

Supplementary Table 1. Descriptive Statistics of 39 Blood Metabolites in HCC Patients and Matched Healthy Controls Based on NMR Metabolomics.

Index	Healthy Controls	HCC Patients
2-Aminobutyric acid (mmol/L)	0.02 (0.01, 0.02)	0.01 (0, 0.02)
2-Hydroxybutyric acid (mmol/L)	0 (0, 0.01)	0.03 (0.02, 0.07)
2-Oxoglutaric acid (mmol/L)	0 (0, 0)	0.01 (0, 0.02)
3-Hydroxybutyric acid (mmol/L)	0.03 (0.02, 0.05)	0.04 (0.02, 0.12)
Acetic acid (mmol/L)	0 (0, 0.01)	0.03 (0.02, 0.04)
Acetoacetic acid (mmol/L)	0.01 (0.01, 0.01)	0.01 (0.01, 0.02)
Acetone (mmol/L)	0.03 (0.02, 0.05)	0.02 (0.01, 0.03)
Alanine (mmol/L)	0.44 (0.38, 0.52)	0.36 (0.31, 0.4)
Asparagine (mmol/L)	0.06 (0.05, 0.07)	0.11 (0.09, 0.13)
Choline (mmol/L)	0.04 (0.03, 0.06)	0.87 (0.09, 1.85)
Citric acid (mmol/L)	0.19 (0.18, 0.2)	0.13 (0.11, 0.15)
Creatine (mmol/L)	0.01 (0.01, 0.02)	0.03 (0.02, 0.04)
Creatinine (mmol/L)	0.07 (0.06, 0.08)	0.07 (0.06, 0.08)
D-Galactose (mmol/L)	0.06 (0, 0.33)	0 (0, 0.01)
Dimethylsulfone (mmol/L)	0.01 (0, 0.01)	0 (0, 0)
Ethanol (mmol/L)	0.02 (0, 0.05)	0.11 (0.04, 0.24)
Formic acid (mmol/L)	0.02 (0.02, 0.02)	0.02 (0.01, 0.02)
Glucose (mmol/L)	5.13 (4.67, 5.81)	3.6 (2.96, 4.42)
Glutamic acid (mmol/L)	0.14 (0.13, 0.17)	0.44 (0.32, 0.55)
Glutamine (mmol/L)	0.67 (0.61, 0.72)	0.32 (0.22, 0.51)
Glycerol (mmol/L)	0.17 (0.14, 0.22)	0 (0, 0.03)
Glycine (mmol/L)	0.25 (0.23, 0.27)	0.57 (0.5, 0.67)
Histidine (mmol/L)	0.09 (0.08, 0.09)	0.13 (0.11, 0.15)
Isoleucine (mmol/L)	0.06 (0.05, 0.07)	0.05 (0.04, 0.05)
Lactic acid (mmol/L)	2.34 (1.95, 2.66)	3.32 (2.56, 4.19)
Leucine (mmol/L)	0.12 (0.1, 0.13)	0.08 (0.07, 0.1)
Lysine (mmol/L)	0.2 (0.19, 0.21)	0.23 (0.19, 0.29)
Methionine (mmol/L)	0.03 (0.02, 0.05)	0.02 (0.01, 0.04)

Index	Healthy Controls	HCC Patients
N, N-Dimethylglycine (mmol/L)	0 (0, 0.01)	0.01 (0.01, 0.02)
Ornithine (mmol/L)	0.06 (0.05, 0.07)	0.16 (0.09, 0.21)
Phenylalanine (mmol/L)	0.05 (0.04, 0.05)	0.05 (0.05, 0.05)
Proline (mmol/L)	0.33 (0.27, 0.4)	0.19 (0.13, 0.25)
Pyruvic acid (mmol/L)	0.13 (0.11, 0.16)	0.17 (0.13, 0.22)
Sarcosine (mmol/L)	0.02 (0.01, 0.02)	0 (0, 0)
Succinic acid (mmol/L)	0.01 (0, 0.01)	0.01 (0.01, 0.05)
Threonine (mmol/L)	0.28 (0.2, 0.42)	0.1 (0.05, 0.13)
Trimethylamine-N-oxide (mmol/L)	0.03 (0.02, 0.04)	0.03 (0, 0.04)
Tyrosine (mmol/L)	0.05 (0.05, 0.06)	0.04 (0.04, 0.04)
Valine (mmol/L)	0.26 (0.24, 0.29)	0.21 (0.18, 0.25)

Abbreviations: HCC, Hepatocellular carcinoma; NMR, Nuclear magnetic resonance.

Supplementary Table 2. Descriptive Statistics of 112 blood-lipid indicators in HCC Patients and Matched Healthy Controls Based on NMR Metabolomics.

Index	Healthy Controls	HCC Patients
Apo-B/Apo-A1 (-/-)	0.7 (0.61, 0.78)	0.62 (0.46, 0.78)
HDL-1 Apo-A1 (mg/dL)	17.05 (12.88, 21.71)	31.28 (24.23, 43.11)
HDL-1 Apo-A2 (mg/dL)	0.62 (0.16, 1.37)	2.42 (1.77, 3.37)
HDL-1 Cholesterol (mg/dL)	13.26 (11.09, 16.65)	27.98 (21.5, 35.61)
HDL-1 Free Cholesterol (mg/dL)	3.09 (2.32, 3.72)	5.64 (4.09, 6.82)
HDL-1 Phospholipids (mg/dL)	13.81 (10.78, 17.11)	28.52 (23.11, 37.2)
HDL-1 Triglycerides (mg/dL)	3.36 (2.43, 4.89)	2.32 (0.13, 3.94)
HDL-2 Apo-A1 (mg/dL)	11.32 (9.12, 14.5)	18.12 (14.96, 21.25)
HDL-2 Apo-A2 (mg/dL)	1.44 (1.01, 2.3)	2.78 (1.77, 3.53)
HDL-2 Cholesterol (mg/dL)	6.29 (5.08, 7.75)	11.1 (9.43, 13.85)
HDL-2 Free Cholesterol (mg/dL)	1.06 (0.66, 1.42)	2.11 (1.6, 2.87)
HDL-2 Phospholipids (mg/dL)	8.71 (6.74, 11.27)	16.21 (13, 19.24)
HDL-2 Triglycerides (mg/dL)	1.76 (1.39, 2.46)	1.29 (0.29, 2.37)
HDL-3 Apo-A1 (mg/dL)	20.55 (18.09, 23.94)	23.6 (19.76, 27.25)
HDL-3 Apo-A2 (mg/dL)	4.48 (3.63, 5.28)	6.51 (4.81, 7.77)
HDL-3 Cholesterol (mg/dL)	7.72 (6.77, 9.03)	10.8 (9.48, 12.48)
HDL-3 Free Cholesterol (mg/dL)	1.45 (0.98, 1.85)	1.45 (0.74, 2.11)
HDL-3 Phospholipids (mg/dL)	11.46 (9.38, 13.86)	16.68 (14.33, 19.18)
HDL-3 Triglycerides (mg/dL)	1.94 (1.56, 2.56)	1.88 (1.11, 2.6)
HDL-4 Apo-A1 (mg/dL)	79.03 (69.68, 84.88)	51.39 (38.8, 63.51)
HDL-4 Apo-A2 (mg/dL)	19.27 (16.82, 20.91)	12.58 (8.07, 17.05)
HDL-4 Cholesterol (mg/dL)	20.45 (16.72, 22.54)	14.83 (9.43, 18.4)
HDL-4 Free Cholesterol (mg/dL)	3.67 (2.83, 4.24)	2.49 (1.34, 3.95)
HDL-4 Phospholipids (mg/dL)	25.48 (22.48, 27.6)	19.24 (15.75, 22.89)

Index	Healthy Controls	HCC Patients
HDL-4 Triglycerides (mg/dL)	3.67 (3.07, 4.46)	2.81 (1.92, 3.59)
HDL Apo-A1 (mg/dL)	130.14 (121.23, 147.25)	128.5 (114.43, 142.76)
HDL Apo-A2 (mg/dL)	28.34 (26.32, 31.47)	31.19 (24.47, 35.05)
HDL-C (mg/dL)	48.4 (43.18, 55.5)	66.61 (57.04, 76.28)
HDL Free Cholesterol (mg/dL)	10.58 (8.96, 12.59)	14.66 (12.18, 18.6)
HDL Phospholipids (mg/dL)	59.66 (52.63, 68.33)	80.38 (70.84, 93.52)
HDL Triglycerides (mg/dL)	10.64 (8.65, 14.27)	7.22 (2.7, 11.39)
IDL Apo-B (mg/dL)	3.2 (2.45, 4.14)	3.08 (1.5, 4.84)
IDL Cholesterol (mg/dL)	10.63 (7.97, 12.59)	2.3 (0.23, 5.58)
IDL Free Cholesterol (mg/dL)	3.34 (2.25, 4.07)	0.5 (0, 1.14)
IDL Phospholipids (mg/dL)	7.02 (4.64, 10.12)	3.4 (1.37, 5.5)
IDL Particle Number (nmol/L)	58.04 (44.48, 75.25)	55.95 (27.23, 88.03)
IDL Triglycerides (mg/dL)	9.38 (3.5, 18.46)	4.22 (2.37, 8.05)
LDL-1 Apo-B (mg/dL)	10.61 (8.44, 13.07)	9 (5.55, 13.83)
LDL-1 Cholesterol (mg/dL)	20.56 (16.21, 25.17)	9.27 (4.93, 17.97)
LDL-1 Free Cholesterol (mg/dL)	6.04 (4.86, 7.68)	4.84 (3.04, 7.28)
LDL-1 Phospholipids (mg/dL)	11.32 (9.28, 13.66)	8.14 (5.59, 13.53)
LDL-1 Particle Number (nmol/L)	192.77 (153.38, 237.71)	163.64 (100.88, 251.51)
LDL-1 Triglycerides (mg/dL)	4.7 (3.42, 6.32)	5.7 (4.02, 8.45)
LDL-2 Apo-B (mg/dL)	8.84 (6.73, 10.69)	0 (0, 4.28)
LDL-2 Cholesterol (mg/dL)	15.03 (10.88, 19.48)	0 (0, 7.69)
LDL-2 Free Cholesterol (mg/dL)	4.98 (3.54, 6.05)	1.53 (0, 4.86)
LDL-2 Phospholipids (mg/dL)	8.48 (6.47, 10.46)	0 (0, 5.29)
LDL-2 Particle Number (nmol/L)	160.78 (122.36, 194.29)	0 (0, 77.67)
LDL-2 Triglycerides (mg/dL)	1.99 (1.62, 2.4)	2.3 (1.12, 3.63)
LDL-3 Apo-B (mg/dL)	9.67 (7.16, 11.91)	1.29 (0, 3.87)

Index	Healthy Controls	HCC Patients
LDL-3 Cholesterol (mg/dL)	16.45 (11.47, 21.31)	0 (0, 0.62)
LDL-3 Free Cholesterol (mg/dL)	5.44 (4.16, 7.15)	3.8 (2.46, 4.93)
LDL-3 Phospholipids (mg/dL)	8.95 (6.7, 11.38)	0.43 (0, 2.64)
LDL-3 Particle Number (nmol/L)	175.86 (130.33, 216.51)	23.39 (0, 70.3)
LDL-3 Triglycerides (mg/dL)	1.5 (0.78, 1.9)	3.25 (2.48, 3.96)
LDL-4 Apo-B (mg/dL)	10.68 (7.32, 13.58)	1.14 (0, 6.35)
LDL-4 Cholesterol (mg/dL)	17.58 (11.47, 22.59)	0 (0, 4.59)
LDL-4 Free Cholesterol (mg/dL)	5.56 (4.13, 6.92)	2.34 (0.76, 4.49)
LDL-4 Phospholipids (mg/dL)	9.61 (6.74, 12.07)	0.44 (0, 4.28)
LDL-4 Particle Number (nmol/L)	194.22 (132.97, 246.93)	20.77 (0, 115.5)
LDL-4 Triglycerides (mg/dL)	1.95 (1.47, 2.53)	3.67 (2.01, 5.24)
LDL-5 Apo-B (mg/dL)	13.18 (9.89, 16.8)	18.22 (10.55, 25.06)
LDL-5 Cholesterol (mg/dL)	19.2 (14.08, 24.08)	21.8 (11.9, 33.51)
LDL-5 Free Cholesterol (mg/dL)	5.41 (3.85, 6.36)	7.63 (4.55, 10.63)
LDL-5 Phospholipids (mg/dL)	10.41 (7.68, 12.62)	12.74 (8.02, 18.26)
LDL-5 Particle Number (nmol/L)	239.62 (179.91, 305.54)	331.23 (191.8, 455.65)
LDL-5 Triglycerides (mg/dL)	2.49 (1.66, 3.19)	5.82 (3.48, 7.91)
LDL-6 Apo-B (mg/dL)	21.02 (16.48, 25.99)	29.66 (21.45, 38.89)
LDL-6 Cholesterol (mg/dL)	25.31 (19.55, 31.77)	39.09 (28.16, 52.21)
LDL-6 Free Cholesterol (mg/dL)	6.3 (5.26, 7.85)	10.87 (7.49, 14.14)
LDL-6 Phospholipids (mg/dL)	13.35 (10.56, 16.39)	22.86 (17.24, 29.48)
LDL-6 Particle Number (nmol/L)	382.33 (299.76, 472.49)	539.41 (390.11, 707.18)
LDL-6 Triglycerides (mg/dL)	3.62 (2.84, 4.66)	7.44 (5.73, 9.75)
LDL Apo-B (mg/dL)	75.68 (63.01, 85.6)	62.36 (45.95, 87.48)
LDL-C (mg/dL)	117.17 (95.96, 134.44)	63.94 (44.84, 88.95)
LDL Free Cholesterol (mg/dL)	33.7 (27.23, 39.38)	24.5 (18.74, 34.22)

Index	Healthy Controls	HCC Patients
LDL-C/HDL-C (-/-)	2.3 (1.86, 2.76)	1.06 (0.7, 1.29)
LDL Phospholipids (mg/dL)	62.92 (52.12, 71.27)	45.08 (34.3, 58.67)
LDL Particle Number (nmol/L)	1376.21 (1145.71, 1556.39)	1133.76 (835.54, 1590.72)
LDL Triglycerides (mg/dL)	17.84 (15.06, 20.66)	29.85 (21, 36.39)
Total Particle Number (nmol/L)	1738.87 (1527.45, 1931.77)	1369.36 (1091.98, 1718.61)
Apo-A1 (mg/dL)	137.38 (123.57, 151.86)	125.62 (114, 141.3)
Apo-A2 (mg/dL)	27.75 (25.44, 30.79)	27.81 (21.87, 32.13)
Apo-B (mg/dL)	95.64 (84.01, 106.24)	75.32 (60.06, 94.52)
TC (mg/dL)	118.6 (76.75, 180.19)	139.29 (115.08, 169.45)
TG (mg/dL)	201.73 (180.82, 222.83)	87.83 (73.68, 118.1)
VLDL-1 Cholesterol (mg/dL)	6.55 (2.95, 13.35)	3.16 (1.37, 5.81)
VLDL-1 Free Cholesterol (mg/dL)	2.71 (1.11, 5.58)	0.15 (0, 1.19)
VLDL-1 Phospholipids (mg/dL)	6.38 (3.2, 12.09)	7.62 (6, 9.75)
VLDL-1 Triglycerides (mg/dL)	34.34 (17.66, 67.82)	45.36 (36.38, 54.46)
VLDL-2 Cholesterol (mg/dL)	3.56 (1.83, 5.4)	1.02 (0.15, 2.67)
VLDL-2 Free Cholesterol (mg/dL)	1.77 (0.82, 2.92)	0 (0, 0.38)
VLDL-2 Phospholipids (mg/dL)	4.04 (2.18, 6.24)	2.24 (1.37, 3.67)
VLDL-2 Triglycerides (mg/dL)	14.86 (8.12, 23.45)	10.98 (7.52, 16.5)
VLDL-3 Cholesterol (mg/dL)	4.44 (2.37, 6.56)	0.36 (0, 1.72)
VLDL-3 Free Cholesterol (mg/dL)	2.18 (1.02, 3.34)	0.5 (0.16, 1.34)
VLDL-3 Phospholipids (mg/dL)	4.58 (2.84, 6.49)	1.54 (0.45, 3.18)
VLDL-3 Triglycerides (mg/dL)	13.39 (8.2, 18.72)	7.15 (4.89, 11.25)
VLDL-4 Cholesterol (mg/dL)	4.11 (2.88, 5.75)	2.76 (1.45, 4.05)
VLDL-4 Free Cholesterol (mg/dL)	1.92 (1.31, 2.82)	0.36 (0, 0.98)
VLDL-4 Phospholipids (mg/dL)	4.12 (3.2, 5.33)	2.65 (1.67, 3.81)
VLDL-4 Triglycerides (mg/dL)	8.71 (6.72, 11.13)	7.38 (5.16, 9.88)

Index	Healthy Controls	HCC Patients
VLDL-5 Cholesterol (mg/dL)	1.52 (1.17, 1.93)	1.38 (0.65, 1.91)
VLDL-5 Free Cholesterol (mg/dL)	0.2 (0, 0.44)	0.44 (0, 1)
VLDL-5 Phospholipids (mg/dL)	1.87 (1.46, 2.27)	1.42 (0.76, 2.19)
VLDL-5 Triglycerides (mg/dL)	2.1 (1.77, 2.72)	3.58 (3.09, 4.47)
VLDL Apo-B (mg/dL)	9.5 (6.24, 12.7)	6.5 (5.17, 9.12)
VLDL Cholesterol (mg/dL)	22.73 (13.13, 31.12)	5.31 (0.4, 10.99)
VLDL Free Cholesterol (mg/dL)	10.34 (6.82, 14.15)	5.37 (2.79, 7.74)
VLDL Phospholipids (mg/dL)	22.6 (14.47, 30.3)	18.35 (14.09, 25.29)
VLDL Particle Number (nmol/L)	172.68 (113.52, 230.83)	118.12 (93.9, 165.92)
VLDL Triglycerides (mg/dL)	82.76 (52.91, 132.6)	70.5 (59.11, 93.46)

Abbreviations: HCC, Hepatocellular carcinoma; NMR, Nuclear magnetic resonance; Apo, Apolipoprotein; HDL, High-density lipoprotein; HDL-C, High-density lipoprotein cholesterol; IDL, Intermediate-density lipoprotein; LDL, Low-density lipoprotein; LDL-C, Low-density lipoprotein cholesterol; VLDL, Very low-density lipoprotein; TC, Total cholesterol; TG, Triglycerides.

Supplementary Table 3. Comparative Analysis of 151 Metabolic Indexes in HCC Patients and Matched Healthy Controls Based on NMR Metabolomics.

Index	log2_FC_median	FC_median	Pvalue	VIP
Glycine	1.212386511	2.317206329	6.02522E-31	1.776652405
Glycerol	-inf	0	5.2413E-29	1.767487765
LDL-3 Cholesterol	-inf	0	6.3895E-28	1.665220819
TG	-1.199639939	0.435383929	4.71445E-26	1.651551402
Glutamic acid	1.629628516	3.094333116	6.24298E-23	1.624720029
Glutamine	-1.05283892	0.482018719	2.63862E-24	1.617647759
LDL-3 Phospholipids	-4.396352936	0.047486034	8.62547E-25	1.601802152
LDL-C/HDL-C	-1.127523752	0.457700651	9.49599E-24	1.556414652
Citric acid	-0.510795598	0.701835292	3.64477E-25	1.516637464
LDL-3 Particle Number	-2.910422588	0.133007307	8.94639E-23	1.512571143
LDL-3 Apo-B	-2.906144824	0.133402275	8.943E-23	1.512564236
Histidine	0.570992837	1.485545545	5.95579E-25	1.506028483
LDL-4 Cholesterol	-inf	0	2.57128E-21	1.501696251
Asparagine	0.776302649	1.71273583	6.42957E-20	1.488685954
LDL-3 Triglycerides	1.120294234	2.173913043	1.0642E-23	1.460943792
LDL-6 Triglycerides	1.041306974	2.058091286	1.8671E-23	1.456243706
Ornithine	1.459023388	2.749221959	9.16863E-25	1.446145414
LDL-4 Phospholipids	-4.464698308	0.045288912	1.05384E-18	1.439576619
N,N-Dimethylglycine	1.647806397	3.133568208	2.61331E-20	1.417632837
HDL-1 Cholesterol	1.077057356	2.109728507	1.4519E-21	1.357700068
HDL-1 Phospholipids	1.045485471	2.064060803	8.50226E-22	1.348219186
HDL-4 Apo-A1	-0.620821478	0.650300538	3.69091E-19	1.327871684
Tyrosine	-0.418637325	0.748130926	5.51368E-20	1.320144814
HDL-2 Phospholipids	0.896139467	1.861079219	1.09015E-18	1.316934052
HDL-2 Cholesterol	0.819427754	1.764705882	2.53121E-19	1.314466006
IDL Free Cholesterol	-2.756505781	0.147982063	4.46892E-22	1.283729554
HDL-2 Apo-A1	0.678469945	1.600441501	8.9861E-17	1.268056069
VLDL-2 Free Cholesterol	-inf	0	3.12305E-21	1.259492115
Proline	-0.749658354	0.594744383	3.13658E-16	1.25316642
HDL-1 Apo-A2	1.973364873	3.926829268	4.41941E-19	1.250366525
LDL-4 Apo-B	-3.227805918	0.106741573	9.29167E-15	1.249949933
LDL-4 Particle Number	-3.22511865	0.106940583	9.29194E-15	1.249905664
LDL-5 Triglycerides	1.227773301	2.342052314	4.25865E-16	1.237303479
VLDL-3 Cholesterol	-3.622865293	0.081172492	7.10305E-18	1.225023224
Threonine	-1.545752064	0.342517104	3.30957E-21	1.224746098
Choline	4.388290058	20.94145906	1.48481E-18	1.219399317
HDL Phospholipids	0.429982855	1.347217566	5.89677E-17	1.216457959
LDL-C	-0.873812583	0.545702825	1.11839E-14	1.214181572
HDL-2 Free Cholesterol	1	2	2.40107E-14	1.195735713
Sarcosine	-3.761996522	0.073709965	1.22293E-23	1.191852884

Index	log2_FC_median	FC_median	Pvalue	VIP
IDL Cholesterol	-2.211575538	0.215898401	1.30902E-18	1.188034883
HDL-1 Free Cholesterol	0.869366743	1.826860841	2.36994E-15	1.183043522
VLDL-5 Triglycerides	0.767553914	1.702380952	1.46106E-16	1.177351207
2-Hydroxybutyric acid	3.493052083	11.25935347	4.301E-27	1.167192701
HDL-C	0.460731734	1.376239669	1.7352E-15	1.166865522
HDL-3 Phospholipids	0.540882934	1.454862625	1.25985E-14	1.166283684
Creatine	1.222510334	2.333524046	4.06464E-14	1.165163256
LDL Triglycerides	0.742615316	1.673206278	4.81656E-15	1.152913659
VLDL Cholesterol	-2.096456087	0.23383194	2.84888E-16	1.13799425
2-Oxoglutaric acid	2.352990842	5.108822606	1.41129E-16	1.133488356
HDL-4 Apo-A2	-0.615224649	0.65282823	4.71522E-14	1.118984545
LDL-6 Phospholipids	0.775985662	1.712359551	2.48576E-14	1.113851726
HDL-1 Apo-A1	0.876122505	1.835435612	6.96946E-16	1.104663619
VLDL-3 Phospholipids	-1.573991383	0.335877863	5.70847E-13	1.101855459
HDL-3 Cholesterol	0.484625181	1.399222294	3.28006E-12	1.076351175
Leucine	-0.452153916	0.730950738	1.59521E-13	1.071134705
VLDL-3 Free Cholesterol	-2.113277987	0.231121281	1.4307E-12	1.05919057
LDL-6 Free Cholesterol	0.785783665	1.724028549	2.10319E-12	1.056872846
Lactic acid	0.505167153	1.419287788	7.10764E-10	1.043315199
LDL-4 Free Cholesterol	-1.250364362	0.420342034	3.18758E-10	1.042584065
VLDL-4 Free Cholesterol	-2.41127558	0.187989556	5.06799E-16	1.041075551
VLDL-2 Cholesterol	-1.798278167	0.287517532	5.75547E-11	1.037339182
LDL-2 Apo-B	-inf	0	1.87783E-17	1.035248149
LDL-2 Particle Number	-inf	0	1.85572E-17	1.035226771
HDL Free Cholesterol	0.471037444	1.38610586	2.50478E-11	1.033986723
D-Galactose	-inf	0	6.06105E-11	1.022456058
LDL-4 Triglycerides	0.912305939	1.882051282	1.16332E-09	1.012182959
IDL Phospholipids	-1.047031529	0.483962937	1.52888E-11	0.981404559
VLDL-1 Free Cholesterol	-4.226827393	0.053406998	1.57852E-16	0.976298184
VLDL Free Cholesterol	-0.945242192	0.51934236	1.02854E-10	0.968157786
HDL-4 Cholesterol	-0.463582245	0.725183374	1.2638E-11	0.968006162
VLDL-2 Phospholipids	-0.849424258	0.55500618	1.83073E-06	0.966670642
LDL-2 Phospholipids	-inf	0	1.37526E-15	0.963273759
HDL-4 Triglycerides	-0.385209933	0.765667575	2.11065E-07	0.961450542
LDL-2 Cholesterol	-inf	0	1.63445E-17	0.95989635
VLDL-3 Triglycerides	-0.904670909	0.534154535	1.53128E-07	0.951239573
HDL-3 Apo-A2	0.539158811	1.453125	2.64955E-09	0.950491972
Alanine	-0.292242149	0.816631912	2.24436E-10	0.949574667
LDL-1 Cholesterol	-1.149549828	0.450765864	1.23572E-12	0.945992976
LDL-6 Cholesterol	0.626991624	1.5443413	1.11704E-09	0.944810508
Succinic acid	0.240637527	1.181514657	7.15233E-05	0.941883513
HDL-4 Phospholipids	-0.404598475	0.755446516	6.0873E-11	0.940081786
LDL-3 Free Cholesterol	-0.51893263	0.697887971	5.86336E-09	0.903121569
HDL-2 Apo-A2	0.941418279	1.920415225	4.12104E-08	0.888093719

Index	log2_FC_median	FC_median	Pvalue	VIP
VLDL-5 Free Cholesterol	1.1740294	2.256410256	0.005502411	0.863460768
Valine	-0.298013991	0.81337131	8.86157E-09	0.855156318
Isoleucine	-0.33463177	0.792986511	8.67211E-08	0.841109757
VLDL Apo-B	-0.547838475	0.684044234	0.000165671	0.834283188
VLDL Particle Number	-0.547805962	0.68405965	0.000167527	0.834224573
VLDL-2 Triglycerides	-0.435899246	0.73923284	0.024849575	0.829042101
LDL-5 Free Cholesterol	0.496054463	1.410351201	3.23713E-06	0.819423938
LDL Phospholipids	-0.481191179	0.716385887	4.63757E-08	0.811367294
Acetic acid	2.865684676	7.288816985	3.08328E-28	0.809373454
VLDL-1 Cholesterol	-1.053854901	0.481679389	6.62203E-07	0.804682054
LDL-6 Apo-B	0.496655982	1.410939358	5.0468E-07	0.796318015
LDL-6 Particle Number	0.49656386	1.410849266	5.01072E-07	0.796287506
Lysine	0.190384939	1.141068134	8.47382E-06	0.784337064
Pyruvic acid	0.368882972	1.291352595	2.18374E-05	0.768234776
IDL Triglycerides	-1.151575692	0.450133333	9.84672E-05	0.739581352
HDL Triglycerides	-0.559427409	0.678571429	1.46042E-06	0.738167838
VLDL Phospholipids	-0.30054271	0.811946903	0.100096149	0.722444392
LDL-2 Free Cholesterol	-1.702614089	0.307228916	2.59725E-08	0.708571212
Dimethylsulfone	-inf	0	1.71788E-34	0.705866949
LDL-5 Apo-B	0.467172589	1.382397572	0.000215619	0.676092555
LDL-5 Particle Number	0.467054914	1.38228482	0.000215628	0.676075086
VLDL-4 Phospholipids	-0.636651978	0.643203883	1.15767E-07	0.660779747
Glucose	-0.510824189	0.701821384	7.45572E-17	0.658602964
Apo-B	-0.344601479	0.787525488	9.57483E-06	0.658582028
Total Particle Number	-0.344649422	0.787499317	9.63672E-06	0.658549655
Formic acid	-0.123164582	0.918171412	0.004222214	0.630103505
VLDL Triglycerides	-0.231310388	0.851860802	0.223726364	0.61640801
VLDL-1 Phospholipids	0.256234574	1.194357367	0.054529005	0.608085117
Acetoacetic acid	0.916125906	1.887041179	3.63084E-13	0.606779933
Apo-A1	-0.129053307	0.914431301	0.000573607	0.597248872
HDL-3 Free Cholesterol	0	1	0.884430919	0.594012678
LDL-5 Phospholipids	0.292088313	1.224411341	0.003763986	0.575078194
LDL Free Cholesterol	-0.459966842	0.727002967	0.000169385	0.541589561
Ethanol	2.372091018	5.176909215	2.08801E-11	0.526200947
LDL-1 Phospholipids	-0.474887354	0.719522968	6.07355E-05	0.51988244
VLDL-5 Phospholipids	-0.393284701	0.761394102	0.002069237	0.507914592
VLDL-4 Cholesterol	-0.574470127	0.671532847	2.48268E-05	0.503365822
HDL-3 Apo-A1	0.199954089	1.1486618	0.005399679	0.49278949
2-Aminobutyric acid	-0.534195558	0.690543614	0.001096763	0.48060099
LDL-1 Triglycerides	0.278570684	1.212992545	0.01827355	0.477508602
HDL-4 Free Cholesterol	-0.564498398	0.676190476	0.000394839	0.472508024
VLDL-4 Triglycerides	-0.238074798	0.847876005	0.010912413	0.471575029
VLDL-1 Triglycerides	0.401320556	1.320716261	0.013693781	0.470562406
HDL-2 Triglycerides	-0.442623331	0.735795455	0.005272484	0.453758087

Index	log2_FC_median	FC_median	Pvalue	VIP
LDL Particle Number	-0.279578994	0.823831392	0.010404617	0.44815862
LDL Apo-B	-0.279502152	0.823875273	0.010446084	0.44815388
HDL-1 Triglycerides	-0.532187961	0.691505216	0.000244056	0.444103815
LDL-5 Cholesterol	0.182846171	1.135121062	0.102657929	0.435869911
HDL Apo-A2	0.13775799	1.100194038	0.043291636	0.421698347
Methionine	-0.434595008	0.73990143	0.002878565	0.408128671
LDL-2 Triglycerides	0.205245115	1.152882206	0.081331413	0.402990078
3-Hydroxybutyric acid	0.123278213	1.08920704	0.193693297	0.401274873
VLDL-5 Cholesterol	-0.134649527	0.910891089	0.031134051	0.400569872
LDL-1 Free Cholesterol	-0.320735292	0.800661704	0.002842512	0.386250412
TC	0.231987677	1.174451939	0.007646788	0.351863906
LDL-1 Particle Number	-0.236436608	0.84883932	0.011716695	0.339708169
LDL-1 Apo-B	-0.236747714	0.848656294	0.01167041	0.339666201
Apo-A2	0.002856052	1.001981625	0.707579271	0.338873959
HDL Apo-A1	-0.018239965	0.987436607	0.09533239	0.328582801
Acetone	-0.759226649	0.590812949	1.49727E-07	0.308045526
Phenylalanine	0.089964719	1.064344154	0.001750502	0.301980229
HDL-3 Triglycerides	-0.05287956	0.964010283	0.11456661	0.272958243
Apo-B/Apo-A1	-0.185355042	0.879432624	0.020923081	0.228650493
IDL Apo-B	-0.05288558	0.96400626	0.189432785	0.155958032
IDL Particle Number	-0.052909388	0.963990351	0.190843911	0.155808846
Creatinine	-0.116379631	0.922499714	0.078531667	0.110798294
Trimethylamine-N-oxide	-0.057988757	0.96060235	0.125920035	0.051751245

Abbreviations: HCC, Hepatocellular carcinoma; NMR, Nuclear magnetic resonance; FC, Fold change; VIP, Variable importance in the projection; Apo, Apolipoprotein; HDL, High-density lipoprotein; HDL-C, High-density lipoprotein cholesterol; IDL, Intermediate-density lipoprotein; LDL, Low-density lipoprotein; LDL-C, Low-density lipoprotein cholesterol; VLDL, Very low-density lipoprotein; TC, Total cholesterol; TG, Triglycerides.

Supplementary Table 4. Univariate cox regression analysis identified 11 prognostic features.

Index	HR	HR_lower	HR_upper	Pvalue
HDL-4 Apo-A2	0.880779649	0.811548695	0.955916501	0.002370648
HDL-4 Cholesterol	0.88909605	0.822308159	0.961308456	0.00317404
HDL-4 Apo-A1	0.96592344	0.943366089	0.989020172	0.004031272
VLDL-1 Triglycerides	0.950356464	0.913480998	0.988720521	0.011676797
HDL-4 Phospholipids	0.905662206	0.83816655	0.978593134	0.012156259
HDL-4 Free Cholesterol	0.761408909	0.602809566	0.961735778	0.02217497
Tyrosine	9.87292E-30	1.69434E-55	0.000575297	0.027353395
2-Oxoglutaric acid	4.56009E+20	108.5221716	1.91614E+39	0.029691214
Lysine	46.66298556	1.393051702	1563.067773	0.031953387
LDL-2 Triglycerides	1.289879811	1.018988646	1.63278554	0.034314356
Glycine	0.030669229	0.00112185	0.838437789	0.038983495

Abbreviations: HR, Hazard ratio; Apo, Apolipoprotein; HDL, High-density lipoprotein; VLDL, Very low-density lipoprotein; LDL, Low-density lipoprotein.

Supplementary Table 5. Univariate and multivariate Cox regression analyses confirmed the RS derived from the StepCox[forward]+RSF model as an independent prognostic factor.

Index	Univariate analysis		Multivariate analysis	
	HR(95%CI)	Pvalue	HR(95%CI)	Pvalue
Age	0.98 (0.95-1.01)	0.173		
Gender				
Male	Reference			
Female	1.10 (0.43-2.61)	0.896		
Hepatocirrhosis				
No	Reference			
Yes	1.20 (0.56-2.41)	0.678		
AFP	1.00 (1.00-1.00)	0.049	1.00 (1.00-1.00)	0.491
PIVKA-II	1.00 (1.00-1.00)	0.726		
Tumor Size	1.20 (1.11-1.31)	<0.001	1.15 (1.03-1.27)	0.01
Tumor Number				
Solitary	Reference		Reference	
Multiple	2.60 (1.22-5.36)	0.013	0.77 (0.09-6.45)	0.81
Macrovascular Invasion				
No	Reference			
Yes	1.90 (0.45-7.95)	0.389		
Microvascular Invasion				
No	Reference		Reference	
Yes	2.80 (1.32-6.13)	0.008	0.83 (0.31-2.23)	0.712
Differentiation				
High-Mid	Reference			
Low	1.40 (0.66-3.16)	0.357		
CNLC Stage				
I	Reference		Reference	
II-III	3.50 (1.64-7.56)	0.001	2.05 (0.03-149.00)	0.742
BCLC Stage				
0-A	Reference		Reference	
B-C	3.50 (1.62-7.46)	0.001	1.13 (0.03-48.50)	0.951
StepCox[forward]+RSF Model	1.20 (1.13-1.27)	<0.001	1.20 (1.11-1.30)	<0.001

Abbreviations: HR, Hazard ratio; RS, Risk score; RSF, Random survival forest; AFP, Alpha-Fetal Protein; PIVKA-II, Protein induced by vitamin K absence or Antagonist-II; BCLC Stage, Barcelona clinic liver cancer stage; CNLC Stage, Chinese liver cancer stage.

Supplementary Table 6. Baseline characteristics of patients in the Training Cohort and Test Cohort for predicting MVI in HCC patients.

Characteristics	All Cohort N=86	Train Cohort N=53	Test Cohort N=33	P-value
Age	54.00 [47.25;65.00]	54.00 [45.00;65.00]	55.00 [48.00;65.00]	0.474
AFP	37.42 [6.03;345.50]	23.46 [3.80;335.00]	131.00 [10.40;425.00]	0.177
PIVKA-II	132.17 [37.50;1252.70]	131.62 [56.33;1861.54]	148.22 [22.41;993.70]	0.397
Tumor Size	4.10 [2.52;7.27]	4.30 [2.80;7.20]	3.60 [2.40;7.30]	0.391
Gender				1.000
Female	19 (22.09%)	12 (22.64%)	7 (21.21%)	
Male	67 (77.91%)	41 (77.36%)	26 (78.79%)	
HBV				0.990
No	17 (19.77%)	11 (20.75%)	6 (18.18%)	
Yes	69 (80.23%)	42 (79.25%)	27 (81.82%)	
Hepatocirrhosis				0.483
No	34 (39.53%)	23 (43.40%)	11 (33.33%)	
Yes	52 (60.47%)	30 (56.60%)	22 (66.67%)	
Tumor Number				0.443
multiple	18 (20.93%)	13 (24.53%)	5 (15.15%)	
solitary	68 (79.07%)	40 (75.47%)	28 (84.85%)	
Macrovascular Invasion				0.645
No	81 (94.19%)	49 (92.45%)	32 (96.97%)	
Yes	5 (5.81%)	4 (7.55%)	1 (3.03%)	
Microvascular Invasion				1.000
No	49 (56.98%)	30 (56.60%)	19 (57.58%)	
Yes	37 (43.02%)	23 (43.40%)	14 (42.42%)	
Differentiation				0.773
High-Mid	65 (75.58%)	39 (73.58%)	26 (78.79%)	

	All Cohort	Train Cohort	Test Cohort	
Characteristics	N=86	N=53	N=33	P-value
Low	21 (24.42%)	14 (26.42%)	7 (21.21%)	
CNLC Stage				0.261
I	72 (83.72%)	42 (79.25%)	30 (90.91%)	
II-III	14 (16.28%)	11 (20.75%)	3 (9.09%)	
BCLC Stage				0.187
0-A	71 (82.56%)	41 (77.36%)	30 (90.91%)	
B-C	15 (17.44%)	12 (22.64%)	3 (9.09%)	

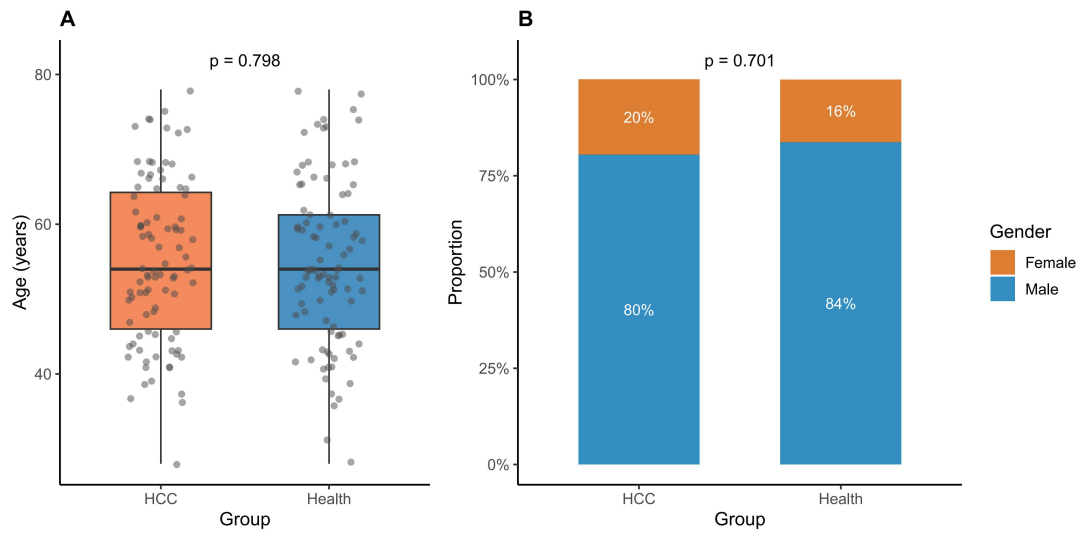
Abbreviations: HCC, Hepatocellular carcinoma; MVI, Microvascular invasion; AFP, Alpha-Fetal Protein; PIVKA-II, Protein induced by vitamin K absence or antagonist-II; BCLC Stage, Barcelona clinic liver cancer stage; CNLC Stage, Chinese liver cancer stage.

Supplementary Table 7. Performance metrics for 10 models predicting MVI in HCC across the training cohort and test cohort.

Cohort	Models	Sensitivity	Specificity	Accuracy	PPV	NPV	F1	AUC
Training cohort	RF	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	RPART	0.913	0.533	0.698	0.600	0.889	0.724	0.723
	LDA	1.000	0.600	0.774	0.657	1.000	0.793	0.832
	GLM	0.957	0.667	0.792	0.687	0.952	0.800	0.833
	NB	1.000	0.833	0.906	0.821	1.000	0.902	0.958
	KNN	0.826	0.633	0.717	0.633	0.826	0.717	0.771
	GLMNET	0.652	0.833	0.755	0.750	0.758	0.698	0.800
	SVM	1.000	0.867	0.925	0.852	1.000	0.920	0.981
	GBM	0.826	1.000	0.925	1.000	0.882	0.905	0.954
	XGB	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Test cohort	RF	0.714	0.895	0.818	0.833	0.810	0.769	0.895
	RPART	0.857	0.368	0.576	0.500	0.778	0.632	0.613
	LDA	0.857	0.474	0.636	0.545	0.818	0.667	0.808
	GLM	0.929	0.579	0.727	0.619	0.917	0.743	0.842
	NB	0.857	0.526	0.667	0.571	0.833	0.686	0.865
	KNN	0.714	0.632	0.667	0.588	0.750	0.645	0.814
	GLMNET	0.714	0.842	0.788	0.769	0.800	0.741	0.805
	SVM	0.857	0.842	0.848	0.800	0.889	0.828	0.921
	GBM	0.714	0.895	0.818	0.833	0.810	0.769	0.816
	XGB	0.786	0.842	0.818	0.786	0.842	0.786	0.895

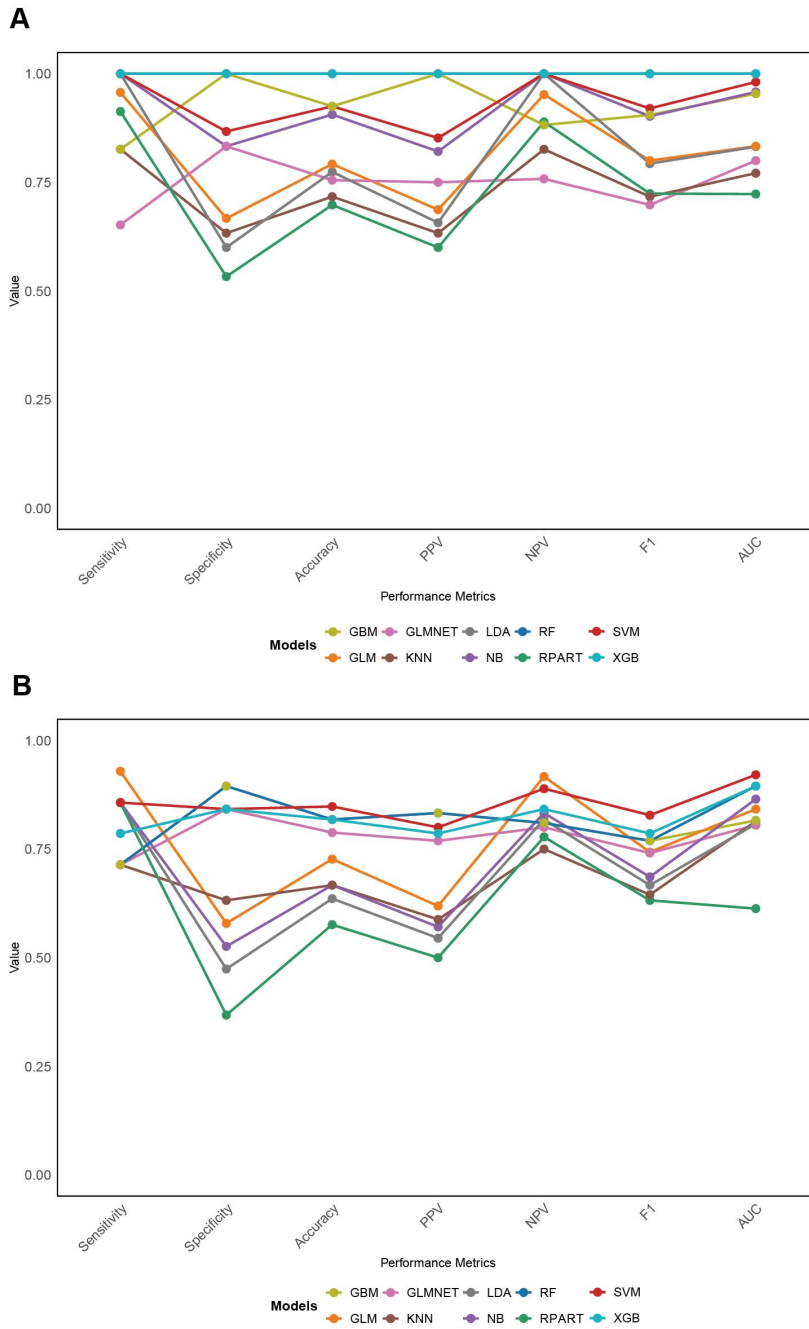
Abbreviations: HCC, Hepatocellular carcinoma; MVI, Microvascular invasion; XGB, XGBoost; RF, Random Forest; SVM, Support Vector Machine; NB, Naive Bayes; GBM, Gradient Boosting Machine; GLM, Generalized Linear Models; GLMNET, Generalized Linear Models with Elastic-Net; LDA, Linear Discriminant Analysis; KNN, k-Nearest Neighbors; RPART, Recursive Partitioning Tree; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

Supplementary Figure 1. Box plot comparing age (A) and proportion plot comparing gender (B) between HCC patients and healthy controls showed no significant differences.



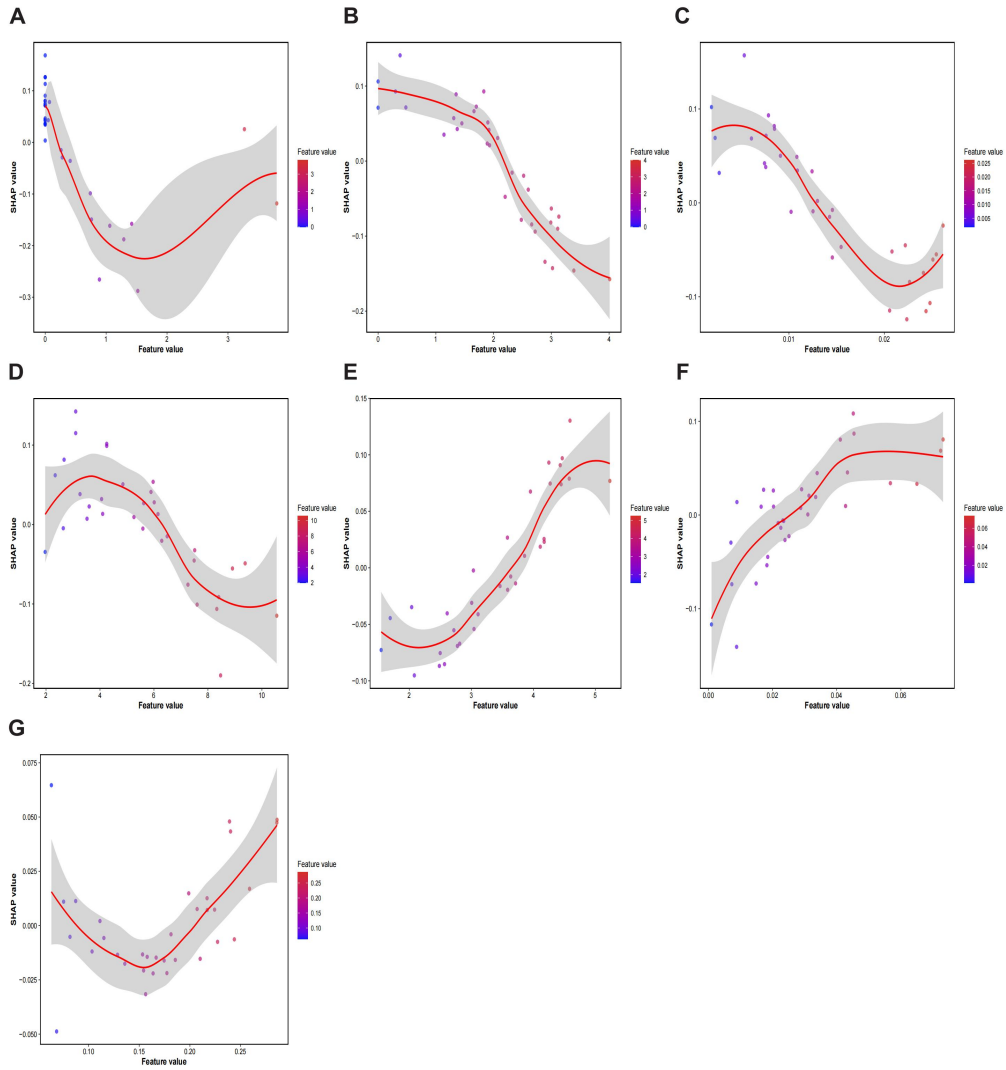
Abbreviation: HCC, Hepatocellular carcinoma.

Supplementary Figure 2. Line chart of performance metrics for 10 models predicting MVI in HCC across the training cohort (A) and test cohort (B).



Abbreviations: HCC, Hepatocellular carcinoma; MVI, Microvascular invasion; RF, Random forest; SVM, Support vector machine; NB, Naïve bayes; GBM, Gradient boosting machine; GLM, Generalized linear model; GLMNET, Generalized linear model with elastic-net; LDA, Linear discriminant analysis; KNN, k-nearest neighbors; RPART, Recursive partitioning tree; PPV, Positive predictive value; NPV, Negative predictive value.

Supplementary Figure 3. SHAP Dependency plot for V2FC (A), H2FC (B), N, N-dimethylglycine (C), H1FC (D), lactic acid (E), creatine (F), and pyruvic acid (G) of the SVM Model to predict MVI in HCC.



Abbreviations: HCC, Hepatocellular carcinoma; MVI, Microvascular invasion; SHAP, SHapley Additive exPlanations; V2FC, VLDL-2 free cholesterol; H2FC, HDL-2 free cholesterol; H1FC, HDL-1 free cholesterol.