Low circulating concentrations of citrulline and FGF19 predict chronic cholestasis and poor survival in adult patients with chronic intestinal failure: development of a Model for End-Stage Intestinal Failure (MESIF risk score)

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ABSTRACT

Background: Patients with chronic intestinal failure (CIF) often develop cholestatic liver injury, which may lead to liver failure and need for organ transplantation.

Objectives: The aim of this study was to investigate whether citrulline (CIT) and the enterokine fibroblast growth factor 19 (FGF19) are associated with chronic cholestasis and survival in adult CIF patients, and to develop a risk score to predict their survival.

Methods: We studied 135 adult CIF patients on intravenous supplementation (>3 mo). Associations of plasma CIT and FGF19 with chronic cholestasis and survival were estimated by logistic and Cox regression models. A predictive risk score was developed and validated internally.

Results: Patients with chronic cholestasis (17%) had a reduced 5-y survival rate compared with patients without chronic cholestasis (38% and 62%, respectively). In multivariable analysis, low FGF19, low CIT, and female sex were associated with chronic cholestasis. Patients with low rather than high CIT or FGF19 also had reduced 5-y survival rates (29% compared with 69%; 54% compared with 66%, respectively). Risk factors identified in multivariable analysis of survival were low FGF19 (HR: 3.4), low CIT (HR: 3.3), and number of intravenous infusions per week (HR: 1.4). These 3 predictors were incorporated in a risk model of survival termed Model for End-Stage Intestinal Failure (MESIF) (C-statistic 0.78). The 5-y survival rates for patients with MESIF scores of 0 to <20 ($n = 47$), 20–40 ($n = 75$), and >40 ($n = 13$) were 80%, 58%, and 14%, respectively.

Conclusions: CIT and FGF19 predict chronic cholestasis and survival in this cohort of adult CIF patients, and the derived MESIF score is associated with their survival. Pending external validation, the MESIF score may help to identify patients for closer clinical monitoring or earlier referral to intestinal transplantation centers. *Am J Clin Nutr* 2019;109:1620–1629.

Keywords: intestinal failure, chronic cholestasis, FGF19, citrulline, home parenteral nutrition

Introduction

Patients with chronic intestinal failure (CIF) require long-term intravenous supplementation (IVS) to maintain adequate protein, energy, fluid, and electrolyte balance; availability of essential micronutrients and minerals; and to achieve longer survival (1, 2). CIF is considered an orphan disease with a prevalence in adults of 12 per million habitants in the Netherlands according to the Dutch Registry of Intestinal Failure and Intestinal Transplantation,

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Abbreviations used: ALP, alkaline phosphatase; CIF, chronic intestinal failure; CIT, citrulline; C-statistic, concordance statistic; FGF, fibroblast growth factor; GGT, γ-glutamyl transferase; HPN, home parenteral nutrition; IF, intestinal failure; IFALD, intestinal failure–associated liver disease; ITx, intestinal transplantation; IVS, intravenous supplementation; MESIF, Model for End-Stage Intestinal Failure; SB, short bowel; TBS, total bile salts.

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launched in February 2013 (3). Care for these patients is complex and requires a multidisciplinary approach (3, 4).

Between 24% and 65% of CIF patients develop liver injury (e.g., steatosis, cholestasis, or fibrosis), collectively known as intestinal failure–associated liver disease (IFALD) (5–9). Ultimately, IFALD may progress to liver failure, which is accompanied by higher rates of referral for intestinal or multivisceral transplantation (ITx) and home parenteral nutrition (HPN)-related mortality (10). Currently, no scoring instruments are available to predict the risk of development of cholestatic liver injury and mortality in adult (or pediatric) CIF patients.

Fibroblast growth factor 19 (FGF19) is an ileum-derived enterokine that is induced by enteral feeding. FGF19 targets the liver to regulate key metabolic processes including energy and lipid metabolism, and maintains hepatic bile salt homeostasis by controlling bile salt synthesis (11, 12). Several studies demonstrated dysregulated bile salt synthesis in experimental and clinical (pediatric) IFALD, indicating an etiologic role of excessive concentrations of hepatic bile salts (13–15). In animal studies, FGF19 ameliorated cholestatic liver injury by restoring bile salt homeostasis or repression of proinflammatory cascades (16–18). Moreover, low concentrations of FGF19 in pediatric patients with short bowel (SB) syndrome were related to hepatic fibrosis and portal inflammation (19).

Citrulline (CIT), a nonproteinaceous amino acid produced in the enterocyte through the glutamine–ornithine pathway, is a powerful marker of the absorptive function of the remnant small bowel (20). Because massive loss of small intestinal tissue is associated with cholestatic liver injury in parenteral nutrition–dependent patients, it could be anticipated that low CIT also predicts development of cholestasis in CIF patients (21).

Taken together, we hypothesized that low FGF19, especially with absent or limited enteral intake or after ileal resection, and inadequate small intestinal absorptive capacity, reflected by low CIT, could accurately predict the risk of cholestatic liver injury and mortality. The aims of this study were *1*) to estimate the predictive performance of the intestinal factors CIT and FGF19 for chronic cholestasis and to assess if these factors are associated with survival in adult CIF patients, and *2*) to develop a prognostic scoring system to predict their survival.

Methods

Study population

This study was a retrospective analysis on a prospectively collected cohort of 193 consecutive adult patients who visited the outpatient clinic of the Department of Gastroenterology of Radboud University Medical Center (Nijmegen, Netherlands)—a tertiary referral center for Intestinal Failure (IF) support—between 2007 and 2017. Patients who had received IVS for ≥ 3 mo at the time of blood collection, and for whom clinical data and a blood sample were available, were considered for inclusion. Before database building, we excluded patients with obstructive cholestasis caused by biliary malignancies or autoimmune diseases (e.g. primary sclerosing cholangitis). All patient plasma samples were obtained as part of routine clinical care during clinic visits and stored surplus plasma samples were analyzed in this study. Blood samples were collected between January, 2007 and February, 2017. Fifty-eight patients were excluded from this study. See **Supplemental Figure 1** for a detailed overview of the excluded patients. This study was approved by the Medical Ethics Committee of Radboud University (no. 2016-2714).

Data collection and definitions

Data were collected from patient medical files. Castor Electronic Data Capture, a web-based electronic platform, was used for data management. The following items were collected: date of birth, sex, body weight, length, BMI, underlying disease, reason for IVS, age at start of IVS, age at day of blood sample, duration of IVS (defined as the difference in time [months] between the start date of IVS and day of blood collection), infused volume per day, frequency of intravenous infusions per week (number between 1 and 7), calories provided by IVS, infusion of intravenous lipids, cholecystectomy, bowel anatomy and oral intake, liver tests, C-reactive protein, Fibroscan value (if available), death and cause of death (if applicable), and hepatitis B and C serologic test results. Chronic cholestasis and survival were the main outcome parameters. Chronic cholestasis was assessed according to Cavicchi et al. (5) as persistent elevation (> 1.5 times the upper limit of the normal range) of ≥ 2 cholestatic markers (alkaline phosphatase [ALP], γ-glutamyl transferase [GGT], and total bilirubin) for ≥ 6 mo. Chronic cholestasis was assessed at the day of blood collection. In case multiple blood samples since the start of IVS were available for a given patient, the most recent blood sample (end date: 22 February, 2017) was used for CIT/FGF19 measurements. Total intravenous energy intake (in kilocalories) and intravenous lipids infused (in grams) per day, adjusted for body weight and number of infusions per week, were calculated according to the manufacturer's formulations. The small bowel anatomy of all patients was assessed, in particular the presence or absence of the terminal ileum. For data analysis small bowel anatomy was dichotomized, i.e., *1*) the terminal ileum was (partially) in situ, or *2*) the complete ileum was resected or the terminal ileum was not preserved. Remnant small bowel length was categorized into 4 groups: *1*) > 200 cm (including patients with no resection), *2*) > 100 to ≤ 200 cm, *3*) ≥ 50 to ≤ 100 cm, and *4*) <50 cm. A cutoff of 107 pg/mL for plasma FGF19 was used for all data analyses (based on the median fasted FGF19 concentrations in 18 healthy males, see below) and a cutoff concentration of 20 μmol/L for plasma CIT was used. The latter was previously shown to be the lower limit for sufficient absorptive function (20).

Blood samples and analytical procedures

Blood was collected in EDTA-coated tubes and derived plasma was stored at −20°C (at Radboud University Medical Center) until further analysis. Plasma FGF19 was assayed by sandwich ELISA as described previously (22). FGF19 cutoffs were derived from analysis of plasma samples ($n = 18$ male healthy volunteers, median [IQR] age: 23 [19, 27] y) obtained after an overnight fast. These samples were collected between 2014 and 2018 in the framework of other studies (MR Soeters, unpublished data). Plasma CIT was measured by HPLC (23). Plasma 7α-hydroxy-4-cholesten-3-one (C4, plasma marker of bile salt synthesis) was assessed by liquid chromatography-mass spectrometry as described previously (22). Plasma total bile salts (TBS) were

measured by an enzymatic cycling method according to the manufacturer's protocol (Diazyme).

Statistical analysis

Data are expressed as frequency (percentage), median [IQR], or mean ± SD as appropriate. For contingency analysis, the chi-square test of independence was used. Differences between 2 groups on continuous variables were tested using the Mann–Whitney *U* test or Student's *t* test, depending on the distribution of the data. The Kruskal–Wallis test with Dunn's multiple-comparison post hoc test was used when comparing ≥ 3 groups. Correlations were evaluated by Spearman rank correlation coefficients (ρ). Univariable and multivariable binary logistic regression analysis was performed to identify predictors of chronic cholestasis. The −2 log-likelihood was used to compare and choose the best fit of the regression models. Survival curves were calculated using the Kaplan–Meier method. Differences between groups were assessed using the log-rank test. In survival analyses, time zero was set as the day of blood collection and subjects were censored by death, end of the follow-up period, or loss to follow-up. The censoring date used for survival analyses was 22 November, 2017. Univariable and multivariable Cox proportional hazard regression analysis was used to identify independent predictors of survival. Selection of covariates for multivariable logistic regression and Cox proportional hazard regression analysis was based on the following criteria: *P* values <0.20 in the univariable analysis or based on the research question. For covariate selection a force entry strategy was used to optimally select relevant covariates. A risk score predicting survival was developed and the model performance was evaluated by assessing the concordance (C) statistic. Internal validation using a bootstrap method was used to correct the C-statistic for optimism. A C-statistic > 0.7 denotes a clinically useful test and values between 0.8 and 0.9 are considered to have excellent predictive value. *P* values <0.05 were considered statistically significant. To study longitudinal differences of FGF19 or CIT in cases where multiple samples were available, the difference between the first and most recent measurements of FGF19 (ΔFGF19) or CIT (ΔCIT) was used and analyzed using linear regression with the time difference (in months) between the 2 measurements as the covariate. Statistical analyses were performed using IBM SPSS Statistics version 24 (IBM Corporation) or R statistical software and associated packages (R Foundation for Statistical Computing).

Results

Patients' characteristics

Data from 135 patients (mean age at start of IVS: 50.3 y, 74% females) were included in this study. Details of the total cohort of patients stratified for chronic cholestasis are displayed in **Table 1**. The duration of IVS therapy (time between the start of IVS and day of blood collection for the FGF19/CIT assay) was 46 [14, 83] mo. Nineteen patients received only intravenous fluids, whereas 116 patients were supplemented with HPN (see **Supplemental Table 1** for a detailed overview of the type of IVS). Ten patients had a history of gastrointestinal malignancy, but none of these patients had residual cancer or signs of recurrence of cancer during IVS. Inherent to stratification criteria, patients with chronic cholestasis had higher GGT, ALP, and total bilirubin concentrations. In addition, transaminases were higher in this group. None of the patients had active hepatitis B or C infection.

Plasma CIT, TBS, FGF19, and C4 concentrations were related to the mechanism of IF

First, we studied plasma concentrations of CIT, TBS, FGF19, and C4 across the different causes of IF (**Table 2**). CIT and TBS concentrations were comparable in all groups. In contrast, FGF19 concentrations were significantly lower in SB patients than in intestinal dysmotility patients ($P < 0.0001$), mechanically obstructed patients ($P = 0.005$), and healthy controls at baseline ($P < 0.0001$). Low FGF19 concentrations in SB patients were accompanied by high C4 concentrations, indicating dysregulated bile salt homeostasis in this group. C4 concentrations in SB patients were notably higher than in patients with intestinal dysmotility ($P < 0.0001$) and patients with mechanical obstruction ($P = 0.016$). FGF19 and C4 were negatively correlated across all patients ($\rho = -0.77$, $P < 0.0001$) and in all cause-of-IF groups (ρ range: −0.41 to −0.96, $P < 0.001$), in line with FGF19 suppressing bile salt synthesis. CIT and FGF19 were not correlated across all patients ($\rho = -0.04$, $P = 0.64$), or in any of the cause-of-IF groups. As expected, both CIT and FGF19 concentrations were associated with small bowel length ($\rho = -0.32$, $P = 0.0004$; $\rho = -0.55$, $P < 0.0001$, respectively) (**Supplemental Figure 2**A). Moreover, FGF19 concentrations were significantly lower in CIF patients who underwent terminal ileum resection than in CIF patients with preserved terminal ileum ($P < 0.0001$). Conversely, C4 concentrations were higher in CIF patients without a terminal ileum than in patients with preserved terminal ileum ($P < 0.0001$) (Supplemental Figure 2B). TBS and CIT concentrations were comparable in patients with resected or preserved terminal ileum.

Low circulating concentrations of CIT and FGF19 predicted chronic cholestasis in adult CIF patients

Next, we investigated the association between selected variables and chronic cholestasis. As shown in Table 1, 23 patients (17.1%) had chronic cholestasis in this cohort. The 5-y survival rate of patients with chronic cholestasis was significantly lower than that of patients without chronic cholestasis (38% compared with 62%, $P = 0.009$) (**Figure 1**). Univariable analysis revealed that terminal ileum resection ($P = 0.021$), small bowel length ($P = 0.002$), prior cholecystectomy ($P = 0.015$), low FGF19 ($P = 0.038$), and low CIT ($P = 0.001$) concentrations were significant predictors of chronic cholestasis (**Table 3**). Multivariable analysis showed that low CIT ($P = 0.002$) and low FGF19 ($P = 0.049$), adjusted for sex ($P = 0.021$), were significant independent predictors of chronic cholestasis (Table 3).

Low CIT and low FGF19 concentrations were associated with reduced survival of adult CIF patients

Because low concentrations of CIT and FGF19 were associated with chronic cholestasis, and patients with chronic

TABLE 1 Patient characteristics[1]

Item	Total cohort	No chronic cholestasis	Chronic cholestasis	*P* value
Patients	135 (100)	112 (83)	23 (17)	
Female	100 (74)	79 (71)	21 (91)	0.038
Age at start of IVS, y	50.3 ± 15.2	49.7 ± 14.5	53.1 ± 17.9	0.353
Age at day of blood sample, y	55.9 ± 14.5	55.3 ± 14.0	58.8 ± 16.7	0.329
BMI, kg/m^2	22.2 ± 3.9	22.1 ± 3.6	22.4 ± 5.0	0.740
Duration of IVS,[2] mo	46.0 [14.0, 83.0]	45.5 [14.0, 88.0]	52.0 [14.0, 81.0]	0.902
Frequency of HPN infusion ($n = 116$)	5.0 [3.5, 7.0]	5.5 [3.5, 7.0]	5 [3.5, 7.0]	0.429
IVS volume, mL/d ($n = 115$)	1408 ± 542	1385 ± 549	1505 ± 516	0.353
Energy intake, kcal · kg^{-1} · d^{-1} ($n = 121$)	22.5 ± 11.6	22.3 ± 12.0	23.5 ± 9.9	0.664
i.v. lipids, g · kg^{-1} · d^{-1} ($n = 115$)	0.72 ± 0.48	0.74 ± 0.48	0.61 ± 0.47	0.245
IVS type				
i.v. fluids only	19 (14)	18 (16)	1 (4)	0.141
Reason for HPN				
Short bowel	58 (43)	43 (39)	15 (65)	0.018
Enterocutaneous fistula	7 (5)	5 (5)	2 (9)	0.341
Intestinal dysmotility	49 (36)	46 (41)	3 (13)	0.011
Mechanical obstruction	3 (2)	2 (2)	1 (4)	0.432
Extensive small bowel mucosal disease	7 (5)	5 (5)	2 (9)	0.341
Other	11 (8)	11 (10)	0 (0)	0.117
Underlying etiology				
Inflammatory bowel disease	28 (21)	24 (21)	4 (17)	0.664
Bowel obstruction	8 (6)	7 (6)	1 (4)	0.725
Mesenteric thrombosis	16 (12)	12 (11)	4 (17)	0.476
Bowel ischemia, nonthrombotic	8 (6)	3 (3)	5 (22)	0.004
Complicated abdominal surgery	2 (2)	1 (1)	1 (4)	0.313
Congenital GI abnormality	1 (1)	1 (1)	0 (0)	1.000
GI malignancy	10 (7)	7 (6)	3 (14)	0.374
CIP	43 (32)	40 (36)	3 (13)	0.034
Volvulus	5 (4)	4 (4)	1 (4)	1.000
Radiation enteritis	6 (4)	6 (5)	0 (0)	0.589
Other	8 (6)	7 (6)	1 (4)	1.000
Surgical anatomy				
Terminal ileum resection, yes	69 (51)	52 (47)	17 (74)	0.014
Small bowel length				
≥ 200 cm	70 (52)	64 (57)	6 (26)	0.007
≥ 100 – <200 cm	19 (14)	14 (13)	5 (22)	0.305
≥ 50 – <100 cm	17 (13)	11 (10)	6 (26)	0.043
<50 cm	13 (10)	8 (7)	5 (22)	0.046
Unknown	16 (12)	15 (13)	1 (4)	0.306
Colon not in continuity with small bowel	39 (29)	31 (28)	8 (35)	0.494
Cholecystectomy	36 (27)	25 (22)	11 (48)	0.012
Liver tests[3]				
ALAT, IU/L	26 [19, 43]	24 [18, 36]	53 [28, 116]	0.007
ASAT, IU/L	27 [22, 39]	25 [21, 33]	43 [30, 53]	0.023
GGT, IU/L	38 [20, 101]	29 [18, 57]	204 [124, 388]	0.001
ALP, IU/L	110 [88, 156]	103 [81, 131]	274 [189, 365]	<0.0001
Total bilirubin, μmol/L	7 [5, 11]	6 [4, 10]	14 [9, 22]	0.007

[1] Values are mean ± SD, median [IQR], or frequency (*n*, %). The chi-square test of independence, Mann–Whitney *U* test, or Student's *t* test (depending on the distribution of the data) was used to compare groups. ALAT, alanine aminotransferase; ALP, alkaline phosphatase; ASAT, aspartate aminotransferase; CIP, chronic intestinal pseudo-obstruction; GGT, γ-glutamyl transferase; GI, gastrointestinal; HPN, home parenteral nutrition; i.v., intravenous; IVS, intravenous supplementation.

[2] Duration of IVS is the time difference between the start of IVS and day of blood collection.

[3] Measured at the day of blood collection.

cholestasis had reduced 5-y survival, we further investigated the association between low CIT or low FGF19 and survival. The survival rates after the start of IVS were 94%, 85%, and 71% at 2, 5, and 10 y, respectively. Twenty-nine patients (22%) died during follow-up, because of their underlying disease ($n = 8$), central venous catheter–related sepsis ($n = 2$), and other causes ($n = 13$). The cause of death was unknown in 6 patients (owing to loss to follow-up) (**Supplemental Table 2**). Patients with low CIT had a reduced 5-y survival compared with patients with CIT concentrations > 20 μM (29% compared with 69%, $P < 0.0001$, **Figure 2**A). Likewise, patients with low FGF19 tended to have a lower 5-y survival than patients with high FGF19 concentrations (54% compared with 66%, $P = 0.060$, Figure 2B).

TABLE 2 CIT, TBS, FGF19, and C4 concentrations related to the mechanism of intestinal failure[1]

Item	CIT (μmol/L)	Adjusted *P* value	TBS (μmol/L)	Adjusted *P* value	FGF19 (pg/mL)	Adjusted *P* value	C4 (ng/mL)	Adjusted *P* value	Correlation FGF19 vs. C4 (ρ, *P* value)
Mechanism of intestinal failure									
SB ($n = 58$)	34 [23, 49]	Ref	4 [3, 9]	Ref	16 [9, 44]	Ref	148 [78, 260]	Ref	−0.59, <0.0001
Intestinal fistula ($n = 7$)	28 [20, 36]	NS	7 [5, 10]	NS	57 [41, 432]	NS	28 [3, 211]	NS	−0.96, <0.0001
Intestinal dysmotility ($n = 49$)	39 [32, 51]	NS	4 [3, 11]	NS	120 [50, 366]	<0.0001	15 [7, 43]	<0.0001	−0.41, <0.0001
Mechanical obstruction ($n = 3$)	41 [33, 44]	NS	9 [1, 13]	NS	287 [129, 691]	0.005	7 [3, 34]	0.016	−0.50, <0.0001
ESMD ($n = 7$)	26 [16, 34]	NS	7 [6, 20]	NS	62 [16, 280]	NS	15 [8, 147]	NS	−0.79, <0.0001
Healthy controls									
Baseline (fasted) ($n = 18$)	N/A	N/A	N/A	N/A	107 [87, 134]	<0.0001	N/A	N/A	N/A

[1] Values are median [IQR]. SB is used as a reference category for the adjusted *P* values. The Kruskal–Wallis test with Dunn's multiple-comparison post hoc test was used to compare between groups with SB as the reference group. Correlations were evaluated by Spearman rank correlation coefficients (ρ). CIT, citrulline; ESMD, extensive small bowel mucosal disease; FGF, fibroblast growth factor; N/A, not available; NS, nonsignificant; Ref, reference group; SB, short bowel; TBS, total bile salts.

Results from univariable and multivariable Cox proportional hazard regression analyses are depicted in **Table 4**. Univariable Cox regressions identified frequency of intravenous infusions per week (HR: 1.32, $P = 0.027$) and low CIT (HR: 3.64, $P < 0.001$) as significant predictors of survival. Low FGF19 tended to be a predictor of survival (HR: 2.81, $P = 0.056$) (Table 4).

In the multivariable Cox regression analysis, low FGF19 became a significant predictor of outcome (HR: 3.35, $P = 0.032$) when adjusting for low CIT (HR: 3.34, $P = 0.004$) and frequency of intravenous infusions per week (HR: 1.39, $P = 0.011$). All variables had a variance inflation factor of 1.0, indicating lack of multicollinearity between variables.

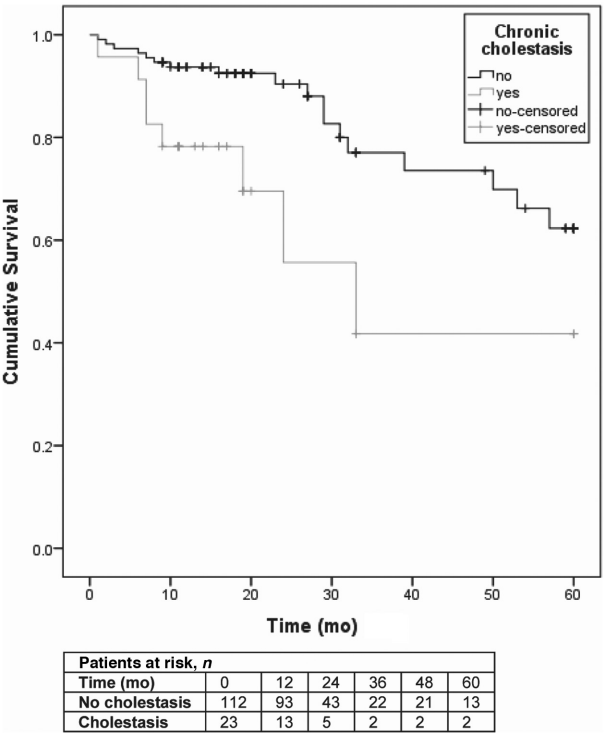


FIGURE 1 Kaplan–Meier curves for adult intestinal failure patients with and without chronic cholestasis during a 5-y observation period. Patients with chronic cholestasis had a significantly lower survival rate than patients without chronic cholestasis (log-rank test, $P = 0.009$).

Development of a scoring system to predict survival in adult CIF patients

Because CIT, FGF19, and frequency of intravenous infusions per week were associated with survival and are simple objective parameters, we developed a scoring system, termed Model for End-Stage Intestinal Failure (MESIF), to predict survival in adult CIF patients. Such a model could be useful to identify potential ITx candidates at an early stage or to stratify patients who need closer clinical monitoring.

The formula for calculating the MESIF score was derived from multivariable Cox proportional hazard regression analysis. The estimates of the regression coefficients were incorporated in a formula and multiplied by 10 to simplify the scoring: MESIF score = 12.05·CIT + 12.09·FGF19 + 3.29·Frequency of intravenous infusions per week (i.e., the number of days per week that IVS is given). CIT is scored as 0 (> 20 μmol/L) or 1 (≤ 20 μmol/L), FGF19 is scored as 0 (> 107 pg/mL) or 1 (≤ 107 pg/mL), and frequency of intravenous infusions per week is a score between 1 and 7. Accordingly, MESIF scores can range between 3 and 47.

We evaluated the predictive performance of the MESIF score by computing the C-statistic, a value that indicates discriminative performance. The C-statistic was 0.78 (95% CI: 0.65, 0.91) for the initial model. Because regression coefficients from multivariable regressions are prone to be overestimated, the final model was validated internally using bootstrap resampling, and resulted in an optimism-corrected C-statistic of 0.76 indicating good discriminative performance. Using the MESIF score, we stratified patients according to their scores into 3 arbitrary risk groups. The 5-y survival rates for groups with scores of 3 to ≤ 20 (low-risk group), 20–40 (intermediate-risk group), or > 40 points (high-risk group) were 80%, 58%, and 14%, respectively ($P < 0.0001$) (**Figure 3**).

The time span between initiation of IVS and blood sampling varied for the FGF19/CIT assay, ranging from 3 to 484 mo. For 80 of the 135 patients, ≥ 2 longitudinal plasma samples covering this interval were available. Linear regression analyses, with ΔFGF19 or ΔCIT (i.e., the difference between the first and most recent plasma values) as the dependent factor and time (ranging between 3 to 484 mo) as the covariate, revealed that time did not have a significant influence on longitudinal FGF19 ($n = 80$; $P = 0.693$) or CIT ($n = 71$; $P = 0.624$) plasma values. Thus, FGF19/CIT values remain quite stable over a longer period of IVS dependency.

Discussion

In this (single-center, Dutch) CIF patient cohort study, we were able to investigate the relation of clinical and gut-derived factors with chronic cholestatic liver injury and survival. The main finding of this study is that low CIT and FGF19, both gut-derived factors, are strongly associated with chronic cholestasis and poor survival in adult patients with CIF. Furthermore, we developed a simple risk score, the MESIF score, to predict survival in adult CIF patients. Of note, a tool to guide clinical practice is currently not available.

Chronic cholestatic liver injury is strongly associated with severe parenteral nutrition–related liver disease and may progress to liver failure (5). In the case of end-stage liver disease, intestine or combined liver–intestine transplantation is the only viable treatment option (10). Previously recognized risk factors for chronic cholestatic liver injury were small bowel length (<50 cm), lipid emulsions containing solely soybean oil, and high-dose parenteral lipids $\geq$ 1 g $\cdot$ kg^{-1} $\cdot$ d^{-1} (5). Since then, multiple strategies have been implemented in clinical care guidelines to reduce the risk of IFALD, including sepsis management, preserving small bowel length, maintaining small bowel–colon continuity, promoting oral/enteral intake, limiting lipid supplementation to <1 g $\cdot$ kg^{-1} $\cdot$ d^{-1}, and minimizing soybean oil content (1). Of note, it has been shown that phytosterols, major constituents of soybean oil, promote cholestatic liver disease, highlighting the need to minimize use of soybean oil–based lipid emulsions to prevent cholestatic liver injury (24, 25). Although liver failure due to IFALD remains the main indication for intestine or combined liver–intestine transplantation, more recent studies showed declines in the prevalence of chronic cholestatic liver injury (20–30%) relative to the 50% prevalence reported in an initial study in 2000 (5, 8, 9). In the large cohort studied here, we found a slightly lower prevalence of 17%. Nonetheless, patients with chronic cholestatic liver injury had reduced survival in our study, underlining the need to identify potential risk factors or predictors.

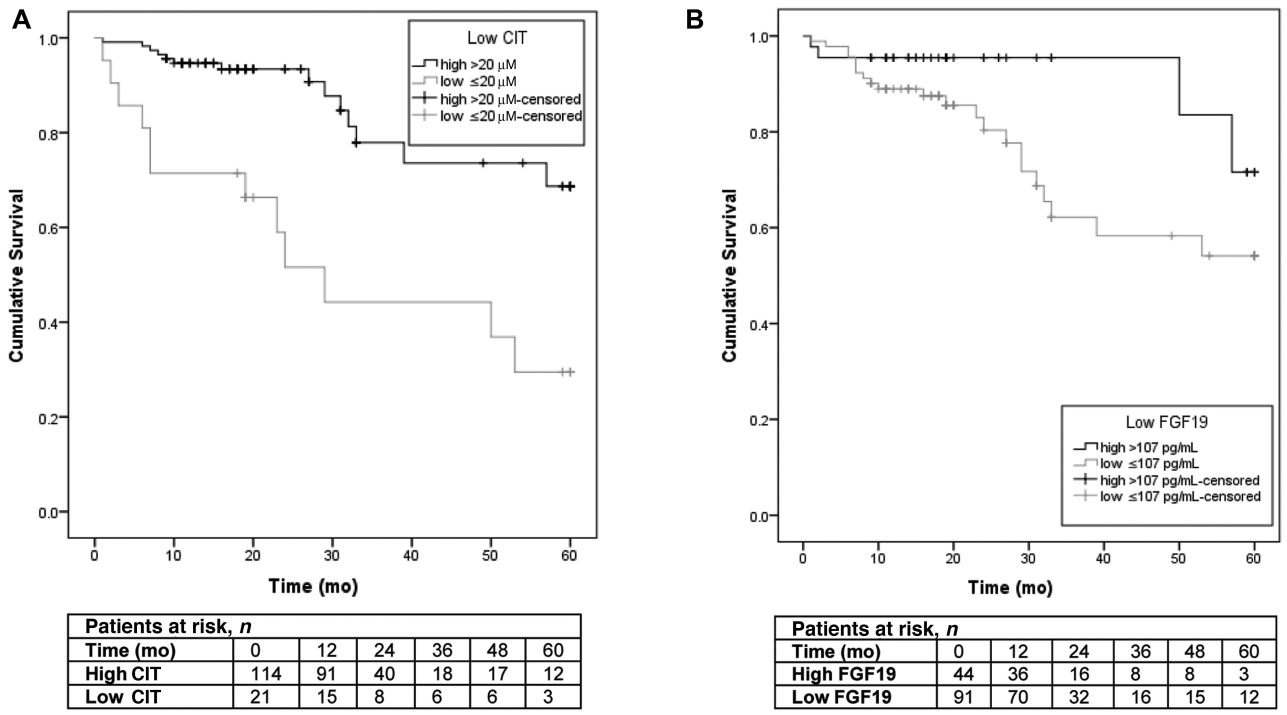
An elegant study in mice receiving parenteral nutrition demonstrated that an intact gut barrier is pivotal to prevent

TABLE 3 Uni- and multivariable logistic regression analysis for the association with chronic cholestasis[1]

ptpt	Univariable analysis		Multivariable analysis	
ptpt				
Item	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
ptpt				
Age at start of IVS, y	1.02 (0.99, 1.05)	0.327	—	
Age at day of blood collection, y	1.02 (0.99, 1.05)	0.284	—	
Sex				
Male	Reference		—	
Female	4.39 (0.97, 19.78)	0.054	6.55 (1.33, 32.30)	0.021
BMI, kg/m^2	1.02 (0.91, 1.14)	0.737	—	
Terminal ileum resection				
No	Reference		—	
Yes	3.33 (1.20, 8.90)	0.021	—	
Small bowel length (n = 119)	1.95 (1.29, 2.96)	0.002	—	
$\geq$ 200 cm (n = 70)	Reference		—	
$\geq$ 100 – <200 cm (n = 19)	3.81 (1.02, 14.26)	0.047	—	
$\geq$ 50 – <100 cm (n = 17)	5.82 (1.59, 21.35)	0.008	—	
<50 cm (n = 13)	6.67 (1.65, 26.93)	0.008	—	
Cholecystectomy				
No	Reference		—	
Yes	3.19 (1.26, 8.10)	0.015	—	
Oral intake (n = 125)				
No	Reference		—	
Yes (n = 117)	0.65 (0.08, 5.59)	0.697	—	
Fibroscan (n = 67)	1.06 (0.98, 1.13)	0.129	—	
Duration of IVS,[2] mo	1.00 (0.99, 1.01)	0.995	—	
Type of IVS				
i.v. fluids only	Reference		—	
HPN	4.21 (0.53, 33.27)	0.173	—	
IVS infusions (n = 116)	1.05 (0.80, 1.36)	0.739	—	
Energy intake, kcal $\cdot$ kg^{-1} $\cdot$ d^{-1}	1.01 (0.97, 1.05)	0.661	—	
i.v. lipids $\geq$ 1 g $\cdot$ kg^{-1} $\cdot$ d^{-1} (n = 115)				
No	Reference		—	
Yes (n = 34)	0.47 (0.15, 1.50)	0.201	—	
IVS volume, mL/d	1.00 (1.00, 1.00)	0.351	—	
FGF19				
High concentrations (> 107 pg/mL)	Reference		—	
Low concentrations ($\leq$ 107 pg/mL)	3.85 (1.08, 12.75)	0.038	3.76 (1.00, 14.10)	0.049
Citrulline				
High concentrations (> 20 μmol/L)	Reference		—	
Low concentrations ($\leq$ 20 μmol/L)	5.36 (1.91, 15.00)	0.001	5.94 (1.89, 18.65)	0.002
C4, ng/mL	0.99 (0.99, 1.00)	0.260	—	
Total bile salts, μmol/L	1.01 (0.98, 1.03)	0.661	—	
CRP, mg/L (n = 120)	1.02 (0.99, 1.06)	0.108	—	

pt [1]Duration of IVS is the time difference between the start of IVS and day of blood collection. CRP, C-reactive protein; FGF, fibroblast growth factor; HPN, home parenteral nutrition; i.v., intravenous; IVS, intravenous supplementation.

[2]HPN only or HPN + i.v. fluid, number of infusions per week.



Patients at risk, *n*						
Time (mo)	0	12	24	36	48	60
High CIT	114	91	40	18	17	12
Low CIT	21	15	8	6	6	3

Patients at risk, *n*						
Time (mo)	0	12	24	36	48	60
High FGF19	44	36	16	8	8	3
Low FGF19	91	70	32	16	15	12

FIGURE 2 Kaplan–Meier curves for patients stratified for CIT (A) or FGF19 (B). Patients with CIT concentrations <20 μM had a significantly lower survival than patients with higher concentrations of CIT (log-rank test, $P < 0.0001$). Patients with FGF19 concentrations <107 pg/mL tended to have a lower survival than patients with high concentrations of FGF19 (log-rank test, $P = 0.060$). CIT, citrulline; FGF, fibroblast growth factor.

cholestatic liver injury, because intestinal inflammation promoted bacterial translocation and LPS-induced Kupffer cell activation and inflammatory sequelae (26). In addition, intestinal inflammation was associated with low concentrations of FGF19 in pediatric IF (13). Another study in pediatric patients with IF due to surgical loss of the ileum showed that reduced FGF19 was associated with severity of fibrosis and liver inflammation (19). Here we show, for the first time to our knowledge, that low concentrations of FGF19 are associated with cholestatic liver injury in adult patients with IF. Because the ileum is the primary source of FGF19 in the circulation, terminal ileum resection was also independently associated with cholestatic liver injury. Interestingly, low CIT was strongly associated with chronic cholestatic liver injury, adding to the notion that adequate gut function is critical in preventing liver injury.

What could be the mechanism underlying the association of low FGF19/CIT with chronic cholestasis? First, recall that low FGF19 concentrations in pediatric IF were related with increased serum and hepatic bile salts and de-repressed bile salt synthesis (13). Analysis of liver biopsies from these pediatric patients revealed downregulation of the master regulator (i.e., Farnesoid X Receptor) of hepatic bile salt homeostasis, and an elevated hepatic bile salt content (13). Hepatic FXR repression was linked to intestinal inflammation and likely resulted in hepatic bile salt toxicity (15, 27). Accumulation of bile salts in the hepatocyte is known to trigger inflammation-linked pathways and results in immune-mediated liver injury (28). In our study, bile salt synthesis was upregulated, as reflected by marked elevation of circulating C4, in patients with loss of the ileum, replicating earlier findings in SB patients (29). However, this was not accompanied by elevation of plasma bile salts. Neither C4 nor TBS concentrations were associated with chronic cholestasis. This suggests that in the studied patients, the normal transport direction of bile salts (i.e., towards the canalicular pole) is maintained. In line, total bilirubin—reflecting liver secretory function—is elevated, but within the normal range, in patients with chronic cholestasis. Hence, chronic cholestasis is unlikely due to hepatotoxic concentrations of bile salts. Alternatively, low FGF19 could contribute to liver injury independently of effects on bile salt synthesis, as its hepatic receptor (FGFR4) has anti-inflammatory actions (30). Hence, loss of enterocytic-derived FGF19 signal could make the liver more susceptible to inflammation (30).

This study revealed a heretofore-unknown association of CIT with chronic cholestasis. CIT is a nonproteinaceous amino acid and urea cycle intermediate. Net release in the circulation occurs exclusively in the intestines. Previous studies showed that CIT reflects the absorptive capacity of the (remnant) small bowel, independently of the degree of intestinal inflammation (20, 31). Apart from stimulation of muscle protein synthesis (32), no liver-specific actions of CIT have been described in humans. An experimental study in septic rats treated with CIT demonstrated hepatoprotective effects in terms of reduced transaminases and lower release of proinflammatory cytokines (33). CIT concentrations were negatively associated with GGT ($n = 115$, $\rho = -0.47$, $P < 0.0001$) and ALP ($n = 131$, $\rho = -0.45$, $P < 0.0001$) in our cohort. Rather than loss of presumed hepatoprotective action, this more likely reflects a reduced functional capacity of the small intestine (reduced bowel length or injured small intestine) in CIF patients, which results in

TABLE 4 Uni- and multivariable Cox proportional hazard regression analysis[1]

	Univariable analysis		Multivariable analysis	
Item	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age at start of IVS, y	1.02 (1.00, 1.05)	0.127	—	
Age at day of blood collection, y	1.02 (1.00, 1.05)	0.111	—	
Sex				
Male	Reference		—	
Female	0.93 (0.41, 2.09)	0.854	—	
BMI, kg/m^2	0.95 (0.86, 1.06)	0.388	—	
Fibroscan ($n = 67$)	0.96 (0.89, 1.14)	0.964	—	
Duration of IVS,[2] mo	1.00 (0.995, 1.005)	0.932	—	
Small bowel resection	1.58 (0.75, 3.33)	0.277	—	
Small bowel length	1.30 (0.88, 1.78)	0.210	—	
≥ 200 cm	Reference		—	
≥ 100 – <200 cm	0.57 (0.07, 4.17)	0.593	—	
≥ 50 – <100 cm	2.98 (1.17, 7.54)	0.022	—	
<50 cm	1.05 (0.24, 4.67)	0.952	—	
Type of IVS				
i.v. fluids only	Reference		—	
HPN	0.77 (0.27, 2.24)	0.630	—	
IVS infusions[3] ($n = 116$)	1.32 (1.03, 1.70)	0.027	1.39 (1.08, 1.79)	0.011
Energy intake, kcal · kg^{-1} · d^{-1} ($n = 118$)	1.03 (1.00, 1.07)	0.057	—	
i.v. lipids ≥ 1 g · kg^{-1} · d^{-1} ($n = 115$)				
No	Reference		—	
Yes	1.02 (0.44, 2.36)	0.960	—	
PN volume, mL/d ($n = 115$)	1.00 (1.00, 1.00)	0.084	—	
FGF19				
High concentrations (> 107 pg/mL)	Reference		Reference	
Low concentrations (≤ 107 pg/mL)	2.81 (0.97, 8.11)	0.056	3.35 (1.11, 10.11)	0.032
Citrulline				
High concentrations (> 20 μmol/L)	Reference		Reference	
Low concentrations (≤ 20 μmol/L)	3.64 (1.71, 7.74)	0.001	3.34 (1.48, 7.51)	0.004
C4, ng/mL	0.99 (0.996, 1.002)	0.533	—	
Total bile salts, μmol/L	1.01 (0.99, 1.03)	0.532	—	
CRP, mg/L ($n = 120$)	1.02 (1.00, 1.05)	0.065	—	

[1]CRP, C-reactive protein; FGF, fibroblast growth factor; HPN, home parenteral nutrition; i.v., intravenous; IVS, intravenous supplementation; PN, parenteral nutrition.

[2]Duration of IVS is the time difference between the start of IVS and day of blood collection.

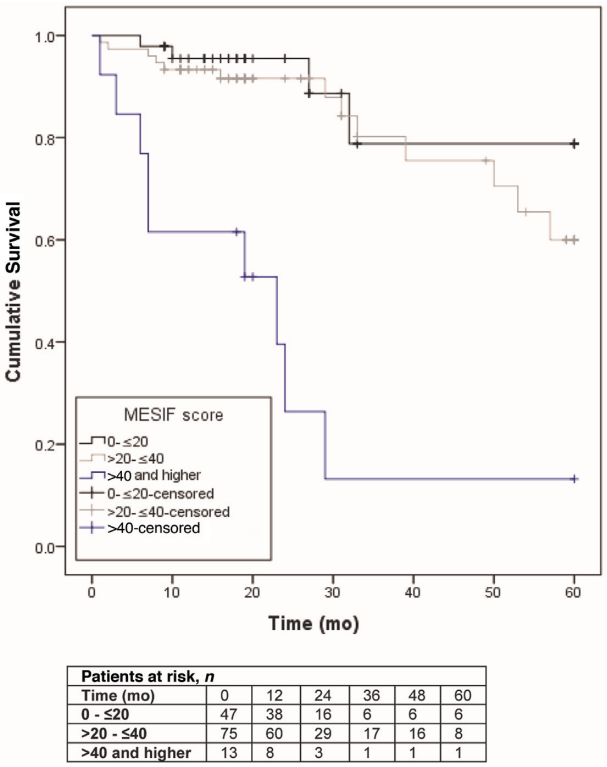
[3]HPN only or HPN + i.v. fluid, number of infusions per week.

low CIT. Ultimately, by the nature of the short gut, patients are at risk of development of IFALD.

In line with earlier findings (8), (remnant) small bowel length and terminal ileum resection were associated with chronic cholestasis in the current study. Unlike earlier reports (5, 34), we (and others [7, 8]) did not observe a relation between high-dose intravenous lipids and chronic cholestasis. Because intravenous lipid mixtures have been improved in composition (in terms of a lower content of proinflammatory mediators derived from n–6 PUFAs in soybean oil) and clinicians are aware of the harmful effects of high doses, intravenous lipids may no longer pose a risk factor for chronic cholestasis. The majority of patients received a lipid emulsion with a reduced amount of soybean oil (ClinOleic: 80% olive oil, 20% soybean oil) as part of their parenteral nutrition (Supplemental Table 1).

In this study, we analyzed the largest cohort of adult CIF patients so far, aiming to identify blood factors that predict survival. The 5-y survival rate (59%) was slightly lower than in other reports, where 5-y survival ranged from 62% to 75% (35–39). Thus far, previous studies did not explore frequency of IVS infusions per week as a predictor of survival. Interestingly, the number of IVS infusions per week was significantly associated with survival ($P = 0.027$) and remained significant in multivariable analyses. Obviously, a higher number of infusions may increase the risk of HPN-related complications. The number of IVS infusions per week, low FGF19, and low CIT, which were incorporated in a risk model, are simple measurements and objective variables and therefore have clinical utility. The MESIF risk score has not been validated yet using an external cohort, and further evaluation and confirmation in future multicenter studies are warranted.

The major strength of our study in this rare patient population was the availability of blood samples and clinical information, allowing us to identify predictors of outcome. Importantly, longitudinal measurements over a long period of time established the stability, and hence validity, of single time point measurements. The study has several limitations. First, a validation cohort was not available and the results thus need to be interpreted with



Patients at risk, *n*						
Time (mo)	0	12	24	36	48	60
0 - ≤20	47	38	16	6	6	6
>20 - ≤40	75	60	29	17	16	8
>40 and higher	13	8	3	1	1	1

FIGURE 3 Kaplan–Meier curves for patients with low, intermediate, and high MESIF scores. Patients with high MESIF scores (> 40) had a significantly lower 5-y survival rate than patients with low (scores between 0 and 20) or intermediate (scores between 20 and 40) MESIF scores (log-rank test, $P < 0.0001$). MESIF, Model for End-Stage Intestinal Failure.

caution. Replication studies should be performed to scrutinize the association of CIT and FGF19 with progressive liver disease and to assess the general validity of the MESIF score. Second, some patients received prescribed drugs, but the potential contribution of these drugs to chronic cholestasis could not be taken into account. Lastly, data from this study are limited by the low event rates of chronic cholestasis (17%) and death (21%), which could potentially lead to overestimation of the reported OR and HR.

Data from this study could be useful for clinicians taking care of adult HPN patients. In particular, patients with a high MESIF score should be monitored more closely or referred earlier for consultation in an intestinal transplantation center. Considering the long waiting time until ITx of ∼275 d (median time, Universitair Ziekenhuis Leuven [Belgium], personal communication), the referral of patients in the intermediate-risk group to ITx centers should be considered. The rehabilitative ITx has a 5-y survival rate of 83%, so early referral should be considered in view of the favorable survival rate. Our study included both SB and non-SB patients (mainly intestinal dysmotility patients), therefore results could be applied to a larger group of patients compared with other studies analyzing only SB patients. It is conceivable that variables in the MESIF risk score could be used as criteria for pre-emptive ITx screening. Further studies exploring this option should be considered, because in a simulation study ITx has been shown to improve the survival of CIF patients and to be more cost-effective in CIF patients with a poor expected survival (40). Because of its rarity, there is a lack of data in the adult CIF population, which makes evidence-based clinical evaluation of CIF challenging. Recently, a European program has been launched (ATLAS Program) to create more awareness of this devastating orphan disease, and to improve the standard care of CIF patients.

In conclusion, low concentrations of FGF19 and CIT predicted chronic cholestasis and were associated with poor survival in our cohort of adult CIF patients. The MESIF score was associated with survival of these patients. Validation studies are warranted to assess the general utility of the MESIF risk score in the clinical management of CIF patients.

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