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

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2 1 **The intravenous supplementation type and volume is associated with one-year outcome and the**
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4 2 **major complications in patients with chronic intestinal failure**
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9 4 Loris Pironi, Ezra Steiger, Francisca Joly, Geert Wanten, Cecile Chambrier, Umberto Aimasso, Anna Simona
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27 13 Nardi, André Van Gossum and Simon Lal.

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29 14 The Home Artificial Nutrition and Chronic Intestinal Failure special interest group of the European Society
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2 27 **What is already known on this subject?**
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- 4 28 • Previous studies have demonstrated that several clinical risk factors are associated with outcome
5
6 29 and the risk of parenteral nutrition/intestinal failure-related major complications in patients on
7
8 30 long-term home parenteral nutrition. However, no objective indicator has yet been identified to
9
10 categorize the severity of chronic intestinal failure.
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13 32 **What are the new findings?**
14

- 15 33 • The one-year odds of major complications of home parenteral nutrition/intestinal failure (liver
16
17 34 disease and catheter-related blood stream infection) and weaning from home parenteral nutrition
18
19 are independently associated with the type and volume of the intravenous supplementation
20 35 required.
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22 36 • The one-year odds of death is non-significantly associated with the type of intravenous
23
24 37 supplementation required; future study is required to determine if the latter significantly impacts
25
26 38 on the longer term risk of death in this patient cohort.
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31 40 **How might it impact on clinical practice in the foreseeable future?**
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- 33 41 • The type and the volume of the intravenous supplementation could be indicators to categorize the
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35 42 severity of chronic intestinal failure in clinical and research settings.
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1
2 43 **Abstract**

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4 44 **Background and aim**

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6 45 No marker to categorize the severity of chronic intestinal failure (CIF) has yet been developed. A one-
7
8 46 year international survey was carried out to investigate whether the European Society for Clinical Nutrition
9
10 47 and Metabolism (ESPEN) clinical classification of CIF, based on the type and the volume of the intravenous
11
12 48 supplementation (IVS) could be an indicator of CIF severity.

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14
15 49 **Methods**

16
17 50 At baseline, participating home parenteral nutrition (HPN)-centers enrolled all adults with ongoing
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19 51 CIF due to non-malignant disease; demographic data, body mass index, CIF mechanism, underlying disease,
20
21 52 HPN duration and IVS category were recorded for each patient. The type of IVS was classified as fluid and
22
23 53 electrolyte alone (FE) or parenteral nutrition admixture (PN). The mean daily IVS volume, calculated on
24
25 54 weekly basis, was categorized as: <1, 1-2, 2-3, >3 L/day. The severity of CIF was determined by patient
26
27 55 outcome (still on HPN, weaned from HPN, deceased) and the occurrence of major HPN/CIF-related
28
29 56 complications: intestinal failure associated liver disease (IFALD), catheter-related venous thrombosis (CVC-
30
31 57 VT) and catheter-related bloodstream infection (CRBSI).

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35 58 **Results**

36
37 59 Fifty-one HPN-centers included 2194 patients. The analysis showed that both IVS type and volume
38
39 60 were independently associated with the odds of weaning from HPN (significantly higher for PN <1 L/day
40
41 61 than for FE and all the PN >1 L/day), patient's death (lower for FE, $p=0.079$), presence of IFALD-
42
43 62 cholestasis/liver failure and occurrence of CRBSI (significantly higher for PN 2-3 and PN >3 L/day).

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47 63 **Conclusions**

48
49 64 The type and the volume of the IVS required by patients with CIF could be indicators to categorize
50
51 65 the severity of CIF in both clinical practice and research protocols.

66 Introduction

67 Intestinal failure (IF) is defined as the reduction of gut function below the minimum necessary for the
68 absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is
69 required to maintain health and/or growth, [1]. Chronic intestinal failure (CIF) is a long-lasting condition
70 that may be reversible or irreversible. Patients with CIF are metabolically stable and receive IVS at home
71 (home parenteral nutrition, HPN) for months, years or lifelong, [2]. Single or multicenter, mostly
72 retrospective, surveys have described risk factors associated with the patient's outcome, such as survival
73 and reversibility of CIF, and with the risk of HPN/IF-related major complications, [3-5]. However, no simple
74 indicator, such as creatinine for kidney disease and SaO₂ for respiratory disease, has yet been identified to
75 categorize the severity of CIF. Such an indicator would be a useful criterion for both clinical practice and
76 research protocols.

77 The European Society for Clinical Nutrition and Metabolism (ESPEN) devised a clinical classification of
78 CIF, to facilitate communication among professionals through an objective categorization of the patients.
79 This was based on patients' requirements for energy and volume of IVS and originally comprised 16
80 categories, [1]. An international cross-sectional survey was carried out to investigate the applicability of this
81 classification and to evaluate factors associated with the IVS requirements of individual patients, [6]. In
82 adult patients with CIF due to non-malignant disease (benign-CIF), the loss of intestinal function appeared
83 more comprehensively represented by IVS volume requirement than by energy requirement. The results
84 enabled the derivation of a new simplified 8-category classification of CIF, based on two types of IVS, either
85 fluid and electrolyte alone (FE) or parenteral nutrition admixture containing energy (PN), and four
86 categories of volume, [6].

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

1
2 92 **Material and methods**

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4 93 *Study design*

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6 94 This was an international survey involving the retrospective collection of data prospectively recorded
7
8 95 during a one-year follow-up period. The severity of CIF was based on both patient outcome and major
9
10 96 complications related to HPN/IF. The patient's outcome was categorized as still on HPN, weaned from HPN
11
12 97 or deceased. The HPN/IF-related complications were described as the occurrence of intestinal failure
13
14 98 associated liver disease (IFALD-cholestasis or liver failure), central venous catheter associated vein
15
16 99 thrombosis (CVC-VT) or central venous catheter related bloodstream infection (CRBSI) at one-year follow-
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20 100 up, [2].

21
22 101 *Baseline HPN center enrollment and patient inclusion*

23
24 102 The baseline data collection was performed on March 1st, 2015. Details regarding HPN-center
25
26 103 enrollment and the patient inclusion criteria have been published in the previous cross-sectional survey
27
28 104 carried out to evaluate the applicability the clinical classification of CIF, [4]. Sixty-five HPN centers from 22
29
30 105 countries enrolled all adult patients (≥ 18 years old) dependent on HPN for CIF on March 1st, 2015. Patients
31
32 106 with either benign or malignant disease were included. Patients with active malignant disease were termed
33
34 107 as having "cancer-CIF". Patients without malignant disease at time of inclusion in the study were termed as
35
36 108 having "benign-CIF". Invasive intra-abdominal desmoid disease was included in the benign group, because
37
38 109 of the chronic nature of the condition and reflecting the fact that it is an established indication for intestinal
39
40 110 transplantation, [2]. A total of 3239 patients, 9.9% with cancer-CIF and 91.1% with benign-CIF were
41
42 111 included, [4]. For the purpose of the present study, only patients with benign-CIF were investigated.

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46 112 *Follow up data collection*

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48 113 The one-year follow up was carried out on patients enrolled in the 2015 baseline cross-sectional
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50 114 study. In February 2016, the study coordinator (LP) sent an email to the HPN centers that participated in
51
52 115 the 2015 cross-sectional survey, to invite them to participate in the follow up. The study protocol
53
54 116 (**Supplemental material 1**) and the structured database for the data collection were attached to the
55
56 117 invitation letter. Centers were asked to include relevant data from the patient's medical records between
57
58 118 March 1st, 2015 and March 1st, 2016 and details of the patient's outcome on March 1st, 2016.

1
2 119 Data were collected into a structured questionnaire embedded in an Excel (Microsoft Co., 2013) database
3
4 120 (the ESPEN CIF Action Day database) (**Supplemental material 2**). Centers were invited to contact the study
5
6 121 coordinator for any additional explanation or instruction.
7

8 9 122 *Ethical statement*

10
11 123 The study was approved by the Home Artificial Nutrition and Chronic Intestinal Failure (HAN&CIF)
12
13 124 special interest group of ESPEN. The research was based on anonymized information taken from patient
14
15 125 records at time of data collection. The study was conducted with full regard to confidentiality of the
16
17 126 individual patient. Each patient was labelled with two anonymized identifications: one given by the HPN-
18
19 127 center and one given by the database manager. Ethical committee approval was obtained by the individual
20
21 128 HPN centers according to local regulations. The collected data were used only for the study purpose.
22
23 129 Contributing centers have been anonymized for data analysis and presentation.
24
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26 27 130 *Statistical analysis*

28
29 131 The term HPN described the provision of IVS, either FE or PN, at the patient's home. Weaning from
30
31 132 equated to stopping IVS [1]. The clinical classification of CIF consisted of 8 categories, based on the type
32
33 133 and volume of IVS, calculated as daily mean of the total volume infused per week: volume per day of
34
35 134 infusion \times number of infusions per week / 7 (mL/day): FE1 or PN1, ≤ 1000 ; FE2 or PN2, 1001–2000; FE3 or
36
37 135 PN3, 2001–3000; FE4 or PN4, >3000 , [6].
38
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40 136 The pathophysiological mechanisms of IF were classified as short bowel syndrome with end-
41
42 137 jejunostomy (SBS-J), with jejunocolic anastomosis (SBS-JC) or with jejunoleileal anastomosis and total colon
43
44 138 in continuity (SBS-JIC), intestinal dysmotility (Dysmotility), intestinal fistulas (Fistulas), mechanical
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46 139 obstruction (Obstruction) and extensive small bowel mucosa disease (Mucosal disease), [6].
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48

49 140 The underlying diseases were grouped as follows: inflammatory bowel disease (IBD), comprising
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51 141 Crohn's disease and ulcerative colitis; mesenteric ischemia, comprising mesenteric arterious or venous
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53 142 infarction and non-occlusive ischemia; acute post-surgical complications; chronic intestinal pseudo-
54
55 143 obstruction, idiopathic or secondary to intestinal or systemic diseases (CIPO); short bowel syndrome due to
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57 144 causes other than mesenteric ischemia, including intra-abdominal adhesions, volvulus, cured cancer,
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59 145 abdominal trauma, intestinal malformation (Other causes of SBS); radiation enteritis; miscellaneous
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1
2 146 (collagenous diseases, intra-abdominal desmoids, intestinal polyposis, autoimmune enteropathy,
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4 147 neurological disease, congenital mucosal disease, celiac disease and other diseases not included in the
5
6 148 above categories).

8
9 149 The reasons for weaning from HPN were categorized as medical and surgical, the latter included non-
10
11 150 transplant procedures and intestinal transplantation. The odds of weaning from HPN were evaluated by
12
13 151 two models of analysis: one including all the weaned patients and one excluding patients weaned because
14
15 152 of non-transplant surgery.

17
18 153 HPN/IF-related complications at March 1st 2016 were categorised as follows: IFALD and CVC-VT
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20 154 reported as prevalent cases, when they were already present at baseline, and as incident case, when they
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22 155 developed during the one-year follow up. CRBSI were categorized as incident cases occurring during the
23
24 156 one-year follow up. The incident or prevalent nature of CVC-TV was collected at time of filling out the
25
26 157 database on March 1st 2016, whereas the incident or prevalent nature of IFALD was collected after
27
28 receiving the filled out database, by asking a specific question to the participating centers.

30
31 159 Practice variation by HPN-center was weighted by including in the statistical analysis the number of
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33 160 patients enrolled in the study by the individual HPN-center. We also estimated a model with center as a
34
35 161 random effect. Although a slight improvement was noted in model fitting (i.e. in terms of percentage of
36
37 162 correctly classified subjects, with subjects correctly classified: 81% vs 80%), the random effect was omitted
38
39 in order to preserve the ease of interpretation of the model.

41
42 164 Data are reported as mean \pm standard deviation (SD), median and range, absolute and relative
43
44 165 frequencies.

46
47 166 Binomial and multinomial logistic regressions were carried out for multivariate analysis. The odds
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49 167 ratio was used to measure the association between the independent variables and the outcome. A
50
51 168 competing risk regression model based on Fine and Gray's proportional subhazards approach was also
52
53 169 performed in order to model the time to occurrence of competing outcomes. Subhazard ratios were
54
55 presented together with the Cumulative Incidence Functions.

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58 171 Missing data were excluded from the analysis. Two-tailed p-values less than 0.05 were considered as
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60 172 statistically significant. All p-values were not corrected for multiple-hypothesis testing.

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The analyses were performed using the IBM SPSS Statistics package for Windows, version 23.0 (BM
Co., Armonk, NY, USA), R software for Windows, version 3.5.1 (<http://cran.r-project.org>) and STATA/IC 16.0
for Windows

Accepted Manuscript

1
2 176 **Results**

3
4 177 *Study population*

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6 178 Fifty-one of the 65 HPN-centers which contributed in the 2015 database collection, participated in
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8
9 179 the 2016 follow up; this included 2194 of the 2919 benign-CIF (75.1%) patients enrolled in 2015. Most of
10
11 180 the patients (79.7%) were from European Countries, the remaining were from Israel, US, Mexico, Argentina,
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13 181 Brazil and Australia. The mean number of patients included in the follow up by center was 43.0 ± 54.1
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15 182 (median: 19; range: 1-231); number of patients by center: ≤ 19 , n. 26 (51.0%) centers, patients n. 198 (9.0%
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18 183 of total); 20-49, n. 8 (15.7%), patients 253 (11.5%); 50-99, n. 10 (19.6%) centers, patients n.657 (29.9%);
19
20 184 ≥ 100 n. 7 (13.7%) centers, patients n. 1086 (49.5%). Nine centers included < 5 patients, each.

21
22 185 **Table 1** shows the baseline characteristics and the one-year outcome of the cohort of patients with
23
24 186 benign-CIF included in the present study. Two-thirds were females. At baseline, the mean \pm SD, (median;
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26
27 187 range) patient age, 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)
28
29 188 kg/m² and 58.0 ± 70.2 (33.2,0-474) months, respectively. SBS-J was the most frequent pathophysiological
30
31 189 mechanism of IF (35.9% of cases). The most frequent underlying disease was Crohn's disease (21.1%). The
32
33 190 type of IVS was FE in 7.9% of patients and PN in 92.1%. The IVS volume was significantly lower in the
34
35
36 191 subgroup of patients receiving FE 1055.8 ± 859.6 mL/day (median 857.1, range 107.1–4800.0) than in those
37
38 192 receiving PN 1055.8 ± 859.6 mL/day (median 1785.7, range 81.7-7542.8) ($P < 0.001$).

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40 193 *One-year outcome*

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42 194 On March 1st, 2016, 1740 (79.3%) patients were still on HPN, 298 (13.6%) were weaned from HPN
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45 195 and 156 (7.1%) were deceased (**Table 1**). The reason for weaning from HPN was reported in 272 cases:
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47 196 spontaneous intestinal adaptation in 138 (50.7%), non-transplant surgery in 114 (41.9%) (surgical intestinal
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49 197 continuity reconstruction in 97 cases), ITx in 14 (5.1%) and intestinal growth factor therapy in 6 (2.2%)
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51 198 cases. The cause of death was reported in 146 cases: HPN/IF-related in 6 (4.1%) patients (CRBSI 5, IFALD 1),
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54 199 underlying disease-related in 64 (43.8%) (4 due to ITx complications) and other causes (neither HPN/IF nor
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56 200 underlying disease-related) in 76 (52.1%) cases.

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58 201 HPN/IF complications were recorded in 1859 of the 2194 (84.7%) patients. The presence of IFALD-
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60 202 cholestasis/liver failure was reported in 97 patients (4.4%), 66 prevalent and 31 of which were incident

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2 203 cases: cholestasis 63 (64.9%), impending liver failure 11 (11.3%), overt liver failure 18 (18.6%), not specified
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4 204 5 (5.1%). A CVC-VT was present in 53 patients (2.9%), 23 prevalent and 30 incident cases. During the follow
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6 205 up, 273 patients (14.7%) had 344 episodes of CRBSI: one episode in 224 (82.0%); two episodes in 40
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8 206 (14.7%); three episodes in 5 (1.8%); four episodes in 2 (0.7%); 7 and 10 episodes in 1 (0.4%) patient each
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11 207 one.

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13 208 A variation of IVS type and volume between baseline and the end of follow up was observed in 317
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15 209 (14.4%) patients: 22 patients changed the IVS type from FE to PN (12.6% of FE), 26 patients changed from
16
17 210 PN to FE (1.3% of PN) and 269 patients changed PN volume (13.3% of PN) (**Supplemental table 1**).

1
2 **Table 1.** Baseline characteristics and one-year outcome and home parenteral nutrition (HPN)/intestinal failure (IF) – related major complications of adult patients
3 with chronic intestinal failure due to benign disease. (IFALD, intestinal failure associated liver disease: cholestasis or liver failure; CVC-VT, central venous catheter-
4 associated deep vein thrombosis; CRBSI, catheter related bloodstream infections). Data are reported as percentages of cases.
5
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Baseline patient cohort n. 2194	One-year outcome			One-year HPN/IF major complications		
	Still on HPN n. 1740	Weaned from HPN n. 298	Deceased n. 156	IFALD n. 97	CVC-VT n. 53	CRBSI 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/m², (%)						
≤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, yrs (%)						
≤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)						

1							
2	Mechanism of IF (%)						
3	SBS-J (n.788)	78.3	14.6	7.1	7.5	2.0	14.6
4	SBS-JC (n.459)	88.2	7.4	4.4	4.0	5.4	12.1
5	SBS-JIC (n.140)	77.9	17.1	5.0	4.4	2.7	18.6
6	Fistulas (n.149)	64.4	23.5	12.1	4.0	0.8	16.8
7	Dysmotility (n.398)	81.7	10.8	7.5	2.9	3.2	15.7
8	Obstruction (n.104)	70.2	18.3	11.5	5.6	1.1	14.4
9	Mucosal disease (n.156)	73.7	17.9	8.3	4.6	2.3	14.6
10							
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12							
13	Underlying disease (%)						
14	IBD (n.480)	79.8	15.0	5.2	4.5	1.9	11.8
15	CIPO (n.299)	85.6	10.4	4.0	3.4	2.7	18.9
16	Other causes of SBS (n.178)	80.7	9.6	9.6	5.8	5.1	19.1
17	Miscellaneous (n.218)	76.4	18.0	5.6	7.3	4.5	19.2
18	Mesenteric ischemia (n.395)	79.2	10.6	10.1	6.4	4.5	13.4
19	Radiation enteritis (n.164)	82.3	10.4	7.3	2.3	1.5	9.8
20	Acute surgical complications (n.306)	70.3	20.6	9.2	7.4	1.2	16.3
21	Not reported (n.154)						
22							
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24							
25	Clinical classification of CIF						
26	(IVS volume/day of infusion) (%)						
27	FE1 (≤1 L) (n.118)	89.8	9.3	0.8	0.9	0.9	6.6
28	FE2 (1-2 L) (n.40)	77.5	12.5	10.0	2.7	0	10.8
29	FE3 (2-3 L) (n.10)	80.0	20.0	0	0	22.2	22.2
30	FE4 (>3 L) (n.6)	83.3	16.7	0	16.7	0	0
31	PN1 (≤1 L) (n.384)	77.1	16.9	6.0	1.9	4.5	10.7
32	PN2 (1-2 L) (n.944)	78.9	13.3	7.7	3.8	3.1	15.0
33	PN3 (2-3 L) (n.482)	78.4	13.5	8.1	8.6	2.0	16.2
34	PN4 (>3 L) (n.210)	81.4	11.0	7.6	12.4	1.6	22.0
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39	Type of IVS (%)						
40	Total FE (n.174)	86.2	10.9	2.9	1.9	1.9	8.2
41	Total PN (n.2020)	78.7	13.8	7.5	12.4	2.9	15.3
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215 BMI, body mass index; HPN, home parenteral nutrition; IF, intestinal failure; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with
216 jejuno-colic anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejunio-ileal anastomosis with intact colon in continuity; CIF chronic intestinal
217 failure; IVS, intravenous supplementation; FE, fluid and electrolytes alone; PN, parenteral nutrition-admixture; IBD (inflammatory bowel disease): Crohn's disease
218 n.462, Ulcerative colitis n.18; CIPO (chronic intestinal pseudo-obstruction): primary n.222, secondary n.77; Other causes of SBS: Intra-abdominal adhesions n.72,
219 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,
220 Intestinal polyposis n.16, Autoimmune enteropathy n.14, Neurological disease n.11, Congenital mucosal disease n.14, Celiac disease n.8, Other diseases n.93

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2 221 *Factors associated with the patient's one-year outcome and HPN/IF-complications*

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4 222 Weaning from HPN, death, presence of IFALD-cholestasis/liver failure or CVC-VT at the end of the
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6 223 follow up, and occurrence of CRBSI during the one-year follow up were considered the dependent
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8 224 variables. The baseline patient's demographics, IF mechanism, underlying disease, IVS characteristics and
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10
11 225 number of patients enrolled in the study by individual HPN-center were included as independent variables.
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13 226 Considering the low number of total patients receiving the FE type as well as the very low number of
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15 227 those receiving FE3 and FE4, patients on FE were grouped in a unique cohort for the outcome analyses.
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17
18 228 **Figure 1** shows the cumulative incidence of weaning off and of death according with the type and the
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20 229 volume of the IVS. When comparing the cumulative incidence function of weaning off and death among
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22 230 groups, non-statistically significant differences were found ($p=0.329$ and $p=0.148$ for weaning off and death
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24 231 respectively): incidence of weaning off was greater in PN1 group and lower in PN4 and FE groups; incidence
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26 232 of death was lower in the FE group .
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29 233 *Odds of one-year outcome*

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31 234 The associations with the IVS type and volume were analyzed in comparison with the PN1 category.
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33 235 The odds of weaning from HPN (**Figure 2 and Supplemental table 2**): a) were lower in the FE type category
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35 236 and in the greatest PN volume categories (PN2, PN3 and PN4); b) were lower in the oldest decades of age,
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38 237 in the longest duration of HPN categories and in the miscellaneous group of underlying diseases; c) were
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40 238 higher in the underweight, overweight and obese BMI categories; d) showed no association with the
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42 239 number of patients included in the study by individual HPN-centers.
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44 240 The results were confirmed when excluding those patients who were weaned because of a non-
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46 241 transplant surgical procedure (**Supplemental table 3**). Furthermore, significant lower odds of weaning off
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49 242 were observed in patients who had SBS-J or SBS-JC as mechanisms of IF and in those who had an underlying
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51 243 disease categorized in the miscellaneous group.
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53 244 The odds of death on HPN (**Figure 2**): a) showed a non-statistically significant decreased risk for the
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55 245 FE type of IVS with respect to PN1 type ; b) were higher in the oldest age categories and in the lowest BMI
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58 246 categories; c) in comparison with SBS-J mechanism of IF, they were lower in the other SBS types and were
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60 247 higher in the other mechanisms of IF, excepting the extensive mucosal disease; d) were increased in the

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2 248 mesenteric ischemia and decreased in the CIPO groups of underlying disease; e) showed a negative
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4 249 association with the number of patients included in the study by individual HPN-centers.
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6 250 The competing risk analysis for the risk of death and of weaning from HPN confirmed the results of
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8
9 251 the multinomial analysis (**Supplemental table 4**).

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11 252 *Odds of major complications of HPN/IF*

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13 253 The results are reported in **table 2**.

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15 254 The odds of the presence of IFALD-cholestasis/liver failure: a) were higher in the greatest PN volume
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18 255 categories in comparison with PN1 and were similar between PN1 and the FE type of IVS; b) were lower in
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20 256 dysmotility mechanism of IF; c) were higher in the group with acute surgical complications as underlying
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22 257 disease; d) showed no association with the number of patients included in the study by individual HPN-
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24 258 centers

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26 259 The odds of the presence of CVC-VT: a) showed no association with the IVS categories; b) were
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29 260 higher in the in the longest HPN duration categories and in the underweight and obese categories of BMI;
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31 261 c) showed a negative association with the number of patients included in the study by individual HPN-
32
33 262 centers.

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35 263 The odds of CRBSI: a) were higher with the increase of the volume of the PN and were similar
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38 264 between PN1 and the FE type of IVS; b) were lower in older patients; c) were higher in the overweight and
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40 265 obese category of BMI and in the CIPO and miscellaneous categories of underlying disease; d) showed a
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42 266 negative association with the number of patients included in the study by individual HPN-centers.
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44 267 The analyses including only the incident cases of IFALD and of CVC-VT showed non-statistically
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47 268 significant odds ratios (**Supplemental table 5**).

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Table 2. Binomial logistic analysis of factors independently associated with the one-year probability of the intestinal failure associated liver disease, cholestasis or liver failure (IFALD), central venous catheter-associated deep vein thrombosis (CVC-VT) and catheter related bloodstream infections (CRBSI) in adult patients on home parenteral nutrition for chronic intestinal failure. Number of analyzed cases due to complete case approach: IFALD-cholestasis/liver failure (presence: 91, absence: 1610), CVC-VT (presence: 49, absence: 1652), CRBSI (presence: 257, absence: 1443).

Independent factors	IFALD-cholestasis/liver failure			CVC-VT			CRBSI		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
IVS type and volume									
PN1 (≤ 1 L)	1			1			1		
PN2 (1-2 L)	1.824	0.738-4.508	0.193	0.784	0.370-1.663	0.527	1.507	0.967-2.346	0.070
PN3 (2-3 L)	3.794	1.522-9.458	0.004	0.513	0.194-1.354	0.178	1.664	1.018-2.721	0.042
PN4 (> 3 L)	4.828	1.792-13.004	0.002	0.437	0.110-1.732	0.239	2.523	1.423-4.475	0.002
FE (total)	0.849	0.202-3.569	0.823	0.384	0.078-1.894	0.240	0.743	0.362-1.525	0.418
Gender									
Male	1			1			1		
Female	0.703	0.449-1.099	0.122	0.798	0.434-1.470	0.470	1.066	0.797-1.427	0.666
Age (years)									
≤ 29	1			1			1		
30-49	0.775	0.355-1.693	0.522	1.875	0.495-7.108	0.355	0.597	0.371-0.961	0.034
50-69	0.694	0.317-1.517	0.360	2.017	0.545-7.461	0.293	0.469	0.291-0.756	0.002
≥ 70	0.822	0.339-1.994	0.665	1.657	0.396-6.939	0.489	0.551	0.319-0.952	0.033
BMI (kg/m²)									
18.5-25.0	1			1			1		
≤ 15.0	1.064	0.233-4.858	0.936	2.705	0.566-12.935	0.212	0.837	0.333-2.106	0.706
15.0-18.5	1.612	0.872-2.983	0.128	2.335	1.093-4.987	0.028	1.061	0.697-1.615	0.782
25.1-30.0	0.611	0.310-1.207	0.156	1.134	0.470-2.738	0.779	1.460	1.012-2.108	0.043
≥ 30.0	0.591	0.172-2.036	0.405	3.124	0.829-11.769	0.092	2.769	1.580-4.851	0.000
Duration of HPN (years)									
≤ 1	1			1			1		

1										
2	1-3	1.025	0.553-1.899	0.938	1.526	0.516-4.515	0.445	1.157	0.787-1.703	0.458
3	3-10	1.070	0.594-1.929	0.821	2.889	1.093-7.636	0.032	1.110	0.762-1.618	0.586
4	>10	0.982	0.470-2.052	0.962	3.477	1.179-10.256	0.024	0.853	0.522-1.393	0.524
5										
6	Mechanism of IF									
7	SBS-J	1			1			1		
8	SBS-JC	0.649	0.338-1.245	0.193	1.926	0.848-4.374	0.117	0.964	0.629-1.479	0.868
9	SBS-JIC	0.629	0.208-1.902	0.411	0.760	0.189-3.060	0.699	1.377	0.754-2.516	0.298
10	Fistulas	0.593	0.219-1.607	0.304	0.580	0.071-4.733	0.611	1.207	0.676-2.154	0.525
11	Dysmotility	0.317	0.115-0.878	0.027	1.431	0.428-4.790	0.561	0.759	0.422-1.365	0.357
12	Obstruction	1.072	0.373-3.083	0.897	0.438	0.050-3.859	0.457	0.800	0.376-1.704	0.563
13	Mucosal disease	0.712	0.260-1.945	0.507	0.868	0.203-3.713	0.849	0.824	0.445-1.526	0.538
14										
15										
16	Underlying disease									
17	IBD	1			1			1		
18	CIPO	1.459	0.481-4.427	0.505	1.244	0.303-5.113	0.762	2.098	1.092-4.03	0.026
19	Other causes of SBS	1.265	0.501-3.192	0.619	2.308	0.742-7.18	0.149	1.490	0.843-2.634	0.170
20	Miscellaneous	2.038	0.909-4.567	0.084	2.308	0.723-7.366	0.158	1.712	1.002-2.924	0.049
21	Mesenteric ischemia	1.468	0.732-2.943	0.280	2.063	0.798-5.333	0.135	1.012	0.626-1.635	0.963
22	Radiation enteritis	0.613	0.170-2.210	0.454	0.824	0.161-4.206	0.816	0.967	0.487-1.918	0.923
23	Acute surgical complications	2.210	1.089-4.482	0.028	0.573	0.142-2.311	0.433	1.143	0.700-1.864	0.593
24										
25										
26	N. of patients included by	0.939	0.765-1.153	0.551	0.580	0.451-0.745	0.000	0.710	0.626-0.806	0.000
27	center									
28										
29										

304 BMI, body mass index; HPN, home parenteral nutrition; IF, intestinal failure; SBS-J, short bowel syndrome with jejunostomy; SBS-JC, short bowel syndrome with jejunocolon
315 anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejunocolon anastomosis with intact colon; IBD, inflammatory bowel disease, CIPO, chronic intestinal
326 pseudo-obstruction; CIF chronic intestinal failure; IVS, intravenous supplementation; FE, fluid and electrolytes alone; PN, parenteral nutrition-admixture.
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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 the volume of the IVS are independently associated with the one-year odds of weaning from HPN and of HPN/IF-associated major complications, as well as with the risk of mortality, albeit the latter observation being based on a non-statistically significant finding. In patients with CIF, the type and the volume of the IVS requirement primarily depends 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 (e.g. drugs and dietary prescriptions) as well as the treatment protocols of the multidisciplinary team caring for him/her, [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 the volume of the 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 the volume of the 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 one-year odds of death depended on the interaction between the 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

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2 305 in the long-term and/or whether a different categorization of the IVS volume will capture any association
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4 306 between IVS volume and risk of death, both in the short and in the long-term.
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6 307 The one-year probability of weaning from HPN was associated with both the type and volume of IVS.
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9 308 The PN1 volume (≤ 1 L/day) showed higher odds of weaning than either the greater PN-volumes or FE-type
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11 309 IVS. There could be several reasons for a longer maintenance of low volume FE than of low volume PN IVS:
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13 310 a more difficult intestinal rehabilitation of fluid and electrolytes than of macronutrient absorption due to
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15 311 concomitant secondary mechanisms of IF causing increased intestinal secretion [1]; the concomitant
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17 312 presence of a reduced kidney function requiring the maintenance of optimal hydration, [2,7]; physician's
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19 313 and/or patient's perception of a lower risk of IVS-associated complications with FE than with PN; patient's
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21 314 better acceptance of FE than of PN, because of shorter duration of FE infusion compared to PN, [2]; the
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24 315 lower cost of FE. All of these factors would make weaning from FE slower/less likely than weaning from PN.
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26 316 The risk of IFALD and of the occurrence of CRBSIs were also associated with both the type and the
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29 317 volume of the IVS, whereas no association was observed with the presence of CVC-VT. The odds of IFALD
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31 318 and of CRBSI were greater in patients receiving the highest volumes of PN in comparison with the lowest
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33 319 PN-volumes and the FE-type of IVS. Furthermore, the odds of these complications were higher in the
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35 320 greater PN volume categories. These data are in keeping with previous studies, [2, 8, 9]. The pathogenesis
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38 321 of IFALD is multifactorial, including factors related to the IVS, underlying gastrointestinal disease and
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40 322 systemic factors, especially episodes of sepsis [2, 10]. Intravenous supplementation overfeeding and a high
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42 323 amount of lipid emulsion are recognized causes of IFALD [2, 10]. Similarly, CRBSI occurrence has also
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44 324 previously been reported to occur more frequently in those dependent on an increased number of days of
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47 325 IVS, [8]; this may relate to more frequent handling of the central venous catheter increasing infection risk
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49 326 or the association between macronutrients, vitamins and trace metals affecting microbial growth in the PN
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51 327 admixture, [11, 12].
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53 328 Most of the other independent factors found to be associated with patient's outcome and HPN/IF
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56 329 complications were in keeping with data from previous studies, [2, 3, 8, 10]. As expected, non-transplant
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58 330 surgery was the cause of weaning off HPN in a large percentage of patients, [13]. Notably, data on the
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60 331 causes of death on long-term HPN are consistent with previous observations, [3-5, 13-15], even though the

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2 332 percentage of HPN-related deaths (4%) was lower than that reported in longer retrospective surveys (10-
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4 333 14%), [3-5,13-15]. This could be due to the short duration of the present follow up, as it is known that the
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6 334 rate of the HPN-related death increases with the duration of the treatment, [4]. The 344 episodes of CRBSI
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8 335 registered in the 1859 patients accounted for a rate of CRBSI of 0.18 per catheter-year, or 0.50 per 1000
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11 336 catheter-days, a rate that is in the range reported in the literature, [2]. The 30 incident cases of CVC-VT
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13 337 observed at one-year follow up, accounted for an incidence rate of 0.016 per catheter-year, that is also in
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15 338 the lower range of the literature (0.02-0.09 cases per catheter-year), [2,16]. The same incidence rate can be
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18 339 accounted for the 31 incident cases of IFALD-cholestasis/liver failure. This data is of some relevance as no
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20 340 prospective study has yet been carried out on this HPN/IF complication, [17].
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22 341 The weakness of the study is mainly represented by the retrospective collection of data prospectively
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24 342 recorded in the previous 12 months, which would imply a risk of some underreporting, and by not using a
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26 343 co-morbidity index to assess the patient's general condition. However, CIF can develop as a complication of
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29 344 a number of gastrointestinal or systemic underlying diseases having different pathogenesis and outcomes,
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31 345 [1]. Therefore, the underlying disease that we collected and included in the statistical analysis, could be
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33 346 considered as a surrogate co-morbidity index, as supported by the finding of an increased risk of death in
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35 347 patients with CIF due to mesenteric ischemia. The strength of the study is clearly reflected by its
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38 348 international multicenter structure and by the study population, which is the largest cohort of patients with
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40 349 CIF ever enrolled in a single survey. These characteristics should avoid the potential bias associated with
41
42 350 the analysis of individual center cohorts, which could be influenced by local practice and expertise and
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44 351 mitigate the impact of the above possible weakness on statistical analyses. Considering that CIF is a rare
45
46 352 disease, [1] the observation of lower odds of death and of HPN/IF complications in HPN-center which
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48
49 353 included the larger number of patients in the study would support the importance of creating networks
50
51 354 facilitating the referral of CIF patients to few but appropriately organized and experienced centers, [18].
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53 355 Finally, the agreement between our results and the risk factors, other than IVS, reported by previous
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55
56 356 studies would support the overall reliability of our findings.
57

58 357 In conclusion, the type of the IVS, either FE or PN, and the volume of the PN-admixture, as
59
60 358 categorized by the ESPEN clinical classification of CIF, were found to be independently associated with the

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2 359 one-year risk of death, of weaning from HPN and of major complications of HPN/IF. These results support
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4 360 the ESPEN categorization of the IVS as potential marker of the severity of CIF.
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2 422 **Figure headings and footnotes**

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7 424 **Figure 1.** Cumulative one-year incidence of weaning from home parenteral nutrition (HPN) and of death
8 425 according to the intravenous supplementation (IVS) type and volume. IVS type: FE, fluid and electrolyte
9 426 alone; PN, parenteral nutrition admixture containing energy. IVS volume (L/day): PN1, ≤ 1 ; PN2, 1-2; PN3, 2-
10 427 3; PN4, >3 . FE1, FE2, FE3 and FE4 were grouped in a unique cohort (FE). The patient risk set is reported in
11 428 **supplemental table 2.**

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18 **Figure 2.** Forest plot of the analysis of factors associated with the one-year probability of weaning from
19 433 home parenteral nutrition (HPN) or of death and of home parenteral nutrition /intestinal failure (HPN/IF) in
20 434 adult patients with chronic intestinal. Number of analyzed cases due to complete case approach: 2035 (Still
21 435 in HPN: 1610, Weaned from HPN: 278, Deceased: 147).

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26 439 Footnote figure 2

27 440 BMI, body mass index; HPN, home parenteral nutrition; IF, intestinal failure; SBS-J, short bowel syndrome
28 441 with jejunostomy; SBS-JC, short bowel syndrome with jejunocolon anastomosis with partial colon; SBS-JIC,
29 442 short bowel syndrome with jejunocolon anastomosis with intact colon; IBD, inflammatory bowel disease,
30 443 CIPO, chronic intestinal pseudo-obstruction; CIF chronic intestinal failure; IVS, intravenous
31 444 supplementation; FE, fluid and electrolytes alone; PN, parenteral nutrition-admixture.

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12 539 LP devised the study protocol, collected the data, analyzed the results and drafted the manuscript.
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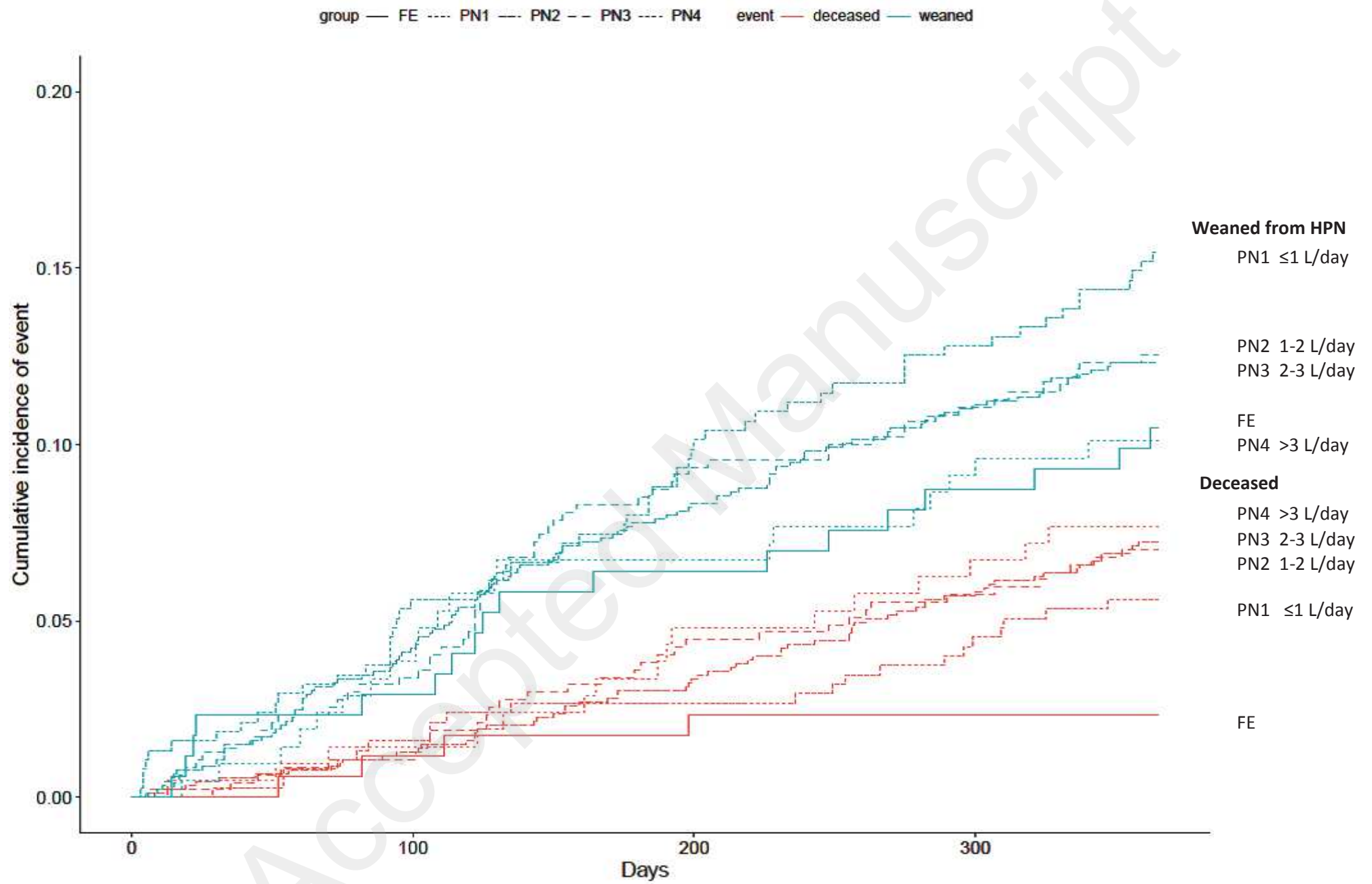
19 542 before submission. All the co-Authors participated in the acquisition of data, revised the final
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22 543 analysis, approved the final version of the manuscript and were accountable for all aspects of the
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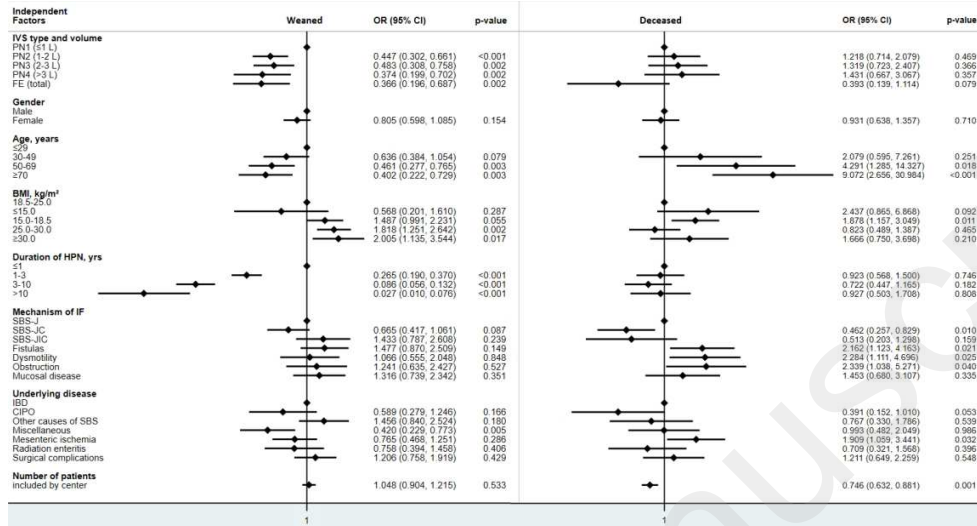


Figure 2

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2 1 **The intravenous supplementation type and volume is associated with one-year outcome and the**
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4 2 **major complications in patients with chronic intestinal failure**
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