Efficacy of Lenvatinib for Unresectable Hepatocellular Carcinoma Based on Background Liver Disease Etiology: Multi-center Retrospective Study

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Abstract

Background/Aim: Hepatocellular carcinoma patients (HCC) related with non-alcoholic steatohepatitis (NASH) has been recently reported to be not responsive to immune-checkpoint inhibitor treatment (ICI). This study aimed to evaluate therapeutic efficacy in non-alcoholic fatty liver disease (NAFLD)/NASH-related unresectable-HCC (u-HCC) treated with lenvatinib.

Material/Methods: Five-hundred-thirty u-HCC with Child-Pugh A were enrolled, and divided into the NAFLD/NASH (n=103) and Viral/Alcohol (n=427) groups. Clinical features were compared in a retrospective manner.

Results: Progression-free survival (PFS) was better in the NAFLD/NASH than the Viral/Alcohol group (median 9.3 vs. 7.5 months, P=0.012), while there was no significant difference in overall survival (OS) (20.5 vs. 16.9 months, P=0.057). In Cox-hazard analysis of prognostic factors for PFS, elevated AFP (≥400ng/mL) (HR1.294, P=0.014), elevated ALT (≥30 U/L) (HR1.247, P=0.029), modified ALBI grade 2b (HR1.236, P=0.047), and NAFLD/NASH etiology (HR0.763, P=0.036) were significant prognostic factors. NAFLD/NASH etiology was not a significant prognostic factor in Cox-hazard analysis for OS (HR0.750, P=0.076), whereas AFP (≥400ng/mL) (HR1.402, P=0.009), later line use (HR0.737, P=0.0137), BCLC C stage (HR1.297, P=0.035), and modified ALBI grade 2b (HR1.875, P<0.001) were significant.

Conclusion: ICI is reportedly not effective for NAFLD/NASH-related HCC, while lenvatinib can improve the prognosis of u-HCC irrespective of HCC etiology or its line of treatment.

Introduction

Molecular targeted agents (MTAs) have recently been introduced for unresectable hepatocellular carcinoma (u-HCC), with sorafenib developed first in 2009 as a first-line MTA based on results presented in the SHARP [1] and Asia-Pacific [2] trials. Following development of that drug, lenvatinib received approval as another first-line treatment in 2018 [3]. Moreover, atezolizumab plus bevacizumab treatment (Atezo+Bev), an immune-checkpoint inhibitor (ICI) and A combination, was recently introduced in September 2020 as a first-line treatment option for u-HCC [4].

In spite of the good therapeutic response noted for Atezo+Bev in the IMbrave 150 trial, a recent report noted that therapeutic responses to ICI treatments differed according to the etiology of the background liver disease [5]. Meta-analysis of that report [5] indicated that patients with HCC with a viral etiology showed therapeutic benefits from ICI use [HR 0.64], whereas those with a nonviral etiology did not [HR 0.92] (P=0.03).Most importantly, results of two validation cohorts treated with ICI clearly showed that overall survival (OS) for non-alcoholic fatty liver disease or non-alcoholic steatohepatitis (NAFLD/NASH)-related HCC patients was significantly worse than that for the non-NAFLD/NASH-related HCC group (11.0 vs. 5.4 months, P=0.023 and 17.7 vs. 8,8 months, P=0.034, resspectively) [5]. This is the first epoch-making and striking results that ICI treatment response differs based on background liver disease etiology,

especially NASH/NAFLD related HCC lacks immune response and immune surveillance to the tumor associated antigen.

Lenvatinib, which was approved after showing non-inferior therapeutic efficacy as compared to sorafenib, has recently come to play a large role as a first-line MTA drug in clinical practice in the world for u-HCC cases. However, therapeutic response in non-viral u-HCC patientswith lenvatinib, especially those with NAFLD/NASH related HCC, has not been adequately elucidated. This study aimed to evaluate differences among background hepatic disease etiology factors for therapeutic response in patients treated with lenvatinib.

Materials And Methods

Patients

The records of 674 patients with u-HCC and treated with lenvatinib at various institutions in Japan between March 2018 and February 2021 (Ehime Prefectural Central Hospital, Kindai University Hospital, Himeji Red Cross Hospital, Kagawa University Hospital, Okayama City Hospital, Osaka Medical School, Nippon Medical School, Ehime University Graduate Hospital, Teine Keijinkai Hospital, Saiseikai Niigata Hospital, Kagawa Prefectural Central Hospital, Asahi General Hospital, Toyama University Hospital, Otakanomori Hospital, Tokushima Prefectural Central Hospital, Matsuyama Red Cross Hospital, Hamamatsu University School of Medicine Hospital, Ogaki Municipal Hospital) were obtained. Those in whom lenvatinib was introduced before March 2018 as part of a clinical trial (n=23), classified as Child-Pugh class B or C (n=91), or with autoimmune liver disease [autoimmune hepatitis (AIH) or primary biliary cirrhosis (PBC)] (n=3) wereexcluded, thus 557 cases were subjected to evaluations performed in a retrospective manner (Figure 1).

Patients positive for hepatitis B virus surface antigen (HBsAg) were judged to have HCC due to the presence of hepatitis B virus (HBV), while those positive for anti-hepatitis C virus (HCV) were judged to have HCC due to HCV. Two patients positive for both HCV and HBV were included in the HCV group for this study because HBV DNA levels were below the detection level. For patients with a history of alcohol abuse of 60 g/day or more [6,7], background liver disease was judged as alcoholic. NAFLD/NASH diagnosis was determined by a medical interview [history of obesity, hyperlipidemia, hypertension, etc and/or no/low alcohol intake (<30 g/day in males, <20 g/day in females)] of fatty liver patients and/or based on pathological findings [8]. Burned-out NASH liver cirrhosis was diagnosed clinically based on the clinical course (e.g., no history of alcohol abuse, history of obesity and/or fatty liver, or past pathological diagnosis) by each institution. Patients other than the above or with autoimmune liver disease (AIH or PBC), or those in whom hepatic fibrosis was not observed pathologically were classified as cryptogenic liver disease.

The therapeutic effects of lenvatinib in all 557 patients with Child-Pugh class A were examined as Study-1. Furthermore, therapeutic responses were compared between patients with NAFLD/NASH (n=103), and

those with chronic hepatic viral infection or alcohol abuse (Viral/Alcohol group) (n=427), after exclusion of cryptogenic patients (n=27), as Study-2 (Figure 1).

HCC diagnosis

HCC was diagnosed based on an increasing trend of alpha-fetoprotein (AFP), as well as typical findings obtained in dynamic CT [9], MRI [10,11], and contrast enhanced ultrasonography (CEUS) with perflubutane (Sonazoid®, Daiichi Sankyo Co., Ltd., Tokyo, Japan) examinations [12,13], and/or pathological findings. To evaluate tumor progression, Barcelona Clinic Liver Cancer (BCLC) stage [14] and tumor node metastasis (TNM) stage were used, and determined as previously reported in a study for TNM staging of HCC conducted by the Liver Cancer Study Group of Japan (LCSGJ) 6th edition [15] (TNM-LCSGJ).

Assessment methods for hepatic reserve function and therapeutic response

Child-Pugh classification [16] and albumin-bilirubin (ALBI) grade were used for assessment of hepatic reserve function [17-19]. To perform more detailed evaluations of patients with the middle ALBI grade of 2, a revised grading system was used that consisted of four levels, with sub-grading for the middle grade of 2 (2a and 2b) based on an ALBI score of −2.27 as the cut-off (modified ALBI, mALBI grade), which was previously reported to result in a predictive value for indocyanine green retention after 15 minutes (ICG-R15) of 30% [20,21].

Progression-free survival (PFS) was analyzed according to the modified Response Evaluation Criteria In Solid Tumors (mRECIST) criteria [22,23], based on results of dynamic CT examinations performed at intervals of 8-12 weeks and rate of discontinuation of lenvatinib medication.

Lenvatinib treatment and assessment of adverse events

After obtaining written informed consent from each patient, lenvatinib treatment was started. The drug was orally administered at 8 mg/day in patients weighing <60 kg or 12 mg/day in those ≥60 kg, and discontinued when any unacceptable or serious adverse event (AE) occurred (any grade 3 or more severe AE, or any unacceptable grade 2 drug-related AE), or radiological tumor progression was observed, according to the guidelines for administration of lenvatinib. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [24]. When a drug-related AE was noted, dose reduction or temporary interruption was maintained until the symptom was resolved to grade 1 or 2, according to the guidelines provided by the manufacturer. AEs of grade 3 or more were defined as severe, and the worst grade for each AE during the present observation period was recorded.

Ethical approval

Written informed consent for lenvatinib treatment was obtained from each patient. This was a retrospective analysis of records stored in a database and official approval was received based on the

Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan. All procedures complied with the declaration of Helsinki.

The study protocol was granted approval by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (IRB No. 30-66) (UMIN000043219).

Statistical analysis

Continuous variables are expressed as median values (first-third quartile). Statistical analyses were performed using Welch's t-test, Student's t-test, Fischer's exact test, or Mann-Whitney's U test, as appropriate. Cox hazard analysis (stepwise regression method), the Kaplan-Meyer method, and a log-rank test were used to analyze prognosis factors.

A P value less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using Easy R (EZR) version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [25], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study-1

Clinical features of all 557 patients are shown in Table 1. PFS and OS were 7.8 months (95%CI 7.0-8.6 months) and 17.8 months (95%CI 16.3-19.5 months), respectively (Figure 2a, 2b), and were well stratified according to mALBI grade (median PFS and OS: grade 1:2a:2b = 9.8:8.0:6.3 months, P=0.002, and 21.0:20.0:11.2, months, P<0.001, respectively) (Figure 3a, 3b), while there were no significant differences for those according to treatment line (first, second, third or greater) using lenvatinib (median PFS and OS: 7.6:8.2:7.7 months, P=0.080, and 16.7:18.3:23.2 months, P=0.091, respectively) (Supplemental Figure S1a, S1b)]. A comparison between initial and later line (second or greater) showed no significant difference regarding PFS (7.6 vs. 8.1 months, P=0.752), while a significant difference was noted for OS (16.7 vs. 19.6 months, P=0.029) (Supplemental Figure S1c, S1d).

Median PFS after dividing patients into HCV, HBV, alcohol, NAFLD/NASH, and cryptogenic groups was 7.0, 7.9, 7.4, 9.3, and 11.9 months, respectively, (P=0.154) (Figure 4a), while median OS was 18.3, 16.3, 15.3, 20.5 months, and not reached, respectively (P=0.052) (Figure 4b). There were no significant differences in regard to PFS (7.5 vs. 8.3 months, P=0.092) or OS (17.2 vs. 18.5 months, P=0.226) between the viral HCC and nonviral (NAFLD/NASH, cryptogenic, alcohol) groups (Figure 4c, 4d). However, in comparisons between the Viral/Alcohol group and others (NAFLD/NASH, and cryptogenic), both PFS and OS for the Viral/Alcohol group were significantly worse (median PFS: 7.5 vs. 9.3 months, P=0.012; median OS: 16.9 vs. 21.0 months, P<0.001) (Figure. 4e, 4f).

Study-2

In comparisons between the NAFLD/NASH and Viral/Alcohol groups, platelet count was lower in the former ($13.1x10^4$/μL vs. $15.3x10^4$/μL, P=0.005). On the other hand, a larger percentage of patients in the NAFLD/NASH group started lenvatinib at a reduced dose (36.9% vs. 26.0%, P=0.037), while there was no significant difference observed in regard to hepatic function (Child-Pugh score, ALBI score, mALBI grade), tumor burden (TNM-LCSGJ, BCLC stage), or malignancy grade of HCC (elevated AFP: ≥400 ng/mL) between them (Table 2).

Following exclusion of cryptogenic patients, PFS was better in the NAFLD/NASH than the Viral/Alcohol group (median 9.3 vs. 7.5 months, P=0.012) (Figure 5a), while there was no significant difference in regard to OS (median 20.5 vs. 16.9 months, P=0.057) (Figure 5b). Cox-hazard analysis for prognostic factors of PFS showed elevated AFP (≥400 ng/mL) (HR 1.294, P=0.014), elevated ALT (≥30 U/L) (HR 1.247, P=0.029), mALBI grade 2b (HR 1.236, P=0.047), and NASH/NAFLD (HR 0.763, P=0.036) to be significant prognostic factors (Table 3a). Although NAFLD/NASH was not a significant prognostic factor in that analysis for OS (HR 0.750, P=0.076), the factors AFP (≥400 ng/mL) (HR 1.402, P=0.009), later line introduction of lenvatinib (HR 0.737, P=0.0137), BCLC C stage (HR 1.297, P=0.035), and mALBI grade 2b (HR 1.875, P<0.001) were significant (Table 3b).

Finally, examination of AEs (over 20%) showed that hypothyroid and urine protein conditions were more common in the NAFLD/NASH as compared to the Viral/Alcohol group (P=0.013 and P=0.032, respectively) (Supplemental Table S1).

Discussion

Patients in the IMbrave150study who underwent treatment with Atezo+Bev, a newly developed ICI and anti-VEGF-antibody combination, showed an overwhelmingly superior therapeutic efficacy as compared with those who received sorafenib (median OS: 19.2 vs. 13.4 months, HR 0.66, 95%CI 0.52-0.85) (ORR/CR by mRECIST: 35%/12% vs. 14%/3%) [26]. Although pooled analysis of the SHARP and Asia-Pacific trials found that positive for HCV was a predictive factor for therapeutic response to sorafenib [HR 0.47, 95%CI 0.32-0.69, P=0.035] [27], IMbrave150 study showed superiority for the therapeutic effect (both OS and PFS) of Atezo+Bev as compared with sorafenib in HCV-HCC cases (HR 0.43, 95%CI 0.25-0.73 and HR 0.68, 95%CI 0.42-1.10, respectively) [26]. On the other hand, that study did not demonstrate superior findings for Atezo+Bev in regard to OS in HCC with nonviral etiology (HR 1.05, 95%CI 0.68-1.63 and HR 0.80, 95%CI 0.55-1.17) as compared to viral HCC cases. However, these results do not indicate that Atezo+Bev is not effective for non-viral HCC, as the OS in patients who received that treatment was 17.0 months, similar to that in patients with HBV HCC (19.0 months). Rather, the worse OS HR can be attributed to better efficacy of sorafenib even in non-viral HCC (18.1 months) as compared with HBV-HCC (12.4 months) and HCV-HCC (12.6 months) cases, though the reasons are unknown.

In a meta-analysis by Pfister, patients with a viral etiology showed therapeutic benefits with ICI treatment [HR 0.64], whereas those with nonviral etiology HCC did not [HR 0.92] (P=0.03) [5]. That study also presented results of two different validation studies of ICI treatment for HCC, in which NAFLD-HCC cases

showed significantly worse OS than HCC with other etiology (HR 2.6 95%CI 1.2-5.6, P=0.017; median 8.8 vs. 17.7 months, P=0.034) [5]. In patients undergoing ICI treatment, background liver disease etiology might be a biomarker ofefficacy. Immunotherapy may be ineffective for NAFLD HCC, but not for all nonviral HCC cases. Rather, sorafenib given as initial treatment seemed to be effective for nonviral HCC patients in the IMbrave 150 trial (Atezo+Bev for PFS: HR: 0.80, 95%CI 0.55-1.17; Atezo+Bev for OS: HR 1.05, 95%CI 0.68-1.63) [26]. Currently, subsequent sequential therapy with multiple MTAs including lenvatinib has been reported [28] and sequential MTAs treatment is considered to be one of the possible causes of such favorable results in non-viral HCC cases in the trial.

Differences regarding therapeutic efficacy among various background liver disease etiology in patients receiving lenvatinib treatment have yet to be evaluated. The present study showed that lenvatinib provided better PFS as well as a trend of better OS in NAFLD/NASH-related HCC patients as compared to patients with HCC with other etiology. An explanation for these findings is not clear, though liver fibrosis in the background of NAFLD/NASH HCC may be milder as compared to that in non-viral liver parenchyma cases, which might then lead to increase subsequent use of effective therapies. This can be said in the sorafenib arm in the non-viral HCC group of the IMbrave150 trial [26].

Despite of this retrospective analysis, it is possible to speculate that cryptogenic HCC is a subgroup of NAFLD/NASH HCC. In the present Study-1, patients with u-HCC due to alcohol abuse had PFS and OS similar to those with viral HCC, thus viral and alcoholic HCC were treated as a single group in comparisons of PFS and OS with those of NAFLD/NASH/cryptogenic HCC patients. In Study-2, after excluding cryptogenic HCC, NAFLD/NASH and other etiology (Viral/Alcohol) groups were compared to confirm response to lenvatinib in clinically diagnosed NAFLD/NASH patients. The NAFLD/NASH showed better PFS (P=0.012), whereas there was no significant difference in OS (P=0.057). On the other hand, OS in the NAFLD/NASH-HCC patients treated with lenvatinib was very favorable (20.5 months) and tended to be better than that in the viral HCC cases (16.9 months).

It was recently been proposed by Hessheier et al. that metabolic factors may be risk factors for development of liver diseases and cirrhosis [29], while Eguchi et al. found “lean-NASH” (non-obese NASH, body mass index: BMI <25 kg/m^2) existing in 20% to >35% in patients in Japan [30]. Of the present cryptogenic HCC patients (n=26), diabetes was observed in 44.4% (n=12), hypertension in 51.9% (n=14), and overweight (BMI ≥25 kg/m^2) in 25.9% (n=7), while 70.4% (n=19) had at least one of those co-factors (Supplemental Table S2). Thus, cryptogenic HCC might be categorized as NAFLD/NASH HCC without severe hepatic fibrosis. When cryptogenic HCC cases are included with NAFLD/NASH, in other words, without hepatitis viral infection or alcohol abuse history, such patients might receive benefit from lenvatinib treatment (Figure 4e, 4f).

Since 2004, the number of adults with NASH awaiting liver transplantation in the United States has nearly tripled and NASH has become the second leading etiology of liver disease among such cases [31]. In meta-analysis results, the NAFLD incidence rate was reported to be 25.24% (overall regions, 95%CI 22.1-28.65) and pooled overall NASH prevalence among biopsied NAFLD patients was estimated to be 59.10%

(95%CI 47.55-69.73), while the annual rate of liver carcinogenesis from NAFLD was estimated to be approximately 0.04% (95%CI 0.29-0.66) [32]. Similarly in Japan, a rapidly increasing rate of HCC patients without hepatitis viruses has been reported [33], with most cases of non-B, non-C HCC shown to be related to lifestyle/metabolic factors, such as obesity or diabetes, including cryptogenic HCC [34]. Recently, liver-related diseases, such as cirrhosis and HCC, have been reported to be the third leading cause of death in patients in Japan with type 2 diabetes mellitus, which is associated with NAFLD [35]. Also, a recent review article of HCC related to NAFLD mentioned that the impact of metabolic syndrome and its relevance for those patients is not clear [36]. Nevertheless, establishment of an effective treatment strategy for u-HCC related with NAFLD/NASH is considered to be a critical clinical issue. As we have previously reported [37,38], good treatment results can be obtained with lenvatinib, even when given as later line therapy, as shown in the present study, if liver function is good (mALBI 1 or 2a) at the time of introduction of the drug [39]. Thus, for NAFLD/NASH u-HCC cases, lenvatinib might be an effective therapeutic option and can be selected for administration at any time in patients with good hepatic function (mALBI 1 or 2a).

It is anticipated that the number and percentage of NAFLD-HCC cases will continue to increase, though liver cirrhosis is not present in all of those. However, HCC is often detected in an advanced stage because no surveillance program for NAFLD-HCC patients has been established. As a result, it is important to confirm which systemic treatment (e.g. MTAs or ICI combination) is a more effective therapeutic option in patients with NAFLD HCC as well as viral hepatitis related HCC.

The present study has some limitations, including its design as a retrospective multicenter study. Furthermore, the pathological diagnosis of disease etiology for the present patients without viral hepatitis was not adequately assessed. A future study in which prospective comparisons between lenvatinib and ICI treatment in NASH/NAFLD HCC patients is needed.

In conclusion, while ICI might not be effective for NAFLD/NASH-related HCC, lenvatinib was found to be effective for improving the prognosis of u-HCC patients irrespective of HCC etiology or line of treatment.

Declarations

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available due to reasons why data are not public.

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Conflicts of interest:

Atsushi Hiraoka, MD, PhD – Lecture fees: Bayer, Eisai, Eli Lilly, Otsuka

Takashi Kumada, MD, PhD – Lecture fees: Eisai

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None of the other authors have potential conflicts of interest to declare.

Authors' contributions

AH, TK, and MK conceived the study, and participated in its design and coordination. AH, TK, ToT, JT, Kka, SF, MA, MH, KTs, TI, KTak, EI, KTaj, NS, HS, HOc, KK, SY, HT, TAo, TaT, HOh, KN, AT, TN, NI, KH, TAr, MI, YK, SN, KM, KJ, and YH performed data curation. AH performed statistical analyses and interpretation. AH, TK, and MK drafted the text. All authors have read and approved the final version of the manuscript.

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Tables

Table 1. Clinical features of all u-HCC patients

	n=557
Age, years *	73.0 (67.0-79.0)
Gender, male:female	430:127
Etiology, HCV:HBV:alcohol:NAFLD/NASH:cryptogenic	236:88:103:103:27
ECOG PS, 0:1:2:3	474:73:9:1
Body mass index (kg/m^2)	22.98 (20.74 to 25.55)
ALBI score * (mALBI grade 1:2a:2b)	-2.49 (-2.18 to -2.74) (217:161:179)
Child-Pugh score, 5:6	359:198
AFP, ≥400 ng/mL (%)	167 (30.0%)
TNM-LCSGJ, I:II:III:IVa:IVb	6:74:207:81:189
BCLC stage, 0:A:B:C:D	4:10:221:321:1
Lenvatinib treatment line, first:second:third:fourth:fifth	355:132:63:6:1
Deaths (%)	301 (54.0%)
Observation period, months	12.2 (6.9-19.2)

*Median (interquartile range). **Duplication. HCV: hepatitis C virus, HBV: hepatitis B virus, NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis, ECOG PS: Eastern Cooperative Oncology Group performance status, ALBI score: albumin-bilirubin score, mALBI grade: modified ALBI grade, AFP: alpha-fetoprotein, TNM LCSGJ 6th: tumor node metastasis stage by Liver Cancer Study Group of Japan 6th edition, BCLC stage: Barcelona Clinic Liver Cancer stage

Table 2: Comparison of clinical features between NAFLD/NASH and Viral/Alcohol groups after exclusion of cryptogenic HCC

	NAFLD/NASH (n=103)	Viral/Alcohol (n=427)	P value
Age, years *	75 (69 to 80)	73 (66 to 79)	0.078
Gender, male:female	77:26	334:93	0.434
Etiology, HCV:HBV:alcohol:NAFLD/NASH	0:0:0:103	236:88:103:0	<0.001
ECOG PS, 0:1:2	89:11:3	364:58:5	0.270
Body mass index, kg/m^2	24.93 (22.79 to 27.41)	22.65 (20.32 to 25.04)	<0.001
Platelets, $10^4/\mu L$ *	15.3 (11.2 to 20.0)	13.1 (9.5 to 17.6)	0.005
AST, U/L *	40 (28 to 57)	41 (29 to 62)	0.273
ALT, U/L *	28 (21 to 41)	30 (19 to 47)	0.403
T-bilirubin, mg/dL *	0.68 (0.5 to 0.90)	0.70 (0.54 to 1.0)	0.094
Albumin, g/dL *	3.70 (3.50 to 4.00)	3.80 (3.45 to 4.10)	0.998
Prothrombin time, % *	89.0 (84.0 to 101.0)	88.0 (80.0 to 97.0)	0.142
eGFR, $nL/min/1.73m^2$ *	66.0 (50.2 to 77.3)	66.4 (56.0 to 79.4)	0.367
ALBI score * (mALBI grade 1:2a:2b:3)	-2.48 (-2.21 to -2.48) (41:31:31:0)	-2.48 (-2.17 to -2.76) (164:123:140:0)	0.603 (0.869)
Child-Pug score, 5:6	72:31	269:158	0.208
AFP, ≥400ng/mL	25 (24.3%)	136 (31.9%)	0.152
MVI, none:Vp1:Vp2:Vp3:Vp4 ** (none:Vv1:Vv2:Vv3) **	89:1:4:7:2 (90:8:4:1)	350:12:29:24:12 (391:22:9:5)	0.663 (0.417)
Positive for EHM	40 (38.8%)	140 (32.8%)	0.249
TNM-LCSGJ, I:II:III:IVa:IVb	2:12:37:12:40	4:60:157:66:140	0.537
BCLC stage, 0:A:B:C	1:2:39:61	3:8:171:245	0.933
Initial dose of lenvatinib, 4:8:12mg *	5:55:43	36:240:151	0.174
reduced starting dose	38 (36.9%)	111 (26.0%)	0.037
Lenvatinib treatment line: first:second:third:fourth:fifth	73:18:11:0:1	262:108:51:6:0	0.093
Deaths (%)	51 (49.5%)	244 (57.1%)	0.185

Observation period, months	13.5 (7.5-21.3)	11.9 (6.8-18.9)	0.124

*Median (interquartile range). **Duplication. HCV: hepatitis C virus, HBV: hepatitis B virus, NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis, ECOG PS: Eastern Cooperative Oncology Group performance status, AST: aspartate transaminase, ALT: alanine aminotransferase, ALBI score: albumin-bilirubin score, mALBI grade: modified ALBI grade, AFP: alpha-fetoprotein, MVI: macrovascular invasion, EHM: extra-hepatic metastasis, TNM LCSGJ 6^{th}: tumor node metastasis stage by Liver Cancer Study Group of Japan 6^{th} edition, BCLC stage: Barcelona Clinic Liver Cancer stage

Table 3. Prognostic factors for progression-free survival and overall survival in Study-2

a. Cox hazard analysis for PFS			
	HR	95%CI	P value
Age ≥75 years	1.083	0.887-1.324	0.433
Female gender	1.024	0.812-1.292	0.840
ECOG PS 2	0.922	0.368-2.312	0.863
NAFLD/NASH	0.722	0.556-0.937	0.014
ALT ≥30 U/L	1.240	1.016-1.513	0.034
Platelet count ≥10 (10^4/μL)	0.892	0.711-1.119	0.324
mALBI grade 2b	1.185	0.656-1.468	0.122
AFP ≥400 ng/mL	1.273	1.032-1.570	0.024
TNM-LCSGJ stage IV	1.192	0.817-1.740	0.362
BCLC stage C	1.048	0.712-1.534	0.808
Reduced starting dose	1.216	0.981-1.507	0.074
Treatment as later line	0.874	0.714-1.071	0.195
Results of stepwise regression method			
NAFLD/NASH	0.763	0.594-0.982	0.036
ALT ≥30 U/L	1.247	1.023-1.520	0.029
mALBI grade 2b	1.236	1.003-1.523	0.047
AFP ≥400 ng/mL	1.294	1.055-1.588	0.014

b. Cox hazard analysis for OS			
	HR	95%CI	P value
Age ≥75 years	1.191	0.930-1.526	0.1651
Female gender	1.152	0.871-1.522	0.321
ECOG PS 2	1.087	0.388-3.048	0.874
NAFLD/NASH	0.750	0.545-1.0.1	0.076
ALT ≥30 U/L	1.187	0.933-1.511	0.162
Platelet count ≥10 (10^4/μL)	0.998	0.759-1.313	0.990
mALBI grade 2b	1.776	1.386-2.276	<0.001
AFP ≥400 ng/mL	1.366	1.058-1.763	0.167
TNM-LCSGJ stage IV	1.185	0.763-1.840	0.450
BCLC stage C	1.172	0.755-1.821	0.479
Reduced starting dose	10.51	0.804-1.373	0.718
Treatment as later line	0.732	0.571-0.939	0.014
Results of stepwise regression method			
mALBI grade 2b	1.875	1.481-2.375	<0.001
AFP ≥400 ng/mL	1.402	1.089-1.805	0.009
BCLC stage C	1.297	1.019-1.652	0.035
Treatment as later line	0.737	0.578-0.939	0.014

ALT: alanine aminotransferase, NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis, ECOG PS: Eastern Cooperative Oncology Group performance status, ALBI score: albumin-bilirubin score, mALBI grade: modified ALBI grade, AFP: alpha-fetoprotein, TNM LCSGJ 6^{th}: tumor node metastasis stage by Liver Cancer Study Group of Japan 6^{th} edition, BCLC stage: Barcelona Clinic Liver Cancer stage

Figures

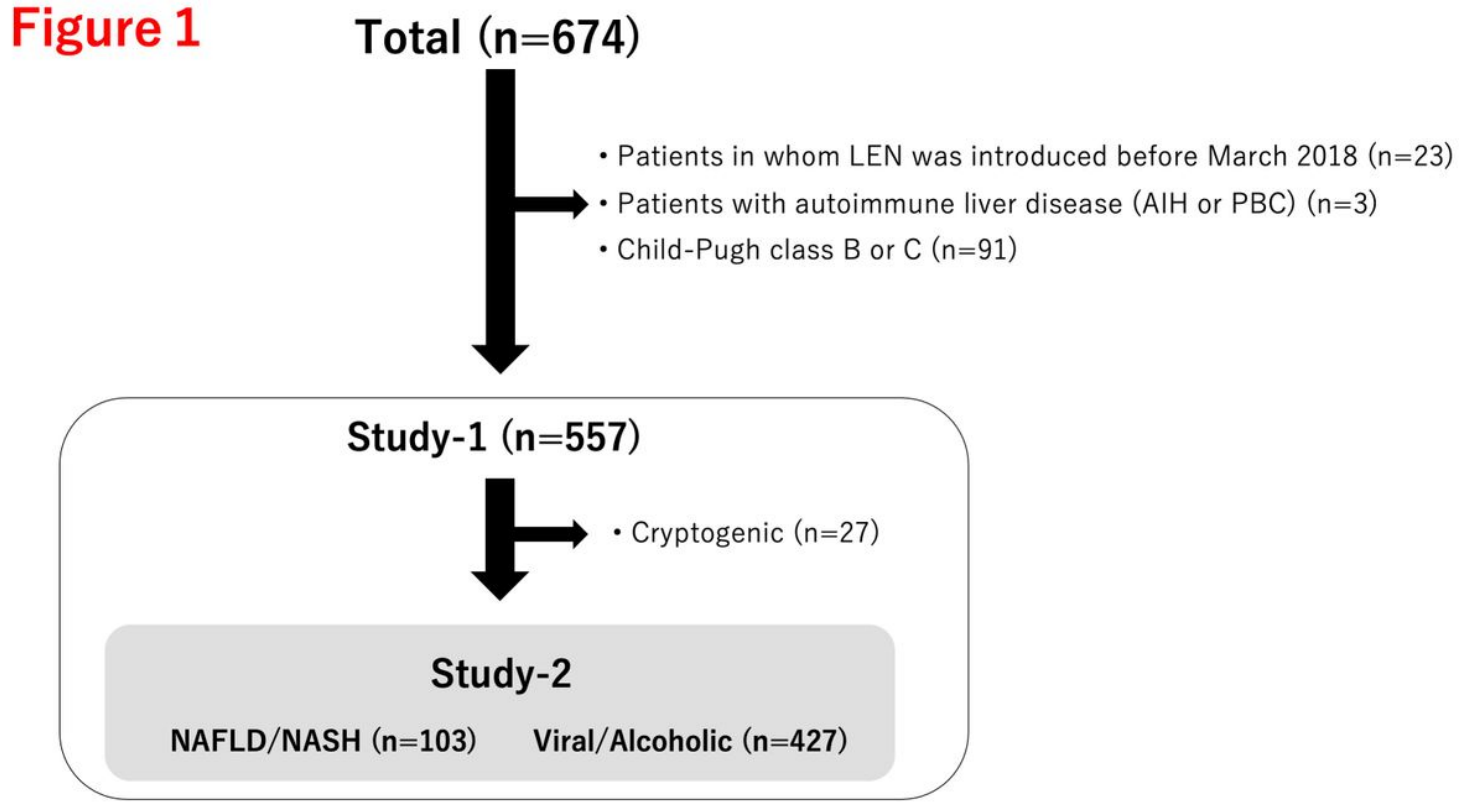

Figure 1

Flow of patient enrollment. LEN: lenvatinib, AIH: autoimmune hepatitis, PBC: primary biliary cirrhosis

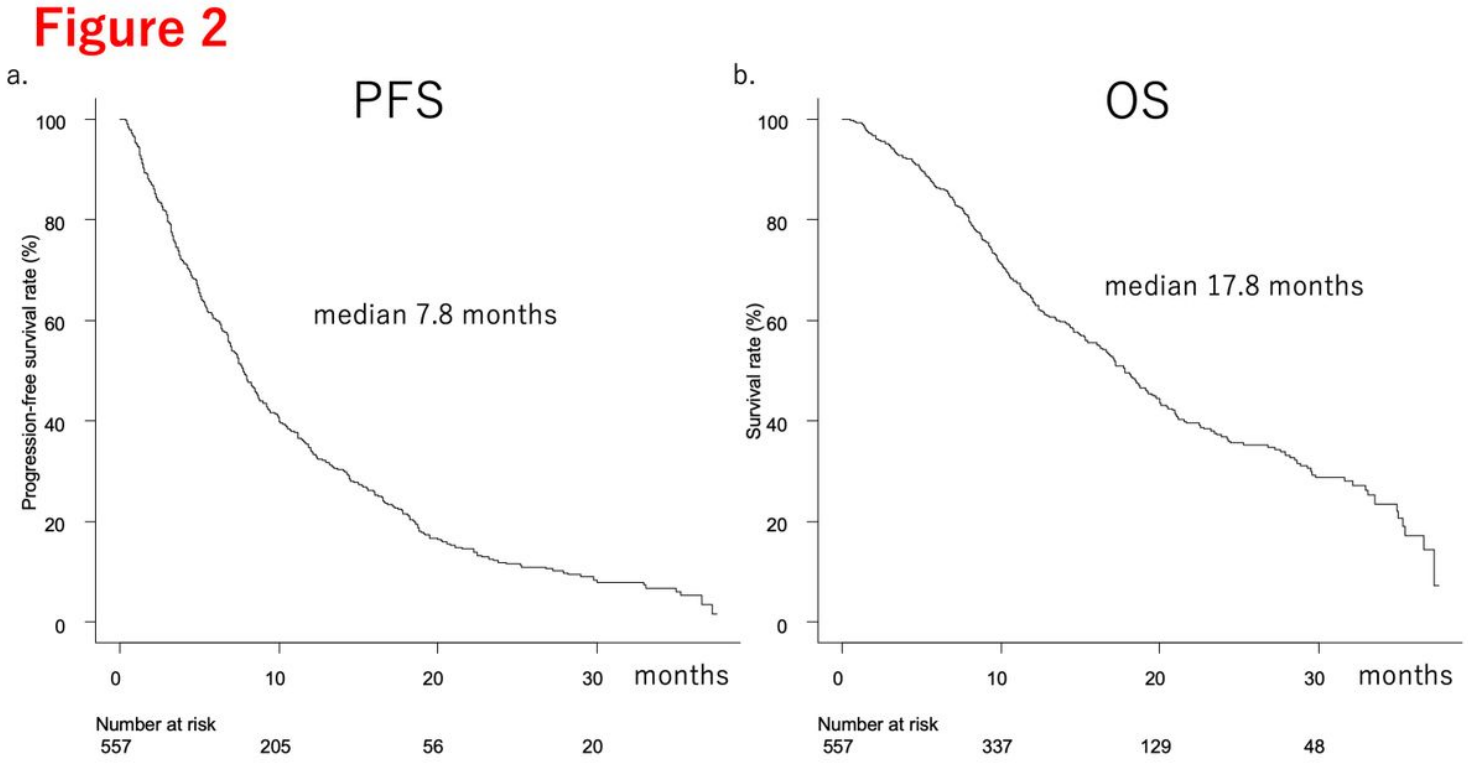

Figure 2

Progression-free and overall survival in all unresectable hepatocellular carcinoma patients with Child-Pugh class A (n=557).

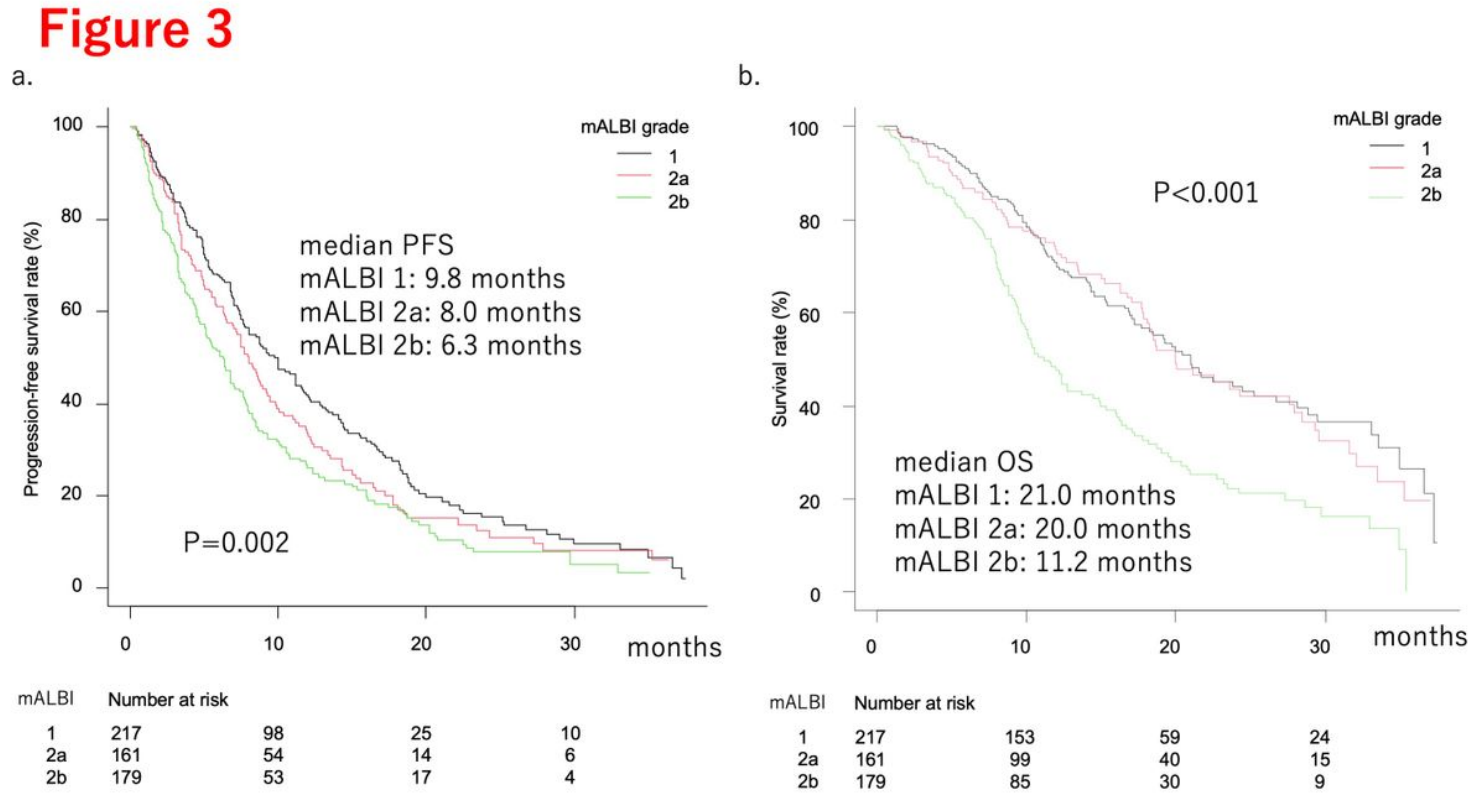

Figure 3

Progression-free and overall survival according to modified ALBI grade.

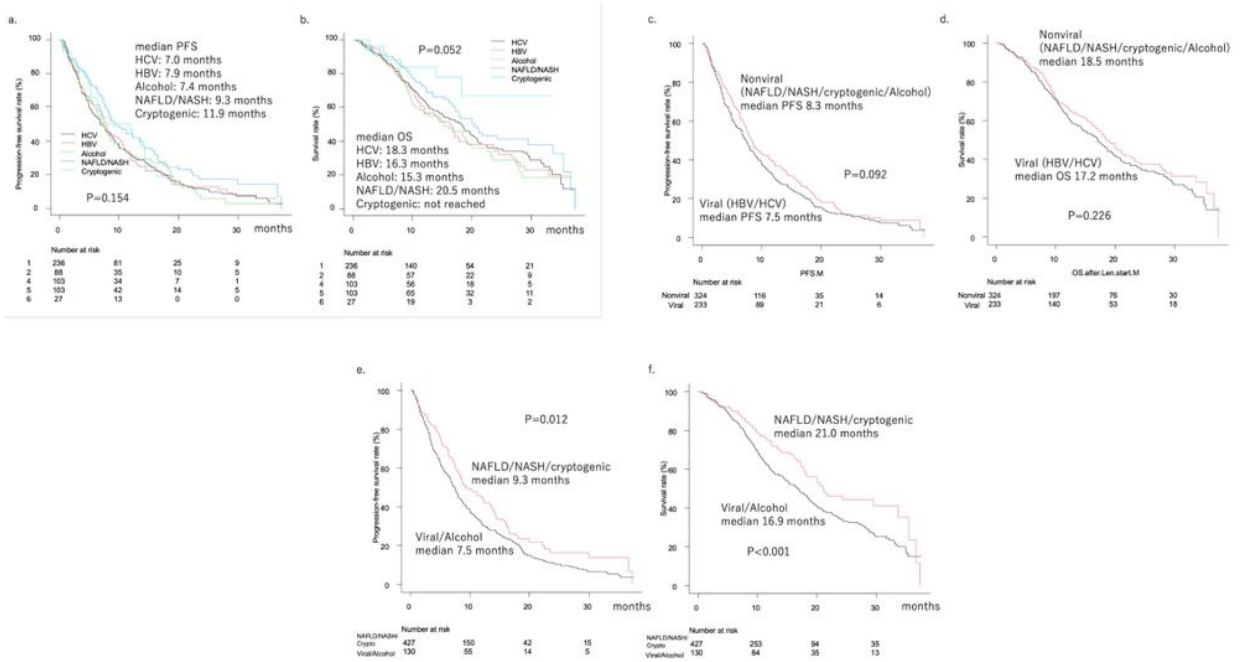

Figure 4

Progression-free and overall survival according to basal liver disease etiology.

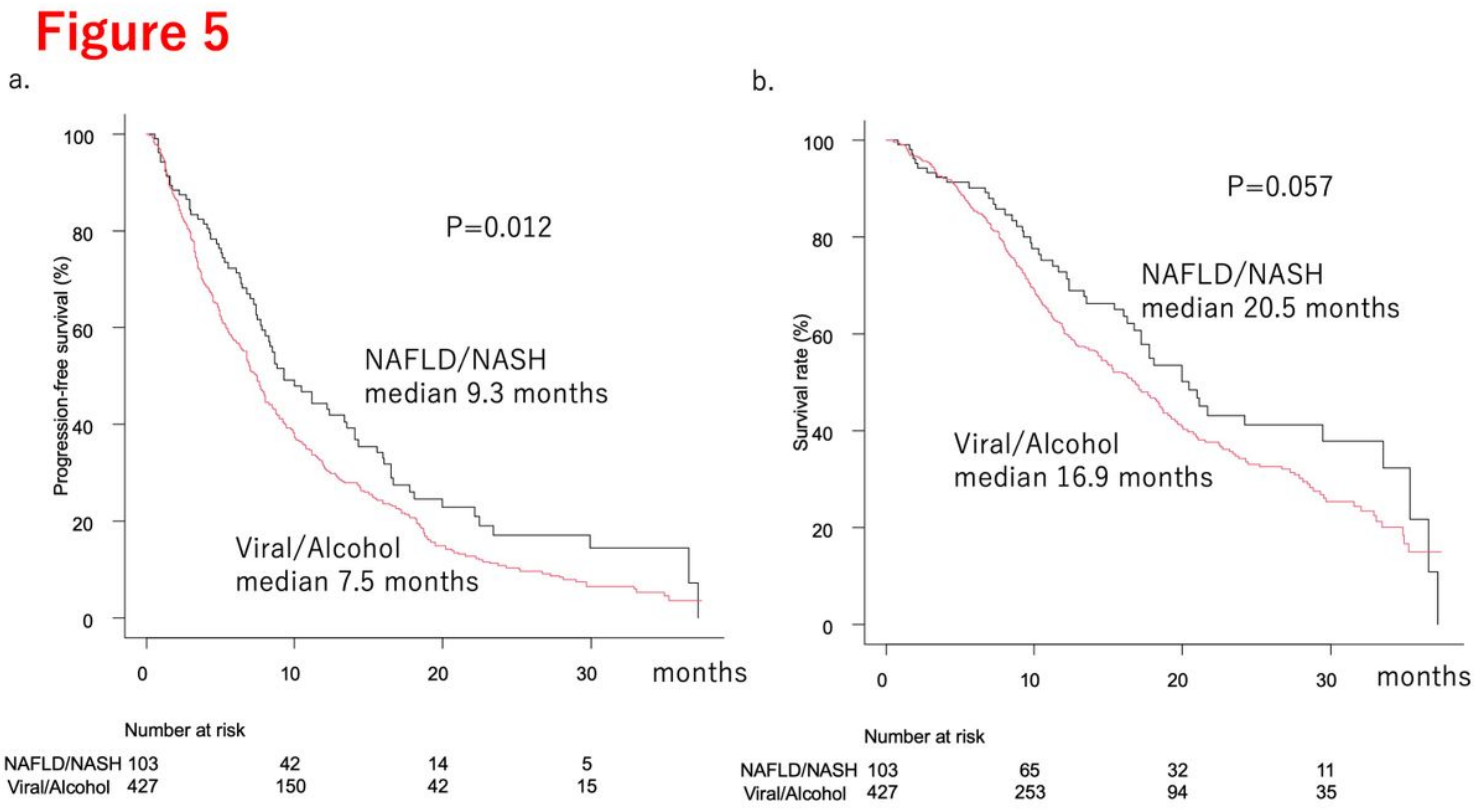

Figure 5

Progression-free and overall survival of NAFLD/NASH and Viral/Alcohol groups.

Supplementary Files

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