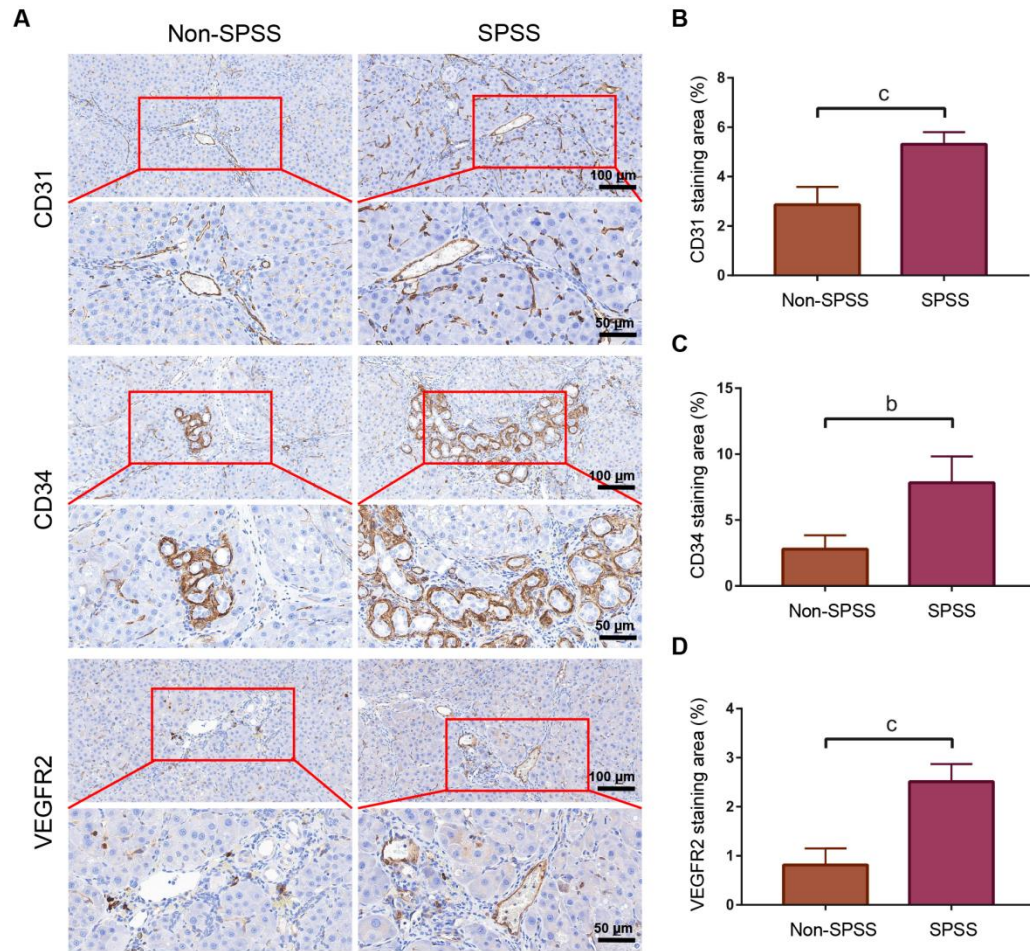
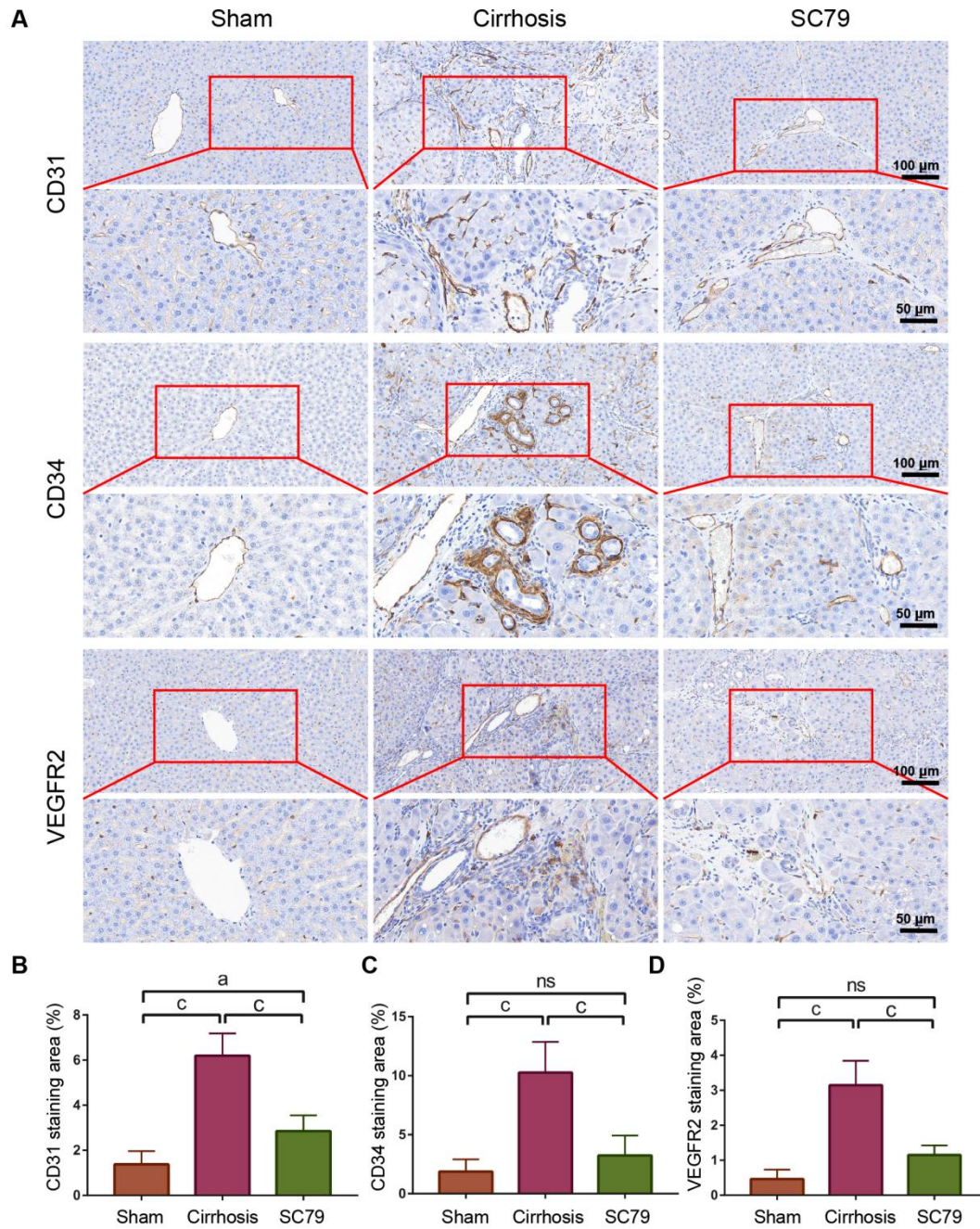




Supplementary Figure 1 Angiogenesis-related markers in rat liver tissues with and without spontaneous portosystemic shunts. A: Representative immunohistochemical staining of CD31, CD34, and VEGFR2; B: Quantification of CD31 staining; C: Quantification of CD34 staining; D: Quantification of VEGFR2 staining. Data are presented as mean $\pm$ SD (n = 5 per group). ^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$; ns, not significant.



Supplementary Figure 2 Angiogenesis-related markers in rat liver tissues across the sham, cirrhosis, and SC79-treated groups. A: Representative immunohistochemical staining of CD31, CD34, and VEGFR2; B: Quantification of CD31 staining; C: Quantification of CD34 staining; D: Quantification of VEGFR2 staining. Data are presented as mean $\pm$ SD (n = 5 per group). ^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$; ns, not significant.

Supplementary Table 1 Clinical characteristics of patients with and without spontaneous portosystemic shunts

Characteristics		Non-SPSS	SPSS	<i>P</i> Value
		(n=291)	(n=418)	
Age	years	52.76 ± 11.47	54.53 ± 10.95	0.038
Gender	Female	51 (17.5%)	97 (23.2%)	0.067
	Male	240 (82.5%)	321 (76.8%)	
White blood cell count	x10 ⁹ /L	5.08 [4.04, 6.62]	4.25 [3.13, 6.03]	<0.001
Hemoglobin		138.00 [116.50, 151.00]	111.00 [90.00, 129.00]	<0.001
Platelet count	x10 ⁹ /L	119.00 [83.50, 163.00]	76.00 [52.25, 106.75]	<0.001
INR	g/L	1.09 [1.00, 1.42]	1.35 [1.17, 1.61]	<0.001
PT	s	14.20 [13.10, 17.30]	16.60 [14.90, 19.20]	<0.001
PTA	%	87.00 [59.00, 100.00]	64.00 [50.00, 78.00]	<0.001
Albumin	g/L	37.00 [31.00, 42.00]	31.00 [27.00, 35.00]	<0.001
Total bilirubin	μmol/L	23.70 [15.65, 66.15]	42.65 [24.72, 85.03]	0.003
Child-Pugh score		6.00 [5.00, 9.00]	9.00 [7.00, 11.00]	<0.001
Child-Pugh grade	A	153 (52.6%)	65 (15.5%)	<0.001
	B	78 (26.8%)	188 (45.0%)	
	C	60 (20.6%)	165 (39.5%)	
MELD score		9.00 [7.00, 16.00]	14.00 [11.00, 18.00]	<0.001
MPV diameter	mm	13.60 [12.23, 15.00]	14.20 [11.86, 15.90]	0.076
LPV diameter	mm	9.24 [8.00, 10.32]	10.00 [8.35, 11.75]	<0.001
RPV diameter	mm	10.20 [9.21, 11.50]	10.00 [7.90, 11.76]	0.012
SV diameter	mm	9.30 [8.18, 10.88]	10.30 [8.54, 12.00]	<0.001

SMV diameter	mm	10.98 [9.88, 12.09]	11.96 [10.50, 13.30]	<0.001
Baseline EGV	No	152 (52.2%)	57 (13.6%)	<0.001
	Yes	139 (47.8%)	361 (86.4%)	
Baseline EGVB	No	276 (94.9%)	353 (84.4%)	<0.001
	Yes	15 (5.1%)	65 (15.6%)	
Baseline PVT	No	287 (98.6%)	379 (90.1%)	<0.001
	Yes	4 (1.4%)	39 (9.0%)	
Baseline HE	Absent	218 (74.9%)	268 (64.1%)	0.002
	Present	73 (25.1%)	150 (35.9%)	
Baseline ascites	No	199 (68.4%)	150 (35.9%)	<0.001
	Mild	34 (11.7%)	67 (16.0%)	
	Moderat			
	e-severe	58 (19.9%)	201 (48.1%)	
Baseline HCC	Absent	276 (94.8 %)	372 (89.0%)	0.006
	Present	15 (5.2%)	46 (11.0%)	

Notes: SPSS, spontaneous portosystemic shunts; INR, international standardization rate; PT, prothrombin time; PTA, prothrombin activity; MPV, main portal vein; LPV, left branch of portal vein; RPV, right branch of portal vein; SV, splenic vein; SMV, superior mesenteric vein; MELD, the model for end-stage liver disease; EV, esophageal varices; GV, gastric varices; EGV, gastroesophageal varices; EGVB, esophageal-gastric variceal bleeding; PVT, portal vein thrombus; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma.

Supplementary Table 2 Multivariable logistic regression of factors associated with portal hypertension-related complications and mortality

Characteristic	Hazard Ratio	Lower 95%	Upper CI	95% P Value
Model predicting EGVB				
Presence of SPSS	3.41	1.63	7.11	0.001
Baseline moderate-severe ascites	2.51	1.31	4.83	0.006
Baseline EV/GV/EGV	4.30	1.29	14.29	0.017
Model predicting PVT				
Age	1.04	1.01	1.07	0.006
Presence of SPSS	3.54	1.40	8.96	0.008
Baseline EGVB	3.02	1.48	6.16	0.002
Model predicting HE				
Age	1.03	1.01	1.05	0.001
Presence of SPSS	4.74	2.44	9.21	<0.001
SMV diameter	1.18	1.08	1.29	<0.001
Child-pugh score	1.23	1.05	1.43	0.011
Baseline HE	2.52	1.66	3.84	<0.001
Model predicting ascites				
Age	1.02	1.01	1.03	0.005
Presence of SPSS	2.89	1.97	4.25	<0.001
Baseline EV/GV/EGV	2.17	1.36	3.45	0.001
Baseline mild ascites	1.94	1.26	2.99	0.003
Baseline moderate-severe ascites	1.78	1.17	2.71	0.007
Model predicting HCC				
Presence of SPSS	2.18	1.28	3.70	0.004
RPV diameter	1.11	1.01	1.22	0.042

Baseline HE	0.53	0.28	0.98	0.048
Baseline HCC	2.32	1.27	4.25	0.006
Model predicting mortality				
Age	1.04	1.02	1.06	<0.001
Presence of SPSS	2.52	1.35	4.71	0.004
MELD score	1.05	1.01	1.10	0.035
Baseline HE	1.95	1.22	3.12	0.005

Notes: SPSS, spontaneous portosystemic shunt; EGVB, esophageal-gastric variceal bleeding; EV, esophageal varices; GV, gastric varices; EGV, gastroesophageal varices; RPV, right branch of portal vein; SMV, superior mesenteric vein; MELD, the model for end-stage liver disease; PVT, portal vein thrombus; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma.

Supplementary Table 3 Clinical characteristics of patients with and without SPSS in the proteomic cohort

Characteristic		Non-SPSS (n=5)	SPSS (n=5)	P Value
Age	years	43.80 ± 12.15	44.40 ± 9.76	0.934
Gender	Female	1 (20.0%)	1 (20.0%)	1
	Male	4 (80.0%)	4 (80.0%)	
INR	g/L	1.18 ± 0.16	1.61 ± 0.26	0.012
PT	s	15.98 ± 3.44	18.00 ± 3.17	0.362
Albumin	g/L	37.40 ± 3.97	32.60 ± 7.09	0.223
Total bilirubin	μmol/L	22.68 ± 7.29	30.46 ± 11.57	0.239
Child-Pugh score		6.00 ± 0.71	9.00 ± 1.87	0.010
Child-Pugh grade	A	4 (80.0%)	0 (0.0%)	0.048
	B	1 (20.0%)	4 (80.0%)	
	C	0 (0.0%)	1 (20.0%)	
MELD score		9.00 ± 2.12	13.60 ± 2.41	0.013
MPV diameter	mm	17.02 ± 1.91	9.18 ± 4.10	0.005
LPV diameter	mm	12.24 ± 2.09	9.45 ± 3.97	0.202
RPV diameter	mm	13.67 ± 1.31	7.81 ± 2.16	<.001
SV diameter	mm	14.16 ± 1.29	17.19 ± 7.42	0.416
SMV diameter	mm	14.31 ± 1.92	13.75 ± 3.24	0.752
Baseline EGVB	No	4 (80.0%)	2 (40.0%)	0.524
	Yes	1 (20.0%)	3 (60.0%)	
Baseline PVT	No	5 (100.0%)	4 (80.0%)	1
	Yes	0 (0.0%)	1 (20.0%)	
Baseline HE	Absent	4 (80.0%)	2 (40.0%)	0.524
	Present	1 (20.0%)	3 (60.0%)	

Baseline ascites	No	5 (100.0%)	0 (0.0%)	0.008
	Yes	0 (0.0%)	5 (100.0%)	

Notes: SPSS, spontaneous portosystemic shunts; INR, international standardization rate; PT, prothrombin time; MELD, the model for end-stage liver disease; MPV, main portal vein; LPV, left branch of portal vein; RPV, right branch of portal vein; SV, splenic vein; SMV, superior mesenteric vein; EGVB, esophageal-gastric variceal bleeding; PVT, portal vein thrombus; HE, hepatic encephalopathy.

Supplementary Table 4 Clinical characteristics of patients with and without SPSS in the metabolomic cohort

Characteristic		Non-SPSS (n=30)	SPSS (n=50)	P Value
Age	years	53.13 ± 11.15	55.10 ± 11.31	0.451
Gender	Female	5 (16.7%)	11 (22.0%)	0.564
	Male	25 (83.3%)	39 (78.0%)	
INR	g/L	1.05 [1.00, 1.22]	1.37 [1.21, 1.66]	<.001
PT	s	13.60 [12.90, 15.47]	17.10 [15.30, 19.95]	<.001
PTA	%	92.00 [72.50, 100.00]	59.50 [48.00, 74.00]	<.001
Albumin	g/L	37.50 [32.25, 41.75]	32.00 [28.25, 35.00]	<.001
Total bilirubin	µmol/L	19.65 [16.65, 31.60]	44.05 [29.07, 88.80]	<.001
Child-Pugh score		5.50 [5.00, 6.00]	8.50 [8.00, 10.00]	<.001
Child-Pugh grade	A	23 (76.7%)	0 (0.0%)	<0.001
	B	5 (16.7%)	35 (70.0%)	
	C	2 (6.7%)	15 (30.0%)	
MELD score		7.00 [7.00, 10.00]	14.00 [11.00, 18.00]	<0.001
MPV diameter	mm	13.13 ± 2.04	14.22 ± 3.05	0.087
LPV diameter	mm	10.00 [9.11, 10.75]	10.07 [8.36, 11.36]	0.800
RPV diameter	mm	10.28 ± 1.58	10.29 ± 2.95	0.992
SV diameter	mm	9.08 [7.73, 10.04]	10.21 [8.79, 11.71]	0.009
SMV diameter	mm	10.76 ± 1.82	10.49 ± 2.24	0.570

Baseline EGV	No	12 (40.0%)	6 (12.0%)	0.004
	Yes	18 (60.0%)	44 (88.0%)	
Baseline EGVB	No	30 (100.0%)	36 (72.0%)	0.001
	Yes	0 (0.0%)	14 (28.0%)	
Baseline PVT	No	30 (100.0%)	45 (90.0%)	0.190
	Yes	0 (0.0%)	5 (10.0%)	
Baseline HE	Absent	29 (96.7%)	37 (74.0%)	0.010
	Present	1 (3.3%)	13 (26.0%)	
Baseline ascites	No	24 (80.0%)	12 (24.0%)	<0.001
	Yes	6 (20.0%)	38 (76.0%)	

Notes: SPSS, spontaneous portosystemic shunts; INR, international standardization rate; PT, prothrombin time; PTA, prothrombin activity; MELD, the model for end-stage liver disease; MPV, main portal vein; LPV, left branch of portal vein; RPV, right branch of portal vein; SV, splenic vein; SMV, superior mesenteric vein; EGVB, esophageal-gastric variceal bleeding; PVT, portal vein thrombus; HE, hepatic encephalopathy.

Supplementary Table 5 Clinical characteristics of SD rats with and without SPSS

Characteristic	Non-SPSS (N=13)	SPSS (N=20)	<i>P</i> Value
Albumin (g/L)	34.9±1.5	28.0±4.7	<0.001
Total bilirubin (umol/L)	2.00 [1.00, 2.20]	2.20 [1.90, 3.30]	0.143
ALT (U/L)	75.6 ± 17.7	110 ± 17.6	<0.001
AST(U/L)	201 ± 33.9	294 ± 70.2	<0.001
GGT (U/L)	4.00 [2.00, 4.00]	3.00 [2.00, 4.50]	0.566
Urea (mmol/L)	4.6 ±0.5	5.1 ±0.7	0.022
Creatinine(umol/L)	31.0 [30.0, 36.0]	36.0 [32.0, 26.0]	0.174
Liver weight (g)	22.02 [20.47, 25.06]	20.55 [18.50, 21.59]	0.186
Spleen weight (g)	1.27 [1.16, 1.56]	1.65 [1.42, 2.12]	0.014
Liver weight/Spleen weight	16.54 [14.19, 20.31]	10.81 [10.20, 14.91]	0.015
Body weight (g)	611±50.4	593±55.2	0.376
Ascites			
No	9 (69.2%)	8 (40.0%)	0.199
Yes	4 (30.8%)	12 (60.0%)	

Notes: SPSS, spontaneous portosystemic shunts; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase.

Supplementary Table 6 Clinical characteristics of SD rats across sham, cirrhosis, and SC79-treated groups

Characteristic	Sham	Cirrhosis	SC79	P Value
	(n=13)	(n=12)	(n=12)	
Albumin (g/L)	30.0 [28.0, 32.0]	30.0 [27.5, 30.0]	32.0 [32.0, 32.0] ^c	0.008
Total bilirubin (μmol/L)	1.5 [1.1, 2.1]	7.2 [2.5, 15.7] ^a	1.4 [1.00, 2.7] ^c	0.006
ALT (U/L)	52.0 [48.5, 55.5]	77.0[52.5, 109.0]	50.0 [44.0, 72.0]	0.144
AST (U/L)	137.0 [97.0, 157.5]	280.0 [157.0, 401.0] ^a	162.00 [101.00, 211.00]	0.048
GGT(U/L)	3.0 [2.0, 4.0]	4.0 [2.0, 4.5]	4.0 [2.0, 6.0]	0.624
Urea(mmol/L)	5.50 [5.05, 5.75]	5.10 [4.85, 5.40]	4.80 [4.20, 4.90]	0.058
Creatinine (umol/L)	30.0 [28.0, 30.0]	30.0 [26.0, 33.5]	34.0 [33.0, 38.0]	0.061
Liver weight (g)	16.6 [15.7, 22.4] ^b	20.2 [19.0, 21.2]	26.2 [22.6, 31.2]	0.019
Spleen weight (g)	0.9 [0.8, 0.9] ^b	1.8 [1.3, 2.3] ^a	1.8 [1.4, 2.7]	<0.001
Liver weight /Spleen weight	21.1 [18.5, 23.2]	11.2 [9.9, 15.3] ^a	15.6 [10.2, 19.9]	0.002
Body weight (g)	648.25 [612.65, 677.60]	734.40 [664.7, 827.1]	670.2 [632.4, 730.1]	0.074
Ascites No	13 (100.0%)	4 (33.3%) ^a	10 (83.3%) ^c	0.002
Yes	0 (0.0%)	8 (66.7%)	2 (16.7%)	

Notes: SPSS, spontaneous portosystemic shunts; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase. ^a*P* < 0.05, sham group *vs* cirrhosis group; ^b*P* < 0.05, sham group *vs* SC79 group; ^c*P* < 0.05, cirrhosis group *vs* SC79 group.