Research Square

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The Short-Term Efficacy of Tenofovir Alafenamide (TAF) in Acute-On-Chronic Liver Failure: A Single Center Experience

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Research Article

Keywords: Acute-on-chronic liver failure, Tenofovir alafenamide, hepatitis B virus, antiviral efficacy

Posted Date: October 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-900437/v1

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Abstract

Background and aims: Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) reduce hepatic events and death in patients with acute-on-chronic liver failure (ACLF), but the efficacy of Tenofovir alafenamide (TAF) is less well studied. We aimed to assess the effectiveness of TAF in hepatitis B virus (HBV) related ACLF.

Methods: We analyzed 106 patients with HBV-ACLF received TAF (25mg/d), ETV(0.5mg/d) for 12 weeks. The primary endpoints were overall mortality and liver transplantation (LT) at week 12. Other determined factors of biochemical response, virologic response, mortality rate, and drug safety and side-effect were also evaluated.

Results: At 4 weeks and 12 weeks, patients received TAF got significantly higher HBV-DNA reduction (P<0.001), higher rate of HBV-DNA undetectbility (P<0.001), lower HBV-DNA level (P<0.001). Lower CTP scores (P=0.003) at 4 weeks in TAF group, but CTP scores showed no difference in two groups at 12 weeks (P=1.143). Lower ALT levels in TAF group at week 4 and week 12 (P=0.023, P<0.0001). The mortality rate was lower in TAF group after 4 weeks treatment(P=0.038), but two group got similar mortality rate at week 8 and week 12. As for reason cause death in HBV-ACLF patients, we found that two group patients developed similar rates of liver-related complications (P>0.05).

Conclusions: The antiviral efficacy of TAF was superior than ETV for the treatment of HBV-related ACLF. TAF therapy reduced 4-week mortality rate in patients with HBV-related ACLF.

Introduction

Hepatitis B virus infection is one of the most popular cause of chronic liver disease worldwide[1, 2]. Chronic HBV infection could cause different clinical manifestations, including HBV carriers, chronic hepatitis B (CHB), sudden reactivation of CHB, cirrhosis, hepatocarcinoma, and so on[3-5].Acute on chronic liver failure (ACLF) is a syndrome characterized by acute hepatic decompensation, organ system failures[6, 7].In patients with CHB, active viral replication could trigger inflammatory responses and pathological changes in liver, and the reactivation of HBV replication could lead to ACLF. Patients with ACLF have poor prognosis and characterized by high short-term mortality[8, 9]. Liver transplantation is an alternative way for patients with ACLF, butthe higher medical costs are not affordable for every patient. Nucelos(t)ide analogues (NAs) could suppress viral DNA replication, which reduces hepatocyte cell death, and subsequently aiding in the prevention of decompensation-related liver failure. As a result, NAs are recommended as one critical therapy method from the onset of ACLF by many guidelines.

Nowadays, entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are the first-line oral agents recommended by most practice guidelines because of their superior effective and high barriers to viral resistance. Lamivudine (LAM) and entecavir (ETV) were reported as the oral agents in the treatment of ACLF. LAM was the first registered NAs used in CHB patients, and it was also widely used in patients with ACLF several years ago[10–12]. Entecavir (ETV) is a novel NA with potent antiviral activity compared with

LAM. Xiaoshu Li's group found that LAM could reduce short-term mortality in patients with ACLF[13]. Kuang-Wei Huang[14] reported that they analyzed 8 retrospective cohort studies, they found that ETV could yield a more favorable long-term outcome in patients with ACLF than LAM did, and ETV could alleviate the clinical manifestations of ACLF patients. TAF is a kind of NAs recently recommended, it is similar to TDF but has higher cell delivery to the hepatic cells and less systemic exposure. So far, data about the effects of TAF versus other NAs on the clinical outcome of HBV-related ACLF is still ambiguous. There is no study that evaluated the outcomes of TAF in patients with HBV-ACLF with 12 weeks. Therefore, we conducted this retrospective study to invest the outcome of antiviral effect of TAF in HBV-ACLF patients.

Table 1
Baseline characters of enrolled patients

	TAF(n=40)	ETV (n=66)	*P* value
Age (year)	52.35±6.58	53.70±6.28	0.902
Male (n%)	36(90.0)	59(89.39)	0.261
e-antigen positive, %	14(35.0)	32(48.48)	0.833
HBV-DNA $\log_{10}$ IU/mL	5.64± 0.68	5.38± 0.838	0.864
ALT(U/L)	424.79(223-1110)	451.85(221-1106)	0.437
AST(U/L)	410.98 (219-881)	424.9(227-773)	0.106
TBIL(μmol/L)	378.79(223.1-678.9)	380.69(234.1-678.5)	0.935
DBIL(μmol/L)	255.28(112.7-347.3)	240.15(101.3-342.3)	0.300
ALB(g/L)	30.31±2.72	30.65± 2.53	0.509
Platelets ($\times 10^9$ /L)	110.98±27.48	116.62±23.86	0.268
PTA%	29.28±5.54	28.48±6.18	0.509
Ascites (%)	17(42.5)	28(42.42)	0.922
Child-Pugh class C (%)	8(20)	9 (13.64)	0.387

Participants And Methods

Participants

Table 2
Cause of death of the population

Cause of death	TAF group(n=6) n %	ETV group(n=22) n %	*P*-value
ACLF with HRS	2 33.33	6 27.27	0.771
ACLF with SBP	1 16.67	6 27.27	0.595
ACLF with variceal bleeding	1 16.67	6 27.27	0.595
ACLF with septicemia	2 33.33	4 18.18	0.423

Abbreviations: TAF tenofovir alafenamide, *ETV* entecavir, *ACLF* cute-on-chronic liver failure, *HRS* hepatorenal syndrome, *SBP* spontaneous bacterial peritonitis

We evaluated individuals with chronic HBV infection who were admitted to the Department of Infectious Diseases of the First Affiliated Hospital of Zhengzhou University from January 1, 2017 to June 31, 2020. A total of 116 HBV-infected individuals with ACLF were enrolled in this study. The inclusion criteria were as follows: 1) positive HBsAg results for at least 6 months; 2)18 to 60 years of age; 3) negative serum results for anti-HAV IgM, anti-HCV, anti-HEV IgM/IgG, anti-EBV IgM, and anti-CMV IgM. The exclusion criteria were as follow: 1) patients were positive results for anti-HDV and anti-HIV; 2) positive results for antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and anti-mitochondrial antibodies (AMA); 3) patients with hepatocellular carcinoma; 4) patients with alcohol live disease; 5) patients with missing data;6) patients whose age were more than 75 years. Patient consents were not applicable to this study for this study was a retrospective investigation.

Each patient's ALT and HBV DNA levels were monitored monthly for at least 6 months. For ACLF defined as a rise of alanine aminotransferase (ALT) level >5 times upper limit of normal and an HBV DNA level >1.8×10 4 IU/mL; fulfilling the criteria about ACLF by the Asian Pacific Association for the study of the liver (APASL), that is serum total bilirubin ≥5mg/dL, the prothrombin activity <40% at the same time.

Virologic And Liver Functional Tests

The laboratory data from all patients were reviewed retrospectively and included the following parameters: 1) HBV markers: HBsAg and HBV eantigen antibodies (HBeAb) detected by commercially available enzyme immunoassays (Alisei Quality System;RADIM, Rome, Italy); 2) international standardized ratio for prothrombin time determined according to the manufacturer's instructions (CA-7000 System; Sysmex, Kobe, Japan); 3) biochemical tests reflecting hepatocytic damage including serum alanine transaminase (ALT), aspartate transaminase (AST), albumin (ALB), and total bilirubin, all tested by colorimetric method (MODULAR EVO; Hoffmann-La Roche Ltd, Basel, Switzerland); and 4) serum HBV DNA measured by a real-time polymerase chain reaction assay using a COBAS TaqMan® 48 analyzer (Roche Diagnostics, Mannheim, Germany) with a detection limit of 20 IU/mL.

Clinical outcome assessment

The primary endpoint was overall mortality or liver transplantation (LT) by 12 weeks. The secondary endpoints were normalization in ALT levels and bilirubin levels, virologic response, emergence of viral mutation, and HBeAg seroconversion in the patients with HBeAg positivity at baseline.

Management and Follow-up

Patients received nucleoside analog treatment (TAF or ETV) according to the HBV DNA load after clinical evaluation. Patients were given nucleoside analog treatment for at least 3 months till death or receive liver transplantation. The clinical and laboratory data, adverse events, and compliance of all patients were monitored during the follow-up period, the liver function parameters, positivity for hepatitis B e antigen (HBeAg), and serum HBV DNA levels were the regular check in every follow-up visit. The enrollment and treatment distribution data of the study population are summarized in Figure 1.

Statistical analyses

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the clinical data for the patients included in this study. For comparisons of numeric variables with normal distributions from independent groups, the t-test was used. The Chi-square test was used for the comparison of categorical variables. All the tests were two tailed, and the threshold for significance was P <0.05.

Results

Study characteristics

A total of 253 patients with ACLF were screened from January 1, 2017 to June 31, 2020. A total of 106 patients were enrolled in this study. The characteristics of patients enrolled in this study with ACLF were presented in Table 1. The patients were divided into 2 groups, TAF group, ETV group. Ultimately, the number of patients enrolled in TAF and ETV group was 40, and 66, respectively (Fig. 1). There was no significant difference between the groups in the baseline characteristics of gender, age, chemical factors, HBV DNA load, etc. (Table 1).

Virological Response

The TAF group and ETV group got rapid HBV-DNA reduction during the treatment. We observed the HBV DNA load at antiviral baseline, 4 weeks and 12 weeks. And the rate of HBeAg loss at 12 weeks' time-point was observed at the same time. At 4 weeks, compared to baseline, the HBV DNA load from (5.64+0.68) $\log_{10}$ IU/mL decreased to (3.55+0.75) $\log_{10}$ IU/mL in TAF group; the HBV DNA load from (5.38+0.838) $\log_{10}$ IU/mL decreased to (4.34+0.62) $\log_{10}$ IU/mL in ETV group(P<0.001). At 12 weeks, the HBV DNA load decreased to (2.01+1.04) $\log_{10}$ IU/mL in TAF group; the HBV DNA load decreased to (3.53+0.64)

log_{10} IU/mL in ETV group(P<0.001). We compared the HBV DNA load in these two groups and found TAF got quick HBV DNA reduction at 4 weeks and 12 weeks. There were 72.5% patients got >2 log_{10} IU/mL decrease in HBV DNA load in TAF group and 60.6% in ETV group after 4 weeks treatment(P<0.001), and 25% patients got negative HBV DNA load in TAF group and 13.64% in ETV group after 12 weeks antiviral therapy (P<0.001).

Biochemical, And Serologic Responses

We observed the CTP score and ALT levels in TAF group and ETV group. We found that CTP score in these two groups had no difference(P=0.79) at baseline, the CTP scores of patients received TAF therapy were lower than the scores of patients in ETV group(P=0.003) at 4 weeks. And CTP scores declined trend also showed significant difference between these two groups (P=0.004) at week 12(Fig. 2). Compared with baseline CTP score, not only in TAF group but also in ETV group showed significant difference (P<0.0001, P<0.0001). The ALT levels in TAF group and ETV group had no difference(P=0.437) at baseline, ALT levels in TAF group were lower than the ALT levels in ETV group at 4 weeks(P=0.023), similarly, the ALT levels in TAF group were lower than ALT levels after 12 weeks (P<0.0001).

Short-term Mortality Rate In Aclf Groups

To assess the effect on ETV and TAF group in improvement of short-term mortality in ACLF patients, we calculated the death rate in these two groups. None of the subject died within the first 2 weeks. In the first 4 weeks, total of 5 patients died and 6 patients were transferred to the liver transplant department. 1(2.50%) patient in TAF group and 10 (15.15%) patients in ETV group (χ = 4.286, P=0.038). At the end of 12 weeks, there were 6(15%) patients in TAF group and 22(33.33%) patients in ETV group died or received liver transplantation surgery totally (χ = 4.307, P=0.038). The cumulative survival analysis showed no difference between TAF group and ETV group (χ = 0.64, P=0.42) (Fig. 3). We also investigated the reason cause death in TAF and ETV group, such as ALCF related hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), variceal bleeding and septicemia. We found that these two groups of patients developed similar rates of liver-related complications (P>0.05) (Table 2). Comparison of clinical features between patients with and those without mortality or liver transplantation by week 12 of treatment was shown in Table3. Old age, cirrhosis, higher levels of Total bilirubin, CTP score, international normalized ratio (INR) of prothrombin time, lower level of platelet, presence of ascites, hepatic encephalopathy, were associated with mortality or liver transplantation (Table 3).

Table 3
Comparisons of baseline clinical features between patients by week 12 of treatment

Features	Patients survived (n=78)	Died or received liver transplantation (n=28)	*P* value
Age(years)	52.17±6.44	56.25±5.49	<0.0001
Gender(male)	70(89.74%)	25(89.29%)	0.833
Cirrhosis	15(19.23%)	19(67.86%)	<0.0001
ETV/TAF	48/30	18/10	0.492
HBV DNA load(log_{10}IU/ML)	5.27±0.80	5.53±0.60	0.119
HBeAg Positive	46(58.97%)	16(57.14%)	0.830
ALT(U/L)	431.99±169.50	448.04±178.56	0.673
AST(U/L)	384.99±148.06	421.19±157.42	0.269
TBIL(μmol/L)	350.83±100.16	459.39± 118.03	<0.0001
INR	1.41±0.34	1.65±0.23	0.001
PLAT($\times 10^9$/L)	123.15±20.02	90.89±23.14	<0.0001
CTP Score	8.27±2.65	10.79±2.27	<0.0001
Ascites	26(33.33%)	19(67.86%)	0.002
Hepatic encephalopathy	5(6.41%)	8(28.57%)	0.005

Abbreviations: TAF tenofovir alafenamide, *ETV* entecavir, *ALT* glutamic-pyruvic transaminase, *AST* glutamic-oxalacetic transaminase, *TBIL* total bilirubin, *INR* international normalized ratio, *PLAT* platelet, *CTP* Child-Turcotte-Pugh

Safety And Side-effect

During the study, none of the patients adjusted the dosage of antiviral agents or discontinued the antiviral therapy. None of the patients developed severe lactic acidosis, renal impairment or other sever adverse event. All the patients could tolerate the antiviral agents (ETV, TAF).

Discussion

There is growing evidence confirmed that antiviral therapy with NAs in the patients with liver failure is a key treatment[15, 16]. TAF and ETV are two first-line NAs that was recommended by the international liver

disease guidelines[17, 18]. But there was no sufficient evidence about the efficacy of these two agents in treatment of ACLF patients. This study investigated the short-term efficacy of TAF and ETV in patients with ACLF. Ultimately, our data demonstrated the superiority of TAF over ETV in efficacy of viral suppression, HBeAg loss, improvement of CTP score, and survival benefit in the first 4 weeks of treatment.

TAF was recommended as the first line oral agents for antiviral therapy of HBV, in addition, TAF is a phosphonamidite prodrug of tenofovir that shares the same intracellular active metabolite, tenofovir diphosphate. But the data about the efficacy and safety of TAF is rare. This study is based on real world research, the data of 106 patients with ACLF was analyzed. There were some of investigations from other groups, they observed the ALT normalization rates and declined trend of HBV DNA in TDF and ETV group, they found no difference between TDF and ETV treatment[19–21]. In this study, we observed ALT normalization rates and declined trend of HBV DNA in TAF and ETV treatment group. In terms of virological suppression, TAF group got quick HBV DNA suppression compared with ETV group. There were 72.5% patients got >2 $\log_{10}$ IU/mL decrease in HBV DNA load in TAF group and 60.6% in ETV group after 4 weeks treatment. And 25% patients got negative HBV DNA load in TAF group after 12 weeks antiviral therapy. At the same time, our data showed that patients treated with TAF, the ALT, AST normalization rates were much higher than patients treated with ETV. As for CTP score, patients in the TAF group showed apparent decline trend than patients in ETV group during the whole therapy course. The results demonstrated that the antiviral efficacy of TAF is superior than ETV. Our data provided the first evidence that TAF could control the HBV DNA and bring advantage of high ALT normalization and improvement of liver function in ACLF patients, so that achieve high survival rate in HBV-ACLF patients after the first 4 weeks therapy. But the pathogenic mechanisms of ACLF is complicated. Mireia Casulleras group reported that a systemic hyperinflammatory state is the main driver of widespread tissue and organ injury in patients with ACLF. The massive release of inflammatory mediators leads to severe tissue damage[22].Jiang Li[23] group confirmed that HBV exacerbate immune-metabolism disorder in HBV-ACLF patients. Therefore, we thought that although received 12 weeks antiviral therapy making HBV DNA load decrease to lower level, immune and metabolic disorder process still drive the development and progression of HBV-ACLF in the followed time, which was the reason of why these two groups achieved similar survival rate after 12 weeks treatment. And some group showed the similar treatment response and clinical outcome in TDF group and ETV group.

Previous study also investigated several important indicators of poor prognosis in ACLF patients[24–27]. Presence of cirrhosis, HBV DNA load, positive of HBeAg, high CTP score, high ALT, AST, TB level and INR, low platelet count were all included. In this study, we also observed the relationship of these factors with mortality in ACLF patients. Consistent with previous study, our data showed that patients died or received liver transplantation surgery had older age, presence of cirrhosis, high TB level, CTP score and INR, low platelet count, ascites, or hepatic encephalopathy. At the same time, this study also observed the safety and side-effect of the antiviral agents, there was no severe lactic acidosis, renal impairment or other sever adverse event during the treatment.

Our study has some limitations, the most important being is that the follow-up period was relatively short and the study subjects in two groups was relatively small. Therefore, further studies of this cohort with long time follow-up are planned. Furthermore, the choice of antiviral agents depends on the choice of investigators and the data of other agents is limited, TAF and ETV are the two main agents in this study. Moreover, other groups[28] confirmed that early and rapid antiviral therapy contributed to decreasing the short-term mortality in HBV-ACLF. But our data found the mortality rate had no difference in TAF group and ETV group at 8 and 12 weeks. Therefore, larger, randomized, controlled studies are needed to confirm our data.

In conclusion, ACLF patients with chronic HBV infection treated with TAF could get rapid HBV-DNA reduction and high normalization rate of ALT. CTP scores could be released to lower level after TAF therapy compared with ETV treatment group. Older age, presence of cirrhosis, high TB level, CTP score and INR, low platelet count, with ascites, hepatic encephalopathy are predictors for mortality in ACLF patients.

Declarations

Acknowledgements

None.

Authors' contributions

The idea for the manuscript was conceived by Zhiqin Li, and was attended by Yong Liu, Jianxia Dong, Yushu Hu, Jingya Yan and Meng Wang. Zhiqin Li wrote the first draft of the manuscript. Yong Liu, Jianxia Dong and Yushu Hu all reviewed the manuscript and were involved in its critical revision before submission. All authors read and approved the final manuscript.

Funding

No Funding.

Availability of data and materials

Please contact the corresponding author with request for data.

Ethics approval and consent to participate

Informed consent was obtained in writing and verbally from all the participants. The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and approved by Local Ethical Committee of the First Affiliated Hospital of Zhengzhou university.

Consent for publication

Due to the retrospective nature of the study, informed consent was waived.

Competing interests

The authors declare that they have no competing interests.

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Figures

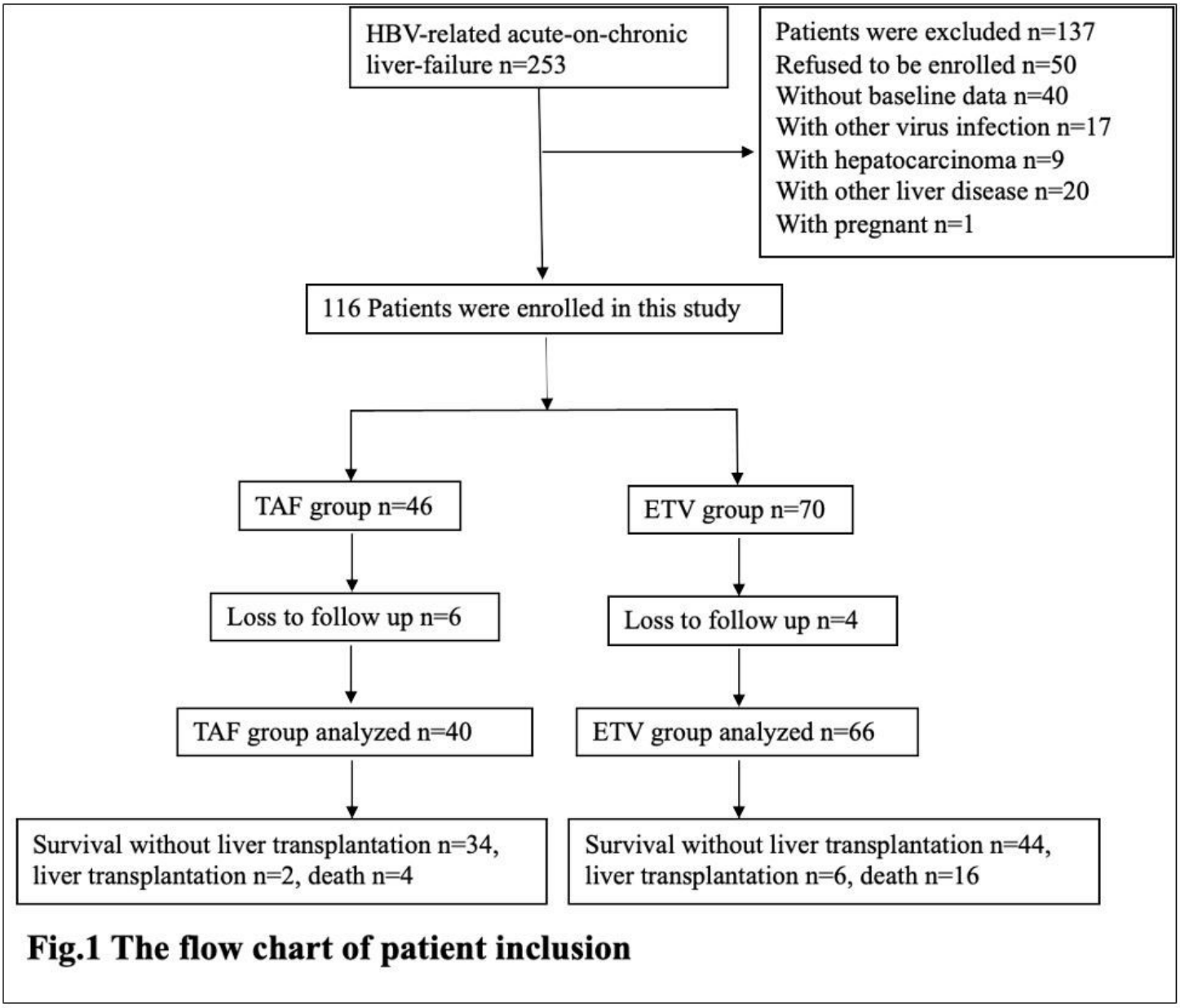

Figure 1

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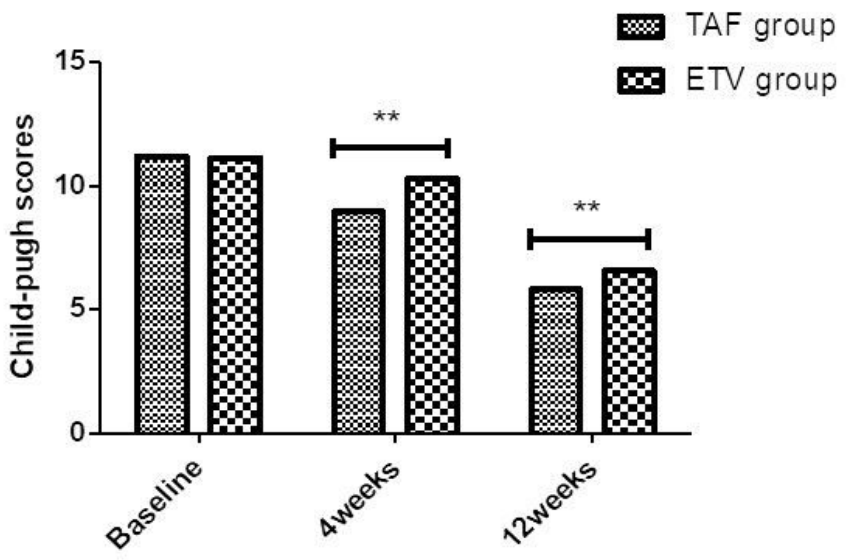

Fig.2 Dynamic changes of Child-pugh scores in TAF group and ETV group.

Figure 2

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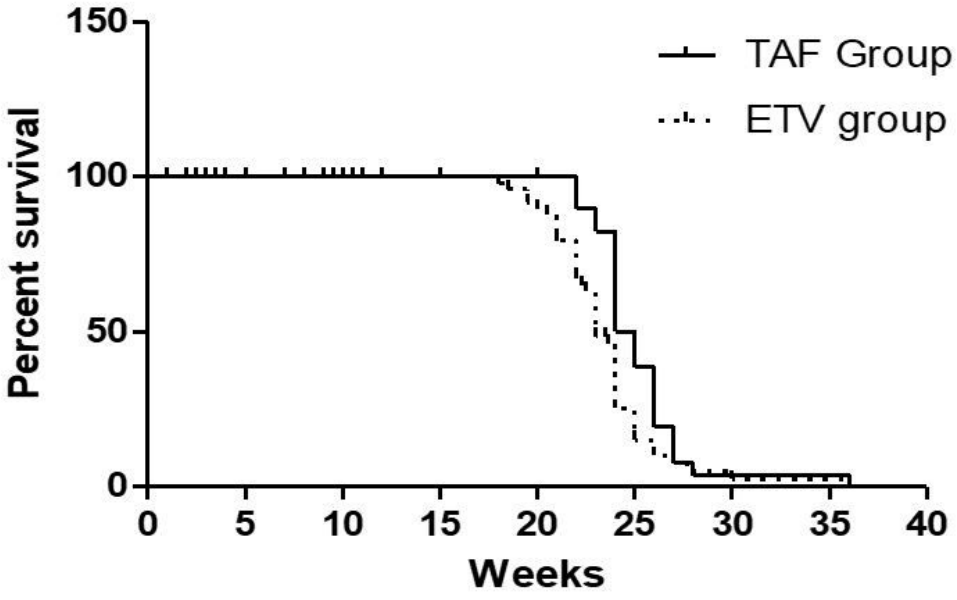

Fig.3 The cumulative survival analysis of patients in TAF group and ETV group

Figure 3

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