ORIGINAL RESEARCH

Intravenous supplementation type and volume are associated with 1-year outcome and major complications in patients with chronic intestinal failure

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ABSTRACT

Background and aim No marker to categorise the severity of chronic intestinal failure (CIF) has been developed. A 1-year international survey was carried out to investigate whether the European Society for Clinical Nutrition and Metabolism clinical classification of CIF, based on the type and volume of the intravenous supplementation (IVS), could be an indicator of CIF severity.

Methods At baseline, participating home parenteral nutrition (HPN) centres enrolled all adults with ongoing CIF due to non-malignant disease; demographic data, body mass index, CIF mechanism, underlying disease, HPN duration and IVS category were recorded for each patient. The type of IVS was classified as fluid and electrolyte alone (FE) or parenteral nutrition admixture (PN). The mean daily IVS volume, calculated on a weekly basis, was categorised as <1, 1–2, 2–3 and >3 L/day. The severity of CIF was determined by patient outcome (still on HPN, weaned from HPN, deceased) and the occurrence of major HPN/CIF-related complications: intestinal failure-associated liver disease (IFALD), catheter-related venous thrombosis and catheter-related bloodstream infection (CRBSI).

Results Fifty-one HPN centres included 2194 patients. The analysis showed that both IVS type and volume were independently associated with the odds of weaning from HPN (significantly higher for PN <1 L/day than for FE and all PN >1 L/day), patients' death (lower for FE, p=0.079), presence of IFALD cholestasis/liver failure and occurrence of CRBSI (significantly higher for PN 2–3 and PN >3 L/day).

Conclusions The type and volume of IVS required by patients with CIF could be indicators to categorise the severity of CIF in both clinical practice and research protocols.

Significance of this study

What is already known on this subject?

- Previous studies have demonstrated that several clinical risk factors are associated with outcome and risk of parenteral nutrition/intestinal failure-related major complications in patients on long-term home parenteral nutrition.
- However, no objective indicator has been identified to categorise the severity of chronic intestinal failure.

INTRODUCTION

Intestinal failure (IF) is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth.[1] Chronic intestinal failure (CIF) is a long-lasting condition that may be reversible or irreversible. Patients with CIF are metabolically stable and receive IVS at home (home parenteral nutrition,

Significance of this study

What are the new findings?

- The 1-year odds of major complications of home parenteral nutrition/intestinal failure (liver disease and catheter-related bloodstream infection) and weaning from home parenteral nutrition are independently associated with the type and volume of the intravenous supplementation required.
- The 1-year odds of death are non-significantly associated with the type of intravenous supplementation required; future study is required to determine if the latter significantly impacts on the longer term risk of death in this patient cohort.

How might it impact on clinical practice in the foreseeable future?

- The type and volume of the intravenous supplementation could be indicators to categorise the severity of chronic intestinal failure in clinical and research settings.

HPN) for months, years or lifelong.[2] Single or multicentre, mostly retrospective, surveys have described risk factors associated with the patient's outcome, such as survival and reversibility of CIF, and with the risk of HPN/IF-related major complications.[3–5] However, no simple indicator, such as creatinine for kidney disease and arterial oxygen saturation for respiratory disease, has yet been identified to categorise the severity of CIF. Such an indicator would be a useful criterion for both clinical practice and research protocols.

The European Society for Clinical Nutrition and Metabolism (ESPEN) devised a clinical classification of CIF to facilitate communication among professionals through an objective categorisation of patients. This was based on patients' requirements for energy and volume of IVS and originally comprised 16 categories.[1] An international cross-sectional survey was carried out to investigate the applicability of this classification and to evaluate factors associated with the IVS requirements of individual patients.[6] In adult patients with CIF due to non-malignant disease (benign CIF), the loss of intestinal function appeared more comprehensively represented by IVS volume requirement than by energy requirement. The results enabled the derivation of a new simplified eight-category classification of CIF, based on two types of IVS, either fluid and electrolyte alone (FE) or parenteral nutrition admixture containing energy (PN), and four categories of volume.[6]

In order to determine whether ESPEN clinical classification categories could be used as indicators of the severity of CIF, a prospective, multicentre international study was carried out to investigate their association with patients' outcome and the major complications related to HPN/IF. The results of the 1-year follow-up are reported.

MATERIALS AND METHODS

Study design

This was an international survey involving the retrospective collection of data prospectively recorded during a 1-year follow-up period. The severity of CIF was based on both patient outcome and major complications related to HPN/IF. Patient outcome was categorised as still on HPN, weaned from HPN or deceased. The HPN/IF-related complications were described as the occurrence of intestinal failure-associated liver disease (IFALD cholestasis or liver failure), central venous catheter-associated vein thrombosis (CVC-VT) or central venous catheter-related bloodstream infection (CRBSI) at 1-year follow-up.[2]

Baseline HPN centre enrolment and patient inclusion

The baseline data collection was performed on 1 March 2015. Details regarding HPN centre enrolment and the patient inclusion criteria have been published in a previous cross-sectional survey carried out to evaluate the applicability of the clinical classification of CIF.[4] Sixty-five HPN centres from 22 countries enrolled all adult patients (≥18 years old) dependent on HPN for CIF on 1 March 2015. Patients with either benign or malignant disease were included. Patients with active malignant disease were termed as having 'cancer-CIF'. Patients without malignant disease at the time of inclusion in the study were termed as having 'benign-CIF'. Invasive intra-abdominal desmoid disease was included in the benign group because of the chronic nature of the condition and reflecting the fact that it is an established indication for intestinal transplantation.[2] A total of 3239 patients, 9.9% with cancer CIF and 91.1% with benign CIF, were included.[4] For the purpose of the present study, only patients with benign CIF were investigated.

Follow-up data collection

The 1-year follow-up was carried out on patients enrolled in the 2015 baseline cross-sectional study. In February 2016, the study coordinator (LP) sent an email to the HPN centres that participated in the 2015 cross-sectional survey to invite them to participate in the follow-up. The study protocol (online supplementary material 1) and the structured database for the data collection were attached to the invitation letter. Centres were asked to include relevant data from patients' medical records between 1 March 2015 and 1 March 2016 and details of patients' outcome on 1 March 2016.

Data were collected into a structured questionnaire embedded in an Excel (Microsoft, 2013) database (the ESPEN CIF Action Day database) (online supplementary material 2). Centres were invited to contact the study coordinator for any additional explanation or instruction.

Statistical analysis

The term HPN described the provision of IVS, either FE or PN, at the patient's home. *Weaning from* equated to stopping IVS.[1] The clinical classification of CIF consisted of eight categories, based on the type and volume of IVS, calculated as daily mean of the total volume infused per week: volume per day of infusion × number of infusions per week/7 (mL/day): FE1 or PN1, ≤1000; FE2 or PN2, 1001–2000; FE3 or PN3, 2001–3000; FE4 or PN4, >3000.[6]

The pathophysiological mechanisms of IF were classified as short bowel syndrome with end-jejunostomy (SBS-J), with jejuno-colic anastomosis (SBS-JC) or with jejuno-ileal anastomosis and total colon in continuity (SBS-JIC), intestinal dysmotility (dysmotility), intestinal fistulas (fistulas), mechanical obstruction (obstruction) and extensive small bowel mucosal disease (mucosal disease).[6]

The underlying diseases were grouped as follows: IBD, comprising Crohn's disease and UC; mesenteric ischaemia, comprising mesenteric arterious or venous infarction and non-occlusive ischaemia; acute postsurgical complications; chronic intestinal pseudo-obstruction, idiopathic or secondary to intestinal or systemic diseases (CIPO); SBS due to causes other than mesenteric ischaemia, including intra-abdominal adhesions, volvulus, cured cancer, abdominal trauma, intestinal

malformation (other causes of SBS); radiation enteritis; and miscellaneous (collagenous diseases, intra-abdominal desmoids, intestinal polyposis, autoimmune enteropathy, neurological disease, congenital mucosal disease, coeliac disease and other diseases not included in the above categories).

The reasons for weaning from HPN were categorised as medical and surgical, the latter included non-transplant procedures and intestinal transplantation. The odds of weaning from HPN were evaluated by two models of analysis: one including all the weaned patients and one excluding patients weaned due to non-transplant surgery.

HPN/IF-related complications on 1 March 2016 were categorised as follows: IFALD and CVC-VT reported as prevalent cases, when they were already present at baseline, and as incident case, when they developed during the 1-year follow-up. CRBSI was categorised as incident cases occurring during the 1-year follow-up. The incident or prevalent nature of CVC-VT was collected at the time of filling out the database on 1 March 2016, whereas the incident or prevalent nature of IFALD was collected after receiving the filled out database, by asking a specific question to the participating centres.

Practice variation by HPN centre was weighted by including in the statistical analysis the number of patients enrolled in the study by the individual HPN centre. We also estimated a model with centre as a random effect. Although a slight improvement was noted in model fitting (ie, in terms of percentage of correctly classified subjects, with subjects correctly classified: 81% vs 80%), the random effect was omitted in order to preserve the ease of interpretation of the model.

Data are reported as mean±SD, median and range, and absolute and relative frequencies.

Binomial and multinomial logistic regressions were carried out for multivariate analysis. The OR was used to measure the association between the independent variables and the outcome. A competing risk regression model based on Fine and Gray's proportional subhazards approach was also performed in order to model the time to occurrence of competing outcomes. Sub-HRs were presented together with the cumulative incidence functions.

Missing data were excluded from the analysis. Two-tailed p values less than 0.05 were considered statistically significant. All p values were not corrected for multiple-hypothesis testing.

Analyses were performed using the IBM SPSS Statistics package for Windows (V.23.0), R software for Windows (V.3.5.1) (http://cran.r-project.org) and STATA/IC V.16.0 for Windows.

RESULTS

Study population

Fifty-one of the 65 HPN centres which contributed in the 2015 database collection participated in the 2016 follow-up; this included 2194 of the 2919 patients with benign CIF (75.1%) enrolled in 2015. Most of the patients (79.7%) were from European countries, and the remaining were from Israel, USA, Mexico, Argentina, Brazil and Australia. The mean number of patients included in the follow-up by centre was 43.0±54.1 (median: 19; range: 1–231); number of patients by centre: ≤19, n=26 (51.0%) centres, patients n=198 (9.0% of total); 20–49, n=8 (15.7%) centres, patients n=253 (11.5%); 50–99, n=10 (19.6%) centres, patients n=657 (29.9%); ≥100, n=7 (13.7%) centres, patients n=1086 (49.5%). Nine centres included <5 patients each.

Table 1 shows the baseline characteristics and the 1-year outcome of the cohort of patients with benign CIF included in the present study. Two-thirds were women. At baseline, the mean±SD (median; range) patient age, body mass index (BMI) and HPN duration were 51.1±16.2 (56.5; 18.0–98.0) years, 22.3±4.4 (21.7; 10.5–59.6) kg/m^2 and 58.0±70.2 (33.2; 0–474) months, respectively. SBS-J was the most frequent pathophysiological mechanism of IF (35.9% of cases). The most frequent underlying disease was Crohn's disease (21.1%). The type of IVS was FE in 7.9% of patients and PN in 92.1%. The IVS volume was significantly lower in the subgroup of patients receiving FE (1055.8±859.6 mL/day) (median 857.1, range 107.1–4800.0) than in those receiving PN (1055.8±859.6 mL/day) (median 1785.7, range 81.7–7542.8) (p<0.001).

One-year outcome

On 1 March 2016, 1740 (79.3%) patients were still on HPN, 298 (13.6%) were weaned from HPN and 156 (7.1%) were deceased (table 1). The reason for weaning from HPN was reported in 272 cases: spontaneous intestinal adaptation in 138 (50.7%), non-transplant surgery in 114 (41.9%) (surgical intestinal continuity reconstruction in 97 cases), intestinal transplantation (ITx) in 14 (5.1%) and intestinal growth factor therapy in 6 (2.2%) cases. The cause of death was reported in 146 cases: HPN/IF-related in 6 (4.1%) patients (CRBSI 5, IFALD 1), underlying disease-related in 64 (43.8%) (4 due to ITx complications) and other causes (neither HPN/IF nor underlying disease-related) in 76 (52.1%) cases.

HPN/IF complications were recorded in 1859 of 2194 (84.7%) patients. The presence of IFALD cholestasis/liver failure was reported in 97 (4.4%) patients, 66 prevalent and 31 incident cases: cholestasis 63 (64.9%), impending liver failure 11 (11.3%), overt liver failure 18 (18.6%) and not specified 5 (5.1%). A CVC-VT was present in 53 (2.9%) patients, 23 prevalent and 30 incident cases. During the follow-up, 273 (14.7%) patients had 344 episodes of CRBSI: one episode in 224 (82.0%), two episodes in 40 (14.7%), three episodes in 5 (1.8%), four episodes in 2 (0.7%), and 7 and 10 episodes in 1 (0.4%) patient each one.

A variation of IVS type and volume between baseline and end of follow-up was observed in 317 (14.4%) patients: 22 patients changed the IVS type from FE to PN (12.6% of FE), 26 patients changed from PN to FE (1.3% of PN), and 269 patients changed PN volume (13.3% of PN) (online supplementary table 1).

Factors associated with patients' 1-year outcome and HPN/IF complications

Weaning from HPN, death, presence of IFALD cholestasis/liver failure or CVC-VT at the end of follow-up, and occurrence of CRBSI during the 1-year follow-up were considered dependent variables. Baseline patient demographics, IF mechanism, underlying disease, IVS characteristics and number of patients enrolled in the study by individual HPN centre were included as independent variables.

Considering the low number of total number of patients receiving the FE type as well as the very low number of those receiving FE3 and FE4, patients on FE were grouped in a unique cohort for outcome analyses.

Figure 1 shows the cumulative incidence of weaning off and of death according to the type and volume of IVS. When comparing the cumulative incidence function of weaning off and death among groups, non-statistically significant differences were found (p=0.329 and p=0.148 for weaning off and death, respectively): the incidence of weaning off was greater in PN1

Table 1 Baseline characteristics and 1-year outcome and HPN/IF–related major complications of adult patients with chronic intestinal failure due to benign disease

	1-year outcome			1-year HPN/IF major complications		
Baseline patient cohort	**Still on HPN**	**Weaned from HPN**	**Deceased**	**IFALD**	**CVC-VT**	**CRBSI**
n=2194	**n=1740**	**n=298**	**n=156**	**n=97**	**n=53**	**n=273**
Gender (%)						
Male (n=811)	77.3	15.4	7.3	6.7	3.1	14.8
Female (n=1383)	80.5	12.5	7.0	4.4	2.7	14.6
Age, years (%)						
≤29 (n=187)	78.6	19.8	1.6	8.1	1.9	24.2
30–49 (n=575)	80.3	16.2	3.5	5.8	3.1	16.4
50–69 (n=990)	80.2	12.5	7.3	4.4	3.0	12.3
≥70 (n=442)	76.2	10.0	13.8	5.1	2.7	13.8
BMI, kg/m^2 (%)						
≤15 (n=57)	80.7	10.5	8.8	6.3	4.2	14.6
15–18.5 (n=324)	74.4	15.7	9.9	6.3	4.7	14.6
18.5–25 (n=1334)	82.5	10.9	6.6	5.5	2.4	13.3
25–30 (n=363)	75.5	18.7	5.8	3.8	2.5	16.8
≥30 (n=111)	67.6	24.3	8.1	3.0	4.0	25.3
Not reported (n=5)						
Duration of HPN, years (%)						
≤1 (n=575)	60	31.7	8.3	5.4	1.3	14.8
1–3 (n=575)	79.1	13.2	7.7	4.9	1.9	16.1
3–10 (n=748)	89.6	4.5	5.9	5.3	4.0	14.7
>10 (n=293)	91.5	1.7	6.8	5.5	4.4	12.2
Not reported (n=3)						
Mechanism of IF (%)						
SBS-J (n=788)	78.3	14.6	7.1	7.5	2.0	14.6
SBS-JC (n=459)	88.2	7.4	4.4	4.0	5.4	12.1
SBS-JIC (n=140)	77.9	17.1	5.0	4.4	2.7	18.6
Fistulas (n=149)	64.4	23.5	12.1	4.0	0.8	16.8
Dysmotility (n=398)	81.7	10.8	7.5	2.9	3.2	15.7
Obstruction (n=104)	70.2	18.3	11.5	5.6	1.1	14.4
Mucosal disease (n=156)	73.7	17.9	8.3	4.6	2.3	14.6
Underlying disease (%)						
IBD (n=480)	79.8	15.0	5.2	4.5	1.9	11.8
CIPO (n=299)	85.6	10.4	4.0	3.4	2.7	18.9
Other causes of SBS (n=178)	80.7	9.6	9.6	5.8	5.1	19.1
Miscellaneous (n=218)	76.4	18.0	5.6	7.3	4.5	19.2
Mesenteric ischaemia (n=395)	79.2	10.6	10.1	6.4	4.5	13.4
Radiation enteritis (n=164)	82.3	10.4	7.3	2.3	1.5	9.8
Acute surgical complications (n=306)	70.3	20.6	9.2	7.4	1.2	16.3
Not reported (n=154)						
Clinical classification of CIF (IVS volume/day of infusion) (%)						
FE1 (≤1 L) (n=118)	89.8	9.3	0.8	0.9	0.9	6.6
FE2 (1–2 L) (n=40)	77.5	12.5	10.0	2.7	0	10.8
FE3 (2–3 L) (n=10)	80.0	20.0	0	0	22.2	22.2
FE4 (>3 L) (n=6)	83.3	16.7	0	16.7	0	0
PN1 (≤1 L) (n=384)	77.1	16.9	6.0	1.9	4.5	10.7
PN2 (1–2 L) (n=944)	78.9	13.3	7.7	3.8	3.1	15.0
PN3 (2–3 L) (n=482)	78.4	13.5	8.1	8.6	2.0	16.2
PN4 (>3 L) (n=210)	81.4	11.0	7.6	12.4	1.6	22.0
Type of IVS (%)						
Total FE (n=174)	86.2	10.9	2.9	1.9	1.9	8.2
Total PN (n=2020)	78.7	13.8	7.5	12.4	2.9	15.3

Data are reported as percentages of cases.
CIPO: primary n=222, secondary n=77.
IBD: Crohn's disease n=462, UC n=18.
Other causes of SBS: intra-abdominal adhesions n=72, volvulus n=46, cured cancer n=21, abdominal trauma n=26, intestinal malformation n=13.
Miscellaneous: collagenous disease n=40, intra-abdominal desmoids n=22, intestinal polyposis n=16, autoimmune enteropathy n=14, neurological disease n=11, congenital mucosal disease n=14, coeliac disease n=8, other diseases n=93.
BMI, body mass index; CIF, chronic intestinal failure; CIPO, chronic intestinal pseudo-obstruction; CRBSI, catheter-related bloodstream infection; CVC-VT, central venous catheter-associated deep vein thrombosis; FE, fluid and electrolytes alone; HPN, home parenteral nutrition; IF, intestinal failure; IFALD, intestinal failure-associated liver disease: cholestasis or liver failure; IVS, intravenous supplementation; PN, parenteral nutrition-admixture; SBS, short bowel syndrome; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with jejuno-colic anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileal anastomosis with intact colon in continuity.

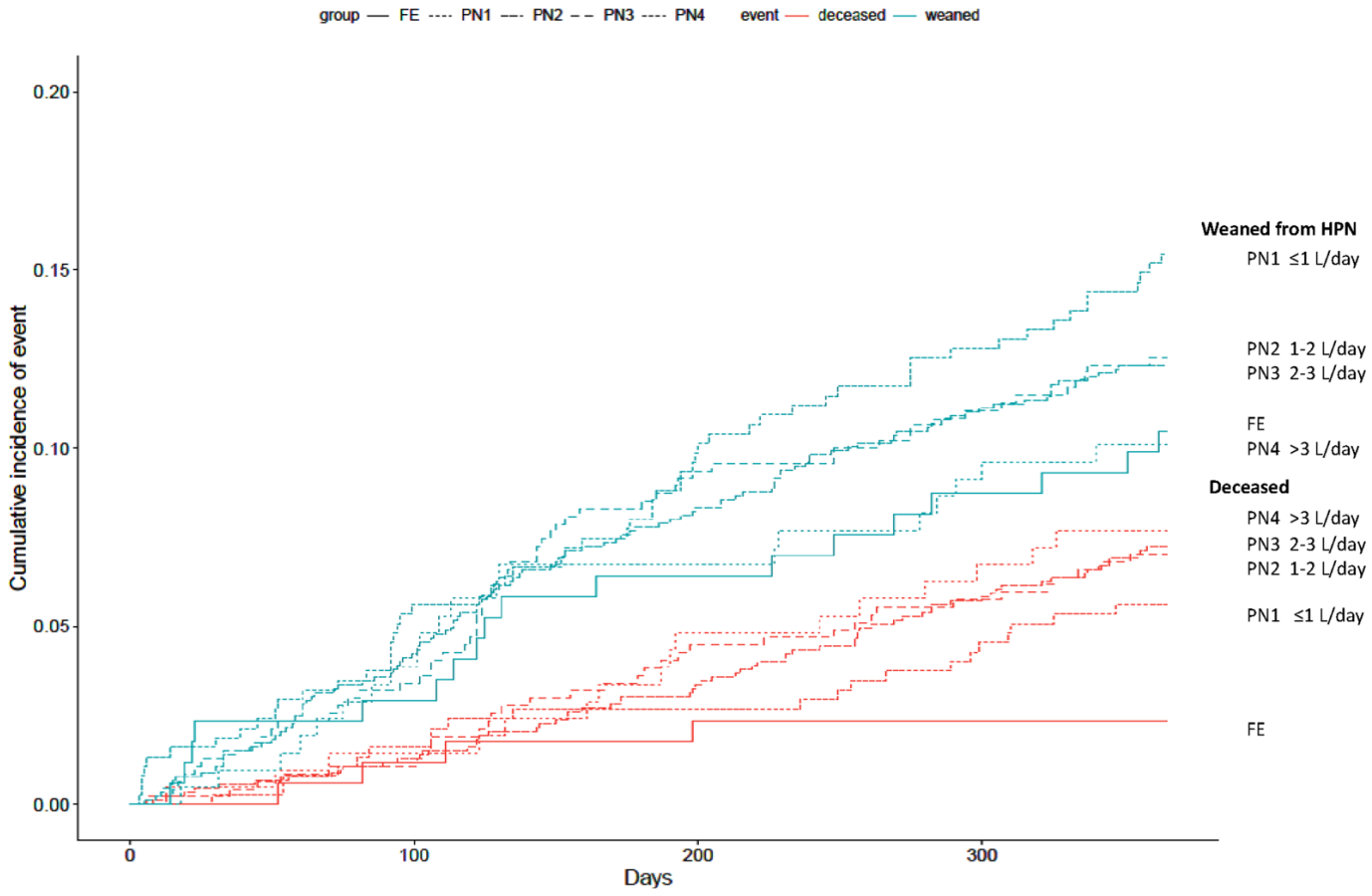

Figure 1 Cumulative 1-year incidence of weaning from HPN and of death according to IVS type and volume. IVS type: FE and PN containing energy; IVS volume (L/day): PN1, ≤1; PN2, 1–2; PN3, 2–3; PN4, >3. FE1, FE2, FE3 and FE4 were grouped in a unique cohort (FE). The patient risk set is reported in online supplementary table 2. FE, fluid and electrolyte alone; HPN, home parenteral nutrition; IVS, intravenous supplementation; PN, parenteral nutrition admixture.

group and lower in PN4 and FE groups; the incidence of death was lower in the FE group.

Odds of 1-year outcome

The associations with IVS type and volume were analysed in comparison with the PN1 category. The odds of weaning from HPN (figure 2 and online supplementary table 2) (1) were lower in the FE type category and in the greatest PN volume categories (PN2, PN3 and PN4); (2) were lower in the oldest decades of age, in the longest duration of HPN categories and in the miscellaneous group of underlying diseases; (3) were higher in the underweight, overweight and obese BMI categories; and (4) showed no association with the number of patients included in the study by individual HPN centres.

The results were confirmed when excluding those patients who were weaned due to a non-transplant surgical procedure (online supplementary table 3). Furthermore, significant lower odds of weaning were observed in patients who had SBS-J or SBS-JC as mechanisms of IF and in those who had an underlying disease categorised in the miscellaneous group.

The odds of death on HPN (figure 2) (1) showed a non-statistically significant decreased risk for the FE type of IVS with respect to PN1 type; (2) were higher in the oldest age categories and in the lowest BMI categories; (3) in comparison with SBS-J mechanism of IF, they were lower in the other SBS types and were higher in the other mechanisms of IF, except the extensive mucosal disease; (4) were increased in the mesenteric ischaemia and decreased in the CIPO groups of underlying disease; and (5) showed a negative association with the number of patients included in the study by individual HPN centres.

The competing risk analysis for the risk of death and of weaning from HPN confirmed the results of the multinomial analysis (online supplementary table 4).

Odds of major complications of HPN/IF

The results are reported in table 2.

The odds of the presence of IFALD cholestasis/liver failure (1) were higher in the greatest PN volume categories in comparison with PN1 and were similar between PN1 and the FE type of IVS; (2) were lower in the dysmotility mechanism of IF; (3) were higher in the group with acute surgical complications as underlying disease; and (4) showed no association with the number of patients included in the study by individual HPN centres.

The odds of the presence of CVC-VT (1) showed no association with IVS categories; (2) were higher in the longest HPN duration categories and in the underweight and obese categories of BMI; and (3) showed negative association with the number of patients included in the study by individual HPN centres.

The odds of CRBSI (1) were higher with the increase of the volume of PN and were similar between PN1 and the FE type of IVS; (2) were lower in older patients; (3) were higher in the overweight and obese categories of BMI and in the CIPO and miscellaneous categories of underlying disease; and (4) showed a

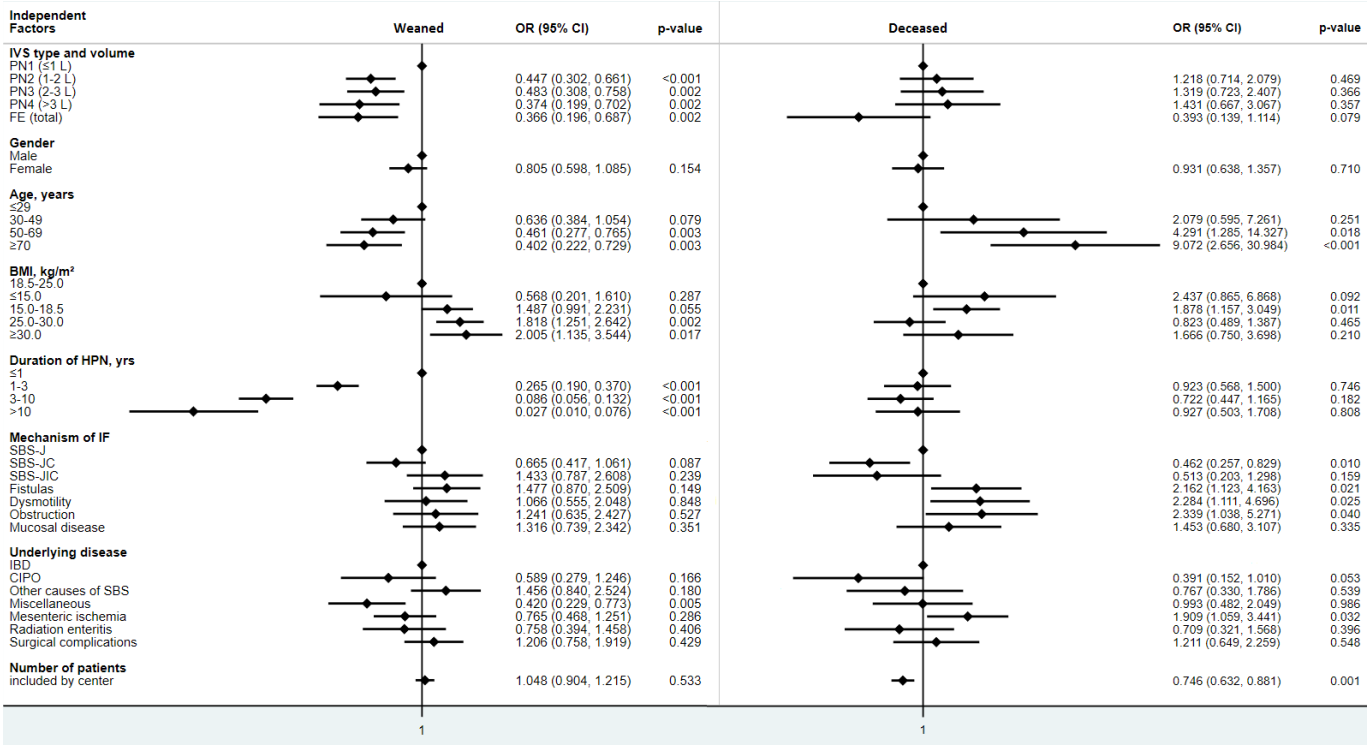

Figure 2 Forest plot of the analysis of factors associated with 1-year probability of weaning from HPN or of death and of HPN/IF in adult patients with CIF. Number of analysed cases due to complete case approach: 2035 (still in HPN: 1610; weaned from HPN: 278; deceased: 147). BMI, body mass index; CIF, chronic intestinal failure; CIPO, chronic intestinal pseudo-obstruction; FE, fluid and electrolytes alone; HPN, home parenteral nutrition; IF, intestinal failure; IVS, intravenous supplementation; PN, parenteral nutrition admixture; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with jejuno-colon anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileal anastomosis with intact colon.

negative association with the number of patients included in the study by individual HPN centres.

The analyses including only the incident cases of IFALD and of CVC-VT showed non-statistically significant ORs (online supplementary table 5).

DISCUSSION

This is the first study aimed at investigating the association between IVS requirement, CIF outcome and the occurrence of major complications in a very large international cohort of HPN-dependent patients with CIF due to benign underlying disease. The results show that both the type and volume of IVS are independently associated with the 1-year odds of weaning from HPN and of HPN/IF-associated major complications, as well as with the risk of mortality, although the latter observation was based on a non-statistically significant finding. In patients with CIF, the type and volume of IVS requirement primarily depend on the degree of the reduction of gut function.[6] However, other factors may be involved, such as the patient's metabolic condition and vital organ function, the patient's compliance with the prescribed treatment (eg, drugs and dietary prescriptions), as well as the treatment protocols of the multidisciplinary team caring for the patient.[1 2] Therefore, while any association between IVS characteristics and the patient's outcome or the occurrence of HPN/IF complications may not be considered causal, they may indicate that the type and volume of IVS reflect comprehensive odds of morbidity and mortality for HPN-dependent patients, independently from the factors that may have determined their prescription. This is further strengthened by the observation that none of the other independent factors entered in the multivariate analysis was contemporaneously associated with odds of weaning from HPN, death, and occurrence of IFALD and CRBSI. These data support the potential role of the ESPEN clinical classification of CIF, based on the type and volume of IVS, as a potential indicator of CIF severity. Further follow-up surveys are required to investigate if this could be translated into a long-term marker of CIF.

The 1-year odds of death depended on the interaction between IVS type and volume rather than on either characteristic alone. Indeed, a non-statistically significant decreased risk of death was observed in those receiving the FE type of IVS, but no association was found with the PN volume alone; since HPN-related deaths were very rare,[3] these results would suggest a less severe clinical condition in patients with CIF requiring only FE supplementation. Future studies will clarify whether the association between the current volume categories of IVS and the risk of death will prove to be statistically significant in the long term and/or whether a different categorisation of the IVS volume will capture any association between IVS volume and risk of death, both in the short and in the long term.

The 1-year probability of weaning from HPN was associated with both the type and volume of IVS. The PN1 volume (≤1 L/day) showed higher odds of weaning than either the greater PN volumes or FE-type IVS. There could be several reasons for a longer maintenance of low-volume FE than of low-volume PN IVS: a more difficult intestinal rehabilitation of fluid and electrolytes than of macronutrient absorption due to concomitant secondary mechanisms of IF causing increased intestinal secretion[1]; the concomitant presence of a reduced kidney function requiring the maintenance of optimal hydration,[2 7] physician and/or patient perception of a lower risk of IVS-associated complications with FE than with PN; patients' better acceptance of FE

Table 2 Binomial logistic analysis of factors independently associated with 1-year probability of IFALD (cholestasis or liver failure), CVC-VT and CRBSI in adult patients on HPN for chronic intestinal failure

	IFALD cholestasis/liver failure			CVC-VT			CRBSI		
Independent factors	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
IVS type and volume									
PN1 (≤1 L)	1			1			1		
PN2 (1–2 L)	1.824	0.738 to 4.508	0.193	0.784	0.370 to 1.663	0.527	1.507	0.967 to 2.346	0.070
PN3 (2–3 L)	3.794	1.522 to 9.458	**0.004**	0.513	0.194 to 1.354	0.178	1.664	1.018 to 2.721	**0.042**
PN4 (>3 L)	4.828	1.792 to 13.004	**0.002**	0.437	0.110 to 1.732	0.239	2.523	1.423 to 4.475	**0.002**
FE (total)	0.849	0.202 to 3.569	0.823	0.384	0.078 to 1.894	0.240	0.743	0.362 to 1.525	0.418
Gender									
Male	1			1			1		
Female	0.703	0.449 to 1.099	0.122	0.798	0.434 to 1.470	0.470	1.066	0.797 to 1.427	0.666
Age (years)									
≤29	1			1			1		
30–49	0.775	0.355 to 1.693	0.522	1.875	0.495 to 7.108	0.355	0.597	0.371 to 0.961	**0.034**
50–69	0.694	0.317 to 1.517	0.360	2.017	0.545 to 7.461	0.293	0.469	0.291 to 0.756	**0.002**
≥70	0.822	0.339 to 1.994	0.665	1.657	0.396 to 6.939	0.489	0.551	0.319 to 0.952	**0.033**
BMI (kg/m^2)									
18.5–25.0	1			1			1		
≤15.0	1.064	0.233 to 4.858	0.936	2.705	0.566 to 12.935	0.212	0.837	0.333 to 2.106	0.706
15.0–18.5	1.612	0.872 to 2.983	0.128	2.335	1.093 to 4.987	**0.028**	1.061	0.697 to 1.615	0.782
25.1–30.0	0.611	0.310 to 1.207	0.156	1.134	0.470 to 2.738	0.779	1.460	1.012 to 2.108	**0.043**
≥30.0	0.591	0.172 to 2.036	0.405	3.124	0.829 to 11.769	0.092	2.769	1.580 to 4.851	**0.000**
Duration of HPN (years)									
≤1	1			1			1		
1–3	1.025	0.553 to 1.899	0.938	1.526	0.516 to 4.515	0.445	1.157	0.787 to 1.703	0.458
3–10	1.070	0.594 to 1.929	0.821	2.889	1.093 to 7.636	**0.032**	1.110	0.762 to 1.618	0.586
>10	0.982	0.470 to 2.052	0.962	3.477	1.179 to 10.256	**0.024**	0.853	0.522 to 1.393	0.524
Mechanism of IF									
SBS-J	1			1			1		
SBS-JC	0.649	0.338 to 1.245	0.193	1.926	0.848 to 4.374	0.117	0.964	0.629 to 1.479	0.868
SBS-JIC	0.629	0.208 to 1.902	0.411	0.760	0.189 to 3.060	0.699	1.377	0.754 to 2.516	0.298
Fistulas	0.593	0.219 to 1.607	0.304	0.580	0.071 to 4.733	0.611	1.207	0.676 to 2.154	0.525
Dysmotility	0.317	0.115 to 0.878	**0.027**	1.431	0.428 to 4.790	0.561	0.759	0.422 to 1.365	0.357
Obstruction	1.072	0.373 to 3.083	0.897	0.438	0.050 to 3.859	0.457	0.800	0.376 to 1.704	0.563
Mucosal disease	0.712	0.260 to 1.945	0.507	0.868	0.203 to 3.713	0.849	0.824	0.445 to 1.526	0.538
Underlying disease									
IBD	1			1			1		
CIPO	1.459	0.481 to 4.427	0.505	1.244	0.303 to 5.113	0.762	2.098	1.092 to 4.03	**0.026**
Other causes of SBS	1.265	0.501 to 3.192	0.619	2.308	0.742 to 7.18	0.149	1.490	0.843 to 2.634	0.170
Miscellaneous	2.038	0.909 to 4.567	0.084	2.308	0.723 to 7.366	0.158	1.712	1.002 to 2.924	**0.049**
Mesenteric ischaemia	1.468	0.732 to 2.943	0.280	2.063	0.798 to 5.333	0.135	1.012	0.626 to 1.635	0.963
Radiation enteritis	0.613	0.170 to 2.210	0.454	0.824	0.161 to 4.206	0.816	0.967	0.487 to 1.918	0.923
Acute surgical complications	2.210	1.089 to 4.482	**0.028**	0.573	0.142 to 2.311	0.433	1.143	0.700 to 1.864	0.593
Number of patients included by centre	0.939	0.765 to 1.153	0.551	0.580	0.451 to 0.745	**0.000**	0.710	0.626 to 0.806	**0.000**

Number of analysed cases due to complete case approach: IFALD cholestasis/liver failure (presence: 91, absence: 1610), CVC-VT (presence: 49, absence: 1652) and CRBSI (presence: 257, absence: 1443).
Bold values indicate statistically significance.
BMI, body mass index; CIPO, chronic intestinal pseudo-obstruction; CRBSI, catheter-related bloodstream infection; CVC-VT, central venous catheter-associated deep vein thrombosis; FE, fluid and electrolytes alone; HPN, home parenteral nutrition; IF, intestinal failure; IFALD, intestinal failure-associated liver disease; IVS, intravenous supplementation; PN, parenteral nutrition admixture; SBS, short bowel syndrome; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with jejuno-colon anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejuno-ileal anastomosis with intact colon.

than of PN, because of shorter duration of FE infusion compared with PN[2]; and the lower cost of FE. All of these factors would make weaning from FE slower/less likely than weaning from PN.

The risks of IFALD and of the occurrence of CRBSIs were also associated with both the type and volume of IVS, whereas no association was observed with the presence of CVC-VT. The odds of IFALD and of CRBSI were greater in patients receiving the highest volumes of PN in comparison with the lowest PN volumes and the FE type of IVS. Furthermore, the odds of these complications were higher in the greater PN volume categories.

These data are in keeping with previous studies.[2 8 9] The pathogenesis of IFALD is multifactorial, including factors related to IVS, underlying GI disease and systemic factors, especially episodes of sepsis.[2 10] IVS overfeeding and a high amount of lipid emulsion are recognised causes of IFALD.[2 10] Similarly, CRBSI occurrence has also previously been reported to occur more frequently in those dependent on an increased number of days of IVS[8]; this may relate to more frequent handling of the central venous catheter, increasing infection risk or the association between macronutrients, vitamins and trace metals affecting microbial growth in the PN admixture.[11 12]

Most of the other independent factors found to be associated with patient outcome and HPN/IF complications were in keeping with data from previous studies.[2 3 8 10] As expected, non-transplant surgery was the cause of weaning off HPN in a large percentage of patients.[13] Notably, data on the causes of death on long-term HPN are consistent with previous observations,[3–5 13–15] even though the percentage of HPN-related deaths (4%) was lower than that reported in longer retrospective surveys (10%–14%).[3–5 13–15] This could be due to the short duration of the present follow-up, as it is known that the rate of the HPN-related death increases with the duration of treatment.[4] The 344 episodes of CRBSI registered in the 1859 patients accounted for a rate of CRBSI of 0.18 per catheter-year, or 0.50 per 1000 catheter-days, a rate that is in the range reported in the literature.[2] The 30 incident cases of CVC-VT observed at 1-year follow-up accounted for an incidence rate of 0.016 per catheter-year, which is also in the lower range of the literature (0.02–0.09 cases per catheter-year).[2 16] The same incidence rate can be accounted for the 31 incident cases of IFALD cholestasis/liver failure. These data are of some relevance as no prospective study has yet been carried out on this HPN/IF complication.[17]

The weakness of the study is mainly represented by the retrospective collection of data prospectively recorded in the previous 12 months, which would imply a risk of some under-reporting, and by not using a comorbidity index to assess the patient's general condition. However, CIF can develop as a complication of a number of GI or systemic underlying diseases having different pathogenesis and outcomes.[1] Therefore, the underlying disease that we collected and included in the statistical analysis could be considered as a surrogate comorbidity index, as supported by the finding of an increased risk of death in patients with CIF due to mesenteric ischaemia. The strength of the study is clearly reflected by its international multicentre structure and by the study population, which is the largest cohort of patients with CIF ever enrolled in a single survey. These characteristics should avoid the potential bias associated with the analysis of individual centre cohorts, which could be influenced by local practice and expertise and mitigate the impact of the above possible weakness on statistical analyses. Considering that CIF is a rare disease,[1] the observation of lower odds of death and of HPN/IF complications in HPN centres which included a larger number of patients in the study would support the importance of creating networks facilitating the referral of patients with CIF to few but appropriately organised and experienced centres.[18] Finally, the agreement between our results and the risk factors, other than IVS, reported by previous studies would support the overall reliability of our findings.

In conclusion, the type of IVS, either FE or PN, and the volume of the PN admixture, as categorised by the ESPEN clinical classification of CIF, were found to be independently associated with the 1-year risk of death, of weaning from HPN and of major complications of HPN/IF. These results support the ESPEN categorisation of IVS as potential marker of the severity of CIF.

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Collaborators The Home Artificial Nutrition and Chronic Intestinal Failure special interest group of the European Society for Clinical Nutrition and Metabolism (ESPEN).

Contributors LP devised the study protocol, collected the data, analysed the results and drafted the manuscript. The Home Artificial Nutrition and Chronic Intestinal Failure Special Interest Group of ESPEN discussed and approved the protocol study, discussed the results and reviewed the manuscript before submission. All coauthors participated in the acquisition of data, revised the final analysis, approved the final version of the manuscript and were accountable for all aspects of the work.

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