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Original article

Assessment of Intestinal Failure Associated Liver Disease according to different diagnostic criteria

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SUMMARY

Background & aims: Intestinal failure associated liver disease (IFALD) has been defined using numerous criteria; however the clinical relevance of these criteria has never been compared. We therefore aimed to evaluate the prevalence, incidence, evolution of IFALD diagnosed by different criteria and to assess any clinical features that may be associated with its occurrence.
Methods: A cross sectional (CS) and retrospective study were carried out on adults on home parenteral nutrition (HPN) for chronic intestinal failure (CIF) managed at a single center. Inclusion criteria at CS: age ≥18 years, benign disease. Collected data included: patient demographics, CIF and HPN characteristics, episodes of central venous catheter related bloodstream infection (CRBSI). IFALD was diagnosed by 9 criteria based on liver function tests and liver ultrasound (US) imaging. IFALD diagnoses were categorized as steatosis (2 criteria), cholestasis (3 criteria) or fibrosis (2 criteria) and unclassified (2 criteria). Prevalence was assessed at CS and at starting HPN (baseline, BS). Evolution was assessed as change of IFALD between BS and CS. Incidence was calculated as patients who developed IFALD from BS to CS.
Results: A total of 113 patients were included. At CS, IFALD prevalence range in each diagnostic categories was: cholestasis 5–15%; steatosis 17–43%; fibrosis 10–20%; unclassified 7–38%. A 28.5% of patients did not have IFALD according to any criteria. Two cholestasis criteria and one fibrosis criterion were significantly ($P < 0.05$) associated with a short bowel syndrome as the pathophysiological mechanism of CIF, HPN requirement and the number of CRBSI episodes. At BS, IFALD prevalence range was: cholestasis 13–40%; steatosis 27–90%; fibrosis 2–5%; unclassified 8–75%. The incidence range of IFALD was: cholestasis 0–7%; steatosis 0–39%; fibrosis 7–18%; unclassified 4–9%. IFALD steatosis diagnosed by US was the most frequent diagnosis at both CS prevalence and incidence assessments. Notably, IFALD criteria normalized in various percentages (2–70%), depending on the diagnostic categories, between BS and CS.
Conclusions: This is the first study to systematically demonstrate that the frequency of IFALD varies greatly depending on diagnostic criteria used, confirming the need for a consensus definition to be used between different national and international IF units. IFALD can be present at HPN initiation but may resolve thereafter; further work is required to evaluate the factors associated with improvement.

1. Introduction

Chronic intestinal failure (CIF) is defined as the "persistent reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth" [1]. The primary and life-saving treatment of CIF is home parenteral nutrition (HPN), that may be required for months or years (reversible CIF) or lifelong (irreversible CIF) [2]. In adult patients with benign CIF, the survival rate on HPN has been reported to be 70% at 5 years, but this will vary according to the underlying disease, which is the principal cause of mortality, with only around 14% of deaths resulting from HPN-related complications, such as central venous catheter (CVC)-sepsis (8%), CVC-thrombosis (2%) and Intestinal Failure Associated Liver Disease (IFALD) (4%) [3].

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IFALD results from liver injury due to factors related to intestinal failure and/or to parenteral nutrition, with no other evident cause [2]. Several studies have reported a varied prevalence of impaired liver function tests (LFTs) in 5–85% of HPN-dependent patients, being more prevalent in children compared to adults [3–6]. IFALD is a multifactorial condition, such that pathogenetic factors can be categorized as "patient/CIF-related" and "HPN-related". Host/CIF factors include CVC related bloodstream infection (CRBSI), intestinal anatomy, especially short bowel syndrome (SBS) with an end-jejunostomy, small bowel bacterial overgrowth and lack of oral/enteral nutrition. HPN-related mechanisms include nutrient deficiencies or excess [4–6]. Reported histologic liver abnormalities include micro- or macro-steatosis, portal inflammation, fibrosis, or cirrhosis. Hepatic fibrosis progressing to cirrhosis is a major concern in these patients [7]; indeed, liver failure due to IFALD can be an indication for a life-saving combined liver-small bowel transplantation [8].

Diagnosing and categorizing IFALD, and determining when it may progress to fibrosis or cirrhosis, are key issues for its timely treatment and, if appropriate, timely referral for transplantation. However, there are no current established consensus criteria for IFALD diagnosis and classification and the evolution of the disease is not well described.

The aims of the present study were to assess the prevalence, incidence and evolution of IFALD as diagnosed by different criteria, and to evaluate factors that may be associated with its occurrence.

2. Material and methods

2.1. Study design

This is a cross sectional and retrospective study carried out on adult patients on HPN for benign CIF cared for at the Center for Chronic Intestinal Failure, Department of Medical and Surgical Science, University of Bologna, Italy.

2.2. Patient cohort

Patients' inclusion criteria: age ≥18 years, on HPN for CIF due to benign disease at 31/12/2015. Exclusion criteria: presence of malignant disease, evident causes of liver injury or disease (viral infection, toxic drugs, autoimmune disease, chronic alcohol abuse).

2.3. Collected parameters

The following data were collected from the patients' clinical charts prospectively filled out during routine clinical outpatient visits: demographic, anthropometric, CIF characteristics (underlying disease and primary mechanism), HPN characteristics [duration, number of infusions per week, volume, energy and macronutrient amounts, type of lipid emulsion (LE)], alcohol consumption, LFTs [(total and conjugated bilirubin, transaminases, γ-glutamyltransferase (γ-GT), alkaline phosphatase (ALP)), liver ultrasound (US) and number of CRBSI.

According to the European Association for the Study of the Liver (EASL) guidelines for non-alcoholic fatty liver disease (NAFLD), the daily alcohol consumption was categorized high when ≥30 g for men and ≥20 g for women [9].

2.4. Diagnostic criteria for IFALD categories

We identified 9 diagnostic criteria for IFALD used thus far in the international literature and in the ESPEN database for CIF [10–17]:

- IFALD-cholestasis
  - Cavicchi et al. criterion [10]: a value ≥1.5 the upper limit of normal (ULN) on two of γ-GT, ALP, and serum conjugated bilirubin for ≥6 months
  - ConBil criterion [11]: conjugated bilirubin >0.3 mg/dL for ≥6 months
  - TotBil criterion [11]: total bilirubin >1 mg/dL and conjugated bilirubin >0.3 mg/dL for ≥6 months
- IFALD-steatosis
  - AAR index, according to Sorbi et al. [12]: AST/ALT ratio <1 when AST and ALT > ULN
  - US criterion, according to the European Association for the Study of the Liver (EASL) guidelines [13]: liver ultrasound echogenic appearance of steatosis.
- IFALD-fibrosis
  - APRI index, according to Rath et al. [14]: AST to platelets (PLT) ratio index = [(AST/ULN AST) × 100]/PLT (10^9/L)] >0.88
  - FIB-4 index, according to Sterling et al. [15]: Fibrosis–4 index = Age (years) × AST)/[PLT (10^9/L) × $ALT^{1/2}$]; advanced fibrosis: ≥2.67:
- IFALD–unclassified
  - Luman et al. criterion [16]: any deranged LFT ≥1.5 the ULN after >6 months of HPN starting
  - Beath et al. criterion [17]: ALP and γ-GT ≥1.5 the ULN and US signs of liver steatosis

2.5. Assessment of epidemiology and evolution of IFALD

The prevalence of IFALD during HPN (cross-sectional, CS) was evaluated by analyzing the above IFALD categories at the date of patients' inclusion in the study.

The prevalence of IFALD at time of starting HPN (baseline, BS) was evaluated by the retrospective analysis of the patients' records for the IFALD criteria at a time range of ±1–3 months from the date the patient commenced HPN.

The evolution of IFALD was evaluated by comparing the IFALD criteria at BS and CS.

The incidence of IFALD was calculated as the percentage of patients with normal LFTs and US image at BS who had positive IFALD diagnostic criteria at CS.

2.6. Ethical statement

The research was based on anonymized information taken from patient records at time of data collection. The study was conducted with full regard to confidentiality of the individual patient. The study was approved by the Local Ethic Committee (n° 63/2017). Voluntary informed written consent was obtained from all patients.

2.7. Statistical analysis

Data on demographic characteristics, anthropometric parameters, underlying disease, cause of CIF and HPN program were reported through descriptive statistics: mean ± standard deviation and percentage. Comparison between groups was performed by non-parametric tests (Mann–Withney and Kruscall–Wallis tests). Frequency comparison was performed by chi square test ($\chi 2$). A significance level of 5% was used ($P < 0.05$). Statistical calculations were carried out using the Statgraphics Centurion XVI program.

3. Results

3.1. Patient cohort at study inclusion (CS)

At CS, 126 patients were evaluated for inclusion in the study. Thirteen were excluded because of age <18 years [2], presence of

cancer [6], previous liver transplantation [1], previous intestinal transplantation [2], viral hepatitis C [2]. A total of 113 subjects were included in the study. The patients', the CIF and the HPN program characteristics at CS are reported in Table 1.

3.2. Prevalence of IFALD at study inclusion (CS)

The prevalence of IFALD according to the each diagnostic criterion is reported in Table 2. The highest prevalence was observed for IFALD-steatosis diagnosed by US (43%), while the lowest prevalence was that of IFALD-cholestasis diagnosed by the TotBil criterion (5%). Notably, 28.5% of patients had no evidence of IFALD at CS, as evidenced by having all LFTs within the normal range and normal US imaging.

3.3. IFALD-associated characteristics at study inclusion (CS)

The association between IFALD categories and the patients' CIF and HPN characteristics were investigated comparing patients with positive and those with negative diagnosis of IFALD. The results are reported in Table 3 as P value of the statistical analysis. Details are shown in the Appendix Tables 1–4.

The presence of IFALD was associated with a statistically significant higher number of HPN infusions/week (cholestasis and fibrosis) and HPN volume/day (cholestasis). IFALD was also significantly associated with the presence of SBS as the mechanism of CIF and with a higher frequency of CRBSIs (cholestasis and fibrosis). Among the IFALD-cholestasis criteria, Cavicchi's criterion showed the greater number of statistically significant associations. ConBil criterion was associated with the same factors as Cavicchi's criterion, but only some achieved statistically significance. No association was found for TotBil criterion. IFALD-steatosis by US criterion was associated only with the duration of the HPN treatment. No associations were found for AAR index. FIB-4 index of IFALD-fibrosis was also associated with numerous risk factors, whereas APRI index showed only few significant associations. Only a few associations were observed for the IFALD-unclassified criteria.

Cholestasis, according to the Cavicchi's criterion or to the ConBil criterion, was more frequent in the subgroup with SBS without-colon continuity than in the other subgroups of CIF mechanisms (Cavicchi's: 20.0% in SBS no-colon and 0% in the other subgroups, $p = 0.011$; ConBil: 26.9% in SBS no-colon, 10.7% in SBS with-colon and 3.2% in other mechanisms, $p = 0.016$).

Among the 7 patients with a daily alcohol consumption higher than recommended (48.5 ± 20.6 g/day; range 28–77), 3 (42.8%) had no IFALD positive criteria and 4 (57.2%) had at least one positive criteria (2 patients with FIB-4 fibrosis alone, 1 patient with US steatosis alone; and 1 patient with FIB-4 fibrosis, US-steatosis and Bil-Dir cholestasis). There was no statistical difference in the occurrence of IFALD positive criteria in those with or without a high alcohol consumption.

3.4. Prevalence of IFALD at starting HPN (BS) and IFALD evolution up to study inclusion (CS)

IFALD criteria at BS were available for 62 patients. Fig. 1 shows the comparison of IFALD diagnosis at BS and at CS, in individual patients.

At BS, the prevalence of IFALD-cholestasis was 40%, 27% and 13% according to Cavicchi, ConBil and TotBil criteria, respectively; IFALD-steatosis was observed in 28% of cases by US and 90% of cases by AAR index assessment; IFALD-fibrosis was reported only in 5% by APRI index and 2% by FIB-4 index; IFALD-unclassified was 75% and 8% by Luman and Beath criteria, respectively.

Table 1
Patients', chronic intestinal failure (CIF) and home parenteral nutrition (HPN) program characteristics, at study inclusion (cross-sectional, CS) and frequency of central venous catheter related bloodstream infection (CRBSI) since starting the HPN treatment.

Patient cohort	
Patients (n.)	113
Gender (M/F)	(51/62)
Age (years)	49.3 ± 17.3
Age at HPN starting (years)	42.3 ± 18.9
Body Mass Index (Kg/m^2)	20.3 ± 3.3
CIF mechanism, n. (%)	
Short Bowel Syndrome (SBS)	77 (68)
- without-colon in continuity	46
- with-colon in continuity	31
Motility Disorder	26 (23)
Mucosal Disease	7 [6]
Intestinal fistula	3 [3]
Underlying disease, n. (%)	
Crohn's disease	26 (23)
Mesenteric ischemia	22 [20]
Chronic intestinal pseudo-obstruction	26 (23)
Mucosal Disease	6 [5]
Radiation Enteritis	6 [5]
Familial polyposis	5 [4]
Other	22 [19]
HPN program	
HPN duration (mo.)	84.2 ± 91.2
Infusions (n./week)	6.0 ± 1.5
Volume (mL/infusion/week)	1695 ± 832
Energy (Kcal/infusions/week)	1039 ± 550
Energy/BEE (%)	81.5 ± 44
Infusions with lipids (n./week)	4.3 ± 2.6
Lipids (g/infusion)	34.3 ± 22.1
Lipids (g/BW/infusion)	0.66 ± 0.44
Glucose (g/infusion)	189 ± 90
Amino acids (g/infusion)	54.7 ± 25.3
Patients with no lipid emulsion (n.)	18 (16%)
CRBSI episodes (n./HPN-year)	0.50 ± 1.22
Alcohol consumption	
Males ≥30 g/day (n.),	6
Females ≥20 g/day (n.)	1

Volume, calculated as daily mean of the total volume infused per week ((volume per day of infusion × number of infusions per week)/7); energy, calculated as daily mean of the total energy infused per week (energy per day of infusion × number of infusions per week)/7); energy/BEE, calculated as (energy/BEE)×100; BEE, calculated by Harris-Benedict formula; BW: body weight.

Table 2
Prevalence of intestinal failure associated liver disease (IFALD) at study inclusion (CS).

IFALD diagnostic categories	Patient cohort (n.)	Prevalence of IFALD n. (%)
IFALD-cholestasis		
• Cavicchi criterion	103	8 [8]
• ConBil criterion	100	15 [15]
• TotBil criterion	100	5 [5]
IFALD-Steatosis		
• AAR index	111	19 [17]
• US criterion	99	43 (43)
IFALD-Fibrosis		
• APRI index	112	11 [10]
• FIB-4 index	110	22 [20]
IFALD-unclassified		
• Luman criterion	104	40 (38)
• Beath criterion	99	7 [7]

Cavicchi criterion: a value ≥1.5 the ULN on two of ɣ-GT, ALP, and serum conjugated bilirubin for ≥6 months; ConBil criterion: conjugated bilirubin >0.3 mg/dL for ≥6 months; TotBil criterion: total bilirubin >1 mg/dL and conjugated bilirubin >0.3 mg/dL for ≥6 months. AAR index: AST/ALT ratio <1 when AST and ALT > ULN; US criterion: liver ultrasound echogenic appearance of steatosis. APRI index: AST to platelets (PLT) ratio index = [(AST/ULN AST) × 100]/PLT (109/L)] >0.88; FIB-4 index: Fibrosis–4 index = Age (years) × AST)/[PLT (109/L) × ALT1/2], advanced fibrosis: ≥2.67. Luman-criterion: any deranged LFT ≥1.5 the upper limit of normal (ULN) after >6 months of HPN starting; Beath criterion: ALP and ɣ-GT ≥1.5 the ULN and US signs of liver steatosis.

Table 3
P values of the Mann–Whitney test and the chi square test for the comparison between patients with positive and those with negative diagnosis of intestinal failure associated liver disease (IFALD) at study inclusion (CS), according to the individual diagnostic criteria. Bold P values highlight the variables that significantly differ between the patients with positive and negative diagnosis of IFALD.

Criteria for IFALD diagnosis	Patient characteristics			CIF Mechanism	HPN-Characteristics					CRBSI episodes
	Gender F	Age (yrs)	BMI (kg/m^2)	SBS	Duration (mo.)	Infusions (n./week)	Lipid Inf. (n./week)	Volume (ml/inf/week)	Energy (kcal/inf/week)	n./HPN-yrs
Cholestasis										
Cavicchi	0.665	0.300	0.946	**0.043**	0.995	**0.020**	0.270	**<0.001**	0.231	**0.017**
ConBil	0.055	0.602	0.629	**0.017**	0.664	0.083	0.353	**0.021**	0.294	0.170
TotBil	0.096	0.580	0.800	0.124	0.950	0.573	0.341	0.424	0.315	0.546
Steatosis										
AAR index	0.430	0.992	0.591	0.280	0.079	0.066	0.108	0.099	0.578	0.348
US	0.717	0.114	0.238	0.473	**0.022**	0.342	0.672	0.729	0.902	0.790
Fibrosis										
APRI index	**0.013**	0.822	1.00	0.540	0.604	0.087	**0.005**	0.275	0.649	0.104
FIB-4 index	0.956	**0.004**	0.069	**0.031**	0.071	**0.032**	0.109	0.216	0.917	**0.046**
Unclassified										
Luman	0.178	0.710	0.487	0.120	0.833	0.076	0.156	0.103	0.405	**0.047**
Beath	0.380	0.316	0.503	0.124	0.322	**0.029**	**0.016**	0.413	0.875	0.494

CIF, chronic intestinal failure; volume, calculated as daily mean of the total volume infused per week ((volume per day of infusion × number of infusions per week)/7); energy, calculated as daily mean of the total energy infused per week (energy per day of infusion × number of infusions per week)/7); SBS, short bowel syndrome; CRBSI, central venous catheter related bloodstream infection since starting the HPN treatment; BMI, body mass index.
Cavicchi criterion: a value ≥1.5 the ULN on two of ɣ-GT, ALP, and serum conjugated bilirubin for ≥6 months; ConBil criterion: conjugated bilirubin >0.3 mg/dL for ≥6 months; TotBil criterion: total bilirubin >1 mg/dL and conjugated bilirubin >0.3 mg/dL for ≥6 months. AAR index: AST/ALT ratio <1 when AST and ALT > ULN; US criterion: liver ultrasound echogenic appearance of steatosis. APRI index: AST to platelets (PLT) ratio index = [(AST/ULN AST) × 100]/PLT (109/L)] >0.88; FIB-4 index: Fibrosis–4 index = Age (years) × AST)/[PLT (109/L) × ALT1/2], advanced fibrosis: ≥2.67. Luman-criterion: any deranged LFT ≥1.5 the upper limit of normal (ULN) after >6 months of HPN starting; Beath criterion: ALP and ɣ-GT ≥1.5 the ULN and US signs of liver steatosis.

In some patients, a positive IFALD diagnostic criterion became negative between BS and CS. This occurred for 70% of positive AAR index score, 40% of the Luman criterion and 20% of Cavicchi IFALD-cholestasis criterion or ConBil criterion and of US steatosis criterion. This also occurred in 4% of patients who had positive Beath criterion, and 2% of those with positive APRI or FIB-4 indices at BS.

The incidence of IFALD was determined by the presence of IFALD at CS in those patients who had previously demonstrated normal LFTs and US imaging at BS. The highest incidence was noted for IFALD-steatosis as defined by US criterion, developing in 39% of patients. IFALD-fibrosis incidence was 18% using the FIB-4 index and 7% with APRI index. IFALD-cholestasis developed in 7% and 6% of cases according to ConBil criterion and Cavicchi criterion, respectively. Incidence of IFALD-unclassified was 9% by Luman criterion and 4% by Beath criterion. No patients developed IFALD after BS according to the TotBil criterion and AAR index.

Table 4 shows the change in lipid emulsion in the PN-admixture, between BS and CS; notably there was a decrease of soy-bean based LE and an increase of alternative LE prescription.

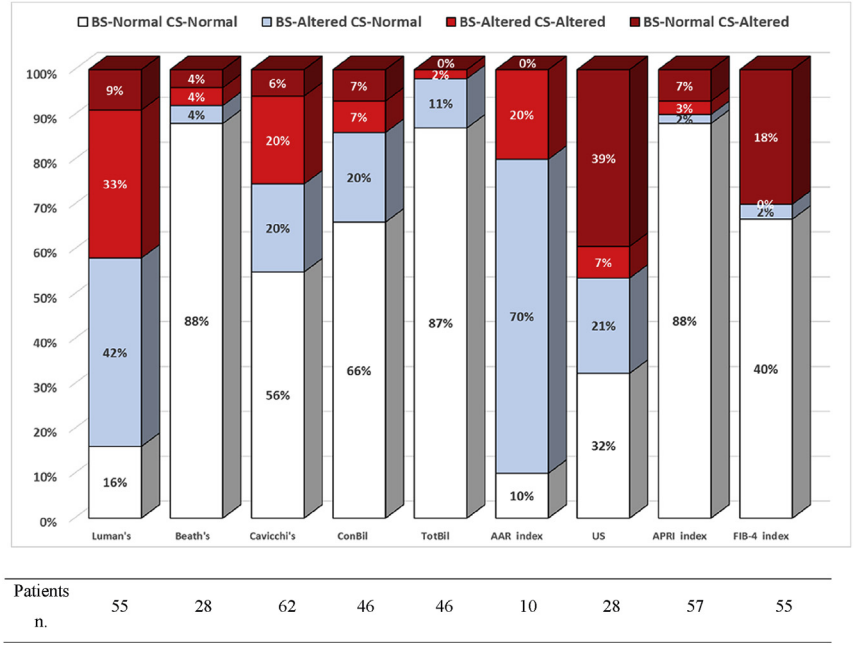

Fig. 1. Number of patients evaluated for each diagnostic criterion, at HPN starting (baseline, BS) and at patients' inclusion in the study (cross sectional, CS). *IFALD-cholestasis:* Cavicchi criterion: a value ≥1.5 the ULN on two of ɣ-GT, ALP, and serum conjugated bilirubin for ≥6 months; ConBil criterion: conjugated bilirubin >0.3 mg/dL for ≥6 months; TotBil criterion: total bilirubin >1 mg/dL and conjugated bilirubin >0.3 mg/dL for ≥6 months. *IFALD-steatosis:* AAR index: AST/ALT ratio <1 when AST and ALT > ULN; US criterion: liver ultrasound echogenic appearance of steatosis. *IFALD-fibrosis:* APRI index: AST to platelets (PLT) ratio index = [(AST/ULN AST) × 100]/PLT (109/L)] >0.88; FIB-4 index: Fib–4 index = Age (years) × AST)/[PLT (109/L) × ALT1/2], advanced fibrosis: ≥2.67. *IFALD–unclassified:* Luman-criterion: any deranged LFT ≥1.5 the upper limit of normal (ULN) after >6 months of HPN starting; Beath criterion: ALP and ɣ-GT ≥1.5 the ULN and US signs of liver steatosis.

4. Discussion

The present investigation shows a number of important findings. Firstly, this is the first study to systematically demonstrate that the prevalence and incidence of IFALD varies significantly, from 5 to 43% according to diagnostic criteria used. Secondly, the study shows that IFALD may resolve despite HPN continuation. Thirdly, the data detail clinical features associated with the IFALD occurrence, including CIF severity, SBS as an underlying cause and the occurrence of CRBSIs, but that the impact of these factors is significantly influenced by the diagnostic criterion used to define IFALD in the individual patient. Thus, the results strongly support the immediate need for an international consensus on definition between different clinical and research domains.

The reported prevalence of IFALD and its association with patient, CIF and HPN program characteristics are in keeping with previously reported observations [4–6,10,16–18]. However, the data clearly demonstrate that the prevalence of IFALD is determined not only by the underlying hepatic pathology considered (for example the occurrence of fibrosis vs. cholestasis), but also by the criterion used to define such pathology. Thus, the highest prevalence was observed for IFALD-steatosis diagnosed by liver US, occurring in around 50% of patients. IFALD-cholestasis was present in only 5% of patients according to TotBil criterion and as many as 15% using the ConBil criteria. IFALD-fibrosis prevalence ranged from 10% with APRI index to 20% with FIB-4 index. Such variation in reported IFALD prevalence clearly support the need for a unified approach to selecting relevant diagnostic criterion according to a specified underlying pathological mechanisms of hepatic injury.

The observed associations between the presence of IFALD and clinical features previously reported to be risk factors for its occurrence may also be considered an indirect validation of the diagnostic criteria adopted [4–6,10,16–18]. For example, IFALD-cholestasis according to Cavicchi criterion or the ConBil criterion and IFALD fibrosis diagnosed by FIB-4 index were significantly associated with SBS as a mechanism of CIF, the severity of CIF and the frequency of CRBSIs. However, IFALD-steatosis diagnosed by ultrasound was associated only with HPN duration. A lower number of statistically significant associations were found for Luman and Beath criteria, the APRI index and the AAR index. These observations might suggest that, until studies comparing IFALD criteria with liver histology and/or investigating their predictive value for the development of liver failure in large patient cohorts, liver US, Cavicchi criterion and/or serum conjugated bilirubin alone and FIB-4 index might be considered as criteria for diagnosis of IFALD-steatosis, IFALD-cholestasis and IFALD-fibrosis, respectively.

Our data also provide information on IFALD prevalence and evolution after HPN commencement since, with the exception of IFALD-cholestasis reported by Cavicchi et al. [10], no previous study has reported on this in the literature to-date. We observed that the criteria for the diagnosis of IFALD can exist at HPN commencement and may disappear during the treatment period. Indeed, around 10–20% of IFALD-cholestasis and steatosis diagnosed by US at the beginning of HPN were not present at time of CS. However, it is notable that fibrosis per se resolved in relatively few cases; these observations are in keeping with the pathophysiological mechanism of IFALD. An improvement of either steatosis or cholestasis observed in an early stage of the disease has been reported to occur in other studies [2,4–6,10,16–18]. On the contrary, fibrosis is typically a feature of the disease progression and is less likely to resolve [2,4–6,10,16–18].

The incidence of IFALD was determined by those patients who had normal LFTs and US imaging at HPN commencement and a positive criteria for IFALD diagnosis at time of inclusion in the study (CS). The incidence data further confirm that in adults with CIF, IFALD is mostly represented by liver steatosis, that chronic cholestasis develops in a low percentage of patients, but that liver fibrosis might develop in a significant proportion of cases. Thus, given the risks of serial liver biopsy, reliable non-invasive tools for diagnosis and follow up of IFALD-fibrosis are now required.

Potential weaknesses of the study include its retrospective design and the lack of any data on liver histology, the gold standard for the diagnosis of liver disease. The analysis of risk factors associated with IFALD onset was not assessable because of the retrospective nature of the study. In particular, the patients' characteristics before HPN commencement could not be known as well as the impact of LEs changes. Indeed, we observed an increase in the use of alternative LEs to soybean-based lipid over the course of the study. This was in line with the most recent recommendations [2] aimed at reducing the delivery of pro-inflammatory fatty acids and to increase anti-inflammatory fatty acids and anti-oxidant α-tocopherol in Les [19,20]. However, the retrospective design of the study precluded evaluation of the reasons for these changes in individual patients. Clearly, a prospective study would be required to investigate this issue. Very few data are available on IFALD liver histology in clinical practice, since liver biopsy is not a routine clinical investigation for CIF patients, given the inherent risks [7,10]. No comparison between biochemical indices with liver histology was performed in Luman [16] or Beath [17] original studies, while liver US is a validated method to assess liver steatosis in non-alcoholic fatty liver disease [13]. AAR ratio [12] has also been found to distinguish between alcoholic and non-alcoholic etiology of steatosis. Furthermore, and when considering fibrosis, a study from Van Gossum et al. [21] on patients on long-term HPN for CIF, found that transient elastography score, APRI index score and FIB-4 index score of fibrosis correlated with the histological score of cholestasis rather than fibrosis. Recently, liver fibrosis in adults on HPN for CIF were analyzed by a retrospective study including patients who underwent liver biopsy for appearance of unexplained chronic liver blood test abnormalities, and/or an assessment before potential intestinal transplantation. The presence of ultra-SBS (<20 cm) and alcohol consumption were found to be the only factors associated with fibrosis. No individual LFT was associated with liver fibrosis, but neither APRI or FIB-4 index were analyzed [22]. Thus, the appropriateness of the biochemical and other indices of liver fibrosis in CIF patients currently requires further investigation.

In conclusion, we have demonstrated that the incidence and prevalence of IFALD vary greatly, as do the identified clinical factors associated with the occurrence of IFALD, depending on the diagnostic criterion used. Furthermore, although we have observed that IFALD may resolve in a significant proportion of people after HPN commencement, the occurrence of fibrosis remains a concern, highlighting the need for non-invasive monitoring of disease progression. These data strongly support the development of an agreed international consensus definition and classification for IFALD in order to facilitate objective comparison between national and international IF units in both the clinical and research arena.

Table 4
Type of lipid emulsions in the parenteral nutrition admixture, at time of starting the home parenteral nutrition program (BS) and at time of inclusion in the study (CS).

Lipid emulsion	BS Patients n. (%)	CS Patients n. (%)	P
Soybean	18 (15.9)	1 (0.9)	<0.001
Soybean/MCT	13 [5,11]	5 (4.4)	
Olive oil/soybean	43 (38.1)	62 (54.8)	
Soybean/MCT/olive/fish	7 (6.2)	20 (17.8)	
Fish oil	2 (1.8)	4 (3.5)	
Olive oil/soybean + fish	0	1 (0.9)	
Soybean/MCT/olive/fish + fish	0	2 (1.8)	
None	10 (8.9%)	18 (15.9%)	
Not available	20 (17.6)	0	

Chi square test.

Statement of authorship

LP devised the study protocol. ASS, FA and CP collected the data. FA and CP revised and approved the manuscript. LP, MC, ASS and SL, analyzed the data and wrote the manuscript.

Conflict of interest

ASS, FA, CP and MG have nothing to disclose.

SL reports grants from Shire, grants from Fresenius Kabi, personal fees from Nutrition-related companies (e.g. Shire & Fresenius Kabi), outside the submitted work.

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Appendix 1. IFALD–cholestasis diagnostic criteria. Bold P values highlight the variables that significantly differ between the patients with positive and negative diagnosis of IFALD.

	Cavicchi criterion			ConBil criterion			TotBil criterion		
	Negative 95 (92%)	Positive 8 (8%)	P	Negative 85 (85%)	Positive 15 (15%)	P	Negative 95 (95%)	Positive 5 (5%)	P
Gender F (n, %)	55 (58%)	4 (50%)	0.665	51 (60%)	5 (33%)	0.055	55 (58%)	1 (20%)	0.096
Age (yrs)	49 ± 17	55 ± 14	0.300	48 ± 18	47 ± 15	0.602	49 ± 18	54 ± 15	0.580
Age at beginning of HPN (yrs)	41 ± 19	48 ± 15	0.365	42 ± 19	41 ± 19	0.870	41 ± 19	48 ± 16	0.420
BMI (kg/m^2)	20 ± 3	20 ± 1	0.946	21 ± 3	21 ± 4	0.629	21 ± 3	21 ± 3	0.800
Primary disease			0.246			0.114			0.171
Cause of CIF			0.250			0.124			0.500
SBS vs Others (n.; %)	62 (65%)	8 (100%)	**0.043**	55 (65%)	14 (93%)	**0.017**	64 (67%)	5 (100%)	0.124
Duration (mo.)	93 ± 94	75 ± 61	0.995	96 ± 96	76 ± 74	0.664	94 ± 101	73 ± 52	0.950
Infusions (n./week)	5.8 ± 1.6	7.0 ± 0.0	**0.020**	5.9 ± 1.6	6.5 ± 1.3	0.083	6.0 ± 1.5	6.0 ± 2.0	0.573
Lipid Infusions (n./week)	4.1 ± 2.7	5.1 ± 2.1	0.270	4.3 ± 2.6	3.4 ± 2.6	0.353	4.1 ± 2.6	5.1 ± 2.7	0.341
Volume (ml/inf/week)	1644 ± 765	2790 ± 850	**<0.001**	1631 ± 791	2217 ± 969	**0.021**	1694 ± 810	2200 ± 1352	0.424
Energy (kcal/inf/week)	1019 ± 548	1291 ± 538	0.231	1019 ± 548	1178 ± 686	0.294	1024 ± 533	1295 ± 710	0.315
Energy/BEE (%)	80.7 ± 45.4	102.6 ± 38.9	0.173	80.3 ± 43.1	90.2 ± 52.9	0.411	81.1 ± 44.4	95.8 ± 50.3	0.438
Lipids (g/infusion)	34.8 ± 22.5	32.7 ± 20.5	0.743	35.2 ± 21.9	31.6 ± 22.5	0.646	34.7 ± 22.3	32.0 ± 16.2	0.721
Lipids (g/BW/infusion)	0.67 ± 0.45	0.60 ± 0.43	0.608	0.68 ± 0.44	0.57 ± 0.45	0.451	0.67 ± 0.45	0.52 ± 0.21	0.388
Glucose (g/infusion)	188 ± 90	213 ± 102	0.617	186 ± 87	217 ± 111	0.208	188 ± 91	244 ± 85	0.191
Amino acids (g/infusion)	54.6 ± 25.6	58.9 ± 25.3	0.911	55.0 ± 24.3	57.4 ± 30.4	0.571	54.9 ± 25.3	64.4 ± 23.2	0.563
Patients with no lipid emulsion (n.)	17 (18%)	0	0.416	13 (15%)	3 (20%)	0.704	16 (17%)	0	0.707
CRSBI episodes (n./HPN-yrs)	0.37 ± 0.68	0.66 ± 0.59	**0.017**	0.39 ± 0.72	0.55 ± 0.66	0.170	0.42 ± 0.73	0.35 ± 0.28	0.546

Cavicchi criterion: a value ≥1.5 the ULN on two of γ-GT, ALP, and serum conjugated bilirubin for ≥6 months.
ConBil criterion: conjugated bilirubin >0.3 mg/dL for ≥6 months.
TotBil criterion: total bilirubin >1 mg/dL and conjugated bilirubin >0.3 mg/dL for ≥6 months.

Appendix 2. IFALD-steatosis diagnostic criteria. Bold P values highlight the variables that significantly differ between the patients with positive and negative diagnosis of IFALD.

	AAR index			US criterion		
	Negative 92 (83%)	Positive 19 (17%)	P	Negative 56 (57%)	Positive 43 (43%)	P
Gender F (n, %)	49 (53%)	12 (63%)	0.430	24 (43%)	23 (53%)	0.717
Age (yrs)	50 ± 17	49 ± 18	0.992	50 ± 16	45 ± 19	0.114
Age at beginning of HPN (yrs)	41 ± 19	45 ± 19	0.520	44 ± 16	36 ± 22	0.072
BMI (kg/m^2)	20 ± 3	20 ± 3	0.591	20 ± 3	21 ± 4	0.238
Primary disease			0.895			**0.035**
Cause of CIF			0.685			0.357
SBS vs Others (n.; %)	61 (66%)	15 (79%)	0.280	39 (70%)	27 (63%)	0.473
Duration (mo.)	92 ± 96	52 ± 59	0.079	76 ± 84	111 ± 103	**0.022**
Infusions (n./week)	5.8 ± 1.6	6.7 ± 0.6	0.066	6.0 ± 1.5	5.8 ± 1.6	0.342
Lipid Infusions (n./week)	4.1 ± 2.6	5.2 ± 2.4	0.108	4.3 ± 2.7	4.2 ± 2.4	0.672
Volume (ml/inf/week)	1632 ± 811	1998 ± 917	0.099	1717 ± 857	1648 ± 824	0.729
Energy (kcal/inf/week)	1029 ± 561	1094 ± 492	0.578	1069 ± 577	1050 ± 500	0.902
Energy/BEE (%)	84.5 ± 45.5	87.3 ± 39.0	0.431	84.8 ± 47.9	80.7 ± 38.2	0.873
Lipids (g/infusion)	35.4 ± 22.6	29.5 ± 18.0	0.212	32.4 ± 20.5	38.4 ± 22.4	0.200
Lipids (g/BW/infusion)	0.68 ± 0.45	0.64 ± 0.38	0.428	0.64 ± 0.46	0.72 ± 0.40	0.216
Glucose (g/infusion)	191 ± 92	178 ± 85	0.559	192 ± 95	198 ± 87	0.689
Amino acids (g/infusion)	55.0 ± 25.3	55.8 ± 23.8	0.916	55.4 ± 26.2	59.0 ± 21.1	0.397
Patients with no lipid emulsion (n.)	15 (16%)	2 (11%)	0.774	9 (16%)	4 (9%)	0.323
CRSBI episodes (n./HPN-yrs)	0.42 ± 1.2	0.83 ± 0.41	0.348	0.65 ± 1.6	0.35 ± 0.50	0.790

AAR index: AST/ALT ratio <1 when AST and ALT > ULN.
US criterion: liver ultrasound echogenic appearance of steatosis.

Appendix 3. IFALD–fibrosis diagnostic criteria. Bold P values highlight the variables that significantly differ between the patients with positive and negative diagnosis of IFALD.

	APRI index			FIB-4 index		
	Negative 101 (90%)	Positive 11 (10%)	P	Negative 54 (49%)	Positive 22 (20%)	P
Gender F (n, %)	52 (52%)	10 (91%)	**0.013**	34 (63%)	14 (64%)	0.956
Age (yrs)	49 ± 17	51 ± 16	0.822	43 ± 16	55 ± 14	**0.004**
Age at beginning of HPN (yrs)	42 ± 19	47 ± 19	0.457	35 ± 18	49 ± 15	**0.007**
BMI (kg/m^2)	20 ± 3	20 ± 2	1.00	19 ± 3	21 ± 3	0.069
Primary disease			0.373			0.068
Cause of CIF			0.740			0.178
SBS vs Others (n.; %)	69 (68%)	8 (73%)	0.540	30 (56%)	18 (81%)	**0.031**
Duration (mo.)	88 ± 95	52 ± 35	0.604	87 ± 91	74 ± 75	0.071
Infusions (n./week)	5.9 ± 1.6	6.7 ± 0.6	0.087	5.9 ± 1.6	6.7 ± .0.6	**0.032**
Lipid Infusions (n./week)	4.0 ± 2.7	6.3 ± 1.3	**0.005**	4.4 ± 2.6	5.0 ± 2.5	0.332
Volume (ml/inf/week)	1663 ± 809	2023 ± 1030	0.275	1624 ± 768	1966 ± 971	0.216
Energy (kcal/inf/week)	1299 ± 591	1270 ± 416	0.649	1368 ± 605	1172 ± 465	0.917
Energy/BEE (%)	79.6 ± 45.5	96.2 ± 31.5	0.153	84.5 ± 46.9	88.2 ± 37.7	0.659
Lipids (g/infusion)	34.4 ± 22.6	29.5 ± 18.0	0.212	36.7 ± 21.5	28.9 ± 19.0	0.109
Lipids (g/BW/infusion)	0.66 ± 0.45	0.65 ± 0.36	0.486	0.73 ± 0.50	0.57 ± 0.40	0.123
Glucose (g/infusion)	189 ± 92	184 ± 83	0.783	197 ± 93	176 ± 75	0.310
Amino acids (g/infusion)	54.6 ± 26.3	55.5 ± 19.4	0.742	54.6 ± 25.8	55.3 ± 20.6	0.809
Patients with no lipid emulsion (n.)	18 (18%)	0	0.126	8 (15%)	2 (9%)	0.503
CRSBI episodes (n./HPN-yrs)	0.45 ± 1.2	0.84 ± 1.60	0.104	0.44 ± 1.5	0.79 ± 1.33	**0.046**

APRI index: AST to platelets (PLT) ratio index = [(AST/ULN AST) × 100]/PLT (109/L)] >0.88.
FIB-4 index: Fibrosis–4 index = Age (years) × AST)/[PLT (109/L) × ALT1/2], advanced fibrosis: ≥2.67.

Appendix 4. IFALD–unclassified diagnostic criteria. Bold P values highlight the variables that significantly differ between the patients with positive and negative diagnosis of IFALD.

	Luman criterion			Beath criterion		
	Negative 64 (62%)	Positive 40 (48%)	P	Negative 92 (93%)	Positive 7 (7%)	P
Gender F (n, %)	33 (52%)	26 (65%)	0.178	50 (54%)	2 (29%)	0.380
Age (yrs)	50 ± 18	49 ± 16	0.710	49 ± 18	43 ± 14	0.316
Age at beginning of HPN (yrs)	42 ± 19	42 ± 19	0.970	41 ± 19	38 ± 17	0.628
BMI (kg/m^2)	20 ± 3	21 ± 3	0.487	20 ± 3	20 ± 3	0.503
Primary disease			0.360			0.767
Cause of CIF			0.454			0.698
SBS vs Others (n.; %)	40 (63%)	31 (78%)	0.120	60 (65%)	6 (86%)	0.124
Duration (mo.)	97 ± 100	82 ± 77	0.833	94 ± 96	54 ± 50	0.322
Infusions (n./week)	5.8 ± 1.6	6.3 ± 1.4	0.076	5.8 ± 1.6	7.0 ± 0.0	**0.029**
Lipid Infusions (n./week)	3.9 ± 2.6	4.7 ± 2.7	0.156	4.2 ± 2.6	6.4 ± 1.5	**0.016**
Volume (ml/inf/week)	1597 ± 790	1878 ± 889	0.103	1669 ± 845	1936 ± 769	0.413
Energy (kcal/inf/week)	1007 ± 551	1095 ± 541	0.405	1058 ± 557	1089 ± 298	0.875
Energy/BEE (%)	79.1 ± 45.5	87.3 ± 44.2	0.321	82.8 ± 44.7	86.4 ± 30.5	0.834
Lipids (g/infusion)	36.0 ± 23.6	32.1 ± 19.8	0.353	35.7 ± 21.3	27.7 ± 22.4	0.169
Lipids (g/BW/infusion)	0.69 ± 0.47	0.62 ± 0.41	0.427	0.69 ± 0.43	0.54 ± 0.46	0.274
Glucose (g/infusion)	193 ± 92	185 ± 88	0.683	198 ± 92	156 ± 68	0.189
Amino acids (g/infusion)	54.9 ± 26.6	55.4 ± 23.7	0.981	57.3 ± 24.7	52.6 ± 13.5	0.966
Patients with no lipid emulsion (n.)	12 (19%)	5 (13%)	0.402	13 (14%)	0	0.627
CRSBI episodes (n./HPN-yrs)	0.28 ± 0.46	0.60 ± 0.96	**0.047**	0.52 ± 1.28	0.48 ± 0.60	0.494

Luman-criterion: any deranged LFT ≥1.5 the upper limit of normal (ULN) after >6 months of HPN starting.
Beath criterion: ALP and γ-GT ≥1.5 the ULN and US signs of liver steatosis.

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