortality and parenteral nutrition weaning in patients with chronic intestinal failure on home parenteral nutrition: a 30-year retrospective cohort study

Chiara D'Eusebio[1]; Fabio Dario Merlo[2]; Marta Ossola [2]; Fabio Bioletto [1]; Mirko Ippolito [1]; Monica Locatelli[3]; Antonella De Francesco[2]; Marta Anrò[2]; Renato Romagnoli [4]; Paolo Strignano [4]; Simona Bo[1,2*]; Umberto Aimasso[2]

*Corresponding author: Simona Bo

[1]Department of Medical Science, University of Torino, c.so AM Dogliotti 14, 10124, Torino, Italy.

[2] Unit of Dietetic and Clinical Nutrition, Città della Salute e della Scienza Hospital, Corso Bramante, 88, 10126 Torino, Italy.

[3] Food Chemistry, Biotechnology and Nutrition Unit, University of Piemonte Orientale, Largo Donegani 2, 28100, Novara, Italy.

[4] General Surgery 2U, Liver Transplantation Unit, Città della Salute e della Scienza Hospital, Corso Bramante, 88, 10126 Torino, Italy.

Abstract

Background: Home parenteral nutrition (HPN) is the standard treatment for patients with chronic intestinal failure (CIF). Mortality and weaning rates of these patients widely differ among cohorts; however, these outcomes were often considered as independent -rather than competing- events, leading to an upward bias of the retrieved estimates.

Objective: This retrospective cohort study evaluated through a competing risk analysis the rates and predictors of mortality and weaning in CIF patients from an Italian referral center.

Methods: All adult patients with CIF receiving >3 months HPN from 1985 until 2016 were enrolled. Clinical information was collected from the database of the Intestinal Failure Unit of Torino. Patients were stratified according to the presence or not of a short bowel syndrome (SBS).

Results: The cumulative incidences of death/weaning were 27.3%/32.3% and 39.0%/33.7% at 5 and 10 years from HPN starting, respectively. At multivariable competing risk analyses, mortality was predicted by age (SHR=1.65 per 10-year increase; 95%CI 1.35-2.01), type 3 SBS (SHR=0.38; 0.15-0.94), small bowel length ≥100 cm (SHR=0.42; 0.22-0.83), and reconstructive surgery (SHR=0.11; 0.02-0.64) in SBS patients, and by age (SHR=1.38 per 10-year increase; 1.16-1.64) and presence of stoma (SHR=0.30; 0.12-0.78) in non-SBS patients. In the same model, weaning was predicted by type 3 SBS (SHR=6.86; 3.10-15.16), small bowel length ≥100 cm (SHR=3.54; 1.99-6.30) and reconstructive surgery (SHR=2.86; 1.44-5.71) in SBS patients, and by age (SHR=0.79 per 10-year increase; 0.66-0.94) and presence of stoma (SHR=2.64; 1.38-5.07) in non-SBS patients.

Conclusions: Surgical procedures strongly affected mortality and weaning risk in CIF patients.

Key words: chronic intestinal failure; competing risk analysis; home parenteral nutrition; mortality rate; short bowel syndrome; weaning rate.

Background

Chronic Intestinal Failure (CIF) is a disabling condition occurring when the gut function is chronically reduced below the minimum necessary for the absorption of macronutrients and/or water and electrolytes and requiring intravenous fluid and/or nutritional supplementation to maintain health and/or growth [1]. Short bowel syndrome (SBS) is the most common cause of CIF; other causes are pseudo-obstructions due to impairment of intestinal motility, mucosal malfunctions, mechanical obstructions, and intestinal fistulas [1]. Home parenteral nutrition (HPN) has dramatically improved the prognosis of these patients [2-4], but it is associated with several complications, including catheter-related infections and thrombosis, and metabolic complications (such as CIF-associated liver disease, metabolic bone disease and impaired renal function [5]. Consequently, increased risks for hospitalization, poor quality of life, and, above all, reduced survival were reported in CIF patients on chronic HPN [4,6-14]. In particular, in nonmalignant CIF patients, survival rates range from 60% to 83% at 5-years [9,15]. An increased mortality risk has been associated with age [4,16-21], presence of stoma [16], absence of colon [20], causes other than SBS [4,20], and underlying diseases other than Crohn's disease [10,16-18,20,22].

HPN dependence has been widely studied in these patients and ranges from 45% to 90% at 5-years [4,8,10,16,18,23-25]. Conditions and procedures associated with HPN weaning were stoma closure and surgical reconstruction of the alimentary tract [14], presence of intestinal fistulas [18],

autologous gastrointestinal reconstruction, and, more recently, intestinal transplantation [8,17,26-27], while pseudo-obstruction [18] reduces weaning rate.

Indeed, in most cases, the employed statistics did not consider the competing risks existing between death and HPN dependency, leading to overestimation of mortality and weaning rates, as recently proven [28].

The present retrospective cohort study aimed to evaluate the rates and predictors of mortality and weaning in a cohort of patients with CIF from an Italian reference center for the care of intestinal failure over a 30-year period of follow-up through a competing risk analysis.

Patients and Methods

This was a retrospective observational study. All the adult patients with CIF who were on HPN and were followed-up at the Intestinal Failure Unit of the "Città della Salute e della Scienza" Hospital of Torino (a tertiary referral center for CIF support) from the 1st January 1985 to the 31st December 2016 were enrolled. The observation was stopped at the end of 2016 to avoid the inclusion of patients treated with glucagon-like peptide (GLP) agonists which might have influenced the results of the present study.

The inclusion criteria were age ≥18 years and a minimum HPN duration of 3 months. Exclusion criteria were active neoplastic disease and/or being under antineoplastic treatment within the previous 5 years, inability to give informed consent, HPN duration less than 3 months, critically ill patients with a <6-month life expectancy.

Ethical aspects

At the time of HPN starting, patients gave their informed consent to the processing of their data. The study was approved by the local Ethics Committee (protocol number CS2/740/2018), and all the procedures were in accordance with the principles of the Declaration of Helsinki.

Outcomes

The primary outcome was the assessment of the mortality and weaning rates of CIF patients on HPN by a competing risk model. The secondary outcome was the assessment of the associations between clinical variables and mortality and weaning rates.

Data collection

The Intestinal Failure Unit database contains information about all patients with CIF since 1985. Patients were followed-up from their first discharge with HPN until weaning or death. All the complications (including death) occurring during this follow-up period were properly recorded. Demographic and clinical data were extracted from the database.

Patients received personalized nutritional support according to their needs. Usually, HPN was administered by an intermittent schedule, at night for, on average, 10–16 h a day and, in most cases, oral nutrition was not forbidden.

Nutritional care, handling of central venous catheters and HPN complications, periodic follow-up and centralized laboratory and radiological exams were performed according to guidelines [1]. Specialized nurses ensured home care through domiciliary visits monthly (or more frequently if necessary).

Definitions

Causes of CIF were classified as SBS, chronic motility disorders, intestinal fistula, and extensive small bowel mucosal disease, according to guidelines [1]. This classification was performed by

two independent researchers (CDE and UA); if the patient could have been classified under more than one pathophysiological category, the most relevant category was chosen.

All patients underwent a barium or Gastrografin follow-through examination performed by the same trained radiologist to estimate the residual intestinal length. If the colon was in continuity, colon length was described according to the method of Cummings [29]. SBS was considered with a remnant small bowel length ≤200 cm [1]. Anatomical types of SBS were defined as: type 1 (end-jejunostomy), type 2 (jejunocolonic anastomosis), type 3 (jejunoileal anastomosis).

Reconstructive surgery consisted in procedures of stoma closure and restoration of intestinal continuity; no patient underwent intestinal transplantation. All surgical procedures were performed by the same team of highly skilled intestinal surgeons.

Patients were divided into three groups based on the decade of HPN initiation (≤2000, 2001-2010, ≥2011). Weaning from HPN was defined as the complete discontinuation of the treatment with the maintenance of the patient clinical stability, i.e., the maintenance of an adequate urine output, stable body weight, and within range serum and urinary electrolyte values for at least 6 months.

Statistical analyses

Data about mortality during HPN and weaning from HPN were analyzed through cumulative incidence functions, obtained using an Aalen-Johansen estimator [30] considering these two outcomes as competing risks; the analysis was stratified according to the pathophysiological mechanism leading to intestinal failure and tested for differences according to the log-rank test [31]. The association between prognostic factors and the outcomes of interest was separately assessed in patients with SBS and non-SBS patients; this stratification was due to the peculiar clinical characteristics of SBS, the availability of a specific classification in anatomical subtypes (which does not apply to non-SBS patients), and the high prevalence of SBS among patients with

CIF. First, a univariate competing risk Cox-regression was performed, with the estimation of sub-distribution hazards (SHRs) [32]; all parameters related to intestinal anatomy were considered as time-dependent variables, due to the possibility of modifications by subsequent surgical interventions. For SBS patients, the cumulative hazards of weaning according to SBS type and small bowel length < or ≥100 cm have been also reported graphically [33]. Afterwards, predictors were assessed for inclusion in a multivariable model using a stepwise backward selection, using $p<0.05$ as the stopping rule [34]. For SBS patients, only the following summary parameters (SBS type, small bowel length < or ≥100 cm, and reconstructive surgery after HPN initiation) have been considered eligible for inclusion in the multivariable regression model, in order to avoid redundant information. Indeed, the anatomical classification of SBS types is based on the presence/absence of stoma, ileocecal valve, and colon; therefore, including these variables in the multivariable model would have led to overlapping information.

Results

Patient characteristics

Out of 409, after exclusion of 78 patients not meeting the inclusion criteria and 7 patients with incomplete data, 324 patients with CIF were included. The flow of the study was reported in Supplementary Figure 1. The median follow-up was 2.8 years (range 0.3-31.1, IQR 1.3-6.2), with a total observation time of 1524.0 person-years.

The baseline characteristics of the patients are shown in Table 1. The majority were women; SBS was the most frequent mechanism leading to CIF and mesenteric ischemia the most common underlying disease.

Mortality during HPN

While receiving HPN, 121 (37.3%) patients died. The cumulative incidence of death was 6.4%, 12.7%, 17.4%, 27.3%, 39.0%, and 52.9% at 1, 2, 3, 5, 10 and 20 years from the beginning of HPN (Figure 1). Cumulative incidence of mortality during HPN was not associated with the pathophysiological mechanism leading to CIF (Supplementary Figure 2).

Mortality in SBS patients

In all analyses, the variables related to intestinal anatomy were considered as time-dependent variables, thus considering the possible modifications by subsequent surgical interventions. In a univariate competing risk Cox-regression, older age at HPN initiation, and mesenteric ischemia conferred a significantly higher risk of death in SBS patients; on the other hand, type 3 SBS, a greater small bowel length (both if considered as a continuous or dichotomous variable), and reconstructive surgery were associated with a reduced mortality risk (Table 2). In the multivariable model, younger age, type 3 SBS, a higher small bowel length, and reconstructive surgery remained significantly associated with lower mortality risk in these patients (Table 2).

Mortality in non SBS patients

In non SBS patients, age at the baseline, other underlying diseases, colon length, were associated with increased risk of mortality, and presence of a stoma with reduced risk at univariate analyses (Table 3). In the multivariable model, older age, and presence of a stoma, respectively, increased and reduced the risk of mortality (Table 3).

Weaning from HPN

One hundred and four (32.1%) patients were weaned from HPN. The cumulative incidence of weaning was 14.2% at 1 year, 22.9% at 2 years, 28.9% at 3 years, 32.3% at 5 years, and 33.7% both at 10 and 20 years from the beginning of HPN (Fig. 1).

Pathophysiological mechanisms leading to CIF were not significantly associated with weaning from HPN (Supplementary Figure 3).

Weaning in SBS patients

In SBS patients, type 3 SBS, a greater small bowel and colon length, and reconstructive surgery were positively associated with the probability of weaning from HPN, while the presence of a stoma reduced this probability at univariate analyses (Table 4). In the multivariable analysis, type 3 SBS, a small bowel length ≥100 cm and reconstructive surgery significantly predicted the probability of weaning (Table 4). The probability of weaning by SBS types and small bowel length is represented in Supplementary Figure 4.

Weaning in non-SBS patients

Older age was associated with a lower probability to be weaned off from HPN both at univariate and multivariable analyses in non-SBS patients (Table 5). On the other hand, the presence of stoma was associated with a higher probability of weaning in both analyses (Table 5).

The morbidity rates linked to reconstructive surgery were low: overall, 10.3%; mortality due to surgery 0%; re-surgery due to complications (such as intestinal obstruction) within and after 30-days from the reconstructive surgery 2.6% and 7.7%, respectively.

Discussion

In a period of around 30-y observation, 37% of patients with CIF deceased during HPN, while 32% of them were weaned from HPN. Intriguingly, surgical procedures significantly affected these outcomes both in patients with and without SBS.

Mortality during HPN

At 5-years and 10-years from the beginning of HPN, we found a cumulative incidence of death of 27% and 39% respectively. These results were very similar to the findings of the previous study employing the competing risk analysis in a cohort of nonmalignant SBS, being the corresponding figures 26% and 35% [28]. In other studies, the reported survival rate ranged from 60% to 83% at 5 years [9,15] and from 52% to 75% at 10 years [4,8,16,20-21,23-24]; however, comparisons with them were difficult, since survival estimates were reported by Kaplan-Meier method, which suffers from potential bias when competing risks are present [35-36], as in the case of the present analysis. In this setting, in fact, the statistical assumptions of Kaplan-Meier method are violated, and its inappropriate use has been shown to lead to an overestimation of both mortality and weaning rates [28].

We have considered patients with SBS separately from those without SBS, because patients with other diseases leading to CIF, such as chronic motility disorders, intestinal fistula, and extensive small bowel mucosal disease, represent a distinct group of individuals with a poorer health status and the possible coexistence of other systemic diseases [37-39].

As expected, younger age was a protective factor against mortality both in SBS and non-SBS patients, in line with literature [3-4,8-10,16,18,20-21,24,28,40]. In SBS patients, a higher small bowel length was inversely associated with the cumulative incidence of death during HPN, in accordance with previous studies [9-10,21,40], suggesting the importance of an intestinal anatomy close to normal for health. Reconstructive surgery during HPN initiation reduced mortality by 90%, a quite impressive result. It is the first time that the role of reconstructive surgery on the survival of these patients has been analyzed and the lack of consideration towards this prognostic factor is rather unexpected, considering these important results. Stoma closure and restoration of intestinal continuity may prevent death by the reduction of most of HPN-related complications,

such as catheter-related infections and thrombosis, and metabolic complications. However, HPN-related complications were reported to be relatively frequent, but not the most common causes of death in CIF patients [4,18,8,10,15,23,41-44]. It can be hypothesized that the recovery of the "gut" in itself leads to a survival advantage, reducing the complications that can occur as a consequence of the intestinal failure. Furthermore, our surgical team is highly specialized and has a long experience in the surgical treatment of patients with CIF, so that our results might not be generalizable. Finally, a selection bias due to the referral of less serious and more performing patients to the surgeon cannot be excluded. Further studies are needed both to confirm these results in other clinical settings and to disentangle the effects due to HPN weaning from those due to reconstructive surgery alone.

In non-SBS patients, presence of a stoma reduced the cumulative incidence of death during HPN by 70%, another result not previously reported in literature. In these patients, creating an intestinal stoma usually occurred after the resection of a pathological tract, such as an intestinal tract with impaired motility, thus leading to many potential benefits, e.g., resolving constipation, reducing bacterial overgrowth and translocation, lowering the risk of systemic infections, increasing food tolerance, and improving the nutritional status [45-47]. Contrary to our results, the presence of a stoma was previously reported to predict a poor survival [16]. However, the authors did not separate their cohort according to the mechanisms of CIF and analyzed together both patients with SBS and non-SBS, for whom we have found that the presence of a stoma play an opposite role.
Our results suggest the importance of considering separately CIF patients according to the underlying disease. The strong survival benefit of the surgical creation of a stoma in non-SBS patients was a further finding supporting the relevant role of surgery in patients with CIF. This

result has never been reported previously and is worthy to be confirmed in larger cohorts for its practical implications.

Weaning from HPN

Cumulative incidences of weaning were 32% at 5 years, and 34% both at 10 and 20 years from HPN starting. Other studies employing the competing risk model found similar results: 34%, and 38% at 5, and 10 years in a cohort of patients with SBS and intestinal fistula [48], and 42% and 44% in nonmalignant SBS patients [28]. Minimal differences between studies may be due to the different characteristics of the analyzed cohort. In analogy with mortality analyses, weaning from HPN was assessed separately in SBS and non-SBS patients, both for the different course of the disease and the specific eligibility for distinct therapeutic options. Most of HPN weaning in our patients occurred within the first 2 years due to the intestinal adaptation usually occurring in the first years after the intestinal circuit modification [10,15,18,25]. Younger age (in individuals without SBS) and increased bowel length (in SBS individuals) were significantly associated with the likelihood of being weaned from HPN in our patients, consistent with the literature [3,8,10,20,24]. However, we have considered intestinal anatomy as a time-dependent datum, allowing a more precise correlation between gut circuit and weaning probability. Type 3 SBS patients had the highest probability of being weaned from HPN, i.e., around 7-fold higher. This finding is not surprising because of their greater absorbing surface, the presence of both the ileocecal valve, which is responsible for the ileal brake slowing the intestinal transit, and the colon in continuity, which is responsible for fluid absorption [49].

Consistent with our mortality results, reconstructive surgery after HPN starting, and presence of a stoma were strong predictors of weaning respectively in SBS, and non-SBS patients. Only one

249 study has assessed the role of surgical reconstruction on HPN autonomy, reporting weaning in
250 92% of patients [16].
251 Much less expected is the fact that the presence of the stoma greatly increased the likelihood of
252 weaning from HPN in non-SBS individuals, suggesting that in the presence of a non-functioning
253 tract, the best option might be its removal. The exclusion of a nonfunctioning tract, by reducing
254 the risk of constipation and inflammations, might increase appetite and food tolerance which, in
255 turn, potentially decrease the need for HPN.
256 ***Clinical implications***
257 Identifying the patients at higher risk of mortality and at lower risk of weaning might allow to
258 personalize the follow-up schedule and the treatment approach. For example, a patient at increased
259 risk of HPN-dependence could be earlier referred to drug treatments with an agonist of glucagon-
260 like-peptide-2 for its hypertrophic effect on bowel mucosa and/or to small bowel lengthening or
261 intestinal transplantation [50-52]. Furthermore, an appropriate surgical approach, when performed
262 in a highly experienced center in collaboration with a specialized multidisciplinary team, can
263 change the prognosis of these patients. It is worth noting the very low incidence of complications
264 after reconstructive surgery in our center which was in line with what reported in other major
265 reference surgical centers [53]. This underlines the importance of these patients being managed in
266 centers with specific expertise.
267 ***Limitations and strengths***
268 The observational nature of the study did not allow to draw definitive conclusions about causality.
269 We did not analyze the causes of death which might have been an interesting information because
270 it would add data about the potential risks of HPN. Indeed, this investigation was beyond the aims
271 of the present study. We analyzed data from a single center of care; nevertheless, this is the regional

referral center and collects patients from the entire Piedmont region. Data relative to volume and type of the intravenous supplementations were lacking; however, these data have been reported as indicators of the severity of intestinal failure rather than as predictors of survival [52].

The strengths of the present study were the long follow-up, the large cohort studied, the high completeness of the data, the centralization of the laboratory analyses, the use of appropriate statistical tools to deal with competing risks and time-dependent variables, in a setting in which traditional survival models have been shown to lead to inaccurate estimations of weaning and mortality over time [28], and the standardization of the measurements (such as bowel length) and practice (such as CIF treatment) by a multidisciplinary team with a long-lasting expertise in the management of these patients.

Conclusions

Home parenteral nutrition is a life-saving treatment in subjects with CIF. Intrinsic individual characteristics predicted their mortality and the possibility of weaning from HPN. However, proper surgical management of these patients significantly contributed to more favorable health outcomes. Different prognostic factors characterized individuals with and without SBS, thus underlining the importance of separately analyzing CIF patient data based on the pathophysiological mechanism leading to intestinal failure. GLP-agonists may change the indication for surgery in the very near future, since the SBS patients currently not considered for surgery for the small length of non-in-transit bowel could receive benefits from reconstructive surgery combined with the subsequent use of these intestinal growth factors.

Legend to Figure

Figure 1. Cumulative incidence functions of mortality during HPN and weaning from HPN, considering mortality and weaning as competing risks.

List of abbreviations

CIF = chronic intestinal failure

GLP = glucagon-like peptide

HPN = Home parenteral nutrition

IQR = inter-quartile range

SBS = short bowel syndrome

SHRs = sub-distribution hazards

Acknowledgments

Not applicable

Authors' contribution

CDE, FDM, UA contributed to the conception, drafting of the manuscript; FB, ML, SB contributed to the statistical analyses, MO, ADF, MA, MI, RR, PS contributed to data collection. All authors contributed to the revision of the manuscript and approved the final version of the manuscript.

Ethical aspects

At the time of HPN starting, patients gave their informed consent to the processing of their data. The study was approved by the local Ethics Committee (protocol number CS2/740/2018), and all the procedures were in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest

The authors declare that they have no conflict of interest.

Statement and Funding sources

Nothing to declare.

Availability of data

The dataset analyzed during the current study is available from the corresponding author on reasonable request

Consent for publication

Not applicable

References

[1] Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr 2015;34:171-180. https://doi.org/10.1016/j.clnu.2014.08.017.

[2] Pironi L, Boeykens K, Bozzetti F, Joly F, Klek S, Lal S, et al. ESPEN guideline on home parenteral nutrition. Clin Nutr 2020;39:1645-1666. https://doi.org/10.1016/j.clnu.2020.03.005.

[3] Pironi L, Paganelli F, Labate AM, Merli C, Guidetti C, Spinucci G, et al. Safety and efficacy of home parenteral nutrition for chronic intestinal failure: a 16-year experience at a single centre. Dig Liver Dis 2003;35:314-324. https://doi.org/10.1016/s1590-8658(03)0074-4.

[4] Lloyd DA, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence on home parenteral nutrition: experience over a 25-year period in a UK referral centre. Aliment Pharmacol Ther 2006;24:1231-1240. https://doi.org/ 10.1111/j.1365-2036.2006.03106.x.

[5] Cuerda C, Pironi L, Arends J, Bozzetti F, Gillanders L, Jeppesen PB, et al. ESPEN practical guideline: Clinical nutrition in chronic intestinal failure. Clin Nutr 2021;40:5196-5220. https://doi.org/10.1016/j.clnu.2021.07.002.

[6] Stanner H, Zelig R, Rigassio Radler D. Impact of infusion frequency on quality of life in patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr 2022;46:757-770. https://doi.org/10.1002/jpen.2317.

[7] Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med 2000;132:525-532. https://doi.org/10.7326/0003-4819-132-7-200004040-00003.

[8] Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. Clin Nutr 2013;32:368-374. https://doi.org/10.1016/j.clnu.2012.08.007.

[9] Scolapio JS, Fleming CR, Kelly DG, Wick DM, Zinsmeister AR. Survival of home parenteral nutrition-treated patients: 20 years of experience at the Mayo Clinic. Mayo Clin Proc 1999;74:217-222. https://doi.org/10.4065/74.3.217.

[10] Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology 1999;117:1043-1050. https://doi.org/10.1016/s0016-5085(99)70388-4.

[11] Ng SC, Clements PJ, Berquist WE, Furst DE, Paulus HE. Home central venous hyperalimentation in fifteen patients with severe scleroderma bowel disease. Arthritis Rheum 1989;32:212-216. https://doi.org/10.1002/anr.1780320216.

[12] Brown M, Teubner A, Shaffer J, Herrick AL. Home parenteral nutrition--an effective and safe long-term therapy for systemic sclerosis-related intestinal failure. Rheumatology (Oxford) 2008;47:176-179. https://doi.org/10.1093/rheumatology/kem329.

[13] Gurbuz AK, Giardiello FM, Petersen GM, Krush AJ, Offerhaus GJ, Booker SV, et al. Desmoid tumours in familial adenomatous polyposis. Gut 1994;35:377-381. https://doi.org/10.1136/gut.35.3.377.

[14] Quintini C, Ward G, Shatnawei A, Xhaja X, Hashimoto K, Steiger E, et al. Mortality of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis: a single center review of 154 patients. Ann Surg 2012;255:511-516. https://doi.org/0.1097/SLA.0b013e31824682d4.

[15] Bonifacio R, Alfonsi L, Santarpia L, Orban A, Celona A, Negro G, et al. Clinical outcome of long-term home parenteral nutrition in non-oncological patients: a report from two specialised centres. Intern Emerg Med 2007;2:188-195. https://doi.org/10.1007/s11739-007-0056-4.

[16] Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, et al. Survival and nutritional dependence on home parenteral nutrition: Three decades of experience from a single referral centre. Clin Nutr 201;36:570-576. https://doi.org/10.1016/j.clnu.2016.01.028.

[17] Pironi L, Goulet O, Buchman A, Messing B, Gabe S, Candusso M, et al. Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr 2012;31:831-845. https://doi.org/10.1016/j.clnu.2012.05.004.

[18] Joly F, Baxter J, Staun M, Kelly DG, Hwa YL, Corcos O, et al. Five-year survival and causes of death in patients on home parenteral nutrition for severe chronic and benign intestinal failure. Clin Nutr 2018;37:1415-1422. https://doi.org/10.1016/j.clnu.2017.06.016.

[19] Howard L, Malone M. Clinical outcome of geriatric patients in the United States receiving home parenteral and enteral nutrition. Am J Clin Nutr 1997;66:1364-1370. https://doi.org/10.1093/ajcn/66.6.1364.

382 [20] Oke SM, Nightingale JM, Donnelly SC, Naghibi M, Willsmore J, Lloyd D, et al. Outcome of
383 adult patients receiving parenteral support at home: 36 years' experience at a tertiary referral
384 centre. Clin Nutr 2021;40:5639-5647. https://doi.org/10.1016/j.clnu.2021.08.025.
385 [21] Salazar E, Clermont-Dejean NM, Schwenger K, Noelting J, Lu Z, Lou W, et al. Patients with
386 severe gastrointestinal dysmotility disorders receiving home parenteral nutrition have similar
387 survival as those with short-bowel syndrome: a prospective cohort study. JPEN J Parenter Enteral
388 Nutr. 2021;45:530-537. https://doi.org/10.1002/jpen.1866.
389 [22] Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term
390 parenteral nutrition. Aliment Pharmacol Ther 2013;37:587-603.
391 https://doi.org/10.1111/apt.12209.
392 [23] Amiot A, Joly F, Alves A, Panis Y, Bouhnik Y, Messing B. Long-term outcome of chronic
393 intestinal pseudo-obstruction adult patients requiring home parenteral nutrition. Am J
394 Gastroenterol 2009;104:1262-1270. https://doi.org/10.1038/ajg.2009.58.
395 [24] Amiot A, Joly F, Lefevre JH, Corcos O, Bretagnol F, Bouhnik Y, et al. Long-term outcome
396 after extensive intestinal resection for chronic radiation enteritis. Am J Gastroenterol 2013;45:110-
397 114. https://doi.org/10.1016/j.dld.2012.10.003.
398 [25] Watanabe Y, Mizushima T, Fujino S, Ogino T, Miyoshi N, Takahashi H, et al. Long-term
399 outcome of patients with Crohn's disease on home parenteral nutrition. Nutrition 2020;78:110903.
400 https://doi.org/10.1016/j.nut.2020.110903.
401 [26] Sier MF, van Gelder L, Ubbink DT, Bemelman WA, Oostenbroek RJ. Factors affecting timing
402 of closure and non-reversal of temporary ileostomies. Int J Colorectal Dis 2015;30:1185-1192.
403 https://doi.org/0.1007/s00384-015-2253-3.

[27] Rege A. The surgical approach to short bowel syndrome - autologous reconstruction versus transplantation. Viszeralmedizin 2014;30:179-189. https://doi.org/10.1159/000363589.

[28] Fuglsang KA, Brandt CF, Scheike T, Jeppesen PB. Differences in methodology impact estimates of survival and dependence on home parenteral support of patients with nonmalignant short bowel syndrome. Am J Clin Nutr 2020;111-161-169. https://doi.org/10.1093/ajcn/nqz242.

[29] Cummings JH, James WP, Wiggins HS. Role of the colon in ileal-resection diarrhoea. Lancet 1973;1:344-347. https://doi.org/10.1016/s0140-6736(73)90131-1.

[30] Aalen O. Nonparametric estimation of partial transition probabilities in multiple decrement models. The Annals of Statistics 1978;6:534–545. http://dx.doi.org/10.1214/aos/1176344198.

[31] Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. The Annals of Statistics 1988;16:1141–1154. https://doi.org/10.1214/aos/1176350951.

[32] Fine JP, Gray RJ Gray. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999;94:496-509. https://doi.org/10.1111/sjos.12167.

[33] Wayne N. Hazard plotting for incomplete failure data. Journal of Quality Technology 2018:1;27-52. https://doi.org/10.1080/00224065.1969.11980344.

[34] Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;W1-W73. https://doi.org/10.7326/M14-0698.

[35] Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? Stat Med 1993;12:737-751. https://doi.org/10.1002/sim.4780120803.

427 [36] van Walraven C, McAlister FA. Competing risk bias was common in Kaplan-Meier risk
428 estimates published in prominent medical journals. J Clin Epidemiol 2016;69;170-3.e8.
429 https://doi.org/10.1016/j.jclinepi.2015.07.006.
430 [37] Downes TJ, Cheruvu MS, Karunaratne TB, De Giorgio R, Farmer AD. Pathophysiology,
431 diagnosis, and management of chronic intestinal pseudo-obstruction. J Clin Gastroenterol
432 2018;52:477-489. https://doi.org/10.1097/MCG.0000000000001047.
433 [38] Nunes G, Martins C, Teixeira C, Borges MF, Oliveira AP, Fonseca J.
434 Hypogammaglobulinemic sprue manifested as chronic intestinal failure: an uncommon but
435 effective indication for home parenteral nutrition. Turk J Gastroenterol 2018;29:717-718.
436 https://doi.org/10.5152/tjg.2018.18234.

[39] Bennett WG, Watson RA, Heard JK, Vesely DL. Home hyperalimentation for common variable hypogammaglobulinemia with malabsorption secondary to intestinal nodular lymphoid hyperplasia. Am J Gastroenterol 1987;82:1091-1095.

[40] Vantini I, Benini L, Bonfante F, Talamini G, Sembenini C, Chiarioni G, et al. Survival rate and prognostic factors in patients with intestinal failure. Dig Liver Dis 2004;36:46-55. https://doi.org/10.1016/j.dld.2003.09.015.

[41] Stokes MA, Almond DJ, Pettit SH, Mughal MM, Turner M, Shaffer JL, et al. Home parenteral nutrition: a review of 100 patient years of treatment in 76 consecutive cases. Br J Surg 1988;75:481-483. https://doi.org/10.1002/bjs.1800750524.

[42] Noelting J, Gramlich L, Whittaker S, Armstrong D, Marliss E, Jurewitsch B, et al. Survival of patients with short-bowel syndrome on home parenteral nutrition: a prospective cohort study. JPEN J Parenter Enteral Nutr 2021;45:1083-1088. https://doi.org/10.1002/jpen.1984.

[43] Messing B, Lémann M, Landais P, Gouttebel MC, Gérard-Boncompain M, Saudin F, et al. Prognosis of patients with nonmalignant chronic intestinal failure receiving long-term home parenteral nutrition. Gastroenterology 1995;108:1005-1010. https://doi.org/10.1016/0016-5085(95)90196-5.

[44] Pironi L, Joly F, Forbes A, Colomb V, Lyszkowska M, Baxter J, et al. Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. Gut 2011;60:17-25. https://doi.org/10.1136/gut.2010.223255.

[45] Billiauws L, Cohen M, Cazals-Hatem D, Joly F. Small intestine motility disorders: chronic intestinal pseudo-obstruction. J Visc Surg 2022; 159:S22-S27. https://doi.org/10.1016/j.jviscsurg.2022.01.001.

[46] Noel RF, Schuffler MD, Helton WS. Small bowel resection for relief of chronic intestinal pseudo-obstruction. Am J Gastroenterol 1995;90:1142-1145.

[47] Lapointe R. Chronic idiopathic intestinal pseudo-obstruction treated by near total small bowel resection: a 20-year experience. J Gastrointest Surg 2010;14:1937-1942. https://doi.org/10.1007/s11605-010-1295-7.

[48] Kopczynska M, Carlson G, Teubner A, Abraham A, Taylor M, Burden ST, et al. Long-term outcomes in patients with intestinal failure due to short bowel syndrome and intestinal fistula. Nutrients 2022;14:1449. https://doi.org/10.3390/nu14071449.

[49] Van Citters GW, Lin HC. Ileal brake: neuropeptidergic control of intestinal transit. Curr Gastroenterol Rep 2006;8:367-373. https://doi.org/10.1007/s11894-006-0021-9.

[50] Kim ES, Keam SJ. Teduglutide: A review in short bowel syndrome. Drugs 2017;77:345-352. https://doi.org/10.1007/s40265-017-0703-7.

[51] Bioletto F, D'Eusebio C, Merlo FD, Aimasso U, Ossola M, Pellegrini M, et al. Efficacy of Teduglutide for parenteral support reduction in patients with short bowel syndrome: a systematic review and meta-analysis. Nutrients 2022;14:1449. https://doi.org/10.3390/nu14040796.

[52] Pironi L, Steiger E, Joly F, Wanten G, Chambrier C, Aimasso U, et al. Intravenous supplementation type and volume are associated with 1-year outcome and major complications in patients with chronic intestinal failure. Gut 2020;69:1787-1795. https://doi.org/10.1136/gutjnl-2018-318172

[53] Abu-Elmagd KM, Costa G, McMichael D, Khanna A, Cruz RJ, Parekh N, et al. Autologous reconstruction and visceral transplantation for management of patients with gut failure after bariatric surgery: 20 years of experience. Ann Surg 2015;262:586-601. doi: 10.1097/SLA.0000000000001440

Table 1. Baseline characteristics of the cohort, stratified according to the pathophysiological mechanism leading to intestinal failure.

	SBS	**Intestinal fistula**	**Malabsorption**	**Mechanical obstruction**	**Pseudo-obstruction**	**All**
N of patients	209	10	49	38	18	324
Age (years)	59.5±15.8	57.8±10.7	54.4±17.0	58.5±14.5	34.2±13.3	57.2±16.6
Females	103 (49.3)	6 (54.5)	27 (55.1)	30 (78.9)	11 (61.1)	177 (54.6)
Year of HPN start						
≤2000	60 (28.7)	3 (30.0)	7 (14.3)	15 (39.5)	4 (22.2)	89 (27.5)
2001-2010	68 (32.5)	3 (30.0)	18 (36.8)	11 (28.9)	4 (22.2)	104 (32.1)
≥2011	81 (38.8)	4 (40.0)	24 (49.0)	12 (31.6)	10 (55.6)	131 (40.4)
Underlying disease						

IBD	37 (17.7)	3 (30.0)	15 (30.6)	1 (2.6)	0 (0)	56 (17.3)
Radiation enteritis	27 (12.9)	3 (30.0)	5 (10.2)	17 (44.7)	0 (0)	52 (16.1)
Surgical complications	38 (18.2)	0 (0)	6 (12.3)	6 (15.8)	0 (0)	50 (15.4)
Mesenteric ischemia	77 (36.8)	1 (10.0)	4 (8.2)	2 (5.3)	0 (0)	84 (25.6)
Fibro adhesive peritonitis	19 (9.1)	2 (20.0)	3 (6.1)	9 (23.7)	0 (0)	33 (10.3)
Pseudo-obstruction	7 (3.4)	0 (0)	1 (2.0)	0 (0)	17 (94.4)	25 (7.8)
Other	4 (1.9)	1 (10.0)	15 (30.6)	3 (7.9)	1 (5.6)	24 (7.5)
Time on HPN (years)	3.3; 5.8	2.85; 3.4	1.8; 2.4	2.3; 4.6	2.8; 3.5	2.8; 4.8
SBS						
Type 1	101 (48.3)	---	---	---	---	---
Type 2	85 (40.7)	---	---	---	---	---
Type 3	20 (9.6)	---	---	---	---	---
Small bowel length						
< 100	130 (62.2)	0	0	2 (5.3)	0	132 (40.7)
≥ 100	77 (36.8)	10 (100.0)	49 (100.0)	36 (94.7)	18 (100.0)	190 (58.7)
Colon length (%)						
<50	111 (53.1)	1 (10.0)	16 (32.6)	4 (10.5)	3 (16.7)	135 (41.7)
≥ 50	98 (46.9)	9 (90.0)	33 (67.4)	34 (89.5)	15 (83.3)	189 (58.3)
Stoma	110 (52.7)	1 (9.0)	13 (26.5)	6 (14.6)	2 (11.1)	132 (40.7)
Ileocecal valve	23 (7.1)	6 (60.0)	27 (55.2)	31 (81.6)	15 (83.3)	102 (31.5)
Reconstructive surgery	34 (16.3)	1 (10.0)	2 (4.0)	1 (2.6)	1 (5.6)	39 (12.0)

Data are presented as: number (percentage), mean±SD, median; interquartile range

Table 2. Predictors of mortality during HPN in SBS patients, considering weaning as a competing risk. All variables related to intestinal anatomy were considered as time-dependent variables.

Variable	**Crude effect SHR (95%CI)**	**p-value**	**Adjusted effect SHR (95%CI)**	**p-value**
Age at baseline (per 10 years increase)	1.70 (1.38-2.09)	<0.001	1.65 (1.35-2.01)	<0.001
Sex				
Female	1		-----	-----
Male	0.97 (0.62-1.51	0.884	-----	-----
Year of HPN initiation				
≤2000	1		-----	-----
2001-2010	0.70 (0.43-1.15)	0.156	-----	-----
≥2011	0.61 (0.34-1.08)	0.090	-----	-----

Underlying disease				
IBD	1		-----	-----
Radiation enteritis	2.20 (0.83-5.81)	0.113	-----	-----
Surgical complications	2.07 (0.74-5.83)	0.168	-----	-----
Mesenteric ischemia	3.08 (1.31-7.21)	0.010	-----	-----
Fibro-adhesive peritonitis	1.13 (0.33-3.89)	0.847	-----	-----
Chronic intestinal pseudo-obstruction Pseudo-	1.23 (0.31-4.91)	0.774	-----	-----
Other	2.39 (0.50-11.37)	0.272	-----	-----
SBS type				
Type 1	1		1	
Type 2	1.20 (0.73-1.97)	0.466	1.07 (0.62-1.86)	0.811
Type 3	0.27 (0.11-0.67)	0.005	0.38 (0.15-0.94)	0.037
Small bowel length				
< 100 cm	1		1	
≥ 100 cm	0.31 (0.17-0.56)	<0.001	0.42 (0.22-0.83)	0.012
Small bowel length (per 10 cm increase)	0.92 (0.88-0.97)	0.001	-----	-----
Colon length (per 10% increase)	0.98 (0.93-1.03)	0.388	-----	-----
Presence of stoma				
No	1		-----	-----
Yes	1.01 (0.64-1.61)	0.958	-----	-----
Reconstructive surgery after HPN initiation				
No	1		1	
Yes	0.07 (0.01-0.45)	0.006	0.11 (0.02-0.64)	0.014

CI: confidence interval; HPN: home parenteral nutrition; IBD: inflammatory bowel disease; SBS: short bowel syndrome; SHR: sub-distribution hazards.

Table 3. Predictors of mortality during HPN in non-SBS patients, considering weaning as a competing risk. All variables related to intestinal anatomy were considered as time-dependent variables.

Variables	**Crude effect SHR (95% CI)**	**p-value**	**Adjusted effect SHR (95% CI)**	**p-value**
Age at baseline (per 10 years increase)	1.37 (1.16-1.62)	<0.001	1.38 (1.16-1.64)	<0.001
Sex				
Female	1		-----	-----
Male	1.05 (0.59-1.86)	0.875	-----	-----
Year of HPN initiation				

≤2000	1		-----	-----
2001-2010	1.01 (0.51-1.98)	0.986	-----	-----
≥2011	1.00 (0.48-2.05)	0.992	-----	-----
Underlying disease				
IBD	1		-----	-----
Radiation enteritis	1.58 (0.55-4.54)	0.397	-----	-----
Surgical complications	1.45 (0.48-4.36)	0.510	-----	-----
Mesenteric ischemia	3.08 (0.88-10.85)	0.080	-----	-----
Fibro-adhesive peritonitis	2.40 (0.86-6.73)	0.096	-----	-----
Chronic intestinal pseudo-obstruction	1.24 (0.38-4.03)	0.718	-----	-----
Other	3.05 (1.09-8.56)	0.034	-----	-----
Pathophysiology				
Intestinal fistula	1		-----	-----
Malabsorption	0.77 (0.32-1.84)	0.551	-----	-----
Mechanical obstruction	1.05 (0.46-2.41)	0.909	-----	-----
Pseudo-obstruction	0.62 (0.20-1.93)	0.410	-----	-----
Small bowel length (per 10 cm increase)	1.02 (0.99-1.05)	0.154	-----	-----
Colon length (per 10% increase)	1.09 (1.00-1.18)	0.044	-----	-----
Presence of stoma				
No	1		1	
Yes	0.30 (0.11-0.81)	0.018	0.30 (0.12-0.78)	0.013

CI: confidence interval; HPN: home parenteral nutrition; IBD: inflammatory bowel disease; SHR: sub-distribution hazards.

Table 4. Predictors of weaning from HPN in SBS patients, considering mortality as a competing risk. All variables related to intestinal anatomy were considered as time-dependent variables.

Variables	**Crude effect SHR (95% CI)**	**p-value**	**Adjusted effect SHR (95% CI)**	**p-value**
Age at baseline (years)	0.89 (0.77-1.02)	0.097	-----	-----
Sex				
Female	1		-----	-----
Male	1.51 (0.91-2.51)	0.109	-----	-----
Year of HPN initiation				
≤2000	1		-----	-----
2001-2010	1.25 (0.66-2.36)	0.502	-----	-----
≥2011	1.32 (0.71-2.47)	0.375	-----	-----
Underlying disease				

IBD	1		-----	-----
Radiation enteritis	0.89 (0.34-2.36)	0.819	-----	-----
Surgical complications	1.84 (0.82-4.14)	0.138	-----	-----
Mesenteric ischemia	0.73 (0.33-1.61)	0.436	-----	-----
Fibro-adhesive peritonitis	1.82 (0.68-4.86)	0.233	-----	-----
Chronic intestinal pseudo-obstruction	0.95 (0.22-4.08)	0.945	-----	-----
Other	No events	-----	-----	-----
SBS type				
Type 1	1		1	
Type 2	1.70 (0.85-3.44)	0.136	1.96 (0.93-4.13)	0.076
Type 3	8.31 (3.97-17.40)	<0.001	6.86 (3.10-15.16)	<0.001
Small bowel length				
< 100 cm	1		1	
≥ 100 cm	3.76 (2.19-6.48)	<0.001	3.54 (1.99-6.30)	<0.001
Small bowel length (per 10 cm increase)	1.10 (1.07-1.14)	<0.001	-----	-----
Colon length (per 10% increase)	1.14 (1.05-1.22)	0.001	-----	-----
Presence of stoma				
No	1		-----	-----
Yes	0.48 (0.27-0.85)	0.012	-----	-----
Reconstructive surgery after HPN initiation				
No	1		1	
Yes	8.00 (4.33-14.80)	<0.001	2.86 (1.44-5.71)	0.003

CI: confidence interval; HPN: home parenteral nutrition; IBD: inflammatory bowel disease; SBS: short bowel disease; SHR: sub-distribution hazards.

Table 5. Predictors of weaning from HPN in non-SBS patients, considering mortality as a competing risk. All variables related to intestinal anatomy were considered as time-dependent variables.

Variables	**Crude effect SHR (95% CI)**	**p-value**	**Adjusted effect SHR (95% CI)**	**p-value**
Age at baseline (years)	0.79 (0.65-0.95)	0.012	0.79 (0.66-0.94)	0.007
Sex				
Female	1		-----	-----
Male	1.13 (0.61-2.09)	0.705	-----	-----
Year of HPN initiation				
≤2000	1		-----	-----
2001-2010	0.72 (0.34-1.54)	0.403	-----	-----
≥2011	0.63 (0.32-1.26)	0.191	-----	-----

Underlying disease				
IBD	1		-----	-----
Radiation enteritis	0.71 (0.29-1.70)	0.439	-----	-----
Surgical complications	0.66 (0.23-1.88)	0.439	-----	-----
Mesenteric ischemia	0.21 (0.03-1.77)	0.151	-----	-----
Fibro-adhesive peritonitis	0.45 (0.13-1.48)	0.188	-----	-----
Chronic intestinal pseudo-obstruction	0.47 (0.16-1.41)	0.178	-----	-----
Other	0.61 (0.25-1.47)	0.271	-----	-----
Pathophysiology				
Intestinal fistula	1		-----	-----
Malabsorption	1.78 (0.55-5.70)	0.334	-----	-----
Mechanical obstruction	1.07 (0.31-3.67)	0.918	-----	-----
Pseudo-obstruction	1.02 (0.25-4.21)	0.980	-----	-----
Small bowel length (per 10 cm increase)	0.98 (0.95-1.01)	0.163	-----	-----
Colon length (per 10% increase)	0.94 (0.87-1.00)	0.052	-----	-----
Presence of stoma				
No	1		1	
Yes	2.60 (1.37-4.92)	0.003	2.64 (1.38-5.07)	0.003

CI: confidence interval; HPN: home parenteral nutrition; IBD: inflammatory bowel disease; SHR: sub-distribution hazards.