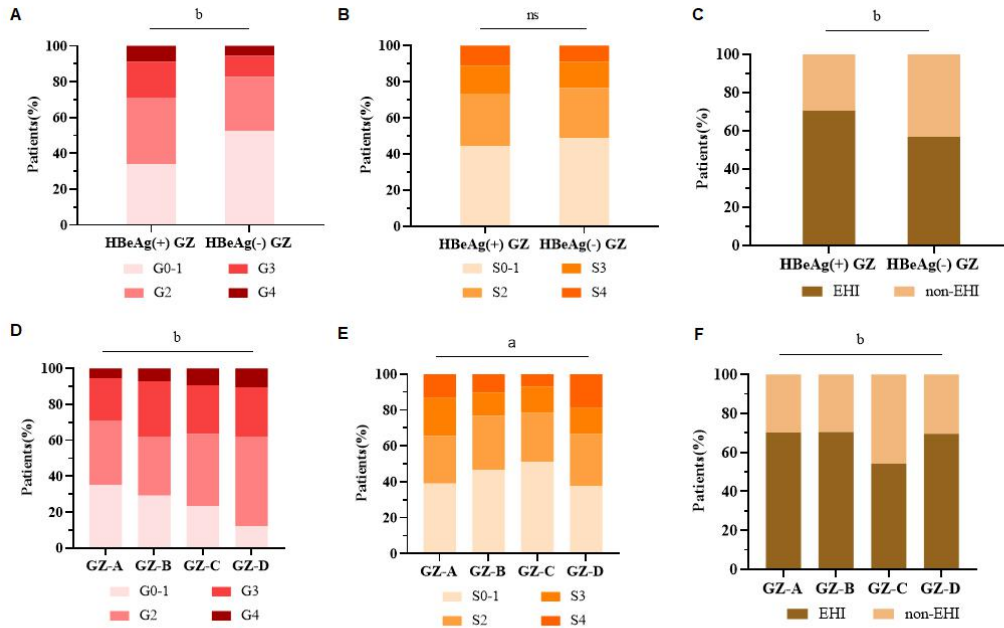


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Supplementary Figure 1 Flowchart of the study design.



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Supplementary Figure 2 Distribution and liver histological features of chronic hepatitis B patients in different grey zones. A: Proportions of liver inflammation grades in HBeAg-positive and HBeAg-negative grey zones; B: Proportions of fibrosis stages in HBeAg-positive and HBeAg-negative grey zones; C: Proportions of significant hepatic injury (SHI) in HBeAg-positive and HBeAg-negative grey zones; D: Proportions of liver inflammation grades in different grey zones; E: Proportions of fibrosis stages in different grey zones; F: Proportions of significant hepatic injury (SHI) in different grey zones. ^a $P < 0.05$, ^c $P < 0.001$; ns: Not significant.

Supplementary Table 1 Definition of different immune states of chronic hepatitis B

	HBeAg	HBV DNA level, IU/ml	ALT, U/L ¹
HBeAg-positive chronic infection	+	$> 10^7$	\leq ULN
HBeAg-positive chronic hepatitis	+	10^4 - 10^7	$>$ ULN
HBeAg-negative chronic infection	-	< 2000	\leq ULN
HBeAg-negative chronic hepatitis	-	> 2000	$>$ ULN
Grey zone A	+	$\leq 10^7$	\leq ULN
Grey zone B	+	$< 10^4$ or $>10^7$	$>$ ULN
Grey zone C	-	≥ 2000	\leq ULN
Grey zone D	-	≤ 2000	$>$ ULN

¹EASL, ALT ULN was 40 U/L.

Supplementary Table 2 Clinical characteristics of chronic hepatitis B patients among different grey zones

Clinical characteristics	Grey zone A (n = 128)	Grey zone B (n = 281)	Grey zone C (n = 334)	Grey zone D (n = 69)	P value
Age (year)	35.0(29.3-39.0)	31.0(26.0-36.0)	40.0(35.0-46.0)	36.0(33.0-44.5)	< 0.001
Male (%)	81(63.3%)	222(79.0%)	236(70.7%)	63(91.3%)	< 0.001
BMI (kg/m ²)	21.3(19.4-24.2)	21.6(19.7-24.5)	22.1(20.1-24.2)	23.5(21.3-25.6)	0.002
Diabetes (%)	2(1.6%)	0(0)	4(5.8%)	6(8.7%)	< 0.001
HBV DNA (log ₁₀ IU/ml)	5.39(4.27-6.11)	7.86(7.38-8.23)	4.40(3.85-5.18)	2.40(2.00-2.77)	< 0.001
PLT (10 ⁹ /L)	200.0(159.0-236.5)	201.0(164.5-240.5)	196.0(163.0-231.0)	195.0(142.5-225.5)	0.602
ALT (U/L)	30.5(23.0-36.0)	70.0(51.0-123.0)	28.0(20.8-34.0)	53.0(45.0-76.0)	< 0.001
AST (U/L)	28.5(24.3-33.0)	51.0(35.5-80.0)	25.0(21.0-30.0)	35.0(29.5-54.5)	< 0.001
GGT (U/L)	27.0(19.0-38.5)	39.0(23.0-80.5)	23.0(17.0-33.0)	47.0(30.0-82.5)	< 0.001
Tbil (umol/L)	12.2(8.7-16.3)	14.8(10.5-20.5)	12.2(9.3-15.8)	14.1(10.2-20.7)	< 0.001
ALB (g/L)	44.6(42.2-46.8)	44.6(41.1-46.6)	45.4(42.9-47.3)	45.4(42.8-48.1)	0.004
AFP (ng/ml)	3.1(2.2-5.1)	3.5(2.2-7.8)	2.8(1.9-4.5)	3.2(1.9-5.5)	0.001
PT (s)	13.4(12.9-14.0)	13.4(12.8-14.1)	13.3(12.9-13.9)	13.3(12.6-14.1)	0.657
APRI	0.36(0.26-0.50)	0.66(0.40-1.21)	0.31(0.25-0.43)	0.48(0.35-0.84)	< 0.001
FIB-4	0.90(0.65-1.35)	0.87(0.57-1.45)	0.99(0.78-1.93)	0.97(0.67-1.49)	0.018

GPR	0.36(0.24-0.52)	0.50(0.26-1.12)	0.30(0.20-0.47)	0.72(0.40-1.34)	<
					0.001
Inflammation					<
					0.001
G0-1	45(35.2%)	94(33.5%)	184(55.1%)	28(40.6%)	
≥G2	83(64.8%)	187(66.5%)	150(44.9%)	41(59.4%)	
Fibrosis					0.047
S0-1	50(39.1%)	131(46.6%)	171(51.2%)	26(37.7%)	
≥S2	78(60.9%)	150(60.9%)	163(48.8%)	43(62.3%)	
SHI					<
					0.001
No	38(29.7%)	83(29.5%)	153(45.8%)	21(30.4%)	
Yes	90(70.3%)	198(70.5%)	181(54.2%)	48(69.6%)	

PLT: Platelet; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; GGT: Gamma-glutamyl transpeptidase; Tbil: Total bilirubin; ALB: Albumin; AFP: α -fetoprotein; PT: Prothrombin time; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis score based on four factors; GPR: Gamma-glutamyl transpeptidase-to-platelet ratio; SHI: Significant hepatic injury.

Supplementary Table 3 Logistic regression analysis of clinical parameters of chronic hepatitis B patients with different grey zones associated with significant hepatic injury.

Variables	Univariable analysis		Multivariable analysis	
	OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value
HBeAg (+) group				
Sex				
Male	Referent			
Female	1.569(0.981-2.508)	0.060		
Age (year)	1.021(0.994-1.050)	0.130		
HBV DNA (log ₁₀ IU/ml)	0.894(0.786-1.016)	0.086		
PLT (10 ⁹ /L)	0.991(0.987-0.995)	<0.001	0.995(0.990-0.999)	0.013
ALT (U/L)	1.006(1.002-1.010)	0.003	0.996(0.989-1.003)	0.230
AST (U/L)	1.022(1.012-1.032)	<0.001	1.017(1.001-1.031)	0.032
GGT (U/L)	1.018(1.010-1.026)	<0.001	1.009(1.000-1.017)	0.048
Tbil (umol/L)	1.052(1.022-1.082)	0.001	1.014(0.986-1.143)	0.335
ALB (g/L)	0.862(0.809-0.918)	<0.001	0.924(0.863-0.990)	0.024
PT (s)	1.479(1.012-1.883)	0.001	1.189(0.890-1.587)	0.242
APRI	6.266(3.161-12.420)	<0.001		
FIB-4	3.569(2.206-5.574)	<0.001		
GPR	4.312(2.352-7.907)	<0.001		
HBeAg (-) group				
Sex				
Male	Referent		Referent	
Female	2.213(1.406-3.483)	0.001	1.731(1.013-2.956)	0.045
Age (year)	1.001(0.978-1.024)	0.962		
HBV DNA (log ₁₀ IU/ml)	1.182(1.008-1.386)	0.039	1.330(1.079-1.640)	0.008

PLT (10 ⁹ /L)	0.990(0.986-0.994)	<0.001	0.993(0.989-0.998)	0.003
ALT (U/L)	1.014(1.003-1.024)	0.011	1.006(0.991-1.022)	0.407
AST (U/L)	1.028(1.009-1.047)	0.003	1.001(0.985-1.017)	0.937
GGT (U/L)	1.020(1.010-1.030)	<0.001	1.015(1.003-1.026)	0.011
Tbil (umol/L)	1.025(1.004-1.047)	0.018	1.010(0.992-1.030)	0.277
ALB (g/L)	0.913(0.862-0.967)	0.002	0.945(0.884-1.010)	0.094
PT (s)	1.599(1.261-2.026)	<0.001	1.260(0.977-1.625)	0.075
APRI	11.945(3.911-36.486)	<0.001		
FIB-4	2.329(1.598-3.376)	<0.001		
GPR	6.561(3.084-13.956)	<0.001		

PLT: Platelet; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; GGT: Gamma-glutamyl transpeptidase; Tbil: Total bilirubin; ALB: Albumin; AFP: α -fetoprotein; PT: Prothrombin time; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis score based on four factors; GPR: Gamma-glutamyl transpeptidase-to-platelet ratio; SHI: Significant hepatic injury.