Higher risk of disease progression in the grey zone relative to inactive Chronic hepatitis B

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Table S1 Definitions of immune states of CHB

	HBeAg	ALT	DNA	APRI/GPR/FIB-4
IC	-	＜40	DNA＜2000IU/mL	normal‡
GZIC	-	＜40	DNA≥2000IU/mL	normal
			DNA＜2000IU/mL	elevated
IA	-	≥80	DNA≥2000IU/mL	normal/elevated
GZIA	-	40≤ALT＜80		normal/elevated
		≥80	DNA＜2000IU/mL	normal/elevated

‡The upper limit of normal of APRI/FIB-4/GPR: APRI＜1.5，GPR＜0.32，FIB-4＜3.25.

Table S2 Baseline clinical characteristics of the group with and without phase changes

Characteristics	Without phase changes	phase changes	P value
n	216	84	
Group, n (%)			< 0.001
IC	163 (75.5%)	38 (45.2%)	
GZIC	53 (24.5%)	46 (54.8%)	
Family history, n (%)			0.889
No	189 (87.5%)	73 (86.9%)	
Yes	27 (12.5%)	11 (13.1%)	
Age, median (IQR)	46 (39, 52)	46 (38, 52.25)	0.969
Sex, n (%)			< 0.001
Female	123 (56.9%)	27 (32.1%)	
Male	93 (43.1%)	57 (67.9%)	
B-ultrasound, n (%)			0.161
No fatty liver	203 (94%)	75 (89.3%)	
Fatty liver	13 (6%)	9 (10.7%)	
DNA, n (%)			0.021
＜2000	192 (88.9%)	66 (78.6%)	
≥2000	24 (11.1%)	18 (21.4%)	
ALT, median (IQR)	20 (15.75, 26)	27 (19, 34)	< 0.001
AST, median (IQR)	22 (19, 26)	26 (22.75, 28)	< 0.001
γ-GT, median (IQR)	16 (13, 22)	22 (16, 31)	< 0.001
TB, median (IQR)	12 (9.275, 15.2)	13 (11.1, 17.725)	0.020
DB, median (IQR)	4.4 (3.4, 5.625)	5.2 (3.875, 6.725)	0.014
IDB, median (IQR)	7.55 (5.6, 10)	8.5 (6.4, 10.7)	0.052
AFP, median (IQR)	3.04 (2.125, 4.185)	3.055 (2.3975, 4.105)	0.283
A, median (IQR)	45.9 (44.6, 47.2)	46.7 (44.775, 48.025)	0.032

RBC, median (IQR)	4.735 (4.4075, 5.0825)	4.895 (4.5675, 5.3125)	0.020
Hb, median (IQR)	142.5 (133, 155)	150.5 (138.75, 157.25)	0.014
WBC, median (IQR)	5.65 (4.985, 6.72)	5.435 (4.685, 6.29)	0.089
N, median (IQR)	3.355 (2.8275, 4.2275)	3.185 (2.6975, 4.04)	0.241
L, median (IQR)	1.71 (1.43, 2.04)	1.695 (1.4575, 1.9825)	0.497
PLT, mean ± sd	191.67 ± 47.919	175.94 ± 48.885	0.012
APRI, median (IQR)	0.29374 (0.22908, 0.37567)	0.35916 (0.28982, 0.45249)	< 0.001
GPR, median (IQR)	0.18253 (0.1352, 0.25142)	0.26393 (0.18101, 0.37772)	< 0.001
FIB4, median (IQR)	1.1827 (0.92345, 1.6164)	1.2727 (0.88624, 1.866)	0.327
NLR, median (IQR)	1.9476 (1.4934, 2.6078)	1.9136 (1.4599, 2.4544)	0.809
PLR, median (IQR)	109.51 (85.665, 133.48)	104.57 (86.761, 122.32)	0.181

Table S3 Cox regression analysis of factors associated with conversion to IA or GZIA

Characteristics	Total(N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Group	300				
GZIC	99	Reference		Reference	
IC	201	0.306 (0.199 - 0.471)	< 0.001	0.683（0.334，1.398）	0.297
Family history	300				
No	262	Reference			
Yes	38	0.944 (0.500 - 1.781)	0.858		
Age	300	0.995 (0.973 - 1.017)	0.644		
Sex	300				
Female	150	Reference		Reference	
Male	150	2.512 (1.586 - 3.977)	< 0.001	2.852（1.096，7.419）	0.032
B-ultrasound	300				
No fatty liver	278	Reference			
Fatty liver	22	2.079 (1.038 - 4.164)	0.039	1.681 （0.723，3.911）	0.228
DNA	300				
＜2000	258	Reference		Reference	
≥2000	42	2.040 (1.209 - 3.442)	0.008	1.813（0.803，4.092）	0.152
ALT	300	1.059 (1.032 - 1.086)	< 0.001	1.010（0.948，1.078）	0.750
ALT1	300				
＞30/19	192	Reference		Reference	
≤30/19	108	0.487 (0.317 - 0.748))	0.001	1.000（0.409，2.445）	1.000
ALT2	300				
＞35/25	52	Reference		Reference	
≤35/25	248	0.390 (0.245 - 0.621)	< 0.001	0.539（0.235，1.239）	0.145

AST	300	1.060 (1.032 - 1.089)	< 0.001	0.970(0.888,1.059)	0.497
γ-GT	300	1.019 (1.013 - 1.025)	< 0.001	1.036(0.994,1.079)	0.095
TB	300	1.018 (0.995 - 1.041)	0.124		
IDB	300	1.014 (0.986 - 1.044)	0.322		
DB	300	1.110 (1.017 - 1.212)	0.020	1.134(0.994,1.248)	0.063
AFP	271	1.081 (1.037 - 1.127)	< 0.001	1.043(0.971,1.121)	0.248
A	300	1.052 (0.954 - 1.161)	0.306		
RBC	300	1.667 (1.070 - 2.597)	0.024	1.046（0.481，2.275）	0.910
Hb	300	1.015 (1.001 - 1.030)	0.032	0.991（0.968，1.014）	0.449
WBC	300	0.910 (0.773 - 1.071)	0.257		
N	300	0.927 (0.766 - 1.121)	0.434		
L	300	0.776 (0.498 - 1.208)	0.261		
PLT	300	0.995 (0.990 - 0.999)	0.026	0.998（0.989，1.006）	0.586
APRI	300	3.423 (1.943 - 6.030)	< 0.001	1.254(0.008,204.798)	0.930
GPRI	300	1.662 (1.319 - 2.093)	< 0.001	0.215（0.025，1.878）	0.165
FIB4	300	1.204 (1.074 - 1.350)	0.001	1.352 (0.843 ，2.168)	0.211
NLR	300	1.008 (0.798 - 1.273)	0.947		
PLR	300	0.997 (0.991 - 1.003)	0.306		

Table S4 Baseline clinical characteristics of the group with and without Antiviral therapy

Characteristics	without Antiviral therapy	Antiviral therapy	P value
n	270	30	
Group, n (%)			< 0.001
IC	193 (71.5%)	8 (26.7%)	
GZIC	77 (28.5%)	22 (73.3%)	
Family history, n (%)			1.000
No	236 (87.4%)	26 (86.7%)	
Yes	34 (12.6%)	4 (13.3%)	
Age, median (IQR)	45 (38.25, 52)	49 (39, 57.75)	0.089
Sex, n (%)			0.248
Female	138 (51.1%)	12 (40%)	
Male	132 (48.9%)	18 (60%)	
B-ultrasound, n (%)			1.000
No fatty liver	250 (92.6%)	28 (93.3%)	
Fatty liver	20 (7.4%)	2 (6.7%)	
DNA, n (%)			0.017
＜2000	237 (87.8%)	21 (70%)	
≥2000	33 (12.2%)	9 (30%)	
ALT, median (IQR)	22 (16, 28)	24 (16.25, 28)	0.708
AST, median (IQR)	23 (20, 27)	26 (21, 29.5)	0.022
γ-GT, median (IQR)	17 (14, 24)	20 (16, 31)	0.098
TB, median (IQR)	12.4 (9.6, 15.3)	12 (10.425, 19.375)	0.374
DB, median (IQR)	4.5 (3.5, 5.975)	4.8 (4.025, 7.325)	0.234
IDB, median (IQR)	7.7 (5.825, 10)	8.45 (5.925, 10.75)	0.405
AFP, median (IQR)	3.01 (2.17, 4.1125)	3.54 (2.55, 4.445)	0.141
A, median (IQR)	46.2 (44.7, 47.5)	45.45 (44, 47.975)	0.481

RBC, mean ± sd	4.8077 ± 0.47703	4.8247 ± 0.58327	0.857
Hb, median (IQR)	145 (134, 156)	145 (135, 156.75)	0.636
WBC, median (IQR)	5.65 (4.9925, 6.65)	5.08 (4.555, 5.97)	0.034
N, median (IQR)	3.335 (2.86, 4.21)	3.12 (2.645, 3.7125)	0.150
L, median (IQR)	1.71 (1.43, 2.04)	1.695 (1.465, 1.9825)	0.516
PLT, mean ± sd	191.54 ± 46.617	148.8 ± 50.206	< 0.001
APRI, median (IQR)	0.30592 (0.24313, 0.38439)	0.40529 (0.30761, 0.57273)	< 0.001
GPR, median (IQR)	0.19103 (0.14286, 0.26924)	0.29764 (0.1912, 0.49869)	< 0.001
FIB4, median (IQR)	1.1742 (0.89529, 1.6093)	1.8368 (1.2201, 2.6887)	< 0.001
NLR, median (IQR)	1.9348 (1.4766, 2.5798)	2.0016 (1.5925, 2.5284)	0.957
PLR, median (IQR)	109.51 (87.222, 132.75)	103.43 (70.78, 112.89)	0.009

Table S5 Baseline clinical characteristics of the group with and without end-stage liver diseases

Characteristics	Without End-stage liver diseases	End-stage liver diseases	P value
n	291	9	
Group, n (%)			0.011
IC	199 (68.4%)	2 (22.2%)	
GZIC	92 (31.6%)	7 (77.8%)	
Family history, n (%)			0.714
No	255 (87.6%)	7 (77.8%)	
Yes	36 (12.4%)	2 (22.2%)	
Age, median (IQR)	46 (38, 52.5)	46 (41, 48)	0.812
Sex, n (%)			0.498
Female	147 (50.5%)	3 (33.3%)	
Male	144 (49.5%)	6 (66.7%)	
B-ultrasound, n (%)			0.501
No fatty liver	270 (92.8%)	8 (88.9%)	
Fatty liver	21 (7.2%)	1 (11.1%)	
DNA, n (%)			0.226
＜2000	252 (86.6%)	6 (66.7%)	
≥2000	39 (13.4%)	3 (33.3%)	
ALT, median (IQR)	22 (16, 28)	27 (27, 32)	0.053
AST, median (IQR)	23 (20, 27)	26 (22, 32)	0.051
γ-GT, median (IQR)	17 (14, 25)	27 (20, 40)	0.008
TB, median (IQR)	12.4 (9.65, 15.5)	11.1 (10.4, 16.4)	0.870
DB, median (IQR)	4.5 (3.5, 6.1)	5.1 (4.1, 6.8)	0.554
IDB, median (IQR)	7.7 (5.75, 10.25)	7.2 (6, 9.5)	0.918
AFP, median (IQR)	3.03 (2.18, 4.15)	3.785 (3.4725, 4.6825)	0.247

A, median (IQR)	46.1 (44.6, 47.5)	46.4 (45.1, 48.6)	0.333
RBC, mean ± sd	4.8079 ± 0.48435	4.8578 ± 0.61577	0.763
Hb, median (IQR)	145 (134, 156.5)	152 (135, 155)	0.512
WBC, median (IQR)	5.59 (4.915, 6.64)	5.19 (4.73, 5.94)	0.385
N, median (IQR)	3.31 (2.825, 4.15)	3.47 (2.7, 3.57)	0.812
L, median (IQR)	1.71 (1.45, 2.04)	1.57 (1.23, 1.7)	0.132
PLT, mean ± sd	188.76 ± 47.27	138.89 ± 68.28	0.002
APRI, median (IQR)	0.31065 (0.2474, 0.38721)	0.625 (0.30726, 0.79268)	0.018
GPR, median (IQR)	0.19444 (0.14316, 0.27086)	0.41221 (0.3125, 0.73394)	0.002
FIB4, median (IQR)	1.1901 (0.8954, 1.6582)	1.6851 (1.0987, 2.929)	0.114
NLR, median (IQR)	1.9209 (1.4743, 2.5646)	2.2203 (1.6752, 3.9512)	0.183
PLR, median (IQR)	108.63 (86.08, 129.97)	104.07 (70, 115.49)	0.268

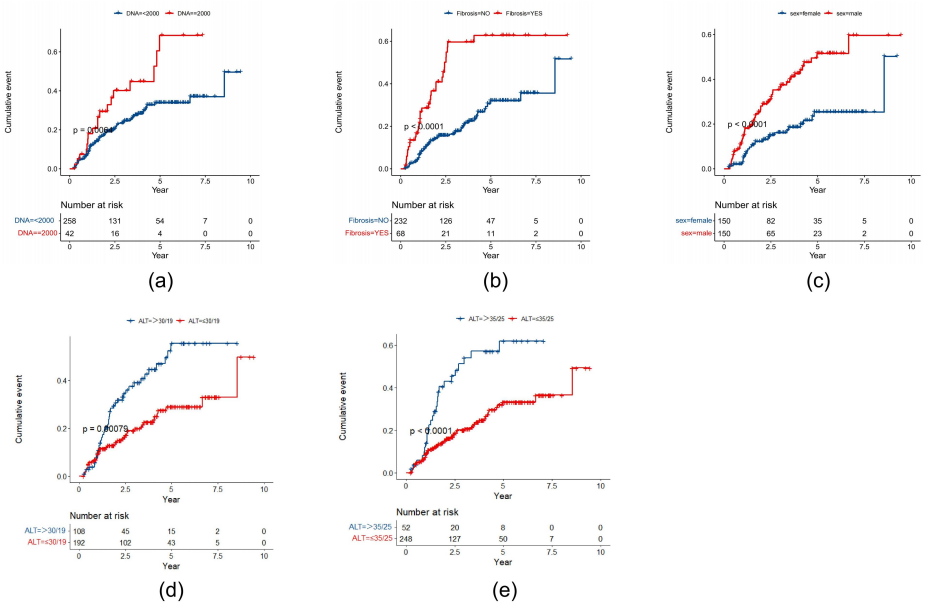

Fig.S1 Cumulative event rates of conversion to IA or GZIA between different groups: (a) DNA <2000IU/ml vs. DNA ≥2000IU/ml; (b) with liver fibrosis (defined by APRI, FIB-4, GPR) vs. without liver fibrosis; (c)male vs. female; (d) ALT >30/19U/L vs. ALT≤30/19U/L; (e) ALT>35/25U/L vs. ALT≤35/25U/L

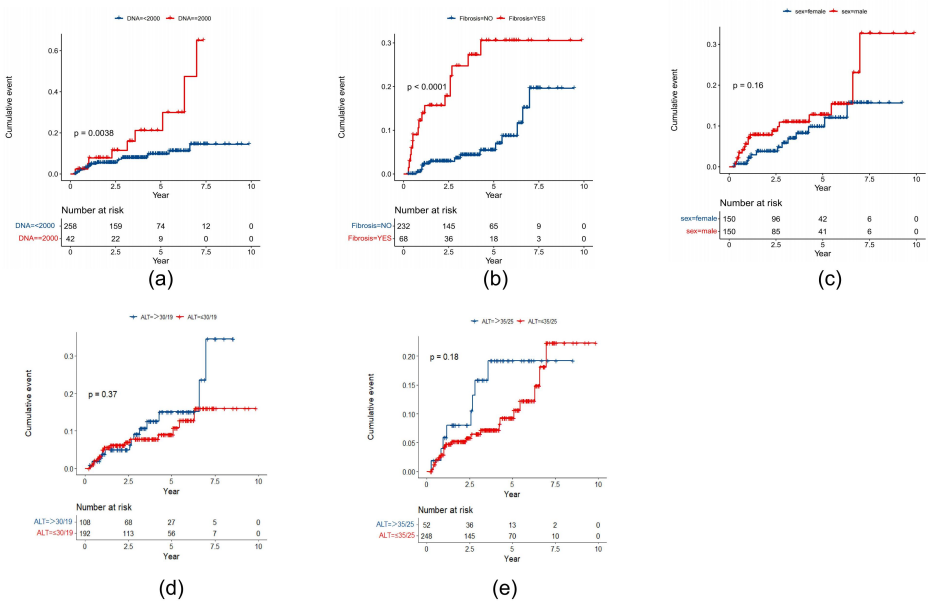

Fig.S2 Cumulative event rates of antiviral therapy between different groups: (a) DNA <2000IU/ml vs. DNA ≥2000IU/ml; (b) with liver fibrosis (defined by APRI, FIB-4, GPR) vs. without liver fibrosis; (c)male vs. female; (d) ALT >30/19U/L vs. ALT≤30/19U/L; (e) ALT>35/25U/L vs. ALT≤35/25U/L

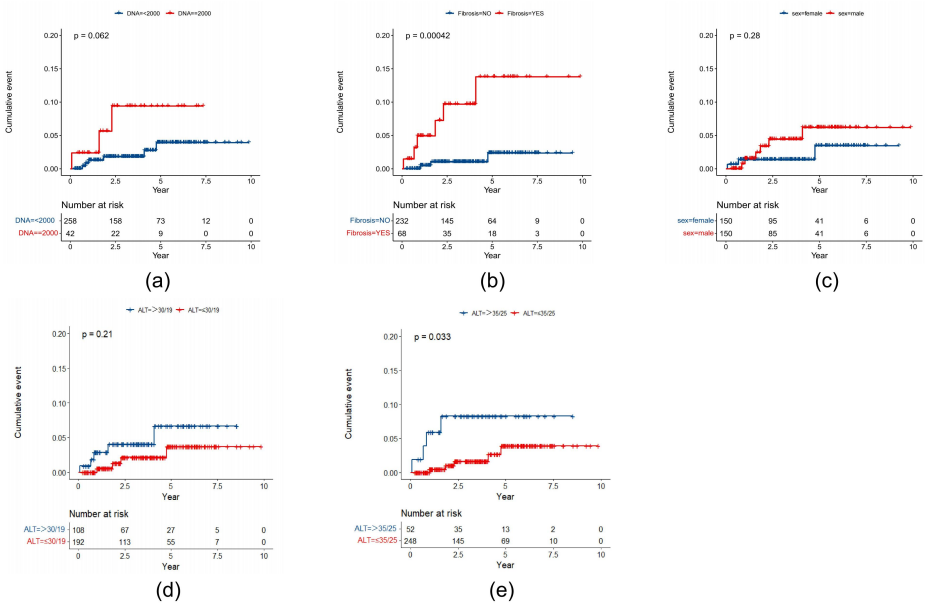

Fig.S3 Cumulative event rates of End-stage liver disease between different groups: (a) male vs. female; (b) DNA <2000IU/ml vs. DNA ≥2000iu/ml; (c) with liver fibrosis (defined by APRI,FIB-4,GPR) vs. without liver fibrosis; (d) ALT >30/19U/L vs. ALT≤30/19U/L; (e) ALT>35/25U/L vs. ALT≤35/25U/L