Non-Achievement of Alanine Aminotransferase Normalization is Associated with the Risk of Hepatocellular Carcinoma during Nucleos(t)ide Analogue Therapies: A Multicenter Retrospective Study

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Supporting information

Figure S1. Response rates for NA therapies based on ALT normalization and HBV DNA undetectability at 1 to 5 years of therapy. Three types of criteria for ALT normalization were as follows. WHO criteria: male, ≤30; female, ≤19. AASLD criteria: male, ≤35; female, ≤25. JSH criteria: ≤30.

Figure S2. Cumulative incidences of HCC according to the achievement of ALT normalization 2 years after the start of NA therapy that were evaluated with different criteria and those according to the viral response. (**a-b**) Comparison of cumulative incidences of HCC between patients who achieved ALT normalization based on the criteria of WHO (**a**) and AASLD (**b**). In these analyses, patients who developed HCC before 24 months and those whose observation periods were less than 24 months were excluded. (**c-d**) Comparison of cumulative incidences of HCC between patients with and without detectable HBV DNA at 1 year (**c**) and 2 years (**d**) of therapy.

Figure S3. Analysis of patients whose ALT was abnormal (>30) at 1 year of therapy but was normalized at 2 years. (**a**) Numbers of patients according to the status of ALT normalization at 1 and 2 years. (**b**) Among only patients without ALT normalization at 1 year of therapy, a comparison of cumulative HCC incidences

between patients with and without ALT normalization at 2 years was performed.

Table S1. Comparison of baseline characteristics between patients with ALT normalization (JSH criteria, ≤30) and those without after propensity score matching at 1 year of NA therapies.

Parameter	**ALT ≤ 30 at 1 year (n = 119)**	**ALT >30 at 1 year (n = 119)**	***p*-Value**
Age (years)	50 (41-58)	50 (40-61)	0.788
Sex (male/female)	90/29	92/27	0.760
Previous IFN (+/-)	14/105	12/107	0.678
DM (+/-)	9/110	6/113	0.424
T-Bil (mg/dl)	0.8 (0.6-1.1)	0.8 (0.6-1.2)	0.347
AST (U/l)	42 (29-82)	51 (35-75)	0.084
ALT (U/l)	56 (34-128)	60 (44-109)	0.295
Alb (g/dl)	4.2 (3.9-4.5)	4.2 (3.9-4.5)	0.879
Cr (mg/dl)	0.77 (0.67-0.88)	0.78 (0.69-0.87)	0.775
PLT ($\times 10^4/\mu l$)	17.6 (13.6-22.4)	16.2 (13.2-21.9)	0.477
AFP (ng/ml)	4.2 (3.0-9.5)	5.6 (3.1-11.4)	0.385
HBV DNA (log IU/ml)	5.3 (4.3-6.7)	5.4 (4.8-6.5)	0.451
HBsAg (IU/ml)	886 (151-2614)	1247 (216-3770)	0.377
HBeAg (+/-)	38/67	40/64	0.734
HBcrAg (log U/ml)	4.4 (3.0-6.4)	3.5 (3.0-6.1)	0.718
FIB-4 index	1.61 (1.08-2.83)	2.10 (1.21-3.00)	0.302
HBV genotype (A/B/C/D)	2/35/60/0	1/32/77/2	0.232
Initial NA (LAM/ETV/TDF/TAF)	16/89/9/5	12/88/13/6	0.705
Observation period (months)	72 (45-110)	72 (44-108)	0.817

Fig. S1

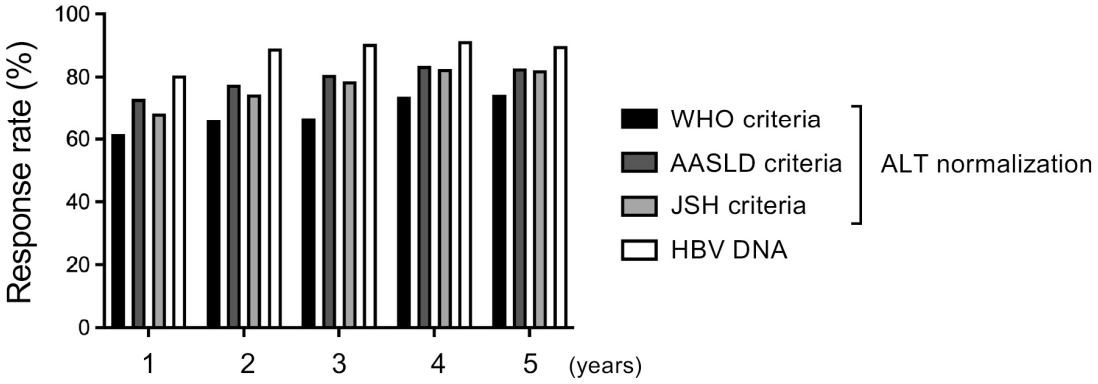

Response rate (%)
100
80
60
40
20
0
1
2
3
4
5
(years)
WHO criteria
AASLD criteria
JSH criteria
HBV DNA
ALT normalization

Fig. S2

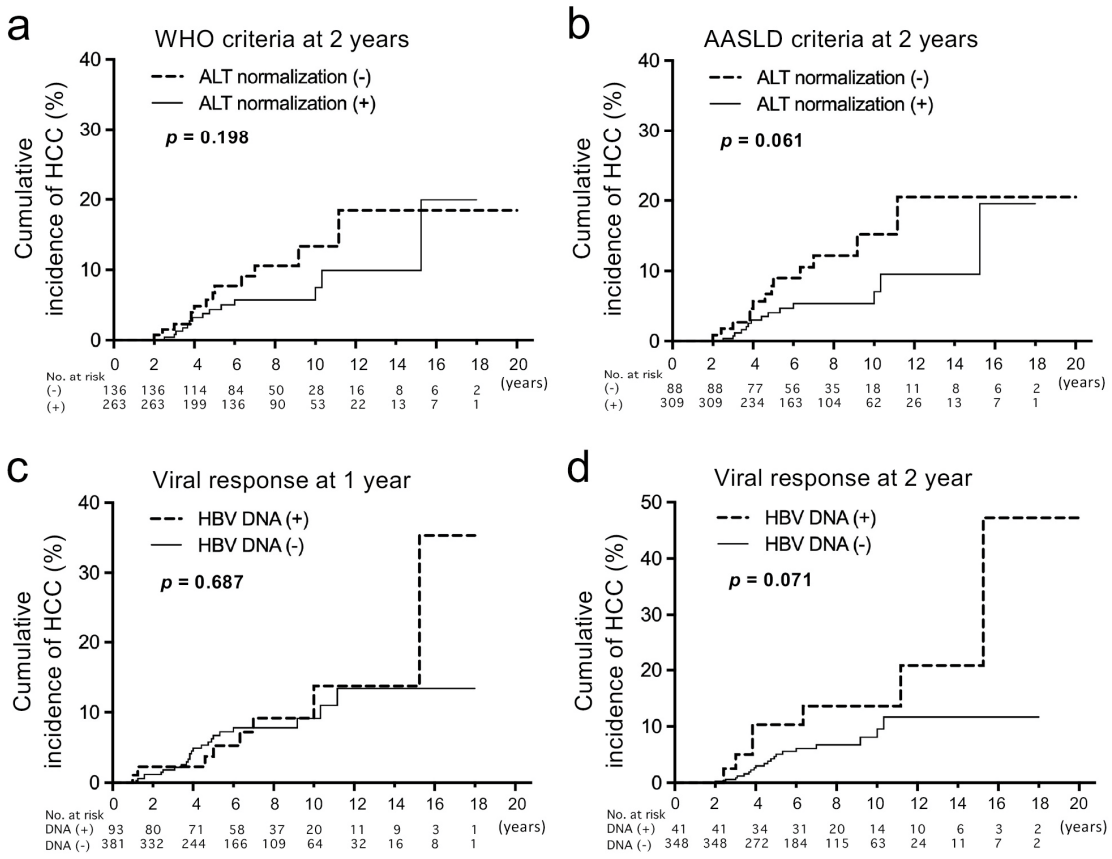
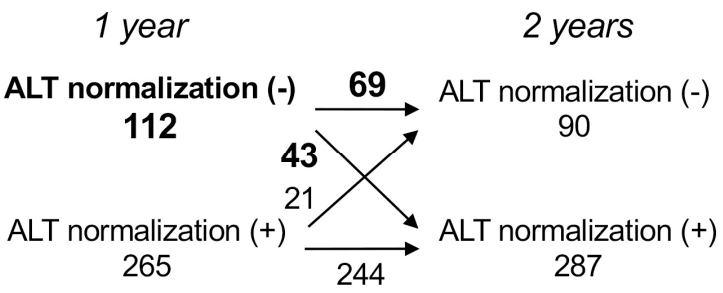
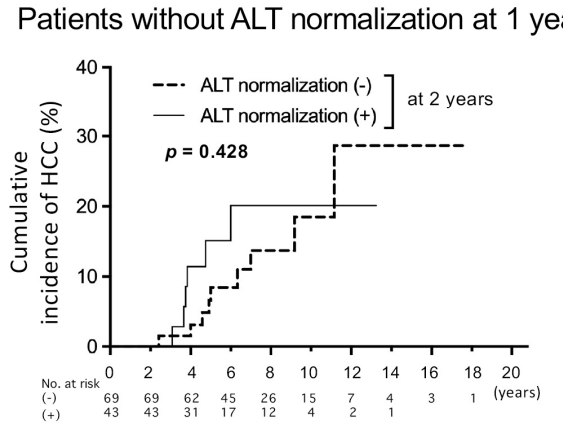

a
WHO criteria at 2 years
ALT normalization (-)
ALT normalization (+)
p = 0.198
Cumulative incidence of HCC (%)
No. at risk
(-) 136 136 114 84 50 28 16 8 6 2
(+) 263 263 199 136 90 53 22 13 7 1
(years)
b
AASLD criteria at 2 years
ALT normalization (-)
ALT normalization (+)
p = 0.061
Cumulative incidence of HCC (%)
No. at risk
(-) 88 88 77 56 35 18 11 8 6 2
(+) 309 309 234 163 104 62 26 13 7 1
(years)
c
Viral response at 1 year
HBV DNA (+)
HBV DNA (-)
p = 0.687
Cumulative incidence of HCC (%)
No. at risk
DNA (+) 93 80 71 58 37 20 11 9 3 1
DNA (-) 381 332 244 166 109 64 32 16 8 1
(years)
d
Viral response at 2 year
HBV DNA (+)
HBV DNA (-)
p = 0.071
Cumulative incidence of HCC (%)
No. at risk
DNA (+) 41 41 34 31 20 14 10 6 3 2
DNA (-) 348 348 272 184 115 63 24 11 7 2
(years)

Fig. S3

a


1 year
2 years
ALT normalization (-)
112
69
ALT normalization (-)
90
43
21
ALT normalization (+)
265
244
ALT normalization (+)
287

b


Patients without ALT normalization at 1 year
ALT normalization (-)
ALT normalization (+)
at 2 years
p = 0.428
Cumulative incidence of HCC (%)
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
(years)
No. at risk
(-) 69 69 62 45 26 15 7 4 3 1
(+) 43 43 31 17 12 4 2 1