Original Article

A randomized open label trial of tenofovir monotherapy versus tenofovir plus telbivudine in spontaneous reactivation of hepatitis B

Ankur Jindal, Ashish Vyas, Manoj Sharma, Guresh Kumar, Shiv K. Sarin

Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

Abstract

Background/Aim: Acute-on-chronic liver failure (ACLF-B) in spontaneous reactivation of chronic hepatitis B (SR-CHB) has high mortality. Tenofovir disoproxil fumarate (TDF) improves survival by ~40% in ACLF-B but is potentially nephrotoxic. Combining telbivudine (LDT) with TDF may negate this risk and could boost rapid viral clearance and improve clinical outcomes.

Patients and Methods: Seventy consecutive patients with SR-CHB were randomized to TDF (300 mg/day, $n = 35$) or TDF plus LDT (600 mg/day; $n = 35$). In all, 25 had ACLF-B and none had option for liver transplantation. Primary endpoint was survival at 3 months. Secondary endpoints were survival at 3 months in ACLF-B, serial reduction in hepatitis B virus (HBV) DNA, hepatitis B surface antigen (HBsAg) loss and liver-related complications.

Results: Overall baseline clinical and laboratory parameters in the two groups were comparable. Reduction in HBV DNA at weeks 2, 4 and 12 was independent of treatment groups and presence of ACLF-B ($P < 0.01$). All six patients with HBsAg loss at 12 weeks had lower HBV DNA at baseline and none had ACLF-B. Patients with no ACLF-B had more rapid decline in bilirubin and alanine aminotraminase at week 2 compared with ACLF-B. Patients on TDF plus LDT showed significant improvement in AKI on follow-up (five of six patients) compared with TDF monotherapy (none of six patients) and had less reduction in estimated glomerular filtration rate at week 12. Eight of 10 patients with liver-related deaths received TDF monotherapy ($P = 0.02$). New-onset septic shock, TDF monotherapy, e-antibody positivity, and higher baseline model for end-stage liver disease score were predictors of mortality in ACLF-B. None had treatment-related severe adverse effects.

Conclusion: Addition of LDT to tenofovir is safe and may be renoprotective in spontaneous reactivation of hepatitis B. Combination therapy improves survival in ACLF-B despite comparable HBV DNA suppression to tenofovir monotherapy.

Keywords: Hepatitis, reactivation, tenefovir and combination therapies, therapy

Address for correspondence: Dr. Ankur Jindal, Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi - 110 070, India.
E-mail: ankur.jindal3@gmail.com

INTRODUCTION

The natural history of chronic hepatitis B (CHB) is punctuated by spontaneous reactivation of the disease.[1] Patients with CHB reactivation can have variable presentation, ranging from a subclinical illness to acute-on-chronic liver failure (ACLF-B).[2] Once ACLF-B develops, the prognosis is extremely poor, with 3-month transplant-free survival of ~50%.[3,4]

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_537_18

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Jindal A, Vyas A, Sharma M, Kumar G, Sarin SK. A randomized open label trial of tenofovir monotherapy versus tenofovir plus telbivudine in spontaneous reactivation of hepatitis B. Saudi J Gastroenterol 2019;25:319-26.

A substantial amount of research is being undertaken to improve the poor outcome of ACLF-B. The main determinants for recovery are liver regeneration and rapid cessation of ongoing necroinflammation. Neither factor is directly dependent on hepatitis B virus (HBV) replication. Patients often need intensive supportive care for close monitoring and treatment of complications. Although liver transplantation should be considered in all patients with ACLF-B, early use of a potent oral nucleoside (tide) analog (NA) is imperative for improving short-term survival.[5] Delay in NA initiation often leads to disease progression and complications including sepsis and multiorgan dysfunction.

Tenofovir disoproxil fumarate (TDF), a potent NA, has been shown to improve transplant-free 3-month survival by ~40% in ACLF-B.[6] However, TDF is potentially nephrotoxic. Nephrotoxicity may result from the apoptotic or mitochondrial toxic effect of TDF in the proximal tubular cells of kidney. Patients with ACLF-B are at a risk of developing renal dysfunction and its presence independently portends poor outcome. The GLOBE study and several real-life studies have revealed that telbivudine (LDT) increases glomerular filtration rate (GFR) in patients with CHB.[7-9]

Although entecavir is often used in patients with HBV with risk of kidney impairment, for this trial, in search of better clinical outcomes, we hypothesized that combining LDT with TDF in patients with severe spontaneous reactivation of CHB (SR-CHB) may negate the risk of TDF-induced nephrotoxicity and could boost rapid viral clearance.

PATIENTS AND METHODS

We conducted a randomized open label study involving patients admitted with SR-CHB at the Institute of Liver and Biliary Sciences (ILBS), New Delhi, India, from January 2013 to January 2017. SR-CHB was defined by spontaneous rise in alanine aminotraminase (ALT) level >5 times upper limit of normal (or >3 times the baseline) in presence of HBV DNA > 1.8×10^4 IU/mL in a previously untreated CHB. Some patients fulfilled the diagnostic criteria for ACLF-B, that is, acute hepatic insult manifesting as jaundice (serum bilirubin >5 mg/dL) and coagulopathy (INR >1.5) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis. Exclusion criteria were as follows: (1) superinfection with hepatitis E, A, D, or C; (2) advanced hepatocellular carcinoma; (3) renal impairment at baseline (serum creatinine >1.5 mg/dL); (4) pregnant and lactating women; (5) human immunodeficiency virus coinfection; (6) peripheral neuropathy; (7) patients who had received a previous course of any antiviral, immunomodulatory or cytotoxic/immunosuppressive therapy within preceding 12 months; (8) those who underwent liver transplantation; (9) serious concurrent medical illnesses (such as malignancy, severe cardiopulmonary disease, uncontrolled diabetes mellitus, alcoholism, psychiatric illness); (10) any contraindication for TDF or LDT therapy; and (11) age <18 years.

It is sometimes difficult to distinguish SR-CHB and acute HBV infection. Inclusion of patients with high HBV DNA at baseline (>10^4 IU/mL) favors SR-CHB. Moreover, 37 of 70 patients had liver biopsy, all showing presence of fibrosis suggestive of underlying chronic HBV infection.

A written informed consent for inclusion in the trial was obtained from all included patients. The potential benefits and risks of use of TDF or LDT were explained, and among patients with ACLF-B, option of early liver transplantation was proposed. The study conformed to the Declaration of Helsinki of 1975 and was duly approved (Clinical Trials.gov NCT01732224) by ethics and review committee of ILBS. Informed consent was obtained before enrolling each patient or their close relatives for inclusion in the study and for conducting various blood tests.

Baseline assessment of patients

Prospectively collected data included patient demographics, clinical, routine laboratory variables, abdominal ultrasound and upper gastrointestinal endoscopy. Percutaneous liver biopsy under fluoroscopic guidance or transjugular liver biopsy (TJLB) in the presence of ascites and/or coagulopathy (INR >1.5/platelets <75,000/mm^3) was done in patients when it was doubtful whether the underlying liver disease was chronic. In ACLF-B, severity of the liver disease was assessed by Child–Turcotte–Pugh score (CTP) and model for end-stage liver disease (MELD) score. Serological tests for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), IgM anti-HBc and total anti-HBc, and anti-HBe were done by commercially available ELISA kits. HBV DNA estimation was done with real-time polymerase chain reaction method (lower limit of detection 6 IU/mL; Roche Taqman assay, Roche Molecular Systems, Inc., Branchburg, NJ).

Study design

Study participants were randomized to TDF [300 mg once daily (OD)] (Group A) or TDF plus LDT (600 mg OD) (Group B) [Figure 1]. Subgroup analysis was done comparing the treatment groups based on presentation

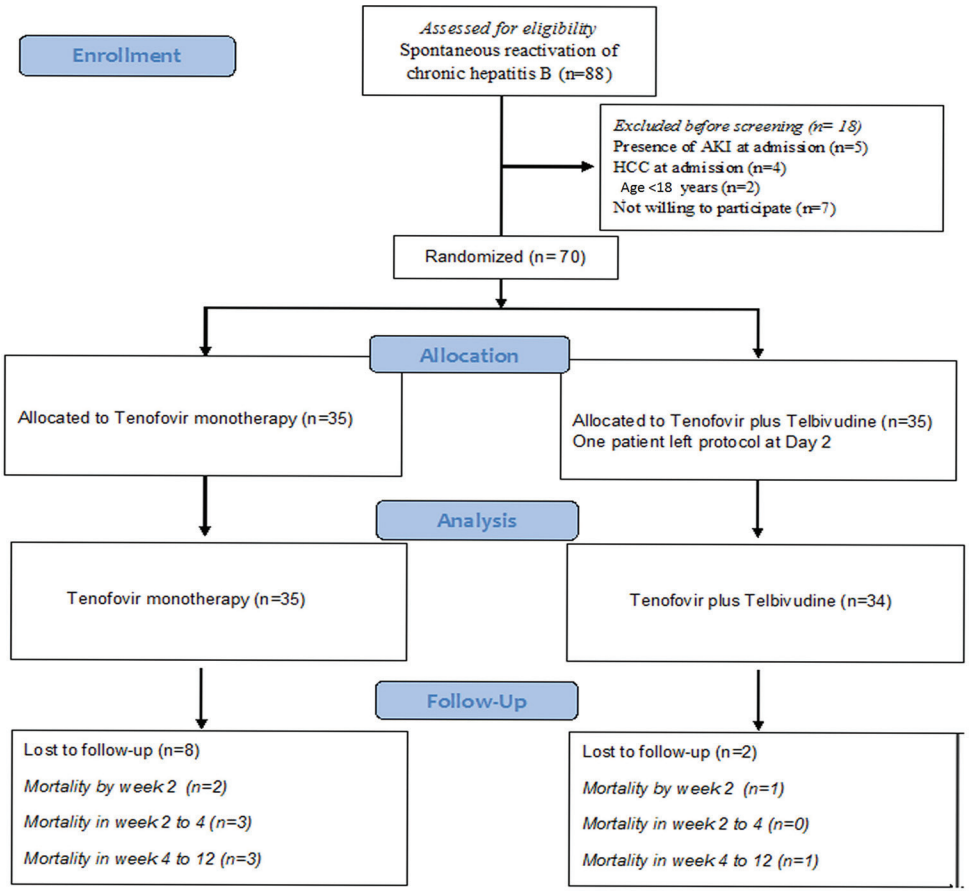


Figure 1: Consort diagram showing patient disposition

as ACLF-B or no ACLF-B. Randomization occurred in outpatient clinic or inpatient ward after patient underwent a baseline investigation.

Follow-up

Clinical assessment and routine investigations were done at weeks 1, 2, 4 and 12 and more frequently as required. HBV DNA and HBsAg levels were repeated at weeks 2, 4 and 12. Child–Pugh score and MELD score were calculated in patients with ACLF-B at each follow-up. Treatment-related side effects were closely monitored. All hospitalized patients with complications were managed with standard medical therapy including albumin, nutritional support, antibiotics, and so on.

Endpoints

The primary endpoint of the study was survival at 3 months, and secondary endpoints were (1) survival at 3 months in patients with ACLF-B; (2) reduction in HBV DNA and HBsAg levels; (3) HBsAg loss; (4) new complications (hepatic encephalopathy, variceal bleed, acute kidney injury, shock) on follow-up; (5) improvement in CTP and MELD scores in ACLF-B; and (6) treatment-related adverse effects.

Statistical analysis

Precise data for calculation of sample size were not available. Based on data by Garg *et al*., where mortality rate in TDF treated ACLF-B group was 43% in comparison to placebo at 3 months.[10] There are no data available on combination of TDF plus LDT therapy in SR-CHB. We hypothesize TDF plus LDT combination as more potent than TDF alone, and the expected mortality rate with combination was taken as 10%. Using comparison of two survivals, taking alpha of 0.05 and power of 80%, the resulting sample size was 32 in each group. So it was decided to enrol 35 cases in each group. Since this study was a time-bound prospective study, we could enroll only 25 patients with ACLF-B. The allocation was done by block randomization method taking block size as 10. Block randomization was done using computer-generated random number list. Descriptive statistics were expressed as median (range) or number (%). Comparison of continuous variables was done by Mann–Whitney *U* test, and categorical variables were compared by Fisher's exact test or Pearson's Chi-square test. The actuarial probability of survival was calculated by Kaplan–Meier graph and compared by log-rank test. All statistical tests were performed using SPSS for Windows version 20 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient disposition

Of 88 patients diagnosed with SR-CHB, 35 patients were randomized to TDF monotherapy (Group A) and 35 patients to TDF plus LDT (Group B). Nineteen patients were excluded after baseline workup [Figure 1]. Eleven patients succumbed to illness before 90 days follow-up.

Baseline parameters

TDF monotherapy versus TDF plus LDT – all patients

The median age was 45 years [interquartile range (IQR) 31–62 years] and 79.7% were male. The two groups were well matched with respect to demographic, clinical, and laboratory parameters as shown in Table 1. Only 11 patients were previously diagnosed to have CHB infection. In all, 37 patients (17 in Group A and 20 in Group B) underwent baseline liver biopsy. Advanced fibrosis (>F4; modified Ishak fibrosis stage) was noted in 10 patients (Group A: 4 patients, Group B: 6 patients; $P = 0.7$). Prominent liver histological findings in two groups include lobular inflammation (58.8% vs. 90%; $P = 0.028$), prominent ductular reaction (52.9% vs. 55%; $P = 0.9$), and cellular/canalicular cholestasis (58.5% vs. 80%; $P = 0.2$). There was no difference in HBV serological and virological parameters based on treatment groups at baseline as shown in Table 1.

TDF monotherapy versus TDF plus LDT – ACLF-B versus no ACLF-B

Twenty-five (36.2%) patients with SR-CHB had ACLF-B at presentation, and of these, 13 patients

Table 1: Baseline demographic and clinical parameters of patients at admission

	Tenofovir (*n*=35)	Tenofovir + Telbivudine (*n*=35)	*P*
Age (yrs) [median (1QR)]	46 (30-63)	43.5 (34-60.25)	0.546
Male: Female	25:10	30:5	0.142
Inpatients- *n*(%)	18 (51.4%)	15 (42.85%)	0.48
ACLF- *n*(%)	13 (37.1%)	12 (34.28%)	0.80
Presenting symptoms- *n*(%)			
Jaundice	29 (82.9%)	31 (88.57%)	0.71
Duration of jaundice	20 (30-63)	20 (10-30)	0.897
Ascites	13 (37.1%)	11 (31.42%)	0.62
Duration of ascites (days)	15 (7-25)	5 (3-13)	0.111
Altered mentation	4 (11.4%)	5 (14.28%)	0.73
Decreased urine output	3 (8.5%)	4 (11.42%)	0.71
GI Bleeding	1 (2.8%)	2 (5.71%)	0.61
Past History- *n*(%)			
History of prior jaundice	14 (40%)	14 (40%)	0.99
Prior known HBV	3 (8.6%)	8 (22.85%)	0.11
Laboratory parameters			
Plasma Hemoglobin (g/L)	12 (11-14)	13 (11-14)	0.186
Total leucocyte count (/mm^3)	8 (6-10)	8 (6-10.25)	0.700
Platelet count (x 10^9)	206 (119-280)	185.5 (125.75-240.75)	0.902
Total bilirubin (mg/dl)	12 (4-25)	13 (5-27.5)	0.897
S. ALT (IU/ml)	598 (193-981)	472 (265.75-1273.25)	0.546
Serum albumin (mg/dl)	3 (2-4)	3 (2.1-4)	0.860
Sodium (MEq/L)	130.24±12.34	132±11.65	0.917
Creatinine (mg/dl)	0.71±0.45	1.06±0.74	0.228
INR	1.37±0.59	1.35±0.54	0.860
Alpha-fetoprotein (ng/ml)	10 (6-25.5)	20 (10-67.25)	0.219
HVPG (mm Hg) (*n*=30)	13 (12-14)	12 (9.5-18.5)	1.0
Liver stiffness (kPa) (*n*=39)	12 (8-19.5)	14.5 (7.75-25)	0.563
Hepatitis B serological profile			
e Antigen positive- *n*(%)	23 (65.7%)	27 (77.14%)	0.30
Median HBV DNA (IU/ml)	3.82 x 10^5 (8.5 x 10^4-9.3 x 10^6)	1.3 x 10^6 (5.5 x 10^4-9.07 x 10^7)	0.401
Median HBsAg (IU/ml)	8.6 x 10^3 (3 x 10^3-2.3 x 10^4)	2.7 x 10^4 (7.6 x 10^3-7.1 x 10^4)	0.071
HbsAg loss at follow up (week 12)	2 (5.7%)	4 (11.7%)	0.372
IgM Anti-HBc positive (*n* %)	12 (60%) (n=20)	12 (80%) (n=15)	ns
Histological variables *n*=37)			
Presence of bile plugs	4 (23.5%)	5 (25%)	0.917
Cellular/canalicular cholestatsis	10 (58.5%)	16 (80%)	0.160
Prominent ductular reaction	9 (52.9%)	11 (55%)	0.901
Stage of fibrosis (modified Ishak's) [Stage 1/2/3/4/5/6]	3/9/1/0/1/3	5/8/0/1/1/5	0.726
Ballooning of hepatocytes	5 (29.4%)	11 (55%)	0.117
Cholestastic pseudorosetting	2 (11.8%)	9 (45%)	0.028
Lobular inflammation	10 (58.8%)	18 (90%)	0.028

received TDF (Group A1) and 12 received TDF plus LDT (Group B1) and all were managed as in-patients for a median duration of 8 days (IQR, 4–13 days). All patients in Groups A1 and B1 had jaundice and ascites. Patients in Group A1 had higher median duration of jaundice [45 days (IQR, 30–60 days)] compared with Group B1 [21.5 (11–33.75) days; $P = 0.04$]. None had acute kidney injury at admission [Supplementary Table 1].

Among ACLF Groups A1 and B1, the mean MELD score [26.23 ± 5.57 vs. 27.42 ± 8.20; $P = 0.6$] and the mean HBV DNA (2.11×10^5 IU/mL vs. 1.32×10^7 IU/mL; $P = 0.11$) were comparable. Among patients with ACLF-B, 9 of 11 patients had advanced fibrosis or cirrhosis on TJLB. Patients with ACLF-B had significant differences in baseline characteristics when compared with patients with no ACLF-B as shown in Supplementary Table 1.

Follow up

Liver-related complications

During the median follow-up of 45 days in patients with ACLF-B, five patients allocated to each treatment group developed HE ($P = 0.9$). All five patients in Group B1 had HE Grade I–II with four patients showing complete HE response on standard medical therapy. In Group A1, four patients had HE Grade III–IV, one had Grade II HE, and only one patient showed complete response on SMT ($P = 0.03$). Six patients with ACLF-B in both the groups developed AKI on follow-up. AKI improved in five of six patients in Group B1 although none with AKI in Group A1 had resolution of AKI (serum creatinine < 1.5 mg/dL; $P = 0.045$) [Supplementary Figure 1]. Despite comparable estimated GFR (eGFR) at baseline, patients on TDF monotherapy had significantly reduced GFR on follow-up in comparison to dual NA therapy (84.8 mL/min vs. 98 mL/min; $P < 0.05$) [Figure 2]. The frequency of other complications such as GI bleeding and SBP in both groups was comparable.

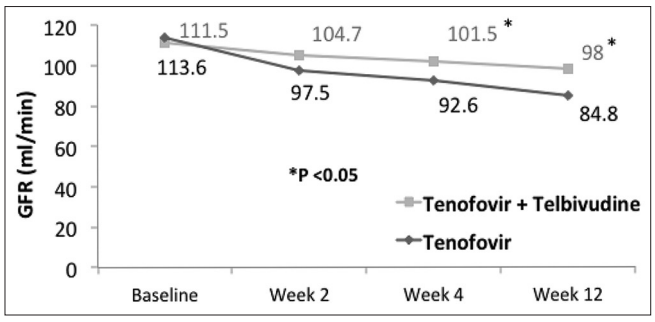


Figure 2: Change in eGFR (calculated by MDRD equation) in patients with ACLF-B in two groups

Liver severity scores – MELD and CTP scores

On follow-up, the mean MELD scores remained comparable in both ACLF-B treatment groups at the end of weeks 2 ($P = 0.8$), 4 ($P = 0.9$), and 12 ($P = 0.4$). No significant change in MELD score at 2 weeks was observed in ACLF-B groups in comparison to baseline (Group A1: 26.23 ± 5.57–24.55 ± 6.23 and Group B1: 27.42 ± 8.20–25 ± 4.92). Significant improvement in MELD scores in both the groups by week 12 was due to patients who had high baseline MELD and died. However, patients in Group B1 in comparison to group A1 had significant reduction in the MELD score at weeks 4 and 12 compared to baseline MELD [Figure 3a]. This is likely related to significant improvement in AKI in patients with ACLF-B in Group B1. The mean CTP scores remain comparable in two treatment groups at the end of weeks 2, 4 and 12.

Biochemical parameters

There was progressive decline in serum bilirubin at weeks 2, 4 and 12 ($P < 0.01$). The percentage change in serum bilirubin from baseline to weeks 4 and 12 was significant in both ACLF-B and no ACLF; however, no significant change in bilirubin at week 2 was noted in patients with ACLF-B compared with baseline [Group A1: 22 mg/dL (11.5–28) to 19 mg/dL (10–27) and Group B1: 26.5 mg/dL (8.75–35.3) to 27 mg/dL (12–38)] [Figure 3b].

In comparison to baseline ALT, reduction of serum ALT at the end of weeks 2, 4 and 12 was significant ($P < 0.01$) but comparable in Groups A and B. Patients with ACLF-B in comparison to no ACLF-B had lesser reduction in ALT at week 2 [reduction from baseline ALT, 80 IU/mL (−45 to 162.5 IU/mL) vs. 183.5 IU/mL (113 to 397 IU/mL; $P = 0.001$)], 4 weeks ($P = 0.004$), and 12 weeks ($P < 0.001$).

Virological parameters – hepatitis B DNA and HBsAg levels

The mean HBV DNA at the end of weeks 2, 4 and 12 was significantly low in comparison to baseline in each individual patient, irrespective of ACLF-B and treatment groups ($P < 0.01$). In patients with ACLF-B, the mean HBV DNA reduction from baseline to the end of 2 weeks in Group A1 (1.45 ± 0.82 IU/mL) was comparable to Group B1 (2.18 ± 1.16 IU/mL); $P = 0.21$ [Figure 3c]. The mean HBV DNA reduction at weeks 2, 4 and 12 were comparable in ACLF-B versus no ACLF-B.

Baseline HBV DNA and HBsAg levels were significantly correlated ($r = 0.259$; $P = 0.035$). Significant reduction of mean HBsAg was present at the end of 12 weeks in comparison to baseline HBsAg in each group ($P < 0.001$).

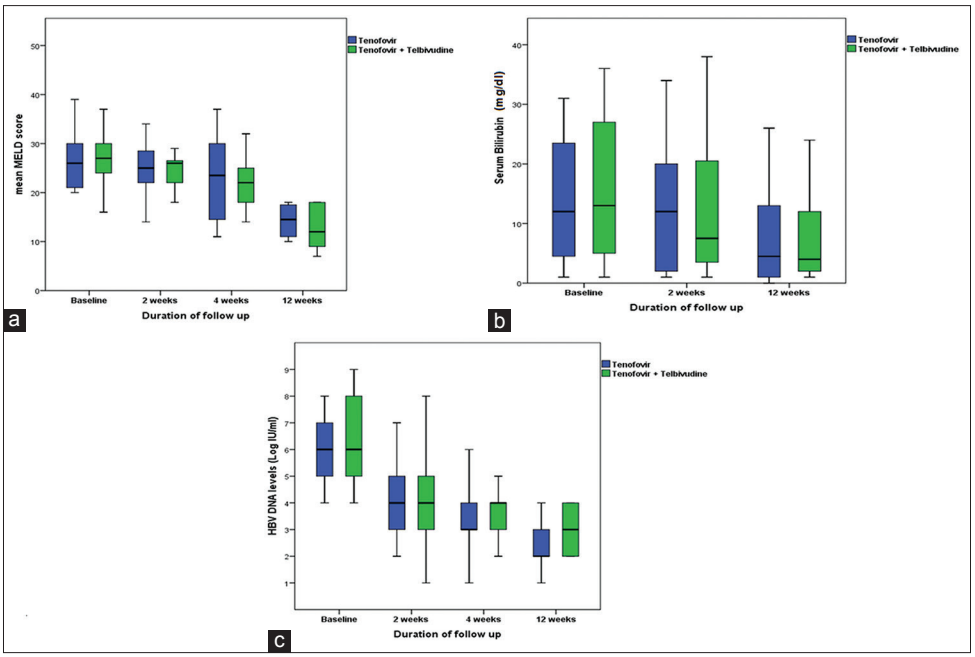


Figure 3: Comparison of (a) MELD score, (b) total bilirubin, and (c) HBV DNA level in patients with ACLF-B on tenofovir vs tenofovir plus telbivudine

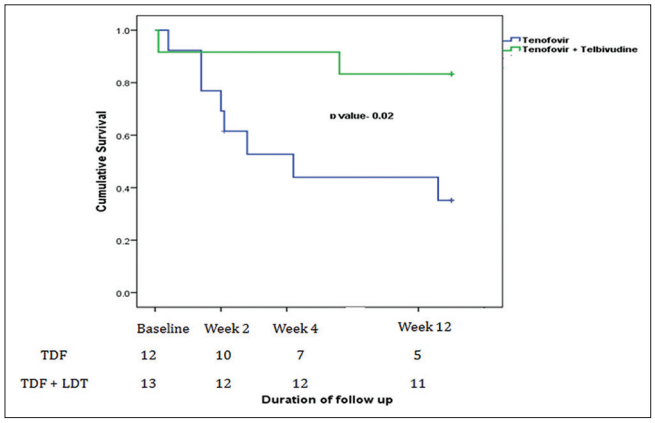


Figure 4: Survival in patients with hepatitis B reactivation-related acute-on-chronic liver failure in tenofovir vs tenofovir plus telbivudine groups over 12 weeks (Kaplan–Meier analysis)

HBsAg loss

Six patients achieved HBsAg loss at the end of 12 weeks, none had ACLF-B, and these patients were continued on antivirals with serial follow-up expecting hepatitis B surface antibody response. Two patients with HbsAg loss were on TDF monotherapy compared with four patients on dual therapy. The only significant predictor of HBsAg loss was baseline HBV DNA. Patients achieving HBsAg loss at 12 week had significantly lower HBV DNA (5.01 ± 1.07 IU/mL) compared with those who remained HBsAg-positive (6.11 ± 1.35 IU/mL, $P = 0.05$).

Survival analysis

Eleven patients died by end of 3-month follow-up. Overall mortality rates in SR-CHB (with or without ACLF) at week 12 were comparable in two groups (Group A: nine patients, Group B: two patients; $P = 0.115$). Of these, 10 had ACLF-B and the primary cause of death was progressive AKI and eventual sepsis and multiorgan failure. In a subgroup of patients with SR-CHB with ACLF-B, patients on dual NA therapy had improved survival at week 12 (11 of 13 patients) in comparison to 5 of 12 patients in TDF monotherapy ($P = 0.02$). A single patient with no ACLF-B had mortality unrelated to hepatic cause. About 80% of patients who died received TDF monotherapy ($P = 0.02$) [Figure 4, Supplementary Figure 2]. All patients who died had <2 Log HBV DNA reduction at 2 weeks. The mean baseline MELD score was high (30.78 ± 7.48) in these patients compared with survivors (24.67 ± 5.65, $P = 0.045$). Presence of septic shock, TDF monotherapy, e-antibody positivity, and high baseline MELD score were predictors of death in patients with ACLF-B on univariate analysis [Supplementary Table 2]. There were no independent predictors of mortality on multivariate analysis.

Safety and tolerability

The proportion of patients reporting at least one adverse event through 3 months, regardless of attributability to study drug, was similar for TDF and TDF plus LDT (67% vs. 56%, respectively). Most were constitutional symptoms, mild, transient and not attributed to study drug. No event was considered treatment-related [Table 2]. There were no reports of myopathy, myositis, rhabdomyolysis, lactic acidosis, pancreatitis or peripheral neuropathy.

DISCUSSION

Despite the advent of potent antiviral agents (TDF and entecavir), patients with hepatitis B reactivation are at risk of hepatic decompensation, organ failure(s) and significant mortality. Once ACLF-B develops, the only definite chance of recovery is liver transplantation. However, considering the ethical and financial limitations as well as lack of deceased donors, this is often inevitable.

In our study, outcome of patients with ACLF-B remained poor despite reduction in HBV DNA. High MELD score and TDF monotherapy were associated with mortality. Kumar *et al.* in a prospective study also showed that although lamivudine significantly decreased HBV DNA in patients with hepatitis B, it did not result in any significant biochemical or clinical improvement compared with placebo.[11] Patients in nonsurvival group had baseline MELD score >28. Many previous studies also demonstrated MELD score as a powerful independent predictor of survival in ACLF-B.[12,13]

We observed that patients on TDF monotherapy had higher mortality despite comparable reduction in HBV viral load at 2, 4 and 12 weeks. Significant improvement in renal parameters on addition of LDT to TDF could have accounted for this. Renal parameters improved in all patients who received combination therapy, while only one of six patients with AKI in tenofovir group had improvement in AKI. The lack of association between change in renal functions and on-treatment virologic response would support a direct beneficial effect on the kidney rather than an indirect effect from HBV suppression.

TDF alone is potentially nephrotoxic. The postulated mechanisms of TDF nephrotoxicity include increased intracellular influx through organic anion transporters and/or a defect in its luminal excretion through multidrug resistance–associated proteins, or mitochondrial toxicity in the proximal tubular cells of the kidney.[14] Acute tubular necrosis with resultant AKI may be seen with antiviral nephrotoxicity, particularly in patients with preexisting renal insufficiency or those exposed to other nephrotoxic agents.[15] In a cohort of 737 TDF-treated CHB patients, serum creatinine increased by >26 μmol/L in 3% of patients after a median of 16 months of therapy.[16]

The exact mechanism for the potential renal protective effect of LDT is unclear, although it appears to be independent of its antiviral effect on HBV. A possible effect of LDT could be on kidney structures or on inflammatory/fibrotic pathways. In the double-blind randomized GLOBE trial of 1397 compensated CHB patients, there was an improvement of 8.5% in the LDT arm compared with −0.5% in those treated with lamivudine ($P < 0.0001$).[7] In a multicenter study from Greece of 131 patients with CHB, GFR was increased in LDT compared with entecavir and LDT treatment.[8,17] A previous Gane *et al.* have shown that even in patients who had achieved complete viral suppression on LAM therapy, switch to LDT resulted in improvement in eGFR and the improvement of eGFR during LDT therapy was maintained even after addition of a second, potentially nephrotoxic NA such as TDF or adefovir.[8] Therefore, it appears that combining LDT with a potential nephrotoxic NA such as TDF can still improve GFR, with more marked effect observed in those with lower baseline GFR.

Table 2: Most common all-cause adverse events through Week 12

	Tenofovir (*n*=35)	Tenofovir plus Telbivudine (*n*=34)
Myalgia	6	9
Headache	3	2
Upper respiratory tract infection	2	1
Dyspepsia	12	10
Arthralgia	2	4
Diarrhea	3	2
Nausea	10	8
Dizziness	2	1
Pain in extremity	6	9
Pyrexia	7	3
Vomiting	9	10
Upper abdominal pain	6	8
Cough	2	1
Acute kidney injury	7	6
Bleed	2	2
Hepatic encephalopathy	6	5
SBP	1	0
Septic shock	7	4

Renal dysfunction can also develop in patients with CHB with advanced liver disease through multiple mechanisms, including functional renal insufficiency and hepatorenal syndrome. Renal function impairment in ACLF-B has been shown to be correlated with impaired liver function and mortality rates. There have been no major studies on the use of LDT alone or in combination with TDF in patients with hepatitis B reactivation. In an study from India in CHB, combination of LDT-TDF was well tolerated with no major side effects.[18]

Although changes in virological response in the two groups were comparable, LDT has been linked to higher HBeAg loss compared with other NAs and rates of HBsAg loss better than interferon.[19] Of six patients achieving HBsAg loss, four were on TDF plus LDT therapy. This effect could

be attributed to enhanced antiviral T-cell reactivity with LDT treatment. The rapid decline in serum HBsAg (as with interferon treatment) was predictive of HBsAg clearance. HBsAg decline on LDT has been comparable to PegIFN-a in a previous study.[20] The association of HBsAg response with dual NA suggests a potential synergistic effect between TDF and LDT that merits longer term investigation in a larger dataset.

Higher ALT level was observed in patients with no ACLF-B in comparison to patients with ACLF. Higher ALT levels reflect a more vigorous immune response and a more extensive hepatolysis with a more robust immune clearance of HBV, and therefore, a higher chance of HBV DNA loss and HBeAg seroconversion and probably HBsAg loss, both in the setting of natural course and drug therapy.[19] Higher HBsAg loss in no ACLF-B group could be accounted by the higher baseline ALT level and its rapid fall in these patients.

Our study has its limitations. Since it was a time-bound prospective study, it was underpowered as we could enroll only 25 patients with ACLF-B. Patients with no ACLF may have acute viral hepatitis which could contribute to HBsAg loss; however, over two-third patients had evidence of chronic hepatitis on liver biopsy. Although early liver transplantation is often warranted in those who develop liver failure as a result of hepatitis B reactivation, antivirals may come to the rescue. Therefore, choosing a right antiviral agent at the earliest is extremely important. TDF has shown some promise, but the quest for a better finite, effective and safe therapy is ongoing. We have shown that combination therapy with TDF-LDT is less nephrotoxic and more effective than TDF monotherapy, and more importantly, it improves survival. However, larger prospective trials with prolonged follow-up are needed to consolidate these initial results.

Acknowledgements

NA.

Author contributions

AJ and AKV involved in writing the manuscript, GK involved in statistical analysis, AJ, MKS and SKS involved in revision and critical review of manuscript draft.

Financial support and sponsorship

This work was partly supported by institutional grant from the Institute of Liver and Biliary Sciences, New Delhi, India.

Conflict of interest

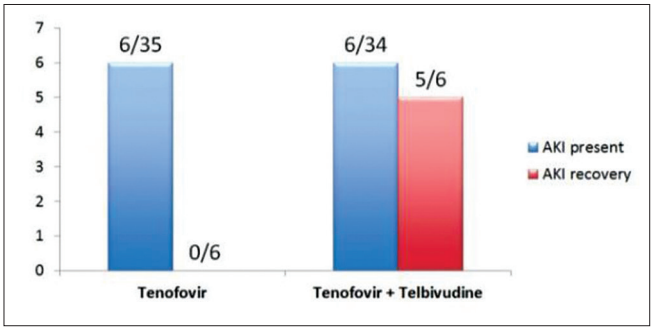
There are no conflicts of interest.

REFERENCES

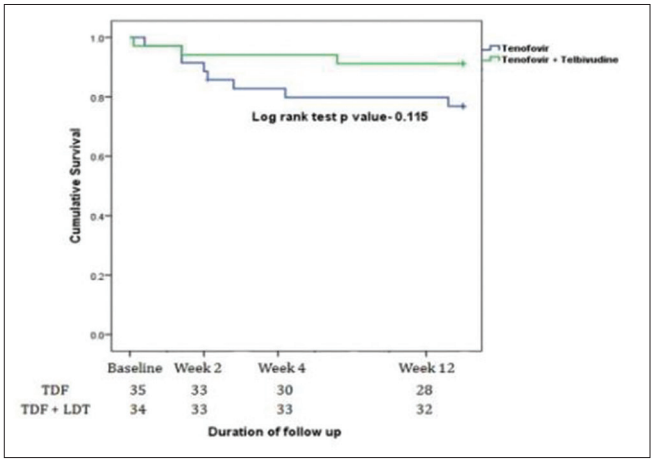
1. Davis GL, Hoofnagle JH, Waggoner JG. Spontaneous reactivation of chronic hepatitis B virus infection. Gastroenterology 1984;86:230-5.
2. Zhao R-H, Shi Y, Zhao H, Wu W, Sheng J-F. Acute-on-chronic liver failure in chronic hepatitis B: An update. Expert Rev Gastroenterol Hepatol 2018;12:341-50.
3. Kumar R, Krishnamoorthy TL, Tan HK, Lui HF, Chow WC. Change in model for end-stage liver disease score at two weeks, as an indicator of mortality or liver transplantation at 60 days in acute-on-chronic liver failure. Gastroenterol Rep 2015;3:122-7.
4. Li H, Chen LY, Zhang NN, Li ST, Zeng B, Pavesi M, *et al*. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to hepatitis B. Sci Rep 2016;6:25487.
5. Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: Benefits of antiviral therapy. J Hepatol 2012;57:442-50.
6. Sun LJ, Yu JW, Zhao YH, Kang P, Li SC. Influential factors of prognosis in lamivudine treatment for patients with acute-on-chronic hepatitis B liver failure. J Gastroenterol Hepatol 2010;25:583-90.
7. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, *et al*. 2-Year GLOBE trial results: Telbivudine is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology 2009;136:486-95.
8. Gane EJ, Deray G, Liaw Y-F, Lim SG, Lai CL, Rasenack J, *et al*. Telbivudine improves renal function in patients with chronic hepatitis B. Gastroenterology 2014;146:138-46.e5.
9. Cholongitas E, Vasiliadis T, Goulis I, Fouzas I, Antoniadis N, Papanikolaou V, *et al*. Telbivudine is associated with improvement of renal function in patients transplanted for HBV liver disease. J Viral Hepat 2015;22:574-80.
10. Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. Hepatology 2011;53:774-80.
11. Kumar M, Satapathy S, Monga R, Das K, Hissar S, Pande C, *et al*. A randomized controlled trial of lamivudine to treat acute hepatitis B. Hepatology 2007;45:97-101.
12. Sun QF, Ding JG, Xu DZ, Chen YP, Hong L, Ye ZY, *et al*. Prediction of the prognosis of patients with acute-on-chronic hepatitis B liver failure using the model for end-stage liver disease scoring system and a novel logistic regression model. J Viral Hepat 2009;16:464-70.
13. Zheng MH, Shi KQ, Fan YC, Li H, Ye C, Chen QQ, *et al*. A model to determine 3-month mortality risk in patients with acute-on-chronic hepatitis B liver failure. Clin Gastroenterol Hepatol 2011;9:351-6.e3.
14. Kohler JJ, Hosseini SH, Green E, Abuin A, Ludaway T, Russ R, *et al*. Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters. Lab Invest 2011;91:852-8.
15. Rifkin BS, Perazella MA. Tenofovir-associated nephrotoxicity: Fanconi syndrome and renal failure. Am J Med 2004;117:282-4.
16. Pan CQ, Trinh H, Yao A, Bae H, Lou L, Chan S. Efficacy and safety of tenofovir disoproxil fumarate in Asian-Americans with chronic hepatitis B in community settings. PLoS One 2014;9:e89789.
17. Chan HL, Shaikh J, Gupta S, Hamed K. Renal function in nucleos (t) ide analog-treated patients with chronic hepatitis B: A systematic literature review and network meta-analysis. Adv Ther 2016;33:862-75.
18. Panda C. Telbivudine plus tenofovir in combination therapy in patients with chronic hepatitis B infection–an Indian experience. J Assoc Physicians India 2013;61:785-8.
19. Liaw YF. Hepatitis flares and hepatitis B e antigen seroconversion: Implication in anti-hepatitis B virus therapy. J Gastroenterol Hepatol 2003;18:246-52.
20. Liver EAFTSOT. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-98.

Supplementary Table 1: Comparison of treatment groups based on presence or absence of ACLF-B

	ACLF-B (*n*=25)		No ACLF-B (*n*=45)	
	Tenofovir (Group A1, *n*=13)	Tenofovir + Telbivudine (Group B1, *n*=12)	Tenofovir (Group A2, *n*=22)	Tenofovir + Telbivudine (Group B2, *n*=23)
Age (yrs) (IQR)	50 (40.5-61.5)	43.5 (40.25-64.25)	41.5 (29-65)	42.5 (30-60.25)
Male: Female	10:3	12:0	15:7	18:4
Inpatients- *n*(%)	11 (84.6%)	12 (100%)	7 (31.8%)	3 (13.6%)
Clinical events				
Jaundice	13 (100%)	12 (100%)	16 (72.7%)	19 (86.4%)
Duration of jaundice	45 (30-60)*	21.5 (11-33.75)	41 (29-65)	42.5 (30-61)
Ascites	13 (100%)	12 (100%)	-	-
Duration of ascites (days)	14 (7-28)	5 (3-13)	-	-
Loss of appetite	13 (100%)	12 (100%)	20 (90.9%)	19 (86.4%)
Fatigue	13 (100%)	12 (100%)	19 (86.4%)	16 (72.7%)
Pedal edema	12 (92.3%)	12 (100%)	-	-
HE on follow up	5 (38.5%)	5 (41.7%)	0	1 (4.5%)
Grade of HE (1/2/3-4)	1/3/1	5/0/0	-	0/1/0
AKI on follow up	6 (46.15%)	6 (50%)	-	2 (9.1%)
GI Bleed on follow up	3 (23.1%)	1 (8.3%)	-	-
Septic Shock on follow up	3 (23.1%)	1 (8.3%)	-	-
Laboratory parameters				
Plasma HB (g/L)	11 (10-12)	12.5 (10.25-14)	13 (12-14)	14 (12-15)
Total leucocyte (mm^3)	9 (8.5-11)	7.5 (5.25-15.25)	6.5 (5-9)	8 (6-9.25)
Platelet count (x 10^9)	119 (65-126)	117 (61.25-186.75)	233 (149-290)	226 (151-258)
Total bilirubin (mg/dl)	22 (11.5-28)	26.5 (8.75-35.5)	8 (2-19.25)	11.5 (4.75-19)
S. ALT (IU/ml)	193 (107-293)	299 (192-490)	840 (545-1236)	624 (319-1483)
Serum albumin (mg/dl)	2.31±0.75	2.33±0.49	3.32±0.90	3.55 0.67
Sodium (MEq/L)	129.3±11.1	131.1±10.9	132.1±11.2	133.2 14.2
Creatinine (mg/dl)	0.77±0.43	1.01±0.42	0.68±0.47	1.09 0.86
INR	2±0.57	1.83±0.57	1.02±0.23	1.09 0.29
AFP (ng/ml)	21 (9-33)	52.5 (14.75-80.75)	7 (4-13)	13 (7-36.5)
Virological parameters				
e Antigen positive- *n*(%)	6 (46.2%)	11 (91.7%)	17 (77.3%)	16 (72.7%)
e Antibody positive- *n*(%)	7 (53.8%)	4 (33.3%)	9 (40.9%)	10 (45.5%)
HBeAg +/anti-HBe -(*n*%)	0	3 (25%)	4 (17.1%)	4 (17.1%)
HBeAg +/anti-HBe + (*n*%)	6 (46.2%)	8 (66.7%)	13 (58.1%)	12 (54.5%)
HBeAg -/anti-HBe + (*n*%)	7 (53.8%)	1 (8.3%)	5 (22.8%)	6 (27.2%)
HBV DNA (IU/ml)	2.11 x 10^5	1.32 x 10^7	6 x 10^5	4.4 x 10^5
	(5.9 x10^4-2.4×10^6)	(1.1 x 10^5-1.1 x 10^8)	(9.1 x10^4-6.4 x10^6)	(5.5 x 10^4-6.1 x 10^7)
HBsAg (IU/ml)	8.6 x 10^3	1.2 x 10^4	9.1 x 10^3	4 x 104 *
	(3 x 10^3-2.1 x 10^4	(4.3 x 10^3-9.6 x 10^4)	(1.1 x 10^3-2.8× 10^4)	(1.2 x 10^4-7.1 x 10^4)
Histological parameters				
Stage of fibrosis [Stage 1/2/3/4/5/6]	0/0/0/0/0/3 (*n*=3)	0/2/0/1/1/4 (*n*=8)	3/9/1/0/1/0 (*n*=14)	5/6/0/0/0/1 (*n*=12)



Supplementary Figure 1: New onset AKI and recovery in AKI in two groups



Supplementary Figure 2: Overall survival in patients with hepatitis B reactivation in tenofovir vs tenofovir plus telbivudine groups over 12 week (kaplan meier analysis)

Supplementary Table 2: Univariate showing showing factors predicting mortality in HBV reactivation in the presence of ACLF-B

	Death (*n*=10)	Alive (*n*=15)	*P*
Age (yrs) [median (1QR)]	51 (14.75-61.25)	41 (35-63)	0.428
Male: Female	7:3	14:1	0.024
Jaundice	10 (100%)	15 (100%)	1
Ascites	9 (90%)	15 (100%)	0.211
HE	5 (50%)	5 (33.3%)	0.405
SBP	4 (40%)	2 (13.3%)	0.126
Septic shock	4 (40%)	0	0.027
AKI	6 (40%)	6 (40%)	0.484
AKI recovery	1/5 (16.7%)	6/6 (100%)	0.028
GI Bleed	2 (20%)	2 (13.3%)	0.484
HBeAg +/anti-HBe -(*n*%)	3 (30%)	11 (73.3%)	0.046
HBeAg +/anti-HBe + (*n*%)	1 (10%)	2 (13.3%)	
HBeAg -/anti-HBe + (*n*%)	6 (60%)	2 (13.3%)	
HBV DNA (IU/ml) baseline	6.01±1.49	6.21±1.62	0.757
HBV DNA (IU/ml) at 2 wk	4±0.82	4.27±1.22	0.608
HBV DNA (IU/ml) at 4 wk	3.75±1.25	3.46±0.97	0.632
HBsAg (IU/ml) baseline	4±0.82	3.93±0.46	0.796
CTP score	11.60±0.96	11.33±0.98	0.508
MELD score	30±7.48	24.67±5.65	0.045
Treatment group	8 (80%)	5 (33.3%)	0.022
Plasma HB (g/L)	11.5 (10-12)	11 (10-14)	1.0
Total leucocyte count (/mm^3)	9.5 (8-13.75)	7 (5-10)	0.422
Platelet count (x 10^9)	120.5 (81.5-297.5)	103 (41-150)	0.428
Total bilirubin (mg/dl)	28 (17-29)	17 (8-30)	0.11
S. AST (IU/ml)	277 (154-539)	331 (165-757)	0.688
S. ALT (IU/ml)	196 (167-461.25)	269 (145-485)	0.688
Serum albumin (mg/dl)	2.39±0.67	2.33±0.62	0.524
Blood Urea (mg/dl)	32.5±15.3	34.5±21.5	0.799
Creatinine (mg/dl)	0.70±284	1.01±0.372	0.465
INR	2.23±0.42	1.73±0.59	0.043
AFP (ng/ml)	30 (14.75-52.5)	35 (18-60)	0.654