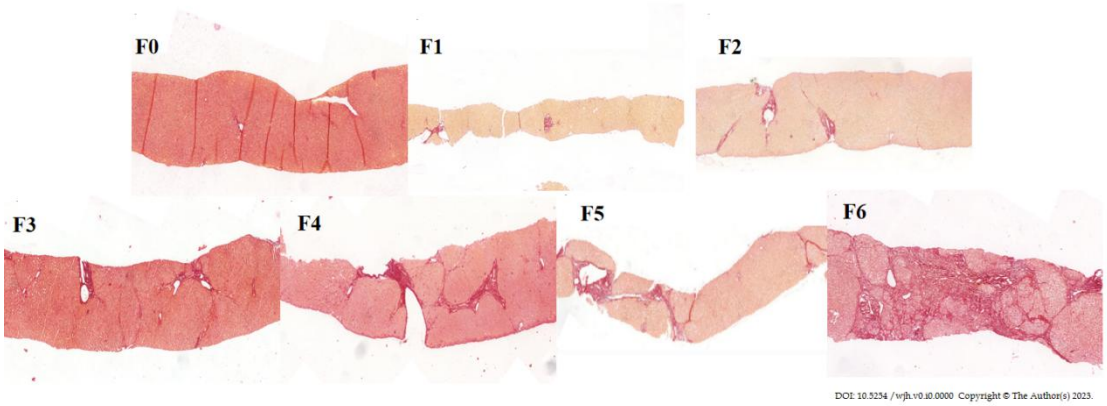
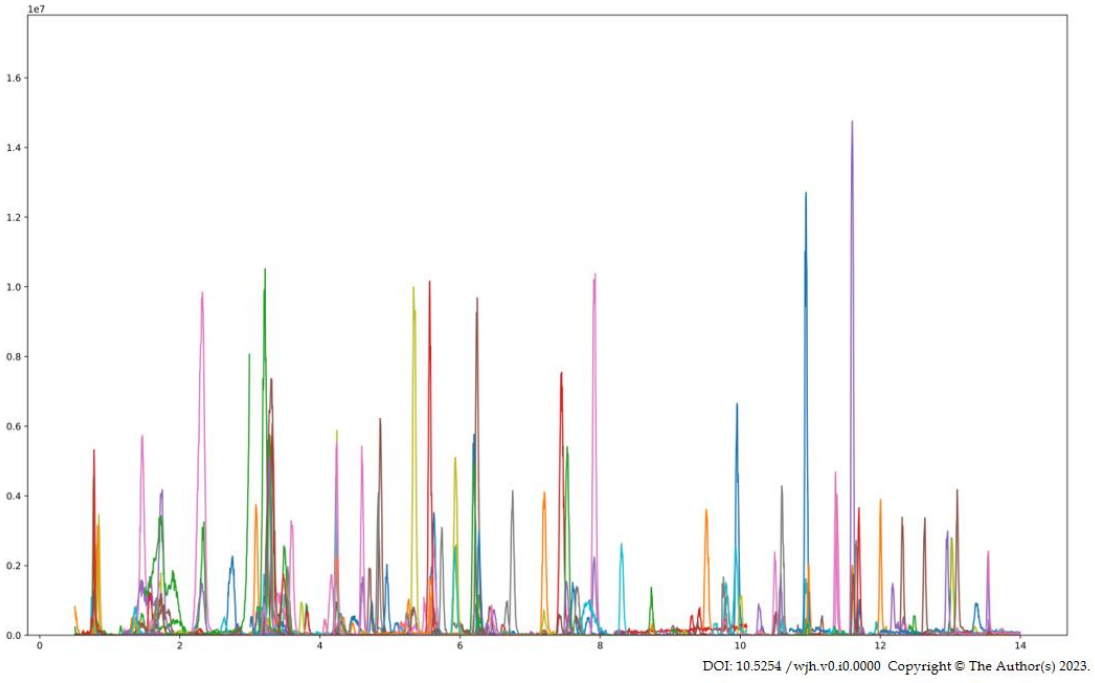
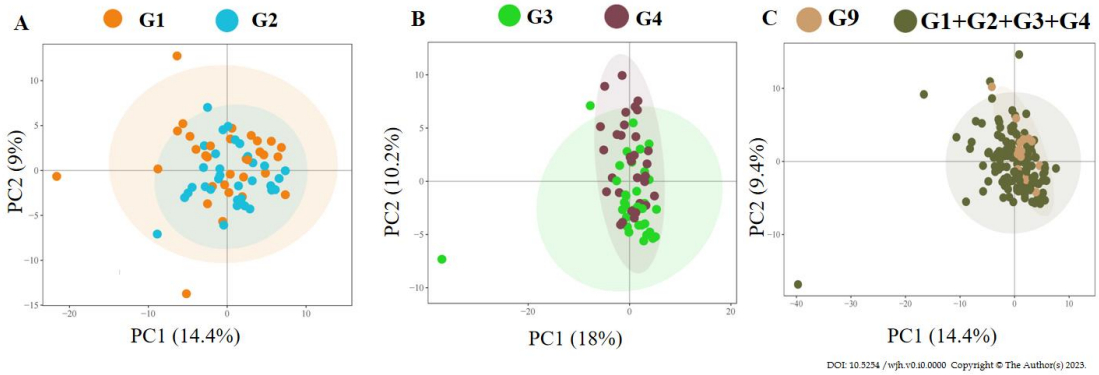


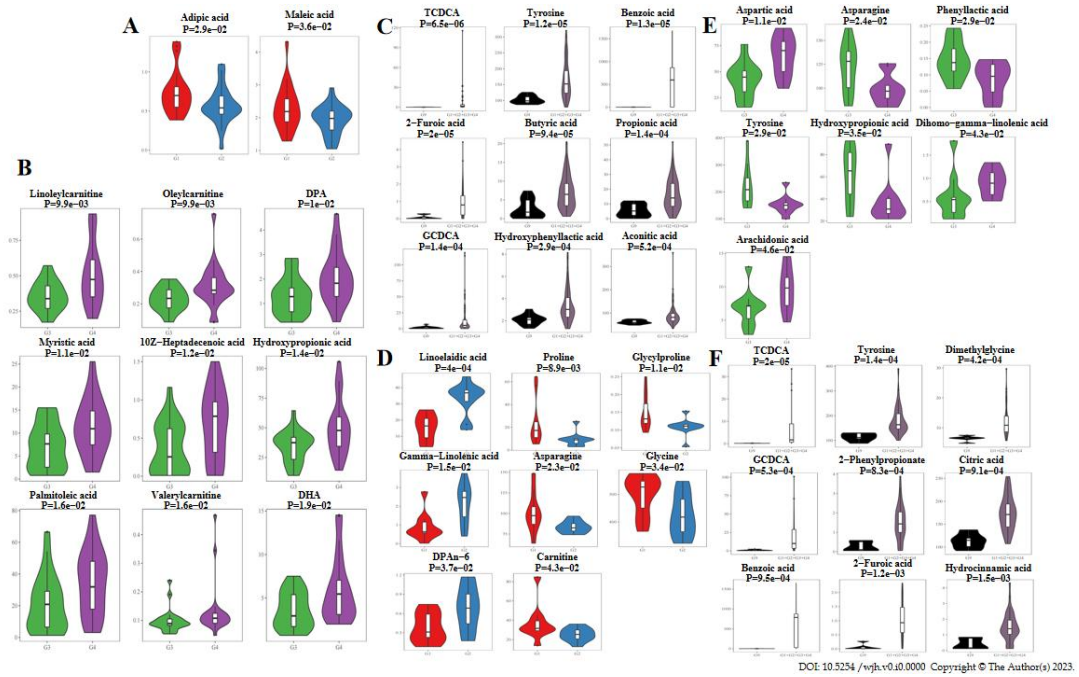
Supplementary Figure 1 Histological characteristics of normal liver and fibrotic liver tissues. F0: Normal liver; F1: Fibrotic portal areas without fibrous septum; F2: Fibrotic portal areas with one fibrous septum; F3: Fibrotic portal areas with two or three fibrous septa; F4: Portal areas with obvious portal-junction bridge fibrosis and more than four fibrous septa; F5: Portal areas with obvious portal-junction bridge or portal-central bridge fibrosis and one to three pseudolobuli; F6: More than three pseudolobuli.



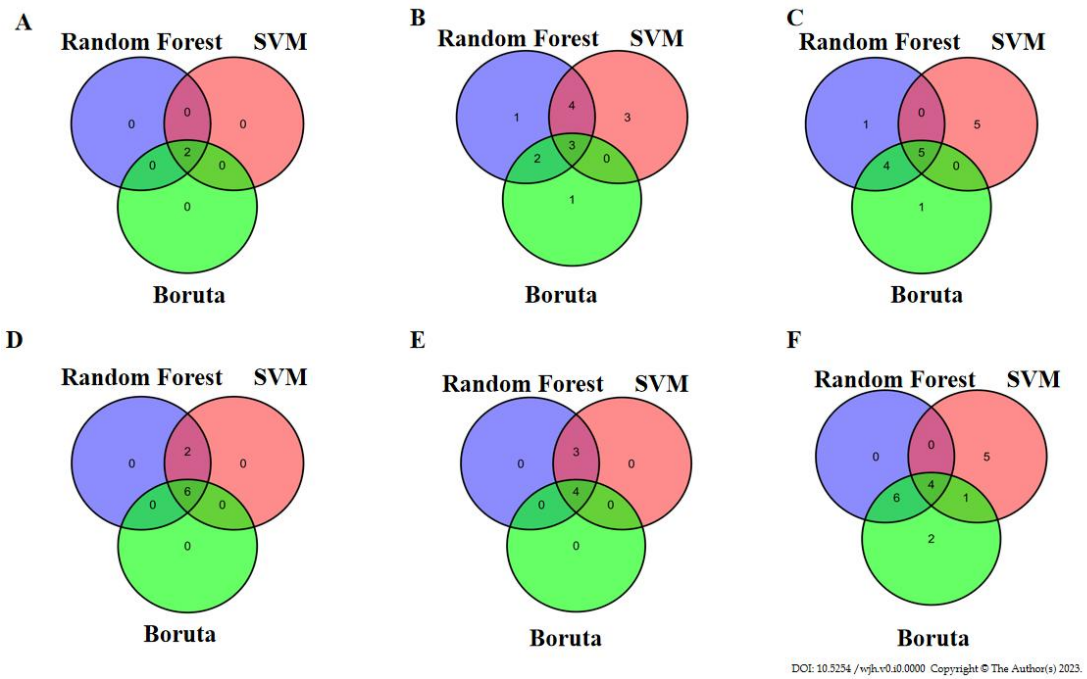
Supplementary Figure 2 Representative nuclear magnetic resonance spectra with targeted metabolites.



Supplementary Figure 3 Principal component analysis. A: Entecavir responders *vs* entecavir no-responders; B: FuzhengHuayu tablet (FZHY) + entecavir responders *vs* FZHY + entecavir no-responders; C: Patients *vs* volunteers.



Supplementary Figure 4 Vioplot of all the potential metabolites. A: Vioplot of entecavir responders (E-R) *vs* entecavir no-responders (E-N) (training set); B: Vioplot of FuzhengHuayu tablet (FZHY) + entecavir responders (F-R) *vs* FZHY + entecavir no-responders (F-N) (training set); C: Vioplot of patients *vs* volunteers (training set); D: Vioplot of E-R *vs* E-N (validation set); E: Vioplot of F-R *vs* F-N (validation set); F: Vioplot of patients *vs* volunteers (validation set). TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid.



Supplementary Figure 5 Venn plot of all the potential metabolites. A: Venn plot of entecavir responders (E-R) *vs* entecavir no-responders (E-N) (training set); B: Venn plot of FuzhengHuayu tablet (FZHY) + entecavir responders (F-R) *vs* FZHY + entecavir no-responders (F-N) (training set); C: Venn plot of patients vs volunteers (training set); D: Venn plot of E-R *vs* E-N (validation set); E: Venn plot of F-R *vs* F-N (validation set); F: Venn plot of patients *vs* volunteers (validation set). SVM: Support vector machine.

Supplementary Table 1 Ultra-high-performance liquid chromatography tandem mass spectrometry instrument settings

UPLC	
Column	Acquity UPLC BEH C18 1.7 μM VanGuard pre-column (2.1 mm × 5 mm) and acquity UPLC BEH C18 1.7 μM analytical column (2.1 mm × 100 mm)
Column temp (℃)	40
Sample manager temp (℃)	10
Mobile phases	A = water with 0.1% formic acid; B = acetonitrile/indolepropionic acid (70:30)
Gradient conditions	0-1 min (5% B), 1-11 min (5-78% B), 11-13.5 min (78-95% B), 13.5-14 min (95-100% B), 14-16 min (100% B), 16-16.1 min (100-5% B), 16.1-18 min (5% B)
Flow rate (mL/min)	0.4
Injection vol (μL)	5.0
Mass spectromete	
Capillary (Kv)	1.5 (ESI +), 2.0 (ESI -)
Source temp (℃)	150
Desolvation temp (℃)	550
Desolvation gas flow (L/Hr)	1000

UPLC: Ultra-high performance liquid chromatography; ESI: Electrospray ionization.