Efficacy and safety of fenofibrate addition therapy in patients with decompensated primary biliary cholangitis refractory to UDCA

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Research Article

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Abstract

Background and aims There is no data regarding the efficacy and safety of fibrates in patients with decompensated liver disease associated with PBC, as published studies have systematically excluded this population. This study aims to evaluate the efficacy and safety of UDCA in combination with fenofibrate in patients with decompensated liver disease related to UDCA-refractory PBC.

Methods We conducted a retrospective analysis comparing the clinical results of additional fenofibrate (FF) therapy and continued UDCA monotherapy in decompensated patients refractory to UDCA.

Results Total of 63 patients included: 32 cases underwent UDCA monotherapy and 31 cases underwent UDCA combined with FF therapy. Among UDCA-refractory patients with decompensated cirrhosis, FF add-on therapy for 60 months significantly improved the Mayo risk score, the Globe risk score and the alkaline phosphatase (ALP) normalization rate. Parallel changes in liver transplant-free survival, the UK-PBC risk score and surrogate serum indices of liver fibrosis were consistent with this effect. During follow-up, serum ALP, aminotransferase and gamma-glutamyl transpeptidase decreased significantly, while total bilirubin, albumin, serum creatinine, blood urea, estimated glomerular filtration rate, APRI index, FIB-4 index and Forns index remained stable in FF-treated cases. Only the Globe risk score, not ALP normalization, was independently and negatively associated with improved outcomes on multivariable analysis (odds ratio, 2.934; confidence interval, 1.046-8.235; p = 0.041). No significant adverse effects associated with FF-related symptoms or nephrotoxicity were observed in our cohort. However, decompensated cirrhosis with deteriorated cholestasis should be considered as potential limiting factors for FF therapy.

Conclusions Additional FF therapy clearly improves the Mayo risk score, the Globe risk score and the ALP normalization rate in patients with decompensated liver disease related to UDCA-refractory PBC. However, the survival rate was not significantly different between the groups. Decompensated cirrhosis with deteriorated cholestasis should be considered as potential limiting factors for FF therapy.

1 Introduction

Primary biliary cholangitis (PBC) is the most common autoimmune liver disease featuring elevated serum cholestasis-related biochemical marker, the seroreactivity of typical disease-specific anti-mitochondrial antibody (AMA) and histology suggestive of granulomatous lymphocytic cholangitis occurring primarily in small bile ducts.[1,2] The only first-line drug presently approved for disease-modifying treatment is ursodeoxycholic acid (UDCA).[3,4] UDCA is extensively administrated and has demonstrated the ability to ameliorate cholestasis-related indicators, delay histological progression and reduce the need for liver transplant (LT) in PBC.[5,6] However, up to 40% of PBC patients treated with UDCA fail to achieve biochemical response in the clinical setting with increased incidence of disease progression and poor consequences, suggesting the clear necessity for add-on therapy.[7,8]

The combination of fibrate, a peroxisome proliferator-activated receptor (PPAR) agonist, with UDCA has been demonstrated efficacy in relieving symptoms, decreasing the levels of cholestasis-related biochemical markers and improving long-term outcomes with relatively good safety features in UDCA-refractory PBC patients.[9-12] Guidance from the American Association for the Study of Liver Diseases recommends off-label therapy is recognized as an alternative in patients with insufficient responses to UDCA, notably with the PPAR agonist fibrates.[13] However, concern remains with regard to their safety profile. Biochemical improvements related to fibrate may be counterbalanced by possible deterioration with rising bilirubin values and negative impact on renal function reported in patients with cirrhosis.[10,14] In addition, fibrates demonstrated limited efficacy in cirrhotic patients with reduced biochemical responses and increased mortality or liver-related outcomes.[10,14] Nevertheless, no data is available on the efficacy and safety features of fibrates in patients with decompensated liver disease associated with PBC, as published studies have systematically excluded this population.

A study was carried out to explore these issues further, including 63 patients with decompensated liver disease related to UDCA-refractory PBC. Our analysis demonstrated that FF add-on therapy clearly improved the Mayo risk score, the Globe risk score, and the alkaline phosphatase (ALP) normalization rate. However, the survival rate was not significantly different between the groups. Decompensated cirrhosis with deteriorated cholestasis should be considered as potential limiting factors for FF therapy.

2 Materials And Methods

2.1 Study design

Retrospective cohort study was conducted. Pooled patients were classified into “the FF group” and “the UDCA group” depending on additional FF therapy or continued UDCA monotherapy. The primary end points were the efficacy profile of FF add-on therapy, including the LT-free survival, the severity and the biochemical response of PBC. Regarding the severity, clinical data were gathered to compute several risk scores prospectively: the Mayo risk score,[15] the Globe risk score[16] and the UK-PBC risk score.[17] Three surrogate serum indices of liver fibrosis were also assessed: APRI index,[18] FIB-4 index[19] and Forns index.[20] Regarding the biochemical response, biochemical data were gathered systemically including specific improvements in ALP, total bilirubin (Tbil), aspartate aminotransferase (AST) and albumin (ALB), which seemed to correlate with improved LT-free survival.[21-24] The secondary end points were the security situation of FF add-on therapy, assessed primarily in terms of FF-related symptoms, hepatotoxicity and nephrotoxicity. To compute the estimated glomerular filtration rate (eGFR), we introduced the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[25] The study design was approved by the ethics committee of the Xijing Hospital of the Air Force Military Medical University.

2.2 Study population

Sixty-three subjects with decompensated liver disease related to PBC who were refractory to prior UDCA monotherapy, were diagnosed and treated in Xijing Hospital of Digestive Diseases (Xi’an, Shanxi, China)

from February 2010 to March 2022. A diagnosis of PBC is made if it meets two of the three standards below: 1) ALP elevation; 2) seroreactivity of AMA or other specific autoantibodies; 3) compatible liver biopsy.[26] Autoimmune hepatitis is determined by the simplified diagnostic criteria.[27] Exclusion criteria included: 1) concurrent with other liver disease, such as alcoholic hepatitis or chronic hepatitis B/C; 2) previous record of LT; 3) evidence of acute liver failure; 4) severe comorbidities (e.g., chronic obstructive pulmonary disease, heart failure and malignant conditions). The definition of refractory to UDCA was failure to meet the ALP cut-off values (serum ALP >1.67× ULN) utilized in Toronto criteria after six months of prior UDCA monotherapy.[20] Decompensated liver disease was defined as cirrhosis with current or previous evidence of liver decompensation (e.g., ascites, portosystemic encephalopathy, spontaneous bacterial peritonitis, or portal hypertensive bleeding).[28] UDCA and FF were administered orally at doses of 13-15 mg/kg/d and 200 mg/d, respectively. For patients with concomitant autoimmune hepatitis, prednisone was administered orally at initial doses of 0.5-1 mg/kg/d, gradually reduced to 5 mg/d for long-term maintenance treatment.

2.3 Data collection and analysis

Clinical information was gathered at the presentation and each follow-up. Biochemical parameters were measured at baseline and repeated at 3-12 months intervals during the study duration. Results of the data were compared annually and the end of therapy to evaluate biochemical improvements. Histology was staged according to a prior report by Ludwig et al.[29] The biopsy specimens were assessed by two qualified and experienced pathologists who were blinked to the results of serological tests. At each visit, an assessment of treatment compliance was made and recorded.

2.4 Statistical analysis

Quantitative variables were described as median or mean and interquartile range or standard deviation (SD), were analyzed with the Mann-Whitney U test or the paired t-test. Qualitative variables were assessed using the chi-squared test. The Kaplan-Meier survival methods were used to estimate the incidence of ALP normalization and LT-free survival; log-rank tests were applied for comparison purposes. To identify independent predictors, we performed logistic regression analyzes using a forward selection procedure, and stepwise regression was used to eliminate multicollinearity. R language version 4.13 (China) and SPSS version 26.0 (IBM) were used for analysis. Two-sided p-values less than 0.05 were regarded as significant.

3 Results

3.1 Study population

Fig 1 gives the study flowchart. A total of 63 (27%) out of 230 patients were eligible for primary analysis. Of these patients with decompensated liver disease related to UDCA-refractory PBC at baseline, 31 (49%) were treated with UDCA along with FF (the FF group) and 32 (51%) continued with UDCA monotherapy (the UDCA group). Nine patients in the FF group concurrent with autoimmune hepatitis while six in the

UDCA group at baseline (29% vs.18%, p = 0.338); eleven patients in the UDCA group developed decompensated liver disease for a median of 36 months (range 20–73 months) after the diagnosis of UDCA-refractory PBC while ten patients in the FF group for a median of 45 months (range 24–72 months) (34% vs.32%, p = 0.859).

Baseline characteristics of the cohort are presented in Table 1. The mean patient age was 55 ± 7 years. The majority of patients were female (84%), Child-Pugh A (75%) and AMA positive (90%). FF was administrated for a median of 12 months (range 6–40 months) after the start of UDCA. The median time of exposure to FF was 36 months (range 12–108 months). The median Mayo risk score, Model for End-Stage Liver Disease (MELD) score, APRI index and FIB-4 index for the study cohort at baseline were 5.2, 1.9, 1.6 and 4.0, respectively. No significant differences except for serum gamma-glutamyl transpeptidase (GGT) levels were identified for both groups at baseline (p = 0.030). Except for patients who experienced LT or death, three patients suffered severe decompensation events during the follow-up period (e.g., large-volume ascites, acute variceal bleeding), FF was temporarily stopped and continued when the condition stabilized.

3.2 The primary end points

3.2.1 LT-free survival

Nine patients were lost in follow-up and no information about their survival was available. In the remaining 54 patients, all-cause death, liver-related death, and LT occurred in 13, 12, and 1 patients, respectively, in the UDCA group and 4, 3, and 3 patients, respectively, in the FF group. Compared to UDCA-treated cases, FF-treated cases reported a lower rate of all-cause and liver-related mortality or need for LT by study end, despite the absence of statistical differences (25% vs.50%, chi-square test, p = 0.082, log-rank test, p = 0.130, Fig 2A; 23% vs. 48%, chi-square test, p = 0.071, log-rank test, p = 0.110, Fig 2B).

Univariate analysis of factors related to LT-free survival of FF showed that four parameters were significantly linked to LT-free survival, namely age (p = 0.048), Mayo (p = 0.041), Globe (p = 0.018) and UK-PBC (p = 0.007) (Table 2). Multivariate analysis incorporating these four indicators revealed that the only independent parameter associated with LT-free survival to FF was the Globe risk score (odds ratio [OR], 2.934; confidence interval [CI], 1.046-8.235; p = 0.041). However, four of the seven patients on FF who experienced died or underwent LT (57%) achieved endpoints with ALP falling to ≤1.00× ULN during follow-up. Achieving ALP normalization at any time point was not an independent parameter associated with LT-free survival.

3.2.2 The severity of PBC

Exposure to FF was associated with a significant decrease in the Mayo and Globe risk score compared to UDCA alone. Similar results were obtained in APRI index, FIB-4 index and Forns index (Fig 3). Higher median UK-PBC risk score was observed in the UDCA group during treatment, but no significant difference

was found between both groups. During follow-up, the Mayo, Globe, UK-PBC risk score, APRI index, FIB-4 index and Forns index remained stable in the FF group ($p > 0.05$, all).

3.2.3 Biochemical response

Of the total cohort, three patients reached normal ALP values before the enrollment of the study. Exposure to FF was associated with a significant increase in the ALP normalization rate compared to UDCA alone in the remaining 60 patients (48% vs.16%, chi-square test, $p = 0.001$, log-rank test, $p < 0.001$, Fig 4A). Of the 42 patients with evidence of decompensation prior to the diagnosis of UDCA-refractory PBC, the ALP normalization rate was obtained in 57% of additional FF-treated cases, versus only 9% of UDCA-treated cases (chi-square test, $p = 0.003$, log-rank test, $p < 0.001$, Fig 4B). Univariate analysis of factors related to the biochemical response of FF showed that five parameters were significantly linked to biochemical response, namely ALB ($p = 0.041$), Tbil ($p = 0.018$), Mayo ($p = 0.012$), Globe ($p = 0.007$) and UK-PBC ($p = 0.034$) (Table 3). Multivariate analysis incorporating ALB, Tbil and Mayo at baseline revealed that the only independent parameter associated with biochemical response to FF was the Mayo risk score (OR, 0.180; CI, 0.040-0.810; $p = 0.025$).

Fig 5 shows the dynamic changes in ALP, Tbil, ALB, alanine aminotransferase (ALT), AST and GGT. At 60 months, the median levels of ALP decreased 65% from baseline in FF-treated cases and 19% in UDCA-treated cases ($p < 0.001$ and $p = 0.050$, respectively). The median levels of Tbil and ALB in the FF group were observed to be 36% lower and 19% higher than baseline at 60 months ($p = 0.126$ and 0.109, respectively), while there was a tendency for serum Tbil and ALB levels to deteriorate in cases treated with UDCA. The median levels of ALT and GGT in both groups and AST in the FF group decreased progressively during follow-up ($p < 0.05$, all). Compared to UDCA-treated cases, significantly lower ALP levels and higher ALB levels were observed in FF-treated cases during follow-up. No significant differences in Tbil, ALT, AST, and GGT were found between both groups. Three patients discontinued FF treatment for a period of 1-2 months, then resumed with reduced ALP levels and one patient reached normal values.

3.3 The secondary end points

Adverse events are listed in Table 4. Elevations of aminotransferase and symptoms of gastrointestinal were the most frequently adverse events. Four patients experienced self-limiting nausea, abdominal pain, cramps and myalgia, and cutaneous rash in the first six months of treatment. One participant in the FF group suffered from severe fatigue at 24 months and resolved after discontinuation of FF. Severely elevated transaminase levels (ALT or AST, 5-7 x ULN) were observed in three patients at 12-24 months of treatment and gradually decreased even after continuing FF treatment with monthly monitoring, and one had concurrent autoimmune hepatitis. One FF-treated case and five UDCA-treated cases experienced first severe progression of Tbil levels (> 100 μmol/L) after enrollment (3% vs. 15%; $p = 0.196$); eight FF-treated cases and one UDCA-treated case reoccurred with severe progression of Tbil levels (25% vs. 3%; $p = 0.013$).

Fig 6 shows the dynamic changes in serum creatinine (SCr), blood urea (BU) and eGFR. Although there was a tendency for eGFR to deteriorate in cases treated with UDCA, median BU, Scr and eGFR remained stable in both groups during follow-up. No significant differences in BU, Scr and eGFR were observed between both groups. However, one 55-year-old patient with Child-Pugh B cirrhosis and normal renal function at baseline, progressed to Child-Pugh C cirrhosis with deteriorating renal function and an eGFR of 28 ml/min/1.73 m^2 at 96 months of follow-up in the FF group, and the only patient with first Tbil progression after enrollment, while two participants in the UDCA group suffered from transient renal deteriorating.

4 Discussion

The results of our study suggested that in patients with decompensated liver disease related to UDCA-refractory PBC, FF add-on therapy for 60 months significantly improved the Mayo risk score, the Globe risk score and the ALP normalization rate. Parallel changes in the survival rate, the UK-PBC risk score and surrogate serum indices of liver fibrosis were consistent with this effect. The biochemical improvements of additional FF therapy can be accessed by the Globe and Mayo risk score. In addition, no significant deterioration in serological indicators of liver or renal function were observed in the FF group as compared with the UDCA group during 60 months of follow-up. However, decompensated cirrhosis with deteriorated cholestasis should be considered as potential limiting factors for FF therapy.

In the current study, the survival rate was higher in FF-treated cases than the UDCA-treated. However, our sample size was too limited to determine whether these changes were related to effective improvements in hard outcomes. Parallel changes in the UK-PBC risk score were consistent with this effect. Importantly, we found these changes in the FF group were accompanied by significantly lower Mayo and Globe risk score, with persistently lower APRI index, FIB-4 index and Forns index than the UDCA group during follow-up. In this way, FF appeared to have extended LT-free survival in patients with decompensated cirrhosis.

Meanwhile, FF has failed to show any significant improvements in the Mayo, Globe and UK-PBC risk score even after 60 months of treatment in decompensated patients, although a disease-stabilizing effect was seen. Similar results were obtained in the surrogate serum indices of liver fibrosis. Our results support previous study in a more general PBC population where addition of FF has not demonstrated any significant reduction in predicted 5-, 10-, and 15-year risk rate by UK-PBC risk score during follow-up.[30] Nevertheless, the salutary effects associated with bezafibrate (pan PPAR agonist) have been reported to improve the incidence of LT-free survival when stratified based on the UK-PBC risk score. These differences in prognosis were probably associated with the broader mechanism of bezafibrate.[31]

These changes in FF-treated cases were accompanied by a rapid and sustained decrease in ALP level and a parallel decrease in AST, with relatively stable levels of ALB and Tbil, the four important prognostic indicators in PBC, which seemed to correlate with improved LT-free survival.[21-24] The salutary effects of FF can also be supported by observing the relapse of ALP levels after discontinuing of the drug. Three

patients discontinued FF but not UDCA, two patients were found to have elevated ALP levels and one patient remained stable, while one patient reached normal values after resuming FF treatment.

Interestingly, 57% of FF-treated cases achieved an endpoint of ALP reduction to ≤1x ULN, and ALP normalization was not an independent predictor of LT-free survival. These discoveries suggested either of the two possibilities: 1) ALP levels may not necessarily be used to evaluate biochemical improvements in patients with established decompensated liver disease or 2) ALP by itself may not be a sufficient responding biomarker to FF in decompensated patients. In contrast, the Globe risk score showed significant differences in death or LT outcomes in the FF group at baseline and could be used as a response criterion. However, the Globe risk score was captured from laboratory values at baseline and 1-year post-treatment. For patients who have been treated with FF for less than one year, we recommend the mayo risk score to evaluate biochemical improvements because univariable analysis has shown that the mayo risk score was significantly associated with overall survival and ALP normalization. Future, prospective therapeutic studies in decompensated liver disease related to UDCA-refractory PBC should assess the validity of ALP, Mayo and Globe risk score as appropriate response criterion for FF treatment.

An important objective of the current study was to determine the safety profile of FF in patients with decompensated liver disease related to PBC. Multiple studies have found that abnormal serum Tbil levels were factors in the poor prognosis of PBC, with Tbil > 30 μmol/L increasing the incidence of LT or death by sixfold.[7,32] Regardless of the initial concerns,[10] we did not identify a deterioration in median Tbil levels in FF-treated cases during follow-up. However, one patient treated with FF who experienced severe progression in Tbil levels after relatively long periods of FF therapy, suggesting the progression seemed to be related to disease progression rather than FF therapy; eight patients who experienced severe progression in Tbil levels before FF therapy, suggesting that they had more severe disease at baseline, and the reoccurrence of severe Tbil progression may be related to disease progression, but there was a significant difference between FF-treated cases and the UDCA treated, decompensated cirrhosis with deteriorated cholestasis should therefore be considered as potential limiting factors for additional therapy with FF.

Nephrotoxicity associated with FF is controversial, with contradictory findings in the PBC population,[11,14,30,33,34] and both serum Scr and eGFR have been reported to deteriorate in cirrhotic patients after 24 months of FF treatment.[14] In our cohort, no significant deterioration in Scr, BU or eGFR was observed even after up to 60 months of FF therapy in decompensated patients. One patient developed stage 4 chronic kidney disease during FF treatment, who had Child-Pugh B cirrhosis at baseline, progressed to Child-Pugh C cirrhosis during follow-up. The progression may be due to the worsening of liver function rather than FF therapy.

In addition, three patients with severe elevated transaminases (5-7× ULN) suffered from decompensated cirrhosis, presumably due to the activation of transaminase gene expression by PPAR-a.[35,36] Instead of discontinuing FF, we observed them closely at monthly reviews and found a gradual decrease in transaminase levels at subsequent follow-ups.

Our study has some notable limitations, such as its single-center, retrospective design, relatively small sample size, and not pure PBC patient nature, which limit the ability to generalize the results. These findings might be caused by the differences between groups or simply by the sampling error; therefore, particular caution is required in the interpretation of our data. Nevertheless, we believe our results are novel and provide further insights into the utility of additional FF therapy in PBC.

In conclusion, the significant improvements in the Mayo risk score, the Globe risk score and the ALP normalization rate compared to UDCA monotherapy suggested that additional FF therapy would lead to more salutary clinical effects in patients with decompensated liver disease related to UDCA-refractory PBC. The biochemical improvements of additional FF therapy can be accessed by the Globe and Mayo risk score. However, decompensated cirrhosis with deteriorated cholestasis should be considered as potential limiting factors for FF therapy. Further studies are needed to evaluate the effectiveness of ALP, Globe and Mayo risk score as an adequate response criterion for treatment with FF in this population.

Declarations

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Author contributions Ying Han, Yulong Shang and Guanya Guo contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yansheng Liu, Linhua Zheng, Gui Jia, Juan Deng, Ruiqing Sun, Xiufang Wang, Xia Zhou, Miao Zhang and Pengwei Ren. The first draft of the manuscript was written by Dawei Ding and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest Dawei Ding, Yansheng Liu, Linhua Zheng, Gui Jia, Juan Deng, Ruiqing Sun, Xiufang Wang, Xia Zhou, Miao Zhang, Pengwei Ren, Guanya Guo, Yulong Shang and Ying Handeclare that they have no conflict of interesting.

Data Availability The data used to support the findings of this study are available from the corresponding author upon request.

Ethical approval The study design was approved by the ethics committee of the Xijing Hospital of the Air Force Military Medical University.

Animal research None.

Consent to Participate None.

Consent to Publish None.

Clinical Trials Registration None.

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Tables

Table 1 Baseline characteristics of patients with decompensated primary biliary cholangitis between "the UDCA group" and "the FF group"

Characteristic	Overall	FF group	UDCA group	p value
	63	N=31	N=32	
Age (mean±SD)	55±7	54±8	56±6	p=0.303
Female (n, %)	53(84)	27(87)	26(81)	p=0.772
Follow-up time (median, range; months)	36(12-108)	36(12-108)	30(12-96)	p=0.390
Concurrent with AIH (n, %)	15(23)	9(29)	6(18)	p=0.338
Child-Pugh A/ B (n, %)	47(75)/ 16(25)	26(83)/ 5(17)	21(66)/ 11(34)	p=0.096
MELD score	1.9(0.6-4.9)	1.7(0.2-5.2)	2.0(0.8-4.7)	p=0.582
AMA positive (n, %)	57(90)	29(93)	28(87)	p=0.672
Mayo risk score	5.2(4.7-6.0)	4.9(4.7-6.0)	5.3(4.9-5.9)	p=0.301
ALP×ULN	2.0(1.7-2.8)	2.2(1.8-3.0)	2.0(1.7-2.8)	p=0.487
GGT×ULN	3.8(2.6-6.5)	4.7(2.7-8.9)	3.4(2.3-4.9)	p=0.030
ALT×ULN	1.1(0.9-1.7)	1.3(1.0-1.8)	1.0(0.8-1.4)	p=0.078
AST×ULN	1.6(1.3-2.3)	1.7(1.4-2.3)	1.6(1.1-2.2)	p=0.274
ALB×LLN	0.9(0.8-1.0)	1.0(0.9-1.1)	0.9(0.8-1.0)	p=0.108
Tbil×ULN	1.1(0.8-1.6)	1.1(0.7-2.0)	1.1(0.8-1.4)	p=0.815
IgG×ULN	0.8(0.7-1.0)	0.8(0.7-0.9)	0.9(0.7-1.0)	p=0.383
IgM×ULN	1.0(0.6-1.5)	1.1(0.6-1.6)	0.9(0.7-1.5)	p=0.874
TG×ULN	0.6(0.4-0.9)	0.6(0.5-0.9)	0.5(0.4-0.7)	p=0.075
CHO×ULN	0.7(0.6-0.9)	0.9(0.6-1.0)	0.7(0.6-0.9)	p=0.307
APRI score	1.8(1.3-2.8)	1.6(1.0-3.0)	1.8(1.4-2.4)	p=0.564
FIB-4 index	5.2(3.5-7.7)	4.0(2.8-8.4)	5.8(4.5-6.9)	p=0.157
Forns index	11.6(10.2-12.6)	10.4(9.9-12.8)	11.6(10.8-12.2)	p=0.211
BU×ULN	0.6(0.5-0.7)	0.5(0.4-0.6)	0.6(0.5-0.7)	p=0.057
Scr×ULN	0.9(0.8-1.0)	0.9(0.7-1.0)	0.9(0.8-1.0)	p=0.443
eGFR (ml/min/1.73m2)	95(89-101)	96(92-101)	94(87-101)	p=0.433

Abbreviations: ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; ALB, albumin; Tbil, total bilirubin; IgG, immunoglobulin G; IgM, immunoglobulin M; TG, triglyceride; BU, blood urea; CHO, cholesterol; Scr, serum creatinine; ULN, upper limit of the normal range; FF, fenofibrate; LLN, lower limit of the normal range; eGFR, estimated glomerular filtration rate; AIH, autoimmune hepatitis; MELD score, Model for End-Stage Liver Disease score; SD, standard deviation

Table 2 Univariable and multivariable analysis of factors that affected the risk of LT and death

Characteristic	Death or LT	No Death or LT	[a]p value	[b]p value	OR (95% CI)
	N=7	N=19			
Age(mean±SD)	57±4	52±9	p=0.048		
Female (n, %)	6(85)	18(94)	p=0.474		
ALP normalization at one year	2(28)	7(36)	p=1.000		
ALP×ULN	2.4(2.1-3.6)	1.8(1.7-2.5)	p=0.135		
GGT×ULN	4.8(3.7-8.7)	3.5(2.4-6.6)	p=0.364		
ALT×ULN	1.1(0.9-1.4)	1.3(1.0-1.9)	p=0.209		
AST×ULN	1.5(1.1-2.0)	1.7(1.4-2.4)	p=0.169		
ALB×LLN	0.9(0.8-1.0)	1.0(0.9-1.0)	p=0.306		
Tbil×ULN	1.2(1.0-2.6)	1.0(0.9-1.5)	p=0.107		
IgG×ULN	0.8(0.7-0.9)	0.8(0.8-0.9)	p=0.364		
IgM×ULN	1.0(0.6-1.3)	0.8(0.5-1.7)	p=0.866		
Mayo	5.8(4.9-6.1)	4.8(4.6-4.9)	p=0.041		
GLOBE	1.4(1.0-2.7)	0.7(0.3-1.2)	p=0.018	p=0.041	2.934(1.046-8.235)
UK-PBC	8.0(6.0-37.0)	3.0(2.0-5.0)	p=0.007		

Abbreviations: FF, fenofibrate; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; ALB, albumin; Tbil, total bilirubin; IgG, immunoglobulin G; IgM, immunoglobulin M; TG, triglyceride; ULN, upper limit of the normal range; FF, fenofibrate; LLN, lower limit of the normal range; LT, liver transplant; OR, odds ratio; CI, confidence interval; SD, standard deviation

a Univariate analysis

b Multivariate analysis: Logistic regression analysis

Table 3 Baseline characteristics of patients with primary biliary cholangitis treated with "FF+UDCA" between "ALP normalization group" and "ALP non-normalization group"

Characteristic	ALP normalization	ALP non-normalization	[a]p value	[b]p value	OR (95% CI)
	N=11	N=10			
Age(mean±SD)	55±9	53±11	p=0.648		
Female (n, %)	10(90)	9(90)	p=1.000		
ALP×ULN	2.1(1.8-2.8)	2.9(2.2-3.3)	p=0.247		
GGT×ULN	3.3(2.3-5.5)	5.4(4.6-7.8)	p=0.247		
ALT×ULN	1.3(0.9-1.8)	1.6(1.2-1.8)	p=0.508		
AST×ULN	1.5(1.3-2.3)	2.2(1.6-2.2)	p=0.310		
ALB×LLN	1.0(0.9-1.1)	0.9(0.8-0.9)	p=0.041		
Tbil×ULN	0.8(0.7-1.1)	2.7(0.9-4.1)	p=0.018		
IgG×ULN	0.9(0.8-1.0)	0.8(0.6-0.8)	p=0.111		
IgM×ULN	0.8(0.3-1.8)	1.2(0.7-1.4)	p=0.554		
Mayo	4.7(4.6-4.8)	5.8(5.5-6.2)	p=0.012	p=0.025	0.18(0.040-0.810)
GLOBE	0.9(0.6-1.0)	1.9(1.4-2.9)	p=0.007		
UK-PBC	3.0(1.7-7.0)	4.9(4.0-63.0)	p=0.034		

Abbreviations: FF, fenofibrate; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; ALB, albumin; Tbil, total bilirubin; IgG, immunoglobulin G; IgM, immunoglobulin M; TG, triglyceride; ULN, upper limit of the normal range; FF, fenofibrate; LLN, lower limit of the normal range; OR, odds ratio; CI, confidence interval; SD, standard deviation

a Univariate analysis

b Multivariate analysis: Logistic regression analysis

Table 4 Adverse events of additional FF therapy in decompensated patients

Adverse event	Number/ Severity	Relationship to FF
Fatigue (Severe)	1 persistent	Possibly related
Cutaneous rash	1 transient	Possibly related
Gastrointestinal disorders	2 transient	Probably not related
Cramps and Myalgias	1 transient	Possibly related
Elevated ALT and AST		Probably related
Severe (5-7×ULN)	3 transient;	
Moderate (2-5×ULN)	3 transient	
Elevated Tbil (≥100μmol/L)		
First occurrence after enrollment	1 died	Probably not related
Reoccurrence after enrollment	3 deterioration (≥200μmol/L): 1 died, 1 fluctuate and 1 lost; 2 persistent; 1 fluctuate; 2 lost	Possibly related
Decreased eGFR		Probably not related
Severe (<30ml/min/1.73m^2)	1 died	

Abbreviations: FF, fenofibrate; ALT, alanine-aminotransferase; Tbil, total bilirubin; AST, aspartate-aminotransferase; eGFR, estimated glomerular filtration rate

Figures

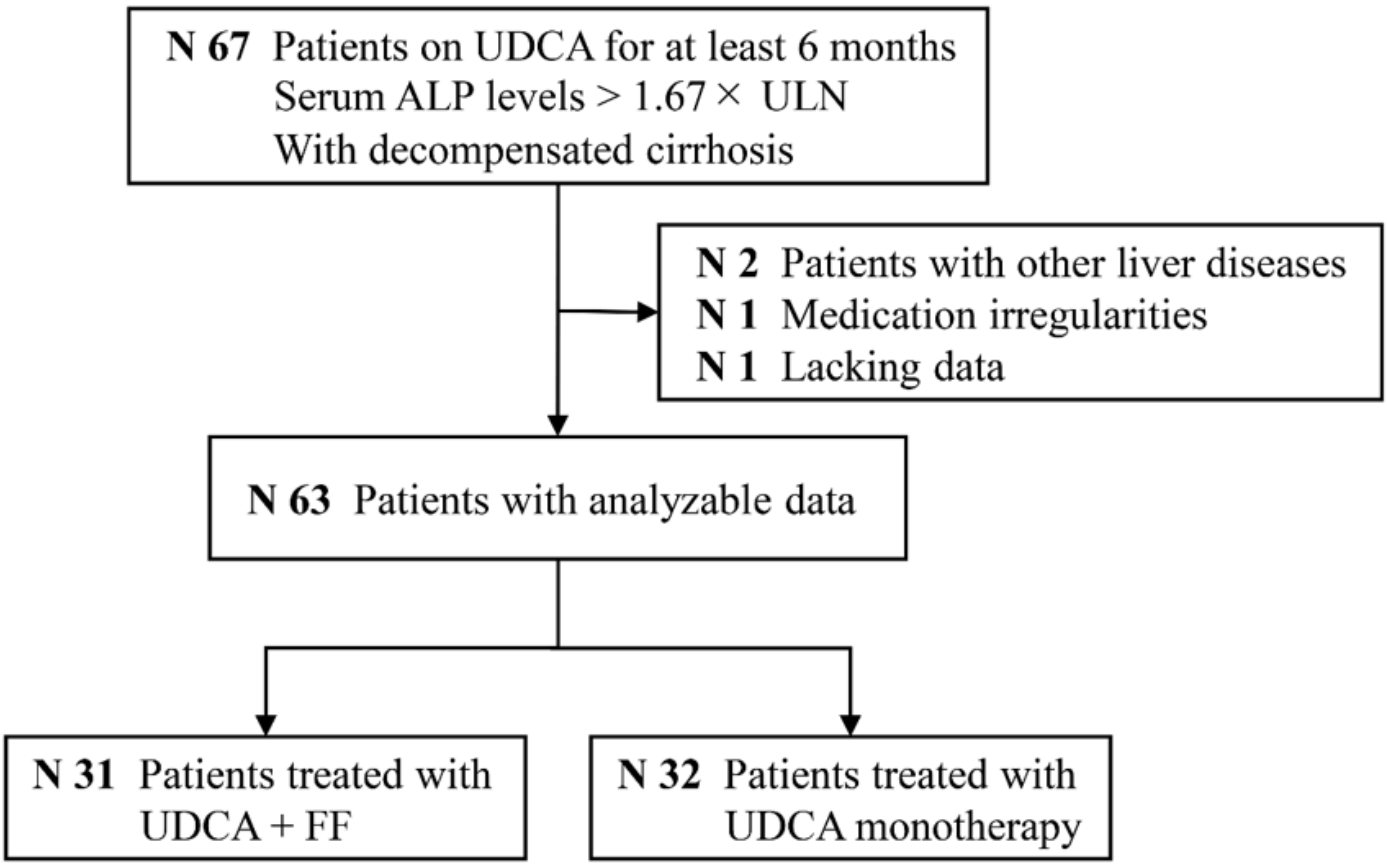

Figure 1

The study flowchart.

Abbreviations: ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; FF, fenofibrate; ULN, upper limit of the normal range

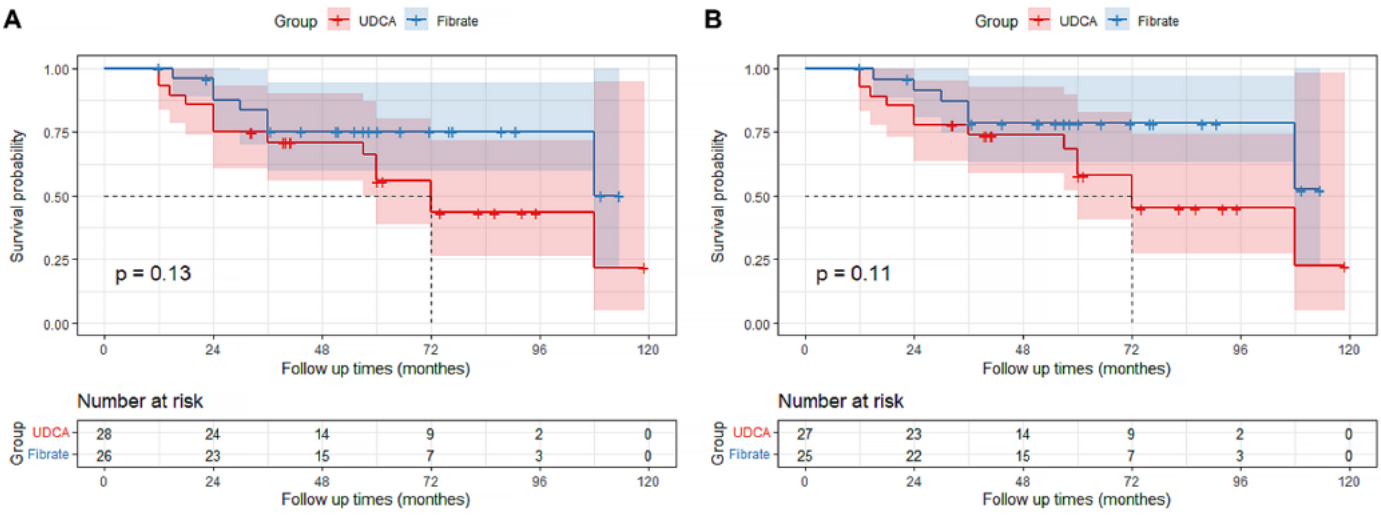

Figure 2

Cumulative incidence of LT-free survival between “the UDCA group” and “the FF group”. (A) All-cause mortality or LT. (B) Liver-related mortality or LT. Shaded areas represent 95% confidence interval. Survival curves were compared with the log-rank test.

Abbreviations: UDCA, ursodeoxycholic acid; Fibrate, fenofibrate; LT, liver transplant

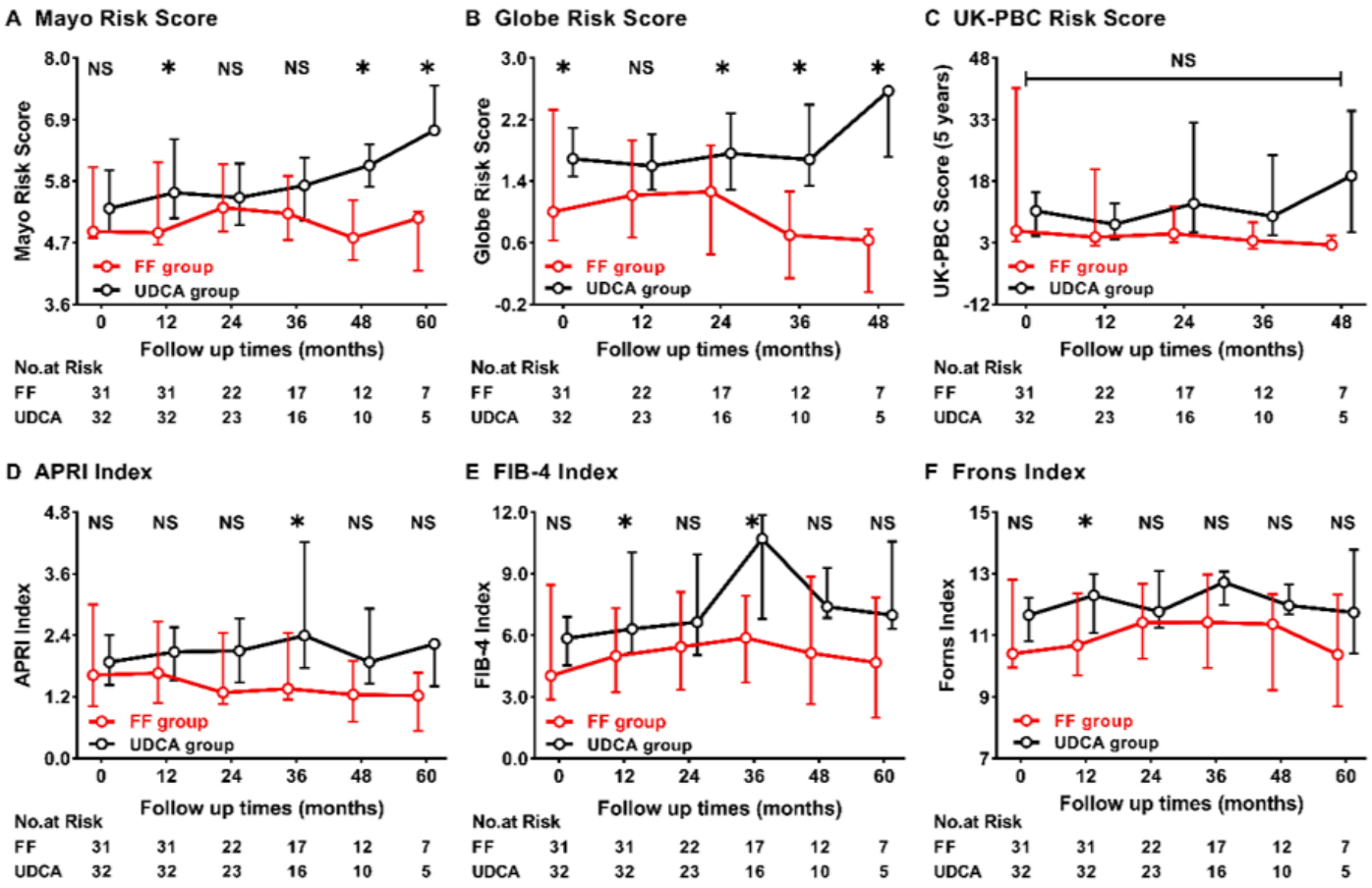

Figure 3

The dynamic changes of Mayo risk score, Globe risk score, UK-PBC risk score, APRI index, FIB-4 index, and Forns index according to follow up time between “the UDCA group” and “the FF group”. Shown are the median values and interquartile ranges at each follow-up visit. Data was compared with the Mann-Whitney U test (*p <0.05).

Abbreviations: UDCA, ursodeoxycholic acid; FF, fenofibrate

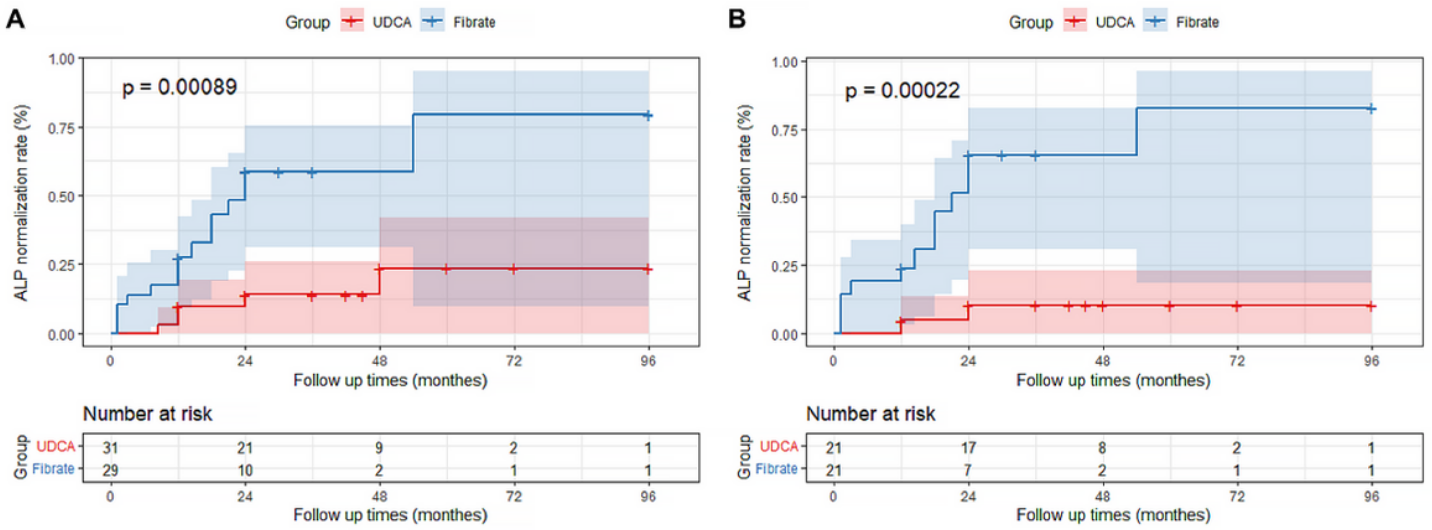

Figure 4

Cumulative incidence of ALP normalization rate between “the UDCA group” and “the FF group”. (A) All patients. (B) Forty-two patients with evidence of decompensation prior to the diagnosis of UDCA-refractory PBC. Shaded areas represent 95% confidence interval. Survival curves were compared with the log-rank test.

Abbreviations: UDCA, ursodeoxycholic acid; Fibrate, fenofibrate

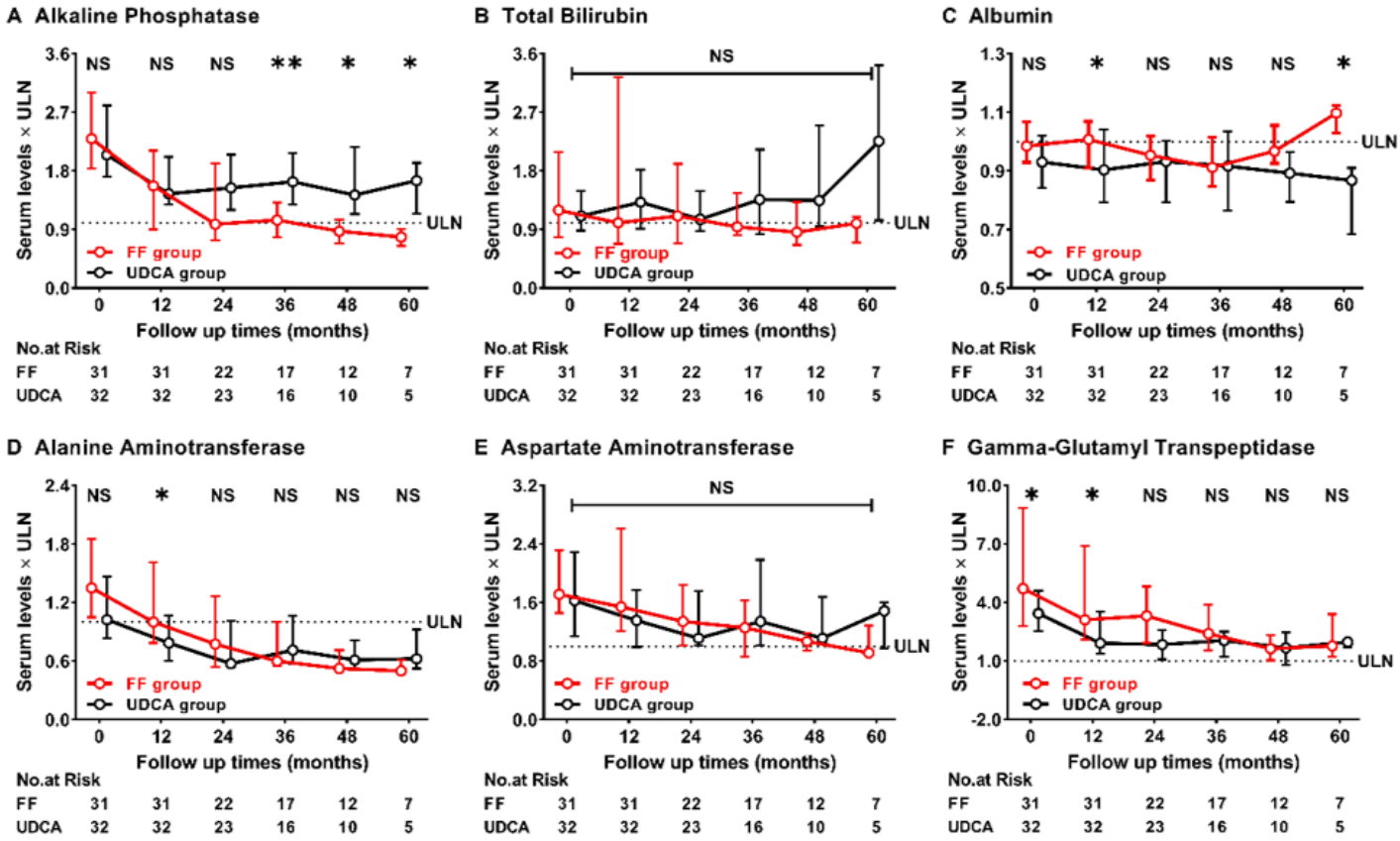

Figure 5

The dynamic changes of alkaline phosphatase, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transpeptidase according to follow up time between “the UDCA group” and “the FF group”. Shown are the median values and interquartile ranges at each follow-up visit. Data was compared with the Mann-Whitney U test (*p < 0.05, **p < 0.01).

Abbreviations: UDCA, ursodeoxycholic acid; FF, fenofibrate; ULN, upper limit of the normal

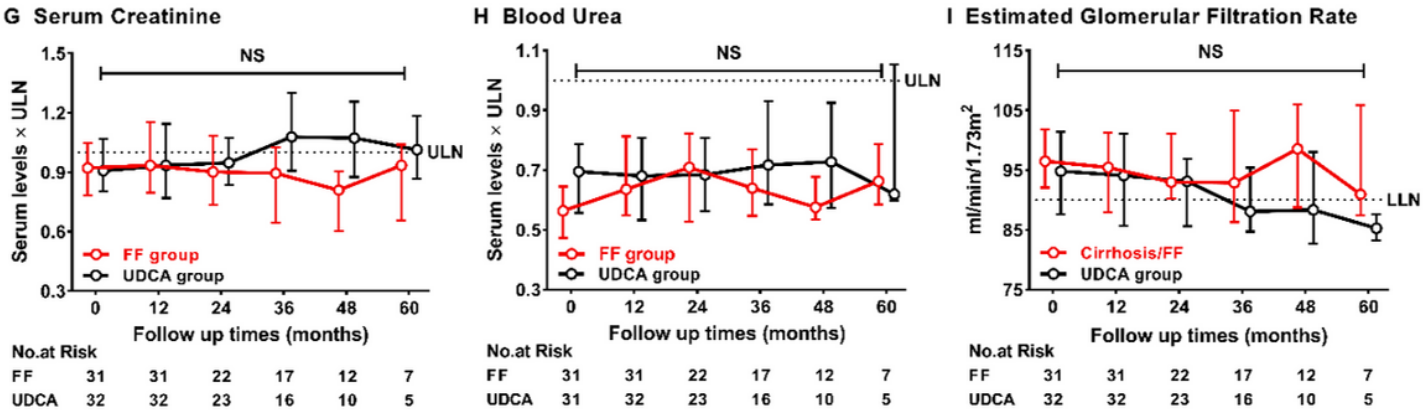

Figure 6

The dynamic changes of serum creatinine, blood urea, and estimated glomerular filtration rate according to follow up time between “the UDCA group” and “the FF group”. Shown are the median values and interquartile ranges at each follow-up visit. Data was compared with the Mann-Whitney U test.

Abbreviations: UDCA, ursodeoxycholic acid; FF, fenofibrate; ULN, upper limit of the normal range; LLN, lower limit of the normal range