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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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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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12  
13 32 **What are the new findings?**  
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- 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.  
21  
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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28 39  
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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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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-  
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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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15 49 **Methods**

16  
17 50 At baseline, participating home parenteral nutrition (HPN)-centers enrolled all adults with ongoing  
18  
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  
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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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34  
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  
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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 SaO<sub>2</sub> 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.



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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  
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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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19  
20 100 up, [2].

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22 101 *Baseline HPN center enrollment and patient inclusion*

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24 102 The baseline data collection was performed on March 1<sup>st</sup>, 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 ( $\geq 18$  years old) dependent on HPN for CIF on March 1<sup>st</sup>, 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  
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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  
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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*

47  
48 113 The one-year follow up was carried out on patients enrolled in the 2015 baseline cross-sectional  
49  
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  
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58 118 March 1<sup>st</sup>, 2015 and March 1<sup>st</sup>, 2016 and details of the patient's outcome on March 1<sup>st</sup>, 2016.

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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*

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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  
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15 125 records at time of data collection. The study was conducted with full regard to confidentiality of the  
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17 126 individual patient. Each patient was labelled with two anonymized identifications: one given by the HPN-  
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19 127 center and one given by the database manager. Ethical committee approval was obtained by the individual  
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21 128 HPN centers according to local regulations. The collected data were used only for the study purpose.  
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23 129 Contributing centers have been anonymized for data analysis and presentation.  
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#### 26 27 130 *Statistical analysis*

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29 131 The term HPN described the provision of IVS, either FE or PN, at the patient's home. Weaning from  
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31 132 equated to stopping IVS [1]. The clinical classification of CIF consisted of 8 categories, based on the type  
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33 133 and volume of IVS, calculated as daily mean of the total volume infused per week: volume per day of  
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35 134 infusion  $\times$  number of infusions per week / 7 (mL/day): FE1 or PN1,  $\leq 1000$ ; FE2 or PN2, 1001–2000; FE3 or  
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37 135 PN3, 2001–3000; FE4 or PN4,  $>3000$ , [6].  
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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  
45  
46 139 obstruction (Obstruction) and extensive small bowel mucosa disease (Mucosal disease), [6].  
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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-  
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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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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 1<sup>st</sup> 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  
21  
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  
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26 157 database on March 1<sup>st</sup> 2016, whereas the incident or prevalent nature of IFALD was collected after  
28  
29 158 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  
32  
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  
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37 162 correctly classified subjects, with subjects correctly classified: 81% vs 80%), the random effect was omitted  
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39 163 in order to preserve the ease of interpretation of the model.

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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  
48  
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  
55 170 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  
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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  $43.0 \pm 54.1$   
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15 182 (median: 19; range: 1-231); number of patients by center:  $\leq 19$ , n. 26 (51.0%) centers, patients n. 198 (9.0%  
16  
17  
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  $\geq 100$  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  $51.1 \pm 16.2$  (56.5;18.0-98.0) years,  $22.3 \pm 4.4$  (21.7; 10.5-59.6)  
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29 188 kg/m<sup>2</sup> and  $58.0 \pm 70.2$  (33.2,0-474) months, respectively. SBS-J was the most frequent pathophysiological  
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31 189 mechanism of IF (35.9% of cases). The most frequent underlying disease was Crohn's disease (21.1%). The  
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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  
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36 191 subgroup of patients receiving FE  $1055.8 \pm 859.6$  mL/day (median 857.1, range 107.1–4800.0) than in those  
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38 192 receiving PN  $1055.8 \pm 859.6$  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 1<sup>st</sup>, 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**).

**Table 1.** Baseline characteristics and one-year outcome and home parenteral nutrition (HPN)/intestinal failure (IF) – related major complications of adult patients with chronic intestinal failure due to benign disease. (IFALD, intestinal failure associated liver disease: cholestasis or liver failure; CVC-VT, central venous catheter-associated deep vein thrombosis; CRBSI, catheter related bloodstream infections). Data are reported as percentages of cases.

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
<b>Gender (%)</b>						
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
<b>Age, years (%)</b>						
≤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
<b>BMI, kg/m<sup>2</sup>, (%)</b>						
≤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)						
<b>Duration of HPN, yrs (%)</b>						
≤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
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13	<b>Underlying disease (%)</b>						
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							
23							
24							
25	<b>Clinical classification of CIF</b>						
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
35							
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39	<b>Type of IVS (%)</b>						
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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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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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  
23  
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;  
30  
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  
36  
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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  
39  
40 265 obese category of BMI and in the CIPO and miscellaneous categories of underlying disease; d) showed a  
41  
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
<b>IVS type and volume</b>									
PN1 ( $\leq 1$ 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	<b>0.004</b>	0.513	0.194-1.354	0.178	1.664	1.018-2.721	<b>0.042</b>
PN4 ( $> 3$ L)	4.828	1.792-13.004	<b>0.002</b>	0.437	0.110-1.732	0.239	2.523	1.423-4.475	<b>0.002</b>
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
<b>Gender</b>									
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
<b>Age (years)</b>									
$\leq 29$	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	<b>0.034</b>
50-69	0.694	0.317-1.517	0.360	2.017	0.545-7.461	0.293	0.469	0.291-0.756	<b>0.002</b>
$\geq 70$	0.822	0.339-1.994	0.665	1.657	0.396-6.939	0.489	0.551	0.319-0.952	<b>0.033</b>
<b>BMI (kg/m<sup>2</sup>)</b>									
18.5-25.0	1			1			1		
$\leq 15.0$	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	<b>0.028</b>	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	<b>0.043</b>
$\geq 30.0$	0.591	0.172-2.036	0.405	3.124	0.829-11.769	0.092	2.769	1.580-4.851	<b>0.000</b>
<b>Duration of HPN (years)</b>									
$\leq 1$	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	<b>0.032</b>	1.110	0.762-1.618	0.586
4	>10	0.982	0.470-2.052	0.962	3.477	1.179-10.256	<b>0.024</b>	0.853	0.522-1.393	0.524
5										
6	<b>Mechanism of IF</b>									
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	<b>0.027</b>	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	<b>Underlying disease</b>									
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	<b>0.026</b>
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	<b>0.049</b>
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	<b>0.028</b>	0.573	0.142-2.311	0.433	1.143	0.700-1.864	0.593
24										
25										
26	<b>N. of patients included by</b>	0.939	0.765-1.153	0.551	0.580	0.451-0.745	<b>0.000</b>	0.710	0.626-0.806	<b>0.000</b>
27	<b>center</b>									
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 ( $\leq 1$  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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23 315 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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37 321 of IFALD is multifactorial, including factors related to the IVS, underlying gastrointestinal disease and  
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39 322 systemic factors, especially episodes of sepsis [2, 10]. Intravenous supplementation overfeeding and a high  
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41 323 amount of lipid emulsion are recognized causes of IFALD [2, 10]. Similarly, CRBSI occurrence has also  
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43 324 previously been reported to occur more frequently in those dependent on an increased number of days of  
44  
45 325 IVS, [8]; this may relate to more frequent handling of the central venous catheter increasing infection risk  
46  
47 326 or the association between macronutrients, vitamins and trace metals affecting microbial growth in the PN  
48  
49 327 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  
54  
55 329 complications were in keeping with data from previous studies, [2, 3, 8, 10]. As expected, non-transplant  
56  
57 330 surgery was the cause of weaning off HPN in a large percentage of patients, [13]. Notably, data on the  
58  
59 331 causes of death on long-term HPN are consistent with previous observations, [3-5, 13-15], even though the  
60

1  
2 332 percentage of HPN-related deaths (4%) was lower than that reported in longer retrospective surveys (10-  
3  
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  
5  
6 334 rate of the HPN-related death increases with the duration of the treatment, [4]. The 344 episodes of CRBSI  
7  
8  
9 335 registered in the 1859 patients accounted for a rate of CRBSI of 0.18 per catheter-year, or 0.50 per 1000  
10  
11 336 catheter-days, a rate that is in the range reported in the literature, [2]. The 30 incident cases of CVC-VT  
12  
13 337 observed at one-year follow up, accounted for an incidence rate of 0.016 per catheter-year, that is also in  
14  
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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17  
18 339 accounted for the 31 incident cases of IFALD-cholestasis/liver failure. This data is of some relevance as no  
19  
20 340 prospective study has yet been carried out on this HPN/IF complication, [17].  
21

22 341 The weakness of the study is mainly represented by the retrospective collection of data prospectively  
23  
24 342 recorded in the previous 12 months, which would imply a risk of some underreporting, and by not using a  
25  
26 343 co-morbidity index to assess the patient's general condition. However, CIF can develop as a complication of  
27  
28  
29 344 a number of gastrointestinal or systemic underlying diseases having different pathogenesis and outcomes,  
30  
31 345 [1]. Therefore, the underlying disease that we collected and included in the statistical analysis, could be  
32  
33 346 considered as a surrogate co-morbidity index, as supported by the finding of an increased risk of death in  
34  
35 347 patients with CIF due to mesenteric ischemia. The strength of the study is clearly reflected by its  
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37  
38 348 international multicenter structure and by the study population, which is the largest cohort of patients with  
39  
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  
43  
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].  
52  
53 355 Finally, the agreement between our results and the risk factors, other than IVS, reported by previous  
54  
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



1  
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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**References**

1. Pironi L, Arends J, Baxter J, et al.; Home Artificial Nutrition & Chronic Intestinal Failure and the Acute Intestinal Failure Special Interest Groups of ESPEN. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. *Clin Nutr* 2015;34:171-80 doi: 10.1016/j.clnu.2014.08.017. Epub 2014 Sep 21
2. Pironi L, Arends J, Bozzetti F, et al.; Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. *Clin Nutr* 2016;35:247-307 doi: 10.1016/j.clnu.2016.01.020. Epub 2016 Feb 8.
3. Pironi L, Goulet O, Buchman A, et al.; Home Artificial Nutrition and Chronic Intestinal Failure Working Group of ESPEN. 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;31:831-45 doi: 10.1016/j.clnu.2012.05.004. Epub 2012 Jun 2.
4. Pironi L, Joly F, Forbes A, et al.; Home Artificial Nutrition & Chronic Intestinal Failure Working Group of the European Society for Clinical Nutrition and Metabolism (ESPEN). Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. *Gut* 2011;60:17-25 doi: 10.1136/gut.2010.223255. Epub 2010 Nov 10.
5. Joly F, Baxter J, Staun M, et al.; ESPEN HAN CIF group. 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 doi: 10.1016/j.clnu.2017.06.016. Epub 2017 Jun 19.
6. Pironi L, Konrad D, Brandt C, et al. Clinical classification of adult patients with chronic intestinal failure due to benign disease: An international multicenter cross-sectional survey. *Clin Nutr* 2018;37:728-738 doi: 10.1016/j.clnu.2017.04.013. Epub 2017 Apr 19.
7. Agostini F, Sasdelli AS, Guidetti M, et al. Outcome of kidney function in adults on long-term home parenteral nutrition for chronic intestinal failure. *Nutrition* 2018, doi: <https://doi.org/10.1016/j.nut.2018.10.005>

- 1  
2 387 8. Dreesen M, Foulon V, Spriet I, et al. Epidemiology of catheter-related infections in adult patients  
3  
4 388 receiving home parenteral nutrition: a systematic review. *Clin Nutr* 2013;32:16-26 doi:  
5  
6 389 10.1016/j.clnu.2012.08.004. Epub 2012 Aug 21.  
7  
8  
9 390 9. Sasdelli AS, Agostini F, Pazzeschi C, et al. Assessment of Intestinal Failure Associated Liver Disease  
10  
11 391 according to different diagnostic criteria. *Clin Nutr* Published online first: 8 May 2018. doi:  
12  
13 392 10.1016/j.clnu.2018.04.019.  
14  
15 393 10. Lal S, Pironi L, Wanten G, et al.; Home Artificial Nutrition & Chronic Intestinal Failure Special Interest  
16  
17 Group of the European Society for Clinical Nutrition and Metabolism (ESPEN). Clinical approach to  
18 394 the management of Intestinal Failure Associated Liver Disease (IFALD) in adults: A position paper  
19  
20 395 from the Home Artificial Nutrition and Chronic Intestinal Failure Special Interest Group of ESPEN. *Clin*  
21  
22 396 *Nutr* 2018;37:1794-1797 doi: 10.1016/j.clnu.2018.07.006. Epub 2018 Jul 9.  
23  
24 397  
25  
26 398 11. Austin PD, Hand KS, Elia M. Systematic review and meta-analyses of the effect of lipid emulsion on  
27  
28 microbial growth in parenteral nutrition. *J Hosp Infect* 2016;94:307-319 doi:  
29 399 10.1016/j.jhin.2016.08.026. Epub 2016 Sep 7.  
30  
31 400  
32  
33 401 12. Buchman AL, Opilla M, Kwasny M, et al. Risk factors for the development of catheter-related  
34  
35 bloodstream infections in patients receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr*  
36 402 2014;38:744-9 doi: 10.1177/0148607113491783. Epub 2013 Jun 6.  
37  
38 403  
39  
40 404 13. Amiot A, Messing B, Corcos O, et al. Determinants of home parenteral nutrition dependence and  
41  
42 405 survival of 268 patients with non-malignant short bowel syndrome. *Clin Nutr* 2013;32:368-74 doi:  
43  
44 406 10.1016/j.clnu.2012.08.007. Epub 2012 Aug 23.  
45  
46  
47 407 14. Dibb M, Soop M, Teubner A, et al. Survival and nutritional dependence on home parenteral nutrition:  
48  
49 408 Three decades of experience from a single referral centre. *Clin Nutr* 2017;36:570-576 doi:  
50  
51 409 10.1016/j.clnu.2016.01.028. Epub 2016 Feb 22.  
52  
53  
54 410 15. Brandt CF, Tribler S, Hvistendahl M, et al. Home Parenteral Nutrition in Adult Patients With Chronic  
55  
56 411 Intestinal Failure: Catheter-Related Complications Over 4 Decades at the Main Danish Tertiary  
57  
58 412 Referral Center. *JPEN J Parenter Enteral Nutr* 2018;42:95-103 doi: 10.1177/0148607116678766. Epub  
59  
60 413 2017 Dec 11.

- 1  
2 414 16. Pironi L, Corcos O, Forbes A, et al.; ESPEN Acute and Chronic Intestinal Failure Special Interest  
3  
4 415 Groups. Intestinal failure in adults: Recommendations from the ESPEN expert groups. *Clin Nutr*  
5  
6 416 2018;37:1798-1809 doi: 10.1016/j.clnu.2018.07.036. Epub 2018 Aug 18..  
7  
8  
9 417 17. Bond A, Huijbers A, Pironi L, Schneider SM, Wanten G, Lal S. Review article: diagnosis and  
10  
11 418 management of intestinal failure-associated liver disease in adults. *Aliment Pharmacol Ther*. 2019  
12  
13 419 Sep;50(6):640-653. doi: 10.1111/apt.15432. Epub 2019 Jul 25. Review. PubMed PMID: 31342540.  
14  
15 420 18. <https://www.engage.England.nhs.uk/consultation/severe-intestinal-failure-services-for-adults/>  
16  
17  
18 421  
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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,  $\leq 1$ ; 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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18 432 **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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## Footnote figure 2

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 anastomosis with partial colon; SBS-JIC, short bowel syndrome with jejunocolon anastomosis with intact colon; IBD, inflammatory bowel disease, CIPO, chronic intestinal pseudo-obstruction; CIF, chronic intestinal failure; IVS, intravenous supplementation; FE, fluid and electrolytes alone; PN, parenteral nutrition-admixture.

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#### 538 **Statement of authorship**

539 LP devised the study protocol, collected the data, analyzed the results and drafted the manuscript.

540 The Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN

541 discussed and approved the protocol study, discussed the results and reviewed the manuscript

542 before submission. All the co-Authors participated in the acquisition of data, revised the final

543 analysis, approved the final version of the manuscript and were accountable for all aspects of the

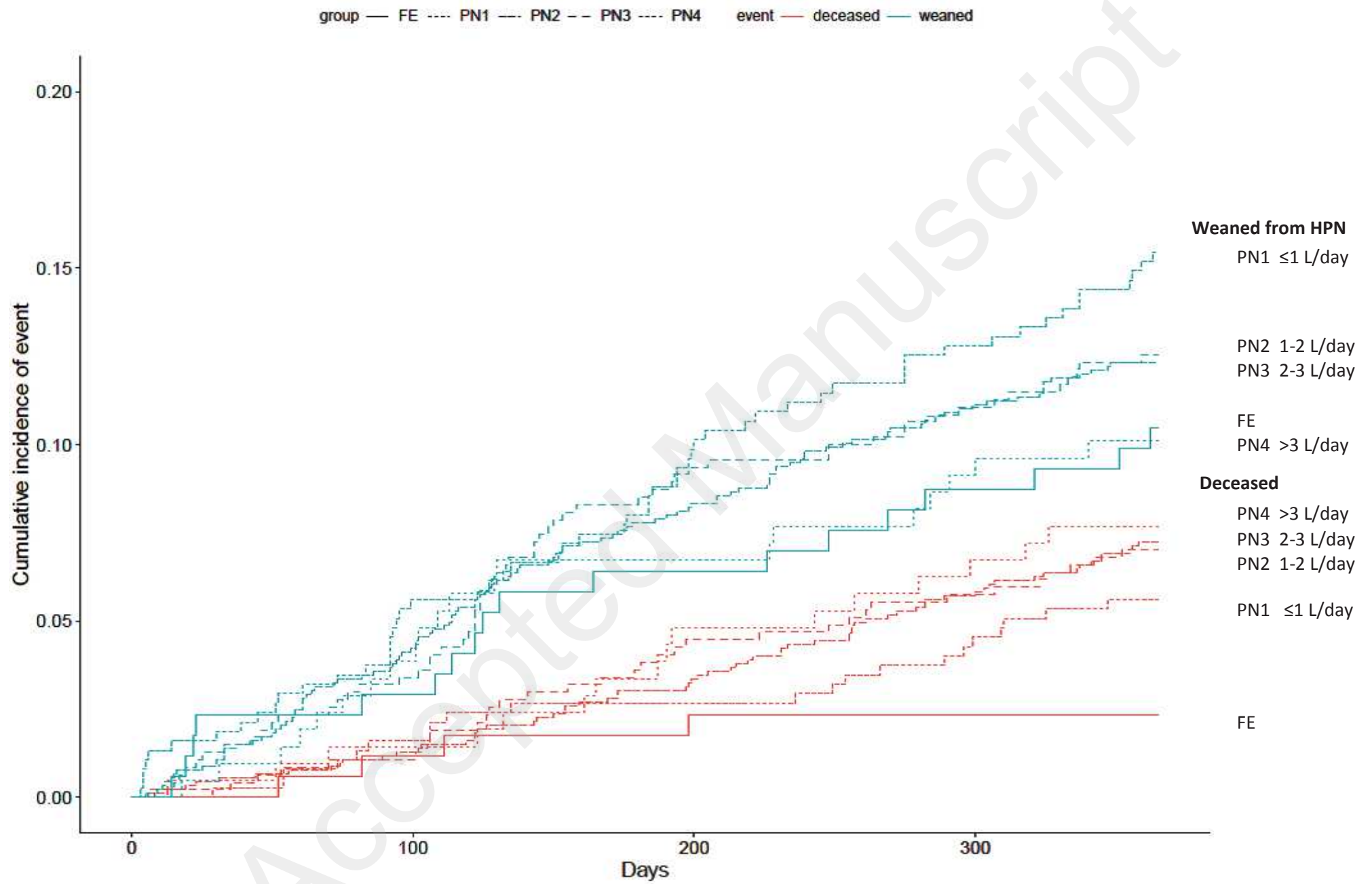
544 work.

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#### 546 **Conflict of interest statements**

547 None declared





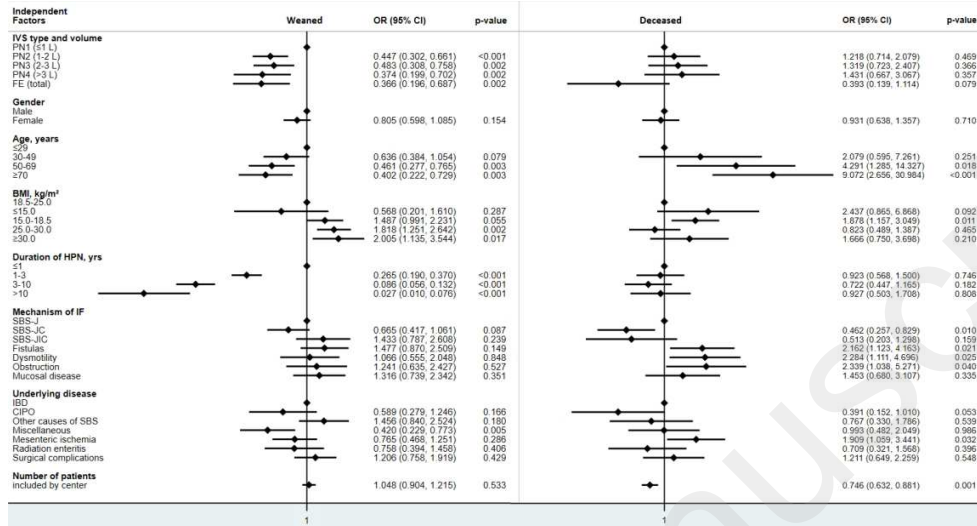


Figure 2

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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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