Table S1 Antiviral outcomes in patients with sustained NAFLD and remission of NAFLD

Efficacy	Sustained NAFLD (n=21)	Remission of NAFLD (n=7)	*P* value
HBV DNA suppression, n (%)			
At week 52	11 (52.4)	4 (57.1)	1.0
At week 104	13 (61.9)	6 (85.7)	0.371
HBeAg seroconversion, n (%)			
At week 52	4 (19.0)	1 (14.3)	1.0
At week 104	5 (23.8)	1 (14.3)	1.0
ALT normalization, n (%)			
At week 52	9 (42.9)	6 (85.7)	0.084
At week 104	12 (57.1)	6 (85.7)	0.364
Histological response			
Change in Knodell score[a]	-3.0 (-3.5 to -0.5)	0 (-3.0 to 0)	0.320
Improvement, n (%)	13 (61.9)	3 (42.9)	0.418
No change, n (%)	8 (38.1)	4 (57.1)	
Progression, n (%)	0 (0)	0 (0)	
Change in Ishak score[b]	0 (-1.0 to 0)	0 (-1.0 to 1.0)	0.658
Improvement, n (%)	9 (42.9)	3 (42.9)	0.432
No change, n (%)	10 (47.6)	2 (28.6)	
Progression, n (%)	2 (9.5)	2 (28.6)	

Note: [a] Necroinflammation improvement was defined as decrease in Knodell score ≥ 2-point, static was defined as change within 1 point, progression was defined as increase ≥ 2-point. [b] Fibrosis improvement was defined as decrease in Ishak score ≥ 1-point, progression was defined as increase in Ishak score ≥ 1-point.

Table S2 Histologic assessment in subgroups

Variable	Without NAFLD at baseline				With NAFLD at baseline		
	Total (n=136)	Sustained non-NAFLD[a] (n=114)	New-onset NAFLD[b] (n=22)		Total (n=28)	Sustained NAFLD[c] (n=21)	Remission of NAFLD[d] (n=7)
Baseline							
Knodell score	5.0 (3.0-7.0)	5.0 (3.0-7.0)	5.0 (3.0-7.0)		5.0 (3.0-8.8)	5.0 (3.0-8.5)	3.0 (2.0-9.0)
Knodell score category							
0-3	38 (27.9)	32 (28.1)	6 (27.3)		10 (35.7)	6 (28.6)	4 (57.1)
4-6	51 (37.5)	41 (36.0)	10 (45.5)		7 (25.0)	7 (33.3)	0 (0)
7-9	35 (25.7)	31 (27.2)	4 (18.2)		6 (21.4)	4 (19.0)	2 (28.6)
10-14	12 (8.8)	10 (8.8)	2 (9.1)		5 (17.9)	4 (19.0)	1 (14.3)
Knodell score ≥7	47 (34.6)	41 (36.0)	6 (27.3)		11 (39.3)	8 (38.1)	3 (42.9)
Ishak score	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-2.0)		2.0 (1.0-2.8)	2.0 (1.0-2.5)	1.0 (1.0-3.0)
Fibrosis stage category							
0	4 (2.9)	3 (2.6)	1 (4.5)		2 (7.1)	1 (4.8)	1 (14.3)
1	37 (27.2)	29 (25.4)	8 (36.4)		9 (32.1)	6 (28.6)	3 (42.9)
2	60 (44.1)	51 (44.7)	9 (40.9)		10 (35.7)	9 (42.9)	1 (14.3)
3	20 (14.7)	17 (14.9)	3 (13.6)		4 (14.3)	2 (9.5)	2 (28.6)
4	7 (5.1)	6 (5.3)	1 (4.5)		1 (3.6)	1 (4.8)	0 (0)
5	7 (5.1)	7 (6.1)	0 (0)		2 (7.1)	2 (9.5)	0 (0)
6	1 (0.7)	1 (0.9)	0 (0)		0 (0)	0 (0)	0 (0)
Significant fibrosis[a]	35 (25.7)	31 (27.2)	4 (18.2)		7 (25.0)	5 (23.8)	2 (28.6)
Week 104							
Knodell score	2.0 (2.0-4.0)	2.0 (2.0-4.0)	2.0 (2.0-4.0)		3.0 (2.0-4.8)	3.0 (2.0-4.5)	3.0 (2.0-6.0)
Knodell score category							
0-3	101 (74.3)	85 (74.6)	16 (72.7)	*	18 (64.3)	13 (61.9)	5 (71.4)
4-6	31 (22.8)	28 (24.5)	3 (13.6)		8 (28.6)	7 (33.3)	1 (14.3)
7-9	3 (2.2)	1 (0.9)	2 (9.1)		2 (7.1)	1 (4.8)	1 (14.3)

10-14	1 (0.7)	0 (0)	1 (4.5)		0 (0)	0 (0)	0 (0)
Knodell score ≥7	4 (2.9)	1 (0.9)	3 (13.6)	*	2 (7.1)	6 (27.3)	1 (14.3)
Ishak score	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (0-2.0)		1.0 (1.0-2.0)	2.0 (1.0-2.0)	1.0 (1.0-2.0)
Fibrosis stage category							
0	22 (16.2)	16 (14.2)	6 (27.3)		4 (14.3)	4 (19.0)	0 (0)
1	71 (52.2)	65 (57.0)	6 (27.3)		11 (39.3)	6 (28.6)	5 (71.4)
2	33 (24.3)	26 (22.8)	7 (31.8)		10 (35.7)	8 (38.1)	2 (28.6)
3	8 (5.9)	5 (4.4)	3 (13.6)		3 (10.7)	3 (14.3)	0 (0)
4	2 (1.5)	2 (1.8)	0 (0)		0 (0)	0 (0)	0 (0)
5-6	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)
Significant fibrosis	10 (7.4)	7 (6.1)	3 (13.6)		3 (10.7)	3 (14.3)	0 (0)

[a] Significant fibrosis was defined as Ishak score ≥3. [b] sustained non-NAFLD was defined as no evidence of NAFLD at either baseline or week 104; [c] new-onset NAFLD was defined as steatosis score ≥1 at week 104. In patients with NAFLD at baseline, [d] sustained NAFLD was defined when the steatosis grade was always ≥S1 both at baseline and week 104, [e] remission of NAFLD was defined when the steatosis grade decreased to S0 and week 104. * Comparison between the new-onset NAFLD and sustained without NAFLD group, $P < 0.05$.

Table S3 Predictors for ALT normalization in CHB patients.

Variable [a]	Univariate analysis		Mutivariate analysis Model 1		Mutivariate analysis Model 2		Mutivariate analysis Model 3	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Gender (Male vs Female)	0.257 (0.027-2.463)	0.238						
Age at first biopsy (years)	0.991 (0.926-1.060)	0.796						
BMI（kg/m^2）at baseline	0.799 (0.705-0.906)	＜0.001	0.805 (0.700-0.925)	0.002	0.775(0.675-0.889)	＜0.001		
ALT (U/L) at baseline	1.006 (0.996-1.015)	0.220						
HBV DNA (log_{10}IU/mL) at baseline	1.784 (1.005-3.166)	0.048	1.558 (0.992-2.446)	0.054	1.556 (0.997-2.431)	0.052	1.408 (0.892-2.223)	0.142
Knodell score at baseline	1.237 (0.988-1.548)	0.064	1.106 (0.919-1.331)	0.286	1.055 (0.877 -1.268)	0.572	1.159 (0.951-1.411)	0.144
Ishak score at baseline	0.754 (0.445-1.277)	0.293						
Optimized therapy[b] (vs mono)	0.647 (0.179-2.341)	0.507						
NAFLD at baseline	0.150 (0.057-0.392)	＜0.001	0.233 (0.082-0.662)	0.006				
NAFLD status change								
Sustained non-NAFLD	Reference							
New-onset NAFLD	0.247 (0.063-0.970)	0.045					0.222 (0.063-0.781)	0.019
Sustained NAFLD	0.051 (0.013-0.193)	＜0.001					0.072 (0.023-0.227)	＜0.001

Note: Logistic regression analysis was used to identify factors associated with ALT normalization, calculating odds ratios (ORs), 95% confidence intervals (95% CIs) and P values.

[a] No significant interactions amongst variables in each model; [b] Optimized therapy was be defined as paients with tibifedine monotherapy had adefovir added;

Table S4 Predictors for fibrosis improvement in CHB patients.

Variable [a]	Univariate analysis		Mutivariate analysis Model 1		Mutivariate analysis Model 2		Mutivariate analysis Model 3	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Gender (Male vs Female)	1.782 (0.564-5.624)	0.325						
Age at first biopsy (years)	0.992 (0.943-1.043)	0.752						
BMI（kg/m^2）at baseline	1.185 (1.030-1.365)	0.018	1.085 (0.967-1.217)	0.164	1.046 (0.942-1.161)	0.401		
ALT (U/L) at baseline	0.998 (0.991-1.004)	0.461						
HBV DNA (log_{10}IU/mL) at baseline	0.950 (0.622-1.451)	0.813						
Knodell score at baseline	0.905 (0.748-1.095)	0.305						
Ishak score at baseline	5.829 (2.851-11.916)	＜0.001	4.346 (2.533-7.456)	＜0.001	3.933 (2.313-6.689)	＜0.001	4.543 (2.591-7.964)	＜0.001
Optimized treatment [b] (vs mono)	0.819 (0.281-2.390)	0.715						
NAFLD at baseline	0.436 (0.190-0.996)	0.049	0.385 (0.140-1.057)	0.064				
NAFLD status change								
Sustained non-NAFLD	Reference							
New-onset NAFLD	0.207 (0.077-0.552)	0.002					0.185 (0.058-0.588)	0.004
Sustained NAFLD	0.332 (0.128-0.860)	0.023					0.247 (0.077-0.800)	0.020
Remission of NAFLD	0.332 (0.071-1.564)	0.163					0.454 (0.064-3.195)	0.428

Note: Logistic regression analysis was used to identify factors associated with fibrosis improvemen, calculating odds ratios (ORs), 95% confidence intervals (95% CIs) and P values.

[†] No significant interactions amongst variables in each model; [‡] Optimized therapy was be defined as paients with tibifedine monotherapy had adefovir added.

Table S5 Antiviral response in subgroups stratified by baseline NAFLD

Efficacy	Without NAFLD (n=136)	With NAFLD (n=28)	*P* value
HBV DNA suppression, n (%)			
Week 52	68 (50.0)	15 (53.6)	0.731
week 104	92 (67.6)	19 (67.9)	1.0
HBeAg seroconversion, n (%)			
week 52	27 (19.9)	5 (17.9)	0.808
At week 104	40 (29.4)	6 (21.4)	0.392
ALT normalization, n (%)			
At week 52	117 (86.0)	15 (53.6)	＜0.001
At week 104	124 (91.2)	18 (64.3)	＜0.001
Histological response			
Change in Knodell score[a]	-3.0 (-4.0 to -1.0)	-3.0 (-3.0 to 0)	0.437
Improvement, n (%)	87 (64.0)	16 (57.1)	0.507
No change, n (%)	44 (32.4)	12 (42.9)	
Progression, n (%)	5 (3.7)	0 (0)	
Change in Ishak score[b]	-1.0 (-1.0 to 0)	0 (-1.0 to 0)	0.066
Improvement, n (%)	86 (63.2)	12 (42.9)	0.113
No change, n (%)	39 (28.7)	12 (42.9)	
Progression, n (%)	11 (8.1)	4 (14.3)	

Note: [a] Necroinflammation improvement was defined as decrease in Knodell score ≥ 2-point, static was defined as change within 1 point, progression was defined as increase ≥ 2-point. [b] Fibrosis improvement was defined as decrease in Ishak score ≥ 1-point, progression was defined as any increase in Ishak score.

Figure S1 Liver necroinflammation grade of patients in the sustained non-NAFLD, new-onset NAFLD and sustained NAFLD group.

(a) Distribution of Knodell necroinflammation scores n the sustained without NAFLD, new-onset NAFLD and sustained NAFLD group at baseline and week 104; (b) Changes in the Knodell necroinflammation score among individual patients in the sustained without NAFLD group; (c) new-onset NAFLD group; and (d) sustained NAFLD group.

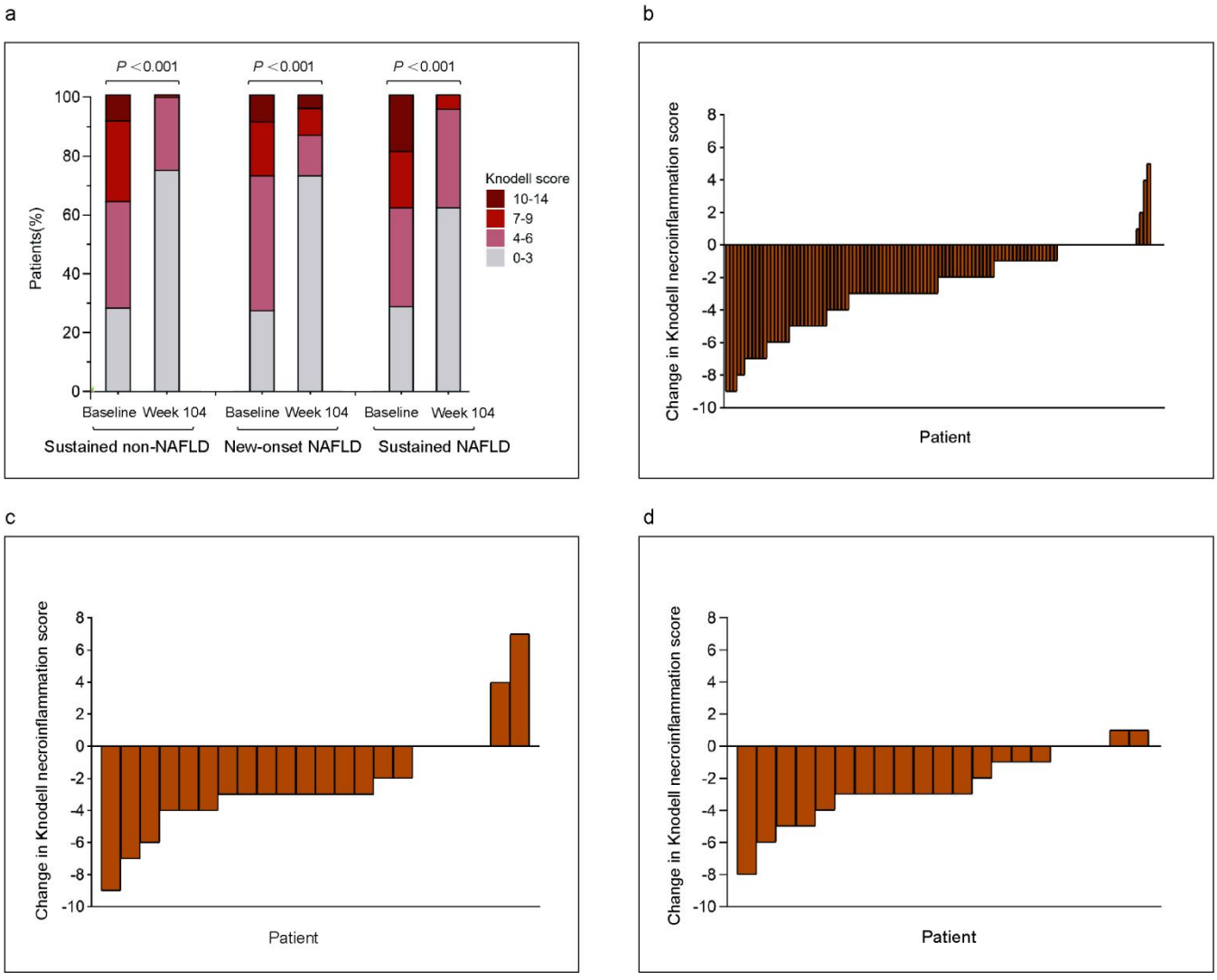


Figure S2　Histological results during antiviral treatment in patients with　sustained NAFLD and remission of NAFLD

Distribution of Knodell necroinflammatory scores in patients with sustained NAFLD and remission of NAFLD at baseline and week 104(a) ; Changes in the Knodell inflammatory score among individual patients in the NAFLD resolution group (b) and sustained NAFLD group(c)；Distribution of Ishak fibrosis scores in patients with sustained NAFLD and remission of NAFLD at baseline and week 104 (d); Changes in the Ishak fibrosis score among individual patients in the sustained NAFLD group (e); and remission of NAFLD group (f).

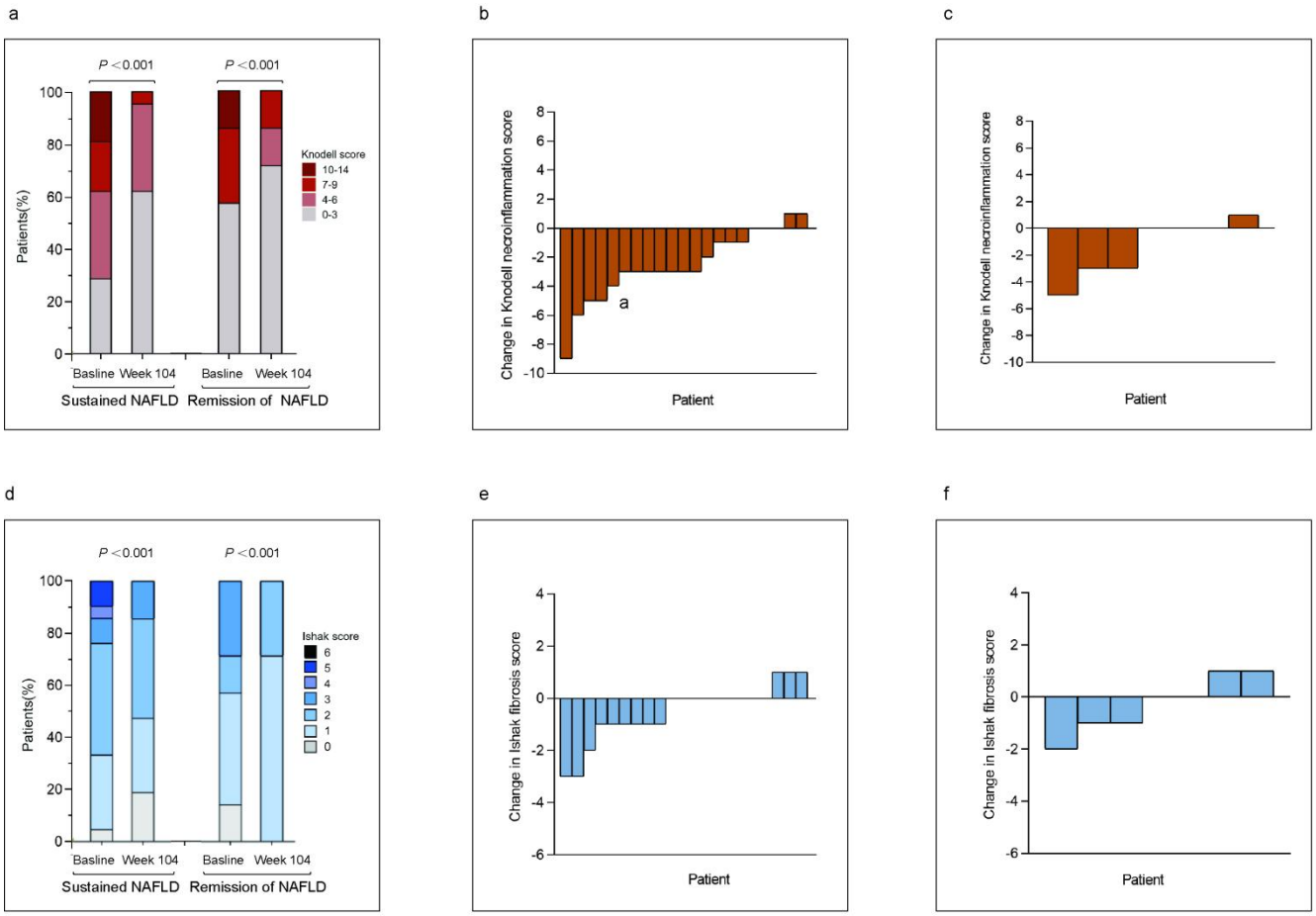
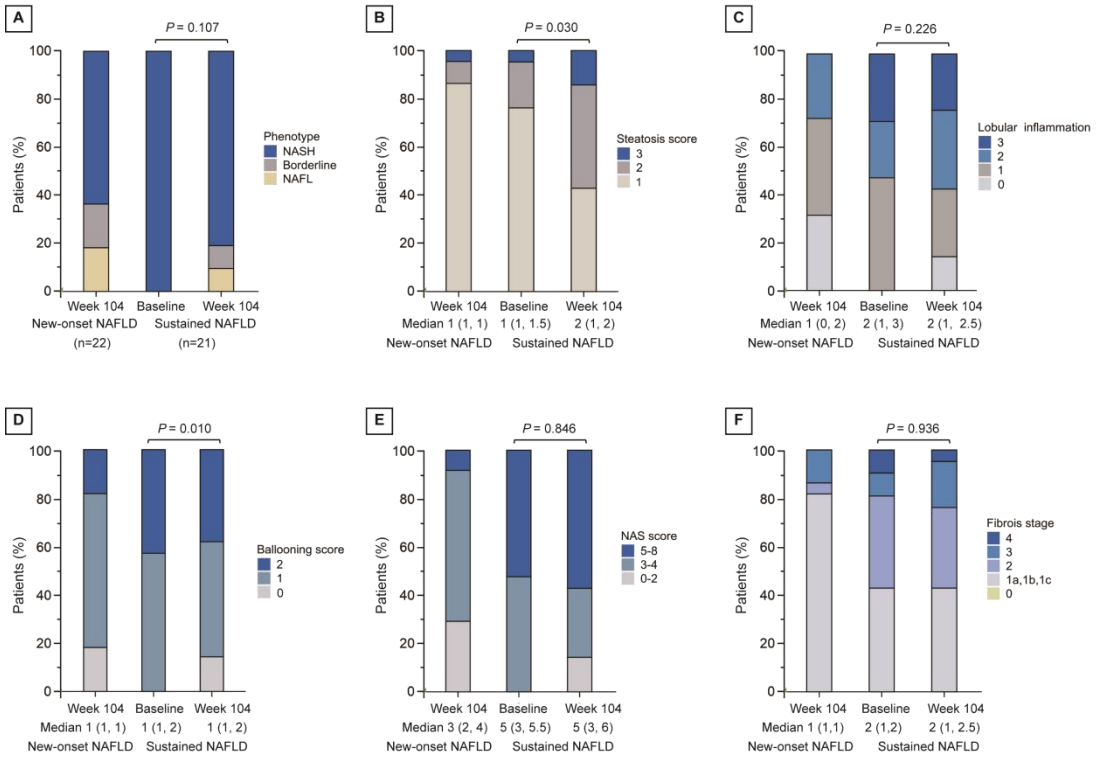


Figure S3 Dynamic changes in the histological characteristics of patients with new-onset and sustained NAFLD during antiviral therapy.

(A) Changes of the proportion of patients with NASH, borderline or NAFL at week 104. Changes in the histological characteristics: steatosis grade (B) , lobular inflammation score (C), ballooning score (D), NAS score (F), and fibrosis stage (E) .



Note: The histopathological features of NAFLD were evaluated according to the system developed by NASH Clinical Research Network.[25] The NAFLD activity score (NAS) ranged from 0 to 8 including steatosis scores (0–3), lobular inflammation scores (0–3) and hepatocellular ballooning scores (0–2). Liver fibrosis for NAFLD was staged 0–4.

Nonalcoholic fatty liver was defined by steatosis with or without inflammation but without ballooning injury. Cases designated as borderline steatohepatitis had some but not all features of definite steatohepatitis, usually consisting of steatosis, inflammation, and appropriate fibrosis without ballooning. Definite steatohepatitis was defined by the presence of macrovesicular steatosis, inflammation, and hepatocellular ballooning in a mainly zone 3 distribution.[25]