

Original article

QuantiFERON-Monitor as prognostic marker of mortality in patients with decompensated cirrhosis: A prospective cohort study

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ABSTRACT

Background: Prognosis in decompensated cirrhosis is heterogeneous and may be influenced by cirrhosis-associated immune dysfunction.

Aims: To assess whether QuantiFERON-Monitor, a whole blood interferon- γ release assay, predicts short-term outcomes in patients with acute decompensated cirrhosis.

Methods: We conducted a prospective cohort study in two hospitals (March 2022-March 2023), enrolling 44 patients hospitalized for acute decompensated cirrhosis. QuantiFERON-Monitor testing measured interferon- γ release after immune stimulation during hospitalization. Patients were followed for 90 days for mortality, bacterial infection, and acute-on-chronic liver failure. Associations between interferon-gamma levels and outcomes were evaluated using Cox proportional hazards and logistic regression models.

Results: The median interferon- γ release was 56 IU/mL (1-366). Each 10 IU/mL increase was associated with a 12% relative reduction in 90-day risk of death or ACLF (HR 0.88, 95% CI 0.79-0.99; $p=0.03$). No deaths occurred in patients with Interferon- $\gamma \geq 100$ IU/mL versus 39% mortality in those below ($p=0.01$). Interferon- γ levels were not significantly associated with infection or acute-on-chronic liver failure. Adding QuantiFERON-Monitor to the MELD-Na improved discrimination for early mortality or acute-on-chronic liver failure.

Conclusions: Baseline interferon- γ release measured by the QuantiFERON-Monitor is a prognostic marker of short-term poor outcome in acute decompensated cirrhosis, reflecting cellular immune dysfunction. This assay may complement existing prognostic tools. Further validation with a larger cohort is required.

1. Introduction

Cirrhosis-associated immune dysfunction (CAID) is a spectrum of immune alterations associated with end-stage liver disease [1]. Bacterial infections are the most common complications and can lead to acute decompensation and multi-organ failure (acute-on-chronic liver failure) associated with high mortality [2].

Trebicka et al. identified three clinical courses of cirrhotic patients with acute decompensation after hospitalization with very different prognoses through the PREDICT study: pre acute-on-chronic liver failure (pre-ACLF) patients who developed ACLF and who had a 1-year mortality rate of 67.4%, unstable decompensated cirrhosis with a 1-year mortality rate of 35.6% and stable decompensated cirrhosis who had a 1-year mortality rate of only 9.5%. Systemic inflammation, often caused

by bacterial infection, is considered the main driver of evolution of the pre-ACLF category of patients [3]. Therefore, identifying patients with a higher risk of infection is essential for the evaluation of prognosis.

QuantiFERON-Monitor (QFM, Qiagen Ltd) is a biological test that was initially developed to evaluate the immunosuppression level of transplanted patients to adjust immunosuppressive treatment and diminish infection risk [4-7]. It was previously assessed in various clinical immunosuppression situations, including HIV [8], organ transplant recipients [4-6,9-12], allogeneic hematopoietic cell transplant recipients [7,13], end-stage kidney disease [14] and cirrhosis [15]. QFM works in a similar manner to QuantiFERON-TB, which is widely used in clinical practice for the diagnosis of tuberculosis. Instead of targeting reactive lymphocytes against *Mycobacterium tuberculosis*, this test allows global stimulation of cellular immunity. Indeed, QFM uses a

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combination of stimulants (QFM LyoSpheres™) that are incubated with whole blood and activate different cell populations from both the innate and adaptative immune systems through Toll-Like Receptor (TLR7/8, R848) and T-cell receptor (TCR) agonists (anti-CD3 monoclonal antibody) [12]. The measurement of interferon- γ (IFN- γ) after stimulation therefore singularly reflects cell-mediated immune function.

A study conducted on cirrhotic patients awaiting liver transplantation assessed QFM to evaluate the relative immunosuppression in these patients. Indeed, they had a significantly lower mean QFM than healthy subjects and lower QFM levels were associated with an increased risk of infection [15].

We evaluated the interest of QFM in predicting infections and mortality, specifically in hospitalized cirrhotic patients with acute decompensation.

2. Methods

2.1. Patients and design

We conducted a bi-centric prospective observational cohort study of 44 patients with cirrhosis hospitalized for acute decompensation. The two centers were a university hospital (CHU of Liège) (n=36) and a regional hospital (CHR Citadelle de Liège) (n=8). Patients were recruited between the 1st of March 2022 and the 22nd of March 2023.

All patients provided written informed consent to participate in the study, which was approved by the Ethics Committee of Liege University and the Institutional Review Board (n°2021/324, amendment 25/11/2022 to recruit with a second center).

Inclusion criteria comprised hospitalized patients with acute decompensation (AD) of an established cirrhosis. The diagnosis of cirrhosis was based on previous liver biopsy findings or a combination of clinical signs and findings provided by laboratory test results, endoscopy, and ultrasonography. Acute decompensation of cirrhosis (AD) was defined as the acute development of ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infection, or any combination of these. Exclusion criteria included immunosuppression factors (transplant patients, immunosuppressive treatment, immune deficiencies, COVID infection at the time of recruitment, history of splenectomy, neutropenia < 1000/mm³, malignant hemopathy with lymphopenia < 800/mm³), and AD defined solely by an isolated bacterial infection.

The QuantiFERON-Monitor assay (QFM, Qiagen Ltd.) was performed according to the manufacturer's instructions. Briefly, 1 mL of heparinized whole blood was collected into dedicated tube and stimulated with the QFM immune ligands in the form of a lyophilized pellet (LyoSpheres). Stimulated blood was incubated overnight at 37°C. Following incubation, the blood was centrifuged and the plasma was harvested. Enzyme-linked immunosorbent assay (ELISA) was then performed. QFM results were measured as interferon-gamma (IFN- γ) production measured in IU/mL. Basal clinical data were collected from patients who were recruited after obtaining consent. The collected data included age, sex, primary cirrhosis etiology, MELD-Na and CHILD-Pugh scores, and history of previous decompensation. Patients were then monitored prospectively through medical files or phone calls for infections, ACLF, transplantation, or death during three months, and for transplantation and death until death or the 16th of September 2024. During hospitalization, bacterial infection was defined by the International Sepsis Forum Consensus [16] including both probable and confirmed infections. For outpatients, bacterial infection was defined as a clinical diagnosis requiring antibiotic prescription from the primary care physician (or another ambulatory specialist). ACLF was diagnosed during follow-up according to the CANONIC study criteria [17] (Table S1). Organ failure and organ dysfunction were defined according to the CLIF consortium (CLIF-C) organ failure (of) score [18] (Table S2). Pre-ACLF, stable decompensated cirrhosis (SDC), and unstable decompensated cirrhosis (UDC) were defined according to the PREDICT study [19].

2.2. Statistical analysis

2.2.1. Descriptive statistics

Discrete variables are described using frequency tables (percentages) and compared using χ^2 or Fisher's exact tests, while continuous variables were described using statistical summaries (median and quartiles, minimum and maximum) and compared using Kruskal-Wallis tests.

Logarithmic transformation was used in the analyses for some biological variables (white blood cells, neutrophils, platelets, CRP, urea, creatinine, and bilirubin).

2.2.2. QFM analysis

QFM was first assessed as a continuous variable. **Time-to-event analysis** was conducted using **univariate Cox proportional hazards models** for all endpoints (3-month mortality, 1-year mortality, 3-month infection and ACLF, 1-year transplantation, and a combined endpoint of 3-month mortality or ACLF). We chose to focus the main analysis on this latter combined endpoint because of its clear clinical relevance. Hazard ratios were expressed in 10 IU/mL increments of IFN- γ . The effect of different factors on survival was studied using the Cox proportional hazards model. For each model, the hazard ratio (HR), its 95% confidence interval (95% CI), and the associated p-values were provided. When necessary, Firth correction was applied to the Cox model. The proportional hazards assumption was assessed using Schoenfeld residuals, and concordance indices were reported to gauge the model discrimination.

Logistic regression analysis at fixed relevant time points of 3 months and 1 year was performed to provide odds ratio estimates. Since no patients were lost to follow-up until one year, we performed a complete-case analysis on the full cohort (n=43) (excluding one patient with incorrect sampling).

Second, we assessed QFM as a dichotomized value, comparing a group with a low IFN- γ response to high responders. The cut-off separating these groups was chosen arbitrarily to reflect the observed bimodal distribution of QFM measurements, with most measurements of IFN- γ $\leq$ 100 IU/mL and a separate group $\geq$ 200 IU/mL. **Time-to-event analyses** were conducted using both **univariate Cox proportional hazards models** and **Kaplan Meier survival curves**. The log-rank test was used to compare survival curves at three months, one year, and for the entire follow-up period.

Subgroup analysis: To address the potential confounding effects of infection at enrollment, we performed a predefined sensitivity analysis restricted to patients without infection at baseline. The prognostic association between QFM and outcomes was re-estimated in this subgroup using the same Cox proportional hazards approach as in the main analysis. Baseline QFM values were also compared between the infected and non-infected patients using Wilcoxon rank-sum test, and the prognostic impact of baseline infection was assessed through univariate Cox models. This analysis aimed to determine whether acute infection at enrollment influenced QFM measurements or modified their prognostic value.

Lastly, to evaluate whether QFM provided independent prognostic information beyond established score, we compared two Cox proportional hazards models for the 90-day combined endpoint (ACLF or death): a univariable model including MELD-Na alone, and a multivariable model including both MELD-Na and QFM (per 10 IU/mL). Hazard ratios were expressed with their 95% confidence intervals. Model performance was assessed using likelihood ratio test and Harrell's C-index. The proportional hazards assumption was verified using Schoenfeld residuals.

The results were considered significant at the 5% uncertainty level (p < 0.05). Calculations and graphs were generated using R software (version 4.3.1).

3. Results

3.1. Description of the cohort

Demographic characteristics and initial data are shown in (Table 1).

Within three months of follow-up, seven patients developed ACLF and were classified in the preACLF group, 17 were classified into the unstable decompensated cirrhosis group (UDC) as they died or were re-admitted to the hospital (non-electively) during the 90-day follow-up, and 19 patients did not die or were not hospitalized and were considered to have stable decompensated cirrhosis (SDC).

Median follow-up was 545 days and ranged from 1 to 858 days.

Fig. S1 shows the Kaplan–Meier curves for overall mortality (A), transplantation (B), infection (C), ACLF (D) and a combined endpoint of death or ACLF (E). Among the cohort of 44 patients, 21 died within a period of 8 days to 2 years. The **probability of survival** was 72.1% (IC95% 59.9–86.8%) at 3 months and 62.8% (IC95%: 0.50–0.79) at 1 year. The cause of death was sepsis or ACLF in eight patients, extrahepatic cancer in two patients (after one year of follow-up), hepatocarcinoma in one patient, and cardiac arrest secondary to rupture of esophageal varices in one patient. The remaining patients died outside the hospital of unknown cause.

Kaplan–Meier curves for mortality in the three different groups according to PREDICT clinical outcomes are shown in **Fig. S2**. The probabilities of death at one year were 86% (n=6/7), 47% (n=8/17), and 16% (n=3/19) for preACLF, UDC and SDC respectively. None of the patients with pre-ACLF underwent transplantation.

3.2. QFM distribution

QFM distribution is shown in **Fig. 1** and varied between 1 IU/mL and 336 IU/mL. The median value was 56 IU/mL (blue line in the figure), and the mean value was 97 IU/mL. The arbitrary cutoff chosen to compare the two populations is indicated by the red line.

3.3. QFM according to different clinical outcomes

QFM values for the different clinical outcomes are shown in **Fig. 2** and summarized in **Table S3**. There were no statistically significant differences between the three groups.

The effect size ($\eta^2 = 0.0795$) suggests a moderate effect, indicating possible biological relevance despite the lack of statistical significance. Dunn's post-hoc test revealed a trend toward a difference between preACLF and SDC ($p = 0.047$, unadjusted); however, this difference was not significant after Bonferroni correction ($p_{adj} = 0.14$).

3.4. QFM correlation to other parameters

Using Spearman's correlation, we found that QFM values were significantly negatively associated with white blood cell count, neutrophil count, bilirubin level, and CHILD score. Blood albumin levels were positively associated with QFM (**Table S4**). Of note, QFM values were not correlated with absolute lymphocyte count ($\rho = -0.03$, $p = 0.83$) nor with the neutrophil-to-lymphocyte ratio (NLR) ($\rho = -0.22$, $p = 0.15$).

3.5. Outcomes and QFM

3.5.1. QFM as a continuous variable

The results of the **univariate Cox proportional-hazards models** on QFM as a continuous variable are shown in **Table 2**. A higher QFM value was significantly associated with a reduced risk of 3-month death or ACLF (HR 0.88, 95%CI 0.791 - 0.991, $p=0.034$). Similar results were found for 3-month mortality (HR 0.89, 95% CI 0.795–0.997; $p = 0.045$) with good discrimination ($C = 0.68$), indicating an 11 % reduction in the instantaneous risk of 3-month mortality per 10 IU/mL increase in QFM. Associations between QFM and one-year mortality (HR 0.94, 95%

Table 1

Baseline characteristics, laboratory parameters, and clinical outcomes of the studied population.

Baseline characteristics	
Age	62 [51.4-70.2]
Sex, M	32 (72.7%)
Site, CHU	36 (81.8%)
Aetiology of cirrhosis	
Alcohol-related	25 (56.8%)
Metabolic dysfunction-associated steatohepatitis	3 (6.8%)
MetALD	6 (13.6%)
Hepatitis C	1 (2.3%)
Alcohol related and hepatitis C	1 (2.3%)
Primary sclerosing cholangitis	2 (4.6%)
Auto-immune hepatitis	2 (4.6%)
Hepatitis B	2 (4.6%)
Other	2 (4.6%)
MELD-Na score	21 [15.5-24] (10-43)
Child-Pugh score	10 [8-11]
Hepatocarcinoma	3 (6.8%)
Obesity	6 (16.2%)
TIPS	3 (7.1%)
Previous hospitalization in the last 3 months	18 (40.9%)
Hospitalization data	
Time between sampling and end of hospitalization (days)	6 [3.5-11]
Ascites	41 (93.2%)
Hepatic encephalopathy	14 (31.8%)
Gastro-intestinal bleeding	2 (4.6%)
Infection at enrollment	11 (28.2%)
QFM (n=43) (IU/mL)*	56 [24-100] (1-336)
White blood cells ($10^3/\text{mm}^3$)	5.58 [4.48-7.56] (2.7-14.68)
Neutrophils ($10^3/\text{mm}^3$)	3.68 [2.71-4.86] (1.48-13.89)
Lymphocytes ($10^3/\text{mm}^3$)	1.12 [0.74-1.58] (0.20-3.28)
Platelets ($10^3/\text{mm}^3$)	82.0 [66.5-158] (38-364)
CRP (mg/dL)	11.2 [7.3-32.5] (1.2-91)
Urea (mg/dL)	39 [23.0-58.0] (9-266)
Creatinine (mg/dL)	0.91 [0.70-1.43] (0.42-5.36)
Albumin (g/L)	27.0 [25-31.5] (16-41)
Sodium	136 [133-138] (123-150)
INR	1.50 [1.30-1.90] (1-2.81)
Bilirubin (mg/dL)	2.80 [1.59-6.11] (0.69-44.82)
Follow-up data	
Infection at enrollment	11 (28.2%)
Infection during follow-up	
0	33 (75%)
1	7 (15.9%)
2	3 (6.8%)
3	1 (2.3%)
Time before infection after enrollment	34.0 [15.0-56.0] (5-90)
Infection site at first infection	
Undefined	5 (45%)
Respiratory	4 (36.4%)
Urinary	1 (9.1%)
Skin	1 (9.1%)
Time from hospitalization to ALCF occurrence (days)	22 [11-35] (6-59)
Liver transplantation	8 (18.2%)
Death	21 (47.7%)
Clinical outcomes	
SDC	19
UDC	17
preACLF	7

Values are presented as median [interquartile range] or number (percentage). Minimum and maximum values are shown in parentheses when relevant. N=44. QFM, QuantiFERON-Monitor; CRP, C-reactive protein; INR, international normalized ratio; TIPS, transjugular intrahepatic portosystemic shunt; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis; pre-ACLF, pre-acute-on-chronic liver failure; ALCF, acute-on-chronic liver failure; metabolic dysfunction-associated steatohepatitis (MASH), combined etiology (MetALD).

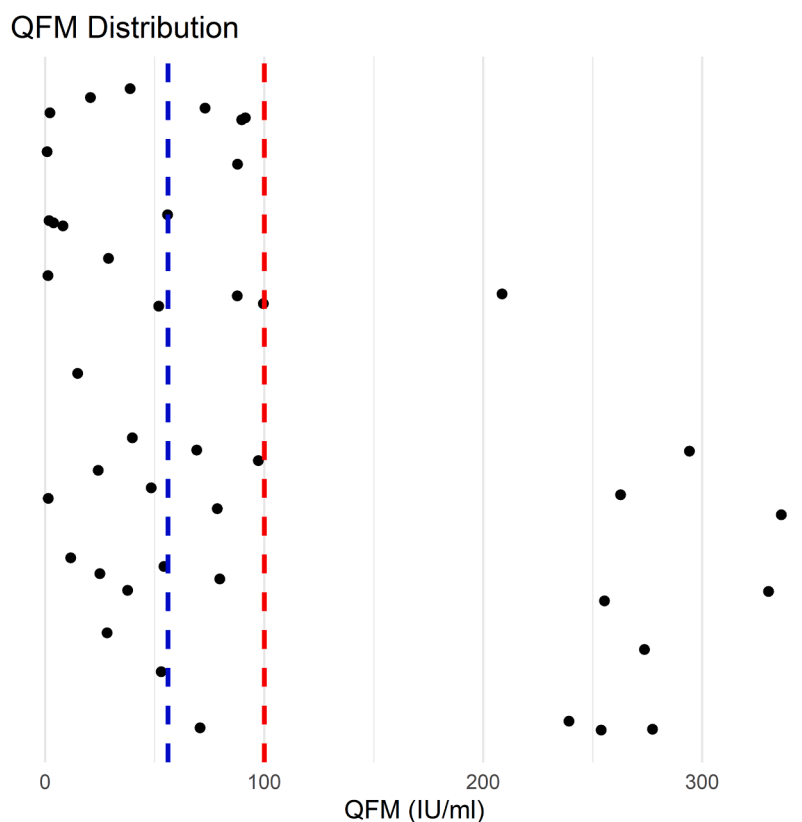


Fig. 1. Distribution of individual QFM values. The blue dashed line represents the median QFM value. The red dashed line corresponds to the arbitrary QFM cutoff (100 IU/mL) used to classify patients into high and low QFM groups.

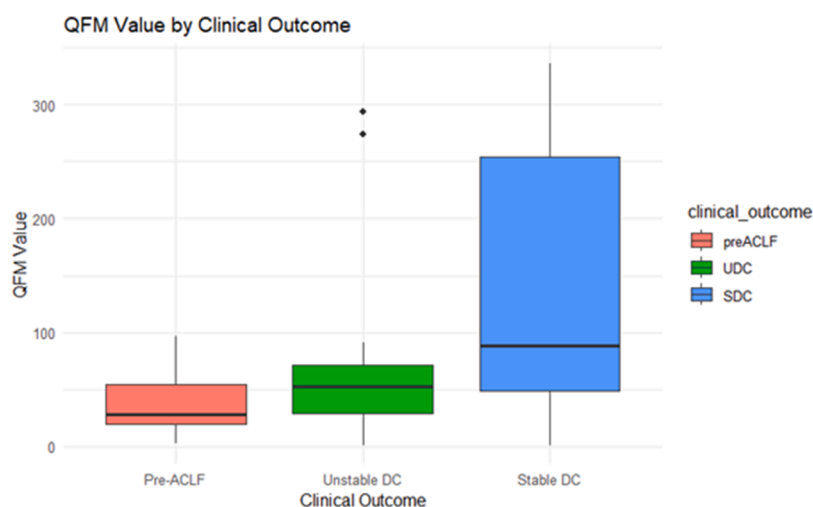


Fig. 2. Distribution of QuantiFERON-Monitor (QFM) values according to clinical outcome categories.

Boxplots display baseline QFM values measured during hospitalization in patients classified as pre-acute-on-chronic liver failure (pre-ACLF), unstable decompensated cirrhosis (UDC), and stable decompensated cirrhosis (SDC), according to PREDICT criteria. Boxes represent the interquartile range (IQR), horizontal lines indicate median values. Individual outliers are shown as points. Comparisons were made using Kruskal-Wallis followed by pairwise comparisons with unadjusted *p*-values.

CI 0.880–1.003; $p = 0.062$) and overall mortality (HR 0.95, 95% CI 0.901–1.003; $p = 0.064$) did not reach statistical significance. No significant relationships were observed between QFM and time to transplantation within 12 months (HR 1.05, IC95% 0.880 – 1.003, $p = 0.14$), infection at 3 months (HR 0.996, $p = 0.89$, 0.940 – 1.055), or ACLF (HR 0.887, 0.754 – 1.045, $p = 0.15$). Schoenfeld tests indicated no violation of the proportional hazard assumption for any model (all $p > 0.05$).

A complete-case logistic regression ($n=43$) was performed for

different outcomes (Table S5) and showed that each 10 IU/mL increase in baseline QFM was associated with a 13% reduction in the odds of 3-months mortality (OR = 0.868, 95% CI 0.753–1.000, $p = 0.049$) and a 14% reduction in the odds of 3-month death or ACLF occurrence (OR=0.86, IC95% 0.74–0.99, $p=0.03$). There was no significant correlation with the other outcomes.

Table 2

Univariate Cox proportional hazards models for clinical outcomes by 10 IU/mL increments of QuantiFERON-Monitor.

Outcome	Events (n)	HR (per 10 IU/mL)	95% CI	p-value
3-month mortality	13	0.890	0.795 – 0.997	0.045
1-year mortality	17	0.940	0.880 – 1.003	0.062
Overall mortality	21	0.951	0.901 – 1.003	0.064
Infection	6	0.996	0.940 – 1.055	0.888
ACLF occurrence	11	0.887	0.754 – 1.045	0.151
Transplantation	7	1.050	0.984 – 1.121	0.141
90-day mortality or ACLF	14	0.88	0.791 – 0.991	0.034

Hazard ratios (HRs) are presented for each 10 IU/mL increase in QuantiFERON-Monitor (QFM) values. Values are expressed as HR with 95% confidence interval (CI) and associated p-value.

ACLF, acute-on-chronic liver failure; QFM, QuantiFERON-Monitor; HR, hazard ratio; CI, confidence interval.

3.5.2. Comparison between QFM groups “low” and “high”

Table 3 shows different variables comparing the groups QFM low and high.

Univariate Cox models comparing the low and high QFM groups are shown in **Table S6**. High-QFM Patients had a markedly lower hazard of death at 3 months (HR 0.09, 95 % CI 0.00–0.64; $p = 0.01$) using Firth’s correction to account for complete separation. In contrast, QFM group was not linked to liver transplant, infection, or ACLF, although all patients who developed ACLF belonged to the low QFM group.

The difference in **mortality** between the two groups (high and low QFM) is illustrated by the **Kaplan-Meier survival curve** in **Fig. 3**. Log-rank was calculated for 3 months, one year and the global follow-up. The group with low QFM values had a lower survival probability at each time point ($p=0.018$, $p=0.021$, and $p=0.023$, respectively). **Fig. 4** shows the difference for the combined endpoint of 90-day mortality or ACLF by QFM groups.

3.6. Other parameters associated with outcomes

Using Cox regression models, we found that in our cohort:

- A high MELD-Na score (HR=1.11, $p=0.0027$) before hospitalization, a higher INR value (HR=3.68, $p=0.0015$), or the presence of a TIPS (HR=4.23, $p=0.026$) were associated with a higher risk of death.
- The presence of a history of acute decompensation of an infectious nature (HR=6.33, $p=0.0076$) and, to a lesser extent, a low platelet count (HR=0.22, $p=0.029$) were aggravating factors for the risk of post-hospitalization infection.
- Neither absolute lymphocyte count (HR 1.03, 95%CI 0.47–2.26, $p = 0.95$, C-index=0.54) nor NLR (HR 1.03, 95%CI 0.97–1.09, $p = 0.40$, C-index=0.63) were associated with our combined endpoint of 90-day death or ACLF.

Extensive results in Supplementary **Table S7** for the association with mortality and in **Table S8** for post-hospitalization infection.

3.7. Multivariate Cox regression and comparison to MELD-Na model

In the **multivariable model** including both QFM and MELD-Na, MELD-Na remained independently associated with the outcome (HR 1.10, 95%CI 1.00–1.20; $p = 0.039$) while QFM showed a borderline protective effect (HR 0.89 per 10 IU/mL, 95%CI 0.79–1.00; $p = 0.057$). As summarized in **Table 4** we compared this model to the univariable

Table 3

Comparison of baseline characteristics, laboratory values, and clinical outcomes in patients with low versus high QuantiFERON-Monitor levels.

Variable	Group low	Group high	p-value
n	32	11	
Anterior data			
Age	60.0 [50.3-68.3]	68.9 [57.2-72.9]	0.242
MELD	21.1 [16.0-24.3]	17.0 [15.0-21.5]	0.083
CHILd	10.2 [9.0-12.0]	8.1 [7.0-9.0]	<
Sex – male (%)	23 (71.9%)	8 (72.7%)	1.000
Hospitalized 3 months before	15 (46.9%)	2 (18.2%)	0.186
History of TIPS	2 (6.7%)	1 (9.1%)	1
At enrollment			
QFM	39.5 [14.3-71.5]	263.0 [246.5-285.5]	<
Ascites	30 (93.8 %)	10 (90.9%)	1
Hepatic encephalopathy (%)	11 (34.4 %)	3 (27.3%)	0.952
Gastrointestinal bleeding	0%	1 (9.1%)	0.571
Infection	8 (26.7%)	4 (36.4%)	0.828
WBC	5.84 [4.54-7.91]	4.54 [3.82-5.96]	0.084
Neutrophils	3.91 [2.83-5.23]	2.85 [2.30-3.71]	0.048
Lymphocytes	1.15 [0.70-1.56]	0.94 [0.82-1.56]	0.835
Platelets	82.00 [67.75-142.75]	79.00 [69.50-165.50]	0.867
CRP	10.45 [7.62-34.17]	12.00 [6.10-30.00]	0.911
urea	39.50 [22.75-58.00]	36.00 [25.50-59.00]	0.790
creatinine	0.98 [0.77-1.26]	0.83 [0.60-1.50]	0.419
albumin	27.00 [24.75-30.00]	32.00 [30.00-35.25]	0.003
Sodium	136.00 [133.00-137.00]	138.00 [134.50-139.00]	0.216
INR	1.58 [1.42-1.94]	1.36 [1.27-1.47]	0.037
Bilirubin	3.23 [1.90-8.89]	1.65 [1.23-2.55]	0.021
Follow-up data:			
Clinical outcomes:			
preACLF	7 (21.9%)	0 (0.0%)	0.012
SDC	10 (31.2 %)	9 (81.8 %)	
UDC	15 (46.9%)	2 (18.2%)	
ACLF occurrence	7 (21.9%)	0 (0.0%)	0.222
Mortality after 3 months	13 (40.6%)	0 (0.0%)	0.032
Overall mortality	19 (59.4%)	2 (18.2%)	0.045
Death or ACLF occurrence after 3 months	14 (56.3%)	0 (0.0%)	0.008
Infection after 3 months	9 (28.1%)	2 (18.2%)	0.801
Transplantation after 1 year	3 (27.3%)	3 (9.4%)	0.330
Time before death (days)	460.50 [52.25-620.75]	669.00 [513.50-731.50]	0.037

Values are presented as median [interquartile range] or number (percentage). N=44. A p-value < 0.05 was considered statistically significant. Comparisons between the low and high QuantiFERON-Monitor (QFM) groups were performed using the Mann–Whitney U test or Fisher's exact test.

ALCF, acute-on-chronic liver failure; CRP, C-reactive protein; INR, international normalized ratio; preACLF, pre-acute-on-chronic liver failure; QFM, QuantiFERON-Monitor; TIPS, transjugular intrahepatic portosystemic shunt; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

model including MELD-Na alone in which each point increase in MELD-Na was associated with a 13% higher hazard of 90-day death or ACLF (HR 1.13, 95%CI 1.03–1.24; $p = 0.009$, C-index=0.67).

The combined model demonstrated improved discrimination (C-index = 0.74) and significantly better fit compared to MELD-Na alone (likelihood ratio test $\chi^2 = 6.24$, $p = 0.012$). The proportional hazards assumption was met for all covariates (global Schoenfeld test $p = 0.37$).

3.8. Non-infected subgroup analysis

Sensitivity analysis: Among the 43 patients, 32 had no infection at

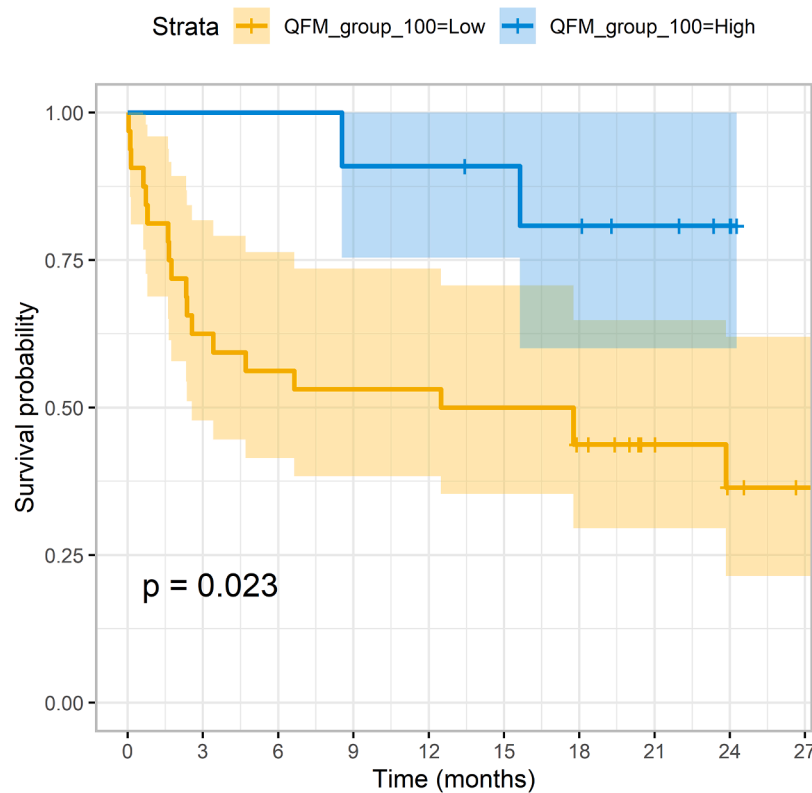


Fig. 3. . Kaplan-Meier survival curves for global survival for high versus low QFM groups. The group QFM low is in blue and the QFM high is in yellow. Confidence intervals are shown as shaded areas. The log-rank p-value is displayed. Time is in months from inclusion.

enrollment. In this subgroup, the association between QFM and the combined endpoint of 90-day mortality or ACLF occurrence remained consistent with the main analysis (HR 0.90 per 10 IU/mL (95%CI 0.79–1.02). The likelihood ratio test reached statistical significance ($p=0.02$), while the score test ($p=0.05$) and the Wald test ($p=0.09$) showed borderline values, reflecting the reduced statistical power but a similar direction.

Besides, baseline QFM values did not differ between patients with and without infection at enrollment, with respectively 52 IU/mL [IQR 33.5–80.5] and median 64.5 IU/mL [IQR 14.25–134.75], Wilcoxon test $p = 0.86$. Moreover, baseline infection was not associated with the combined endpoint of 90-day mortality or ACLF occurrence (HR 1.91, 95%CI 0.64–5.69, $p=0.25$).

4. Discussion

In this prospective cohort of hospitalized patients with acute decompensation of cirrhosis, we evaluated whether a single measurement of QuantiFERON-Monitor (QFM), a whole-blood IFN- γ release assay reflecting global cellular immune responsiveness, was associated with short-term outcomes. We focused primarily on the clinically relevant composite endpoint of 3-month mortality or ACLF. Our findings suggest that QFM provides meaningful prognostic information in the early period, although conclusions must remain cautious given the limited sample size.

QFM measured as a continuous variable showed a significant association with the 3-month risk of death or ACLF, with each 10 IU/mL increase corresponding to a 12% relative risk reduction. Similar trends were observed for 3-month mortality alone. When QFM was dichotomized at 100 IU/mL, an arbitrary cut-off dividing the distribution of QFM into two populations, patients in the high-QFM category were almost entirely protected from early mortality (0 % vs. 39 % at 90 days; HR 0.09). Although the protective signal attenuated over time, trends

persisted for 1-year and overall mortality. These findings support the interpretation that QFM provides a snapshot of immune function at a given moment, and, like other assays, fluctuates over time [7,20] and is more relevant for predicting short-term outcomes.

In multivariable Cox model analysis, MELD-Na remained, as expected, the dominant predictor but the association between higher QFM values and reduced risk of early ACLF or death persisted with a borderline statistical significance. The addition of QFM to MELD-Na compared to MELD-Na alone improved the overall discrimination. While our results should be interpreted cautiously due to the limited sample size, they support the hypothesis that QFM offers complementary prognostic information by quantifying the functional capacity of the immune system.

Although QFM was not associated with the risk of bacterial infection or with transplantation probability, interpretation is limited by the small number of events. All patients who developed acute-on-chronic liver failure (ACLF) belonged to the low-QFM group, suggesting a potential link between impaired inducible IFN- γ response and susceptibility to high-grade inflammatory phenotype characteristic of ACLF. Larger studies are needed to explore this association robustly. Of note, the proportion of transplantations was higher in the high QFM group. This can be explained by the fact that the most severely affected patients in our cohort (preACLF and higher MELD-Na) had an alcohol-related disease and were refused for transplantation because of the absence of abstinence.

QFM correlated with clinically relevant parameters (bilirubin level, Child-Pugh score and neutrophil count), supporting a link between impaired IFN- γ inducibility and deteriorating liver function. In contrast, QFM did not correlate with absolute lymphocyte count or neutrophil-to-lymphocyte ratio, and neither of these simpler hematological parameters predicted short-term mortality in our cohort. This is consistent with the findings of Marx et al. [10], who reported that IFN- γ responses measured with QFM do not directly reflect lymphocyte counts

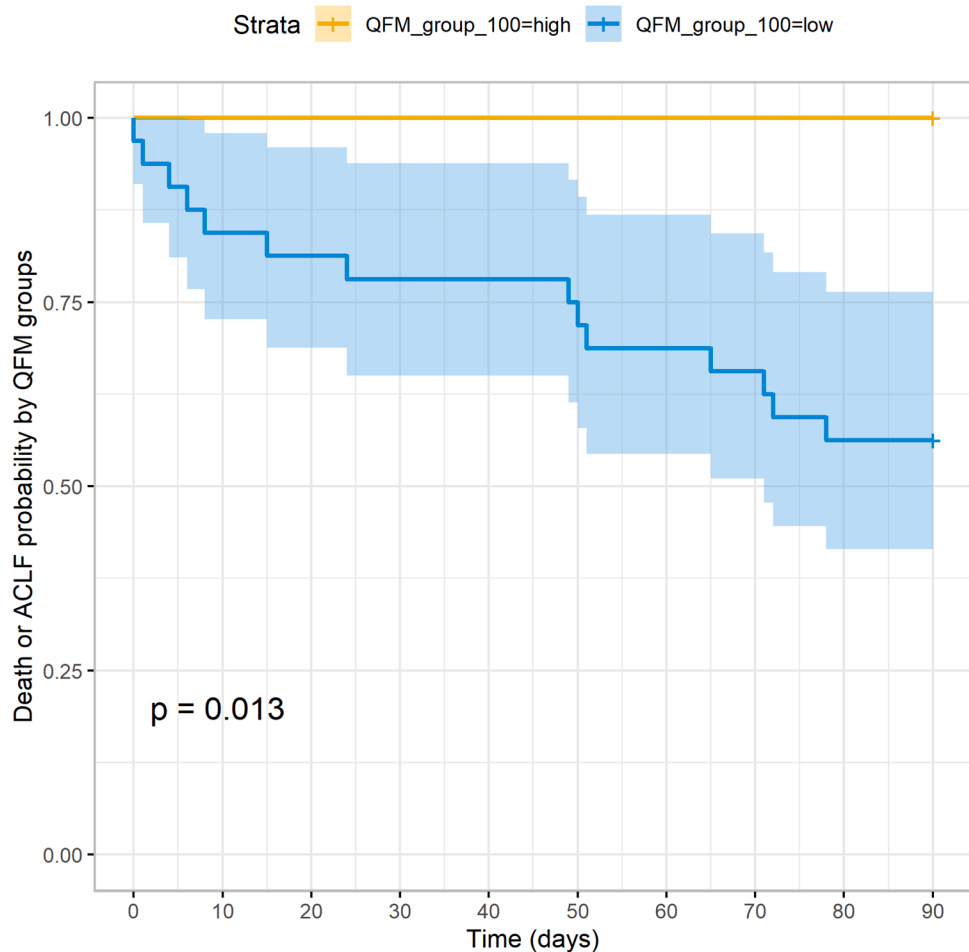


Fig. 4. . Kaplan Meier survival curves for combined endpoint of 90-day death or ACLF by QFM low (in blue) and high (in yellow). *Confidence intervals are shown as shaded areas. The log-rank p-value is displayed. Time is in days from inclusion.*

Table 4
Cox proportional hazards models for the combined endpoint of 90-day death or ACLF.

	HR	95% CI	P value	C-index
QFM	0.88	0.79-0.99	0.03	0.69
MELD-Na	1.13	1.03-1.24	0.01	0.67
MELD-Na + QFM				0.74
MELD-Na	1.10	1.00-1.20	0.04	
QFM	0.89	0.79-1.00	0.06	

Univariable and multivariable Cox models assessing the association between baseline QuantiFERON-Monitor (QFM) values and the 90-day composite endpoint of death or acute-on-chronic liver failure (n = 43; events = 14). QFM was analyzed per 10 IU/mL increments. MELD-Na was analyzed per 1-point increase. Hazard ratios (HRs), 95% confidence intervals (CI), and p-values are reported for each model. Discriminative performance was evaluated using Harrell’s concordance index (C-index).

but rather the functional capacity of multiple cell subsets. Although our study did not assess lymphocyte subpopulations, their work also demonstrated that absolute numbers of IFN-γ-secreting cells was comparable for all three main lymphocyte subpopulation (CD4⁺, CD8⁺ and NK-cells) contributing to the overall QFM signal.

Importantly, in decompensated cirrhosis, systemic inflammation, often associated with leukocytosis or neutrophilia, may coexist with a profound impairment of effective immune responses, a hallmark of CAID. Experimental and clinical studies [1,21] have shown that neutrophils in advanced cirrhosis frequently exhibit qualitative functional

defects (including impaired chemotaxis, phagocytosis, oxidative burst and bacterial killing), despite preserved or increased circulating cell counts, and that these abnormalities are associated with worse outcomes. In this context, the inverse correlation observed between QFM and neutrophil or leukocyte counts likely reflects a dissociation between quantitative inflammatory markers and inducible cellular immune function, rather than a direct relationship with immune competence. These data further support that QFM captures a qualitative dimension of both innate and adaptive immune responsiveness that is not adequately reflected by routine blood counts.

Because QFM assesses global IFN-γ release, **we evaluated whether acute bacterial infection at enrollment could confound the assay.** QFM distributions did not differ between infected and non-infected patients consistently with previous work [9]. Baseline infection showed no association with the early composite outcome. In the subgroup of patients without infection at sampling, the protective association of higher QFM with improved early prognosis persisted with a similar effect size, through statistical significance was attenuated as expected due to reduced power. Taken together, these results suggest that the prognostic signal captured by QFM is not driven by the acute infection but rather reflects underlying Cirrhosis-associated immune dysfunction (CAID) and more advanced disease.

We also confirmed that **decompensated cirrhotic patients had significantly lower QFM values than healthy individuals** (mean value of our cohort was 97 IU/mL vs. healthy controls 423 IU/mL as described before (Wilcoxon test, W= 0, p < 0.01) [21]), in line with previous observations by Sood et al. [15,21]. Our study further extends these findings in terms of clinical outcomes by showing **differences**

across the three clinical outcomes defined by the PREDICT study when comparing QFM low and high groups ($p=0.012$). A larger sample size may be required to confirm these findings.

Overall, our findings align with the concept of CAID and the immune implication in cirrhosis decompensation previously described [17,19,22]. CAID is a dynamic spectrum ranging from low-grade systemic inflammation to the high-grade, sepsis-like immune dysfunction observed in ACLF [23]. CAID severity has a direct impact on the progression of cirrhosis and is closely linked to liver dysfunction, bacterial translocation, and organ failure. Our hypothesis is that the higher mortality rate in patients with lower QFM can be explained by more severe cirrhosis-associated immune dysfunction (CAID).

From a clinical perspective, QFM could provide an additional dimension for assessment of patients with cirrhosis, focusing on immune dysfunction. Beyond its prognostic value, QFM could also guide antibiotic prophylaxis in high-risk patients, complementing the current guidelines for variceal bleeding and spontaneous bacterial peritonitis [24]. Its practical advantages, including minimal laboratory processing and availability, render it a promising candidate for routine use. However, further studies are needed to confirm these findings and to establish the potential role of QFM in clinical decision-making.

Our study has several limitations. The sample size was modest ($n=44$), which restricts statistical power, especially for less frequent outcomes, such as infection and ACLF. QFM was measured at a single time point; serial assessments could better capture the dynamic immune changes. We did not measure lymphocyte subtypes. Our empirical 100 IU/mL cutoff requires external validation in larger, more diverse cohorts. Lastly, while the observed infection rates at enrollment and during follow-up were similar to the PREDICT study rate (28.2% vs. 29.2% at enrollment and 25% vs. 23.9% during the three-month follow up), there was a complete absence of new spontaneous bacterial peritonitis during follow-up. Post-discharge infections were identified based on clinical diagnosis and antibiotic prescription, which may have led to under-ascertainment of milder, undocumented, or outpatient-managed infectious events, and may partly explain the absence of expected specific infection in our cohort.

5. Conclusion

In conclusion, the QFM assay offers a promising method to quantify functional immune capacity in decompensated cirrhosis. In this pilot cohort, lower inducible IFN- γ responses were associated with worse short-term outcomes, particularly 90-day mortality or ACLF. By capturing an immune dimension of disease severity, QFM may provide clinically meaningful prognostic information complementary to traditional liver scores, offering an additional tool to guide patient assessment and clinical decision-making. Larger prospective studies are required to validate these findings and determine how QFM could be integrated into personalized patient care.

Abbreviations

CAID: Cirrhosis-associated immune dysfunction
 QFM: QuantiFERON-Monitor
 IFN- γ : interferon- γ
 AD: acute decompensation
 ELISA: enzyme-linked immunosorbent assay
 ACLF: acute-on-chronic liver failure
 CLIF-C: Chronic Liver Failure Consortium
 OF: organ failure
 SDC: stable decompensated cirrhosis
 UDC: unstable decompensated cirrhosis
 MELD-Na: Model for End-Stage Liver Disease sodium-adjusted score
 TIPS: transjugular intrahepatic portosystemic shunt
 HR: hazard ratio
 CI: confidence interval

OR: odds ratio

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CRediT authorship contribution statement

Alice Dongier: Writing – original draft, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Edouard Louis:** Writing – review & editing, Funding acquisition. **Jean-Philippe Loly:** Writing – review & editing. **Pierre Dandoy:** Resources. **Odile Warling:** Resources. **Anne Vijverman:** Resources. **Jean Delwaide:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinre.2026.102776.

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