Antiviral Research 100 (2013) 300–305

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Predictors of survival in hepatitis B virus related decompensated cirrhosis on tenofovir therapy: An Indian perspective

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ARTICLE INFO

Article history:
Received 27 April 2013
Revised 21 August 2013
Accepted 27 August 2013
Available online 5 September 2013

Keywords:
Decompensated cirrhosis
Prognostic predictor
Survival
Antivirals
MELD
Tenofovir
Mortality
HE

ABSTRACT

Decompensated cirrhosis has low survival rate compared to compensated state. Effective viral suppression due to antiviral therapy (tenofovir) has been shown to slow disease progression and may delay the burden of liver transplantation. We aimed to evaluate the usefulness of various prognostic indicators in predicting the 24-months survival in HBV related decompensated cirrhosis after tenofovir therapy and to evaluate the post-treatment outcome. Ninety-six HBV related decompensated patients on antiviral (tenofovir) therapy were prospectively studied for 24 months survival and mortality. Cutoff levels for several prognostic indicators were generated by ROC. Prediction of overall probability of mortality was also calculated. The overall probability of survival observed at 12 months was 0.947 whereas at 24 months it was found to be 0.833. According to Cox proportional hazards model, the univariate analysis revealed cutoff of >7.4 log copies/ml for HBV DNA, >1.2 mg/dl for serum creatinine, >3.7 mg/dl for total bilirubin, ⩽0.75 for platelets count, >10 for CTP and >20 for MELD as predictors of poor survival. Multivariate analysis showed MELD score of >20 was the most robust predictor of mortality, with 58 times higher risk (HR: 58.73, $p < 0.001$). Post-treatment response with tenofovir for 24 months significantly improved the hepatic functions and reverses decompensation and showed incredible efficacy in improvement of hepatic functional status with reduced viremia in a great majority of decompensated cirrhosis subjects having high MELD and HBV DNA level.

1. Introduction

Hepatitis B virus (HBV) infection is one of the major global concerns because of chronic infection in about two billion and 600,000 deaths due to complications of cirrhosis and hepatocellular carcinoma (HCC) as per WHO FACT SHEET World-Health-Organization (2008). Approximately 15–40% of chronic hepatitis B (CHB) cases are expected to develop cirrhosis, (Beasley, 1998; Bosch et al., 2005) of these 15–20% are likely to decompensate in 5 years (Fattovich et al., 1991). Decompensation and development of HCC is associated with high viral replication (Locarnini, 2005; Lok et al., 2003). Decompensated cirrhosis has 14–35% 5-year survival rate compared to 84% in compensated state. Effective viral suppression in CHB patients has been shown to slow disease progression and improve patient outcomes (Liaw et al., 1989; Lin et al., 1999; Xu et al., 2003). HBeAg loss/seroconversion along with reduction in HBV viral load has been associated with reversal of decompensation and 55% reduction in death rate (de Jongh et al., 1992). Therefore the ultimate goal in HBV related decompensated cirrhosis is viral suppression followed by liver transplantation, wherever required. However limited availability of organ and the exorbitant organ replacement cost remains the main limitations. Suppression of HBV replication has resulted in reduction of hepatic necroinflammation and improvement of liver function in patients with CHB cirrhosis and liver decompensation. If patients likely to have favorable response with antivirals can be identified, based on some prognostic indicators then the limited resource may be utilized more judiciously for definitive treatment i.e. organ transplantation (OLT). Child–Pugh (CTP) classification was considered the keystone prognostic score (Oellerich et al., 1991), but later its limitations in predicting the mortality were recognized (Forman and Lucey, 2001) and Model for End-Stage Liver Disease (MELD) was introduced as reliable tool to predict mortality risk, to evaluate disease severity and was found useful in listing high risk patients for organ allocation (Malinchoc et al., 2000; Yousfi et al., 2001; Chan et al., 2006). However their validity remains to be established in predicting response to antivirals in HBV related decompensated cirrhosis. tenofovir (TDF) has efficacious response in decompensated cases acting as a high genetic barrier as compared to other old generation antiviral therapy which are highly prone to resistance or newer molecules and well tolerated in multiple treatment failure cases with improvement in viologic, biochemical and clinical parameters (Liaw et al., 2011; Kim et al., 2012). So this

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http://dx.doi.org/10.1016/j.antiviral.2013.08.020

prospective study aims to evaluate the usefulness of various prognostic markers in predicting favorable outcome after post-antiviral therapy (TDF) in HBV related decompensated cirrhosis.

2. Patients and methods

2.1. Study population

Hepatitis B-related decompensated cirrhosis (appearance of ascites) patients attending University hospital's gastroenterology services during July 2009 to Aug 2011 were selected. Ninety-six (96) patients with viral load >2000 copies/ml, without access to liver transplantation were included in the study after an informed consent. Untreated control was not considered for this study due to ethical consideration. The follow-up data (3–6 months) were obtained for a period of 24 months through monitoring of patients at our outpatients clinics and inpatients ward. The study was approved by the ethical review committee of the institute and the guidelines were thoroughly followed. The patients received initial therapy of TDF during study period and beyond and were never pre-treated with any other antivirals. This treatment was to be modified only in event of virologic breakthrough (VBTH) which is defined as increase in serum HBV DNA by >1 log10 (10-fold) above nadir after achieving virologic response, during continued treatment (Lok and McMahon, 2009) or intolerance to the drug. Patients with hepatorenal syndrome, spontaneous bacterial peritonitis, co-infection with other hepatotrophic viruses, alcohol consumption to any degree and diabetes diagnosed at baseline were excluded from the study.

2.2. Biochemical and serological markers

Blood samples at inclusion as well as during follow-up were tested by standard laboratory test for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (BIL), total protein, serum albumin (ALB), creatinine (CRET), prothrombin time (PT)/international normalized ratio (INR), median total leukocytes count and differential, hemoglobin and platelets count. Serologic tests like HBsAg, hepatitis B e antigen (HBeAg) and antibodies to hepatitis B e antigen, hepatitis C virus, hepatitis delta virus, hepatitis A virus (IgM) and hepatitis E virus (IgM) were tested using commercially available enzyme linked immunosorbent assays (ELISA) kits (Biorad Laboratories, France) and HIV (SD Elisa kits, Korea).

2.3. HBV DNA Quantification

HBV DNA was extracted from 200 μl serum using High-pure Viral Nucleic Acid Kit (Roche Diagnostics, Mannheim, Germany). Serum HBV DNA was quantitated using Real-time PCR with the help of HBV DNA quantitative kit (Genome Diagnostics, India) as per manufacturer's instructions. The highest and lowest detection limit of this assay was 10^8 and 67 copies/ml respectively.

2.4. End stage liver markers

MELD score was calculated using the UNOS formula i.e.: $9.6 \times \log_e$ (creatinine mg/dl) + $3.8 \times \log_e$ (bilirubin mg/dl) + $11.2 \times \log_e$ (INR) + 6.4 (etiology: biliary or alcoholic 0; others 1). CTP score was calculated (Pugh et al., 1973) for decompensated patients. Endoscopic examination was done for grading oesophageal/gastric varices. Mortality and its causes were recorded.

2.5. Statistical analysis

The baseline demographic and clinical characteristic data were presented as percentage or mean ± SD or median (range). Chi-square and Student's *t*-test was used to compare the mean values of the individual prognostic factor. Categorical data was analyzed using cross-tables. To assess independent associations of the different scores with mortality, univariate analysis of the scores was done for age, sex, HBeAg status, ALT, albumin, platelets, bilirubin, HBV DNA load, CTP and MELD scores. The cut-off level taken for analysis was calculated using ROC (Receiver operating characteristics). Scores with *p*-value less than 0.05 were then included in the second multivariate analysis model. To predict survival prognostic factors proportional hazard Cox-regression analysis was performed. Correlation of the two scores has also been evaluated. A *p*-value of 0.05 and confidence interval of 95% were considered statistically significant. Estimation of hazard rate (λ) was calculated using the formula, $\lambda = d/f + F$ where d: no. of deaths, $f = \Sigma$ti (total time period of death), $F = \Sigma$Ti (sum of censored + alive cases) to predict the overall probability of death at different time interval. Survival analysis was estimated by Kaplan–Meier method using the formula for Pt which stands for the probability of survival at time *t*.

3. Results

3.1. Patient characteristics

Most of the ninety-six patients with decompensated cirrhosis enrolled in this study were males ($n = 81$) and remaining were females ($n = 15$). The mean age of patients included was 41.9 ± 14.4 years. A total of 34.4% patients were HBeAg negative while 65.6% patients were HBeAg positive. The clinical, serological and virological features of the patients at baseline have been shown in Table 1. 67.7% subjects were observed to have MELD score >15 and 26% with >20 respectively.

3.2. Demography and survival

Sixteen of the cases were lost to follow-up (one in first year and fifteen in second year). Sixteen patients died during the study of 24 months (5 in first year and 11 in second year of follow up). The cause of death recorded was hepatic encephalopathy (HE) with hepatic failure in 7 (43.7%), variceal bleed in 4 (25%), development of HCC in 3 (18.7%) and HRS in 2 (12.5%).

3.3. Baseline predictors of survival

The baseline characteristics (age, sex, HBeAg serostatus, total bilirubin, albumin, creatinine, platelets, INR-International Normalized Ratio, CTP score, MELD and HBV DNA) of survivors and those succumbed to the disease, during study period of 24 months, were compared. Significantly higher values of total bilirubin (6.95 ± 5.9 *vs.* 3.3 ± 3.6, $p = 0.002$), serum creatinine (1.62 ± 0.60 *vs.* 1.12 ± 0.37, $p = 0.005$), HBV DNA (7.67 ± 1.2 *vs.* 6.78 ± 1.73, $p = 0.05$), INR (1.9 ± 0.44 *vs.* 1.68 ± 0.43, $p = 0.021$) and lower platelet counts (0.66 ± 0.32 *vs.* 0.91 ± 0.44, $p = 0.031$) were noted in cirrhotic cases who succumbed to the disease than in survivals. Moreover, mean CTP score (10.5 ± 1.70 *vs.* 9.39 ± 1.97, $p = 0.04$) and MELD score (23.72 ± 4.37 *vs.* 15.41 ± 4.86, $p < 0.001$) were also higher in fatal cases than surviving ones. Mortality in HBeAg positive and negative patients was statistically similar (14.8% *vs.* 21.2%, $p = 0.401$) (Table 1). In addition, 30% of 17 subjects with HE had fatal outcome all within a year and none of the cases without HE

Table 1
Comparison of baseline parameter of dead and surviving patients.

Parameters	All patients (n = 96)	Dead (n = 16)	Survived (n = 64)*	p-Value
Age (years)	41.9 ± 14.4	39.3 ± 11.1	42.46 ± 15.0	=0.428
ALT (IU/L)	103.3 ± 128.9	128.8 ± 175.6	98.22 ± 118.2	=0.388
Total bilirubin (mg/dl)	3.92 ± 4.2	6.95 ± 5.9	3.3 ± 3.6	=0.002
Albumin (g/dl)	2.94 ± 0.75	3.0 ± 0.95	2.92 ± 0.71	=0.515
Creatinine (mg/dl)	1.2 ± 0.45	1.62 ± 0.60	1.12 ± 0.37	=0.005
Hemoglobin (g/dl)	10.14 ± 2.4	9.38 ± 2.9	10.28 ± 2.38	=0.181
Platelets/mm	0.87 ± 0.43	0.66 ± 0.32	0.91 ± 0.44	=0.031
HBV-DNA (copies/ml)	6.93 ± 1.69	7.67 ± 1.2	6.78 ± 1.73	=0.05
INR	1.73 ± 0.45	1.9 ± 0.44	1.68 ± 0.43	=0.021
Child–Pugh score	9.57 ± 1.98	10.5 ± 170	9.39 ± 1.97	=0.04
MELD score	16.79 ± 5.6	23.72 ± 4.37	15.41 ± 4.86	<0.001
HBeAg positive	63 (65.6)	9 (56.3)	43 (67.1)	=0.401
HBeAg negative	33 (34.4)	7 (43.7)	21 (32.8)	

HBeAg: Hepatitis B e Antigen; MELD: model for end stage liver disease. Percentage value in parenthesis.
* Total of 64 patients survives after patients lost to follow-up (16) and succumbed to disease (16).

Table 2
Univariate and multivariate analysis for predictive factors of mortality using cut-off values generated via ROC using Cox proportional hazard model.

Parameters		Univariate analysis			Multivariate analysis		
		HR	CI (95%)	p-Value	HR	CI (95%)	p-Value
Age (years)	⩽41	1					
	>41	1.612	0.600–4.329	=0.341	–	–	–
ALT (IU/L)	⩽68.5	1					
	>68.5	1.457	0.542–3.91	=0.455	–	–	–
HBV DNA (copies/ml)	⩽7.4	1					
	>7.4	2.942	1.022–8.468	=0.045	1.041	0.273–3.97	NS
Albumin (g/dl)	>3.2	1					
	⩽3.2	2.384	0.887–6.408	=0.085	–	–	–
Creatinine (mg/dl)	⩽1.2	1					
	>1.2	3.325	1.154–9.578	=0.026	1.951	0.603–6.31	NS
Platelets (lacs/mm)	>0.75	1					
	⩽0.75	3.434	1.107–10.65	=0.033	2.151	0.653–7.78	NS
Total bilirubin (mg/d)	⩽3.7	1					
	>3.7	6.201	1.998–19.24	=0.002	1.694	0.567–5.06	NS
INR	⩽1.72	1					
	>1.72	2.532	0.920–6.966	=0.072	–	–	–
CTP score	⩽10	1					
	>10	3.155	1.146–8.684	=0.026	1.430	0.493–4.14	NS
MELD score	⩽20	1					
	>20	58.739	7.718–447.06	<0.001	36.056	3.76–345.17	0.002

NS: Non-significant; HR: Hazard ratio; CI: Confidence interval.

succumbed to the disease in that period. Among total fatal cases, 43.7% had HE at baseline ($p < 0.001$).

For obtaining the cut-off values of different variable for predicting the survival, ROC curve was plotted. According to Cox proportional hazards model, the univariate analysis revealed that HBV DNA level of >7.4 log copies/ml ($p = 0.045$), serum creatinine of >1.2 mg/dl ($p = 0.026$), total bilirubin of >3.7 mg/dl ($p = 0.002$), platelets/mm of ⩽0.75 ($p = 0.033$), CTP of >10 ($p = 0.026$) and MELD of >20 ($p < 0.001$) were significantly associated with fatal outcome but characteristics including age >41 years ($p = 0.344$), ALT >68.5 IU/ml ($p = 0.455$), serum albumin ⩽3.2 g/dl ($p = 0.085$) and INR >1.72 ($p = 0.072$) does not appear to be the significant predictors for mortality in decompensated cases (Table 2). MELD score of >20 carried an increased risk of 58 times (HR: 58.73, $p < 0.001$).

Multivariate cox regression analysis with baseline confounders showed that among all predictors, baseline MELD was the only independent factor for early mortality with 36 times elevated risk in those patients having MELD score >20 ($p = 0.002$) which was determined to be most sensitive and specific as evaluated by ROC curve analysis (Table 2). Moreover significant correlation was found between the CTP and MELD scores with correlation coefficient of 0.63 ($p < 0.001$).

3.4. Survival analysis

The Kaplan–Meier estimation of survival curve gave the following summary of data i.e. the overall probability of survival observed at 12 month was 0.947 whereas at 24 months it was found to be 0.833. Number of deaths at 0–6 months was 3, at 6–12 months was 2, at 12–18 months was 6 and 18–24 months was 5. The overall survival curve was plotted accordingly (Fig. 1). Survival curve plotted only for 12 and 24 months does not signify any outcome.

3.5. Mortality

The annual hazard rate (λ) of death was 0.0957 i.e. 9.6% patients with decompensated cirrhosis at baseline were likely to succumb to death within a year. Comparing the mortality in patients with MELD score >15 *vs.* ⩽15 was found to be 21.6 *vs.* 0% ($Chi^2 = 9.15$,

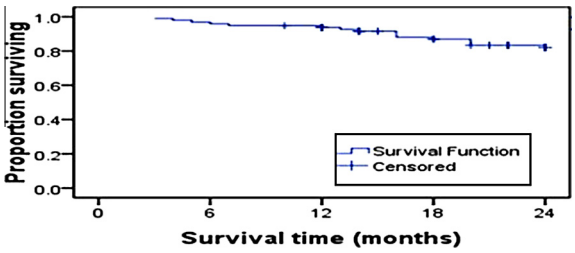

Fig. 1. Overall survival probability of decompensated cirrhosis patients using Kaplan–Meier analysis. Overall probability of survival observed at 12 months was 0.947 whereas at 24 months it was found to be 0.833.

$p = 0.001$) and consequently mortality was elevated in patients having MELD score >20 *vs.* <20 was 60 *vs.* 1.4% ($Chi^2 = 45.70$. $p < 0.001$).

3.6. Post-treatment response with tenofovir

Among survivors, therapeutic outcome with TDF was efficacious, respective mean values at 12 and 24 months for HBV DNA were 4.3 ± 1.3 and 2.4 ± 1.2 logs, serum creatinine 1.2 ± 0.3 and 1.0 ± 0.2 mg/dl, CTP score 8.4 ± 1.8 and 6.5 ± 1.5 and MELD score 14.2 ± 4.5 and 11.2 ± 2.9. Among fatal cases, baseline level of HBV DNA was >7.4 logs (100%), MELD score >20 (94%) and CTP >10 (81%) serum bilirubin >3.7 mg/dl (100%). Among HBeAg positive patients, 45 (70.3%) achieved DNA negativity and 21 (32.8%) were seroconverted at 24 months. Among the seroconverted patients, 9 (42.8%) achieved HBV DNA negative. HBV DNA >7.4 and MELD score >20 (derived by ROC) had poor response at 24 months than those who were below these cutoff levels (Fig. 2). Patients having MELD score >20 were revealed to have constant increment in CTP score at 24 months (i.e. 10.7 *vs.* 12) but the level of DNA, serum bilirubin and creatinine had no significant elevation. Subjects with MELD ⩽20 had constant significant decline in all the parameters defined in the study which proves that TDF had no nephrotoxic activity and show better response even with MELD >20 during therapy. Similarly in patients acquiring HBV DNA >7.4, MELD score raised at 12 months (18.8 *vs.* 24.8, $p < 0.05$) but could not be recorded at 24 months as all the patients succumbed to disease. There was no significant increase in other parameters observed at 12 months (Fig 2).

Subjects with baseline CTP >10, compared to CTP ⩽10 after 24 months of antiviral therapy had significantly higher MELD score ($p < 0.026$), HBV DNA ($p < 0.001$), total bilirubin ($p = 0.032$) and CTP ($p = 0.001$). In 48.6% cases reversal of decompensation was observed at the end of 24 months (i.e. without ascites or any other feature of liver failure). The post-therapeutic outcome revealed that TDF acted as high genetic barrier to resistance during the treatment and disapproves the appearance of nephrotoxicity or any other deterioration in clinical symptoms.

4. Discussion

Decompensated liver cirrhosis is almost an end stage of liver disease and only organ transplantation (OLT) remains the definitive treatment option. Poor survival in HBV-related decompensated cirrhosis has been reported earlier (de Jongh et al., 1992). However, with the limited resources available, identifying the patients who benefit most from transplantation is important. However, MELD score is a dynamic criterion, especially in HBV related cirrhosis where antiviral therapy may improve MELD score to a level where OLT may not be essential. OLT is recommended for patients having CTP class C and MELD score >15. In this study we focused to identify the predictors which are likely to be associated with clinical improvement and survival in decompensated CHB when treated with antivirals alone. Such studies on identifying predictors of response to antiviral therapy are scarce.

TDF was considered for therapy because of rare instances of mutation and clinical deterioration, even on prolonged administration. Decompensated patients cannot afford development of resistance resulting in aggravation of liver dysfunction. Entecavir (ETV) is another effective drug with very low mutation rate but some instances of lactic acidosis has been reported with its use in decompensated state (Shim et al., 2010). However, TDF is safe in decompensated state.

According to univariate Cox's model, predictors of survival up to 24 months, without OLT, were HBV DNA with ⩽7.4 log copies/ml, serum creatinine of ⩽1.2 mg/dl, total bilirubin of ⩽3.7 mg/dl, platelets/mm of ⩾0.75, CTP of ⩽10 ($p = 0.026$) and MELD of ⩽20 ($p < 0.001$). In conformity to our findings, baseline bilirubin, prothrombin time, CTP, MELD and grade III encephalopathy were predictors of early mortality on univariate analysis, however, on multivariate analysis only HE grade III was found as an independent predictor of mortality (Tseng et al., 2005). Though the cases

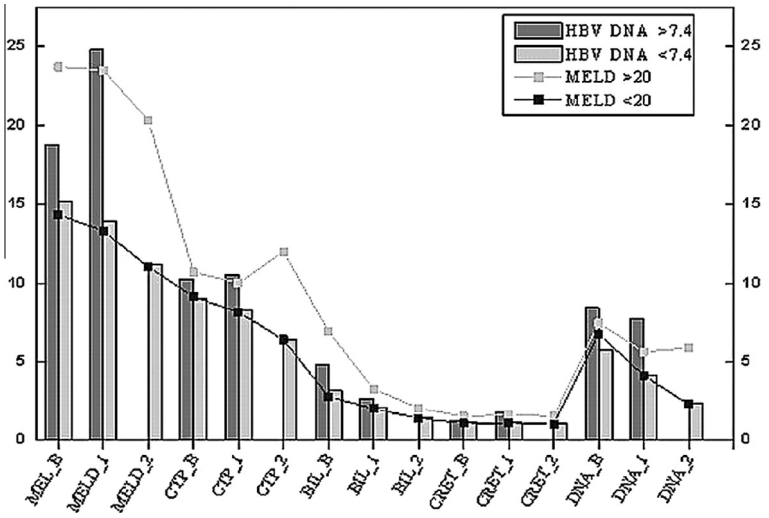

Fig. 2. Post-tenofovir (TDF) therapy outcome based on prognostic indicators (MELD >20 and <20 & DNA >7.4 and <7.4) based on cutoff determined by ROC. MELD: Model for End-Stage Liver Disease; CTP: Child–Pugh score; BIL: Bilirubin; CRET: Creatinine; _B: values at baseline; _1: values at 12 months; _2: values at 24 months.

were not stratified according to grades of encephalopathy, mortality was noted only in those subjects who presented with HE ($p < 0.05$) at 12 months. In addition HE appeared to be additional predictor of mortality as almost one-third subjects succumbed and all in first year ($p = 0.001$). Although CTP score had significant correlation with MELD score ($r = 0.63$, $p < 0.001$), still on multivariate analysis only MELD was an independent predictor of mortality. In another study (Attia et al., 2008), both MELD and CTP were the predictors of mortality on multivariate analysis with significant correlation between these score ($r = 0.57$, $p < 0.001$). A systemic study (Yao et al., 2001; D'Amico et al., 2006) showed that CTP score >10 or its components are robust predictors of mortality in cirrhosis leading to OLT which could not be validated in our observation when results were analyzed via multivariate Cox's model. Unlike our study where serum albumin did not have any potential role in predicting the survival, it was revealed that hypoalbuminemia <2.8 g/dl was significant prognostic indicator of poor survival probability (Hui et al., 2002).

Transplant free survival in HBV related decompensated cirrhosis was 87% at 12 months on ETV therapy (Shim et al., 2010) and 84% on adefovir (ADV) therapy (Schiff et al., 2007) which was almost similar to our results of 95% survival after a year of TDF therapy. Despite Child class C status in 56% and MELD score >15 in 67.7% we observed 83% survival at 24 months; these results were again consistent with other findings (Shim et al., 2010). In a retrospective study, two years survival in decompensated cirrhotics did not depend on antiviral therapy: however most of their patients were in Childs A and B (Hui et al., 2002). Moreover such a high survival without antivirals couldn't be substantiated by other workers (Attia et al., 2008) where survival at one and second year was 49% and 39% respectively while 14% at 5 years (de Jongh et al., 1992).

In addition, on antiviral therapy these predictive parameters (total bilirubin, serum creatinine, HBV DNA, MELD and CTP scores) improved progressively at 12 and 24 months revealing the dynamic status of these predictive parameters. LAM therapy revealed noted improvement in CTP scores in 50% of subjects (Kapoor et al., 2000). Even Yao et al. (2001) and Hann et al. (2003) revealed LAM to be highly effective in reversal of hepatic decompensation and significant improvement. Similarly several investigators (Yao and Bass, 2000; Liaw et al., 2011) have established improvement in one or more of these prognostic factors (serum bilirubin, serum albumin, prothrombin time, MELD and CTP scores) in decompensated cirrhosis when treated with antivirals (LAM, ETV, TDF, Emtricitabin). Das et al. (2010) revealed that decompensation with ascites predicts reduced survival while antiviral therapy beyond 6 months improved the outcome. Similarly Chan et al. (2006) noticed on multivariate analyses that MELD and CTP scores acts as independent predictors of 3 months and 1-year mortality along with LAM acting as effective drug.

Post-treatment response was comparatively poor for cases with cutoff of CTP > 10, MELD > 20, HBV DNA > 7.4 and total bilirubin > 3.7 ($p < 0.05$) (Fig. 2). In the present study, MELD score >20 was revealed as the most potent predictor of mortality among all factors considered and should be considered for OLT. Patients with HBV DNA > 7.4, CTP > 10, encephalopathy at baseline are other risk factors. The clinical efficacy of antiviral (TDF) therapy was proven and showed rescue activity in achieving more than 90% survival at one year and >80% survival at 2 years in decompensated Child C cirrhosis. TDF therapy appears a useful option for candidates on waiting list for OLT particularly with MELD score >15. The present study indeed suggested the efficacy of TDF in improving hepatic decompensation, its safety, tolerability and paucity of viral breakthrough and high genetic barrier to resistance even on prolonged therapy. Still multicentre study on larger patients' size is required to confirm the usefulness of predictors of survival when treated with newer generation antivirals with high barrier to resistance to combat the chronicity of disease and prevent or delay the OLT.

Funding

This work was supported by the DST-PURSE grant Dev. scheme number "4157".

Acknowledgement

The authors thank all the patients for their participation in this study.

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