Source population (*n* = 251)
Newy developed HCC patiet in SNUBH
from March 2012 to April 2016

Exclusions (*n* = 11)
Concurent malignancies (*n* = 9)
Combine chlagiocarinoma (*n* = 2)

Study population (*n* = 240)
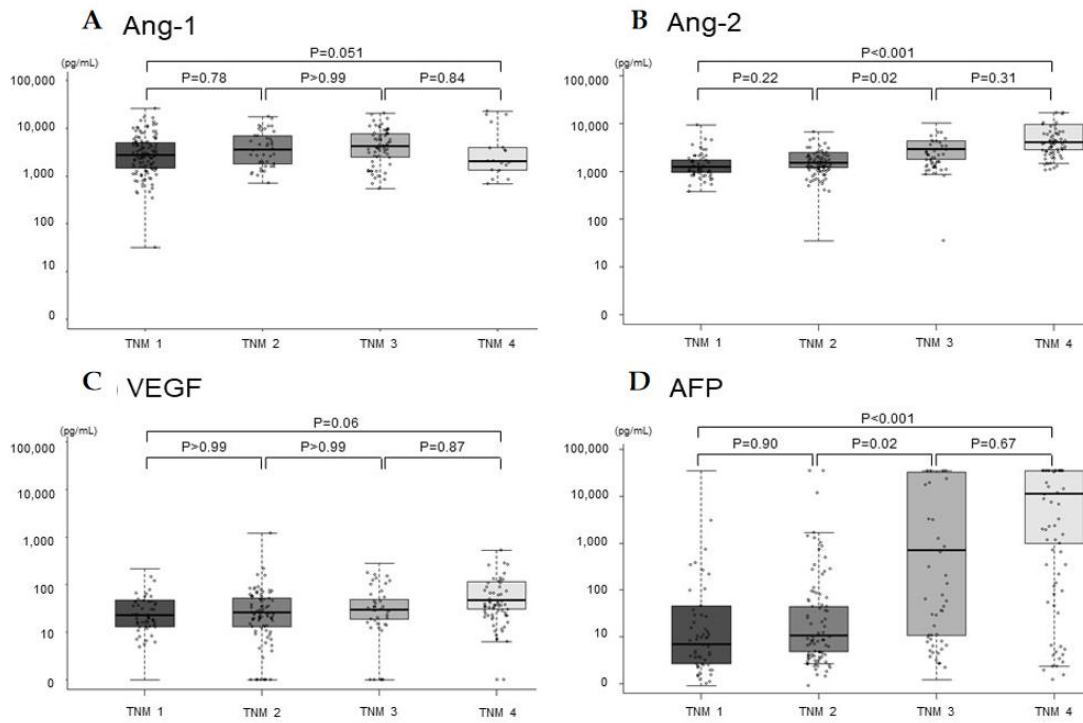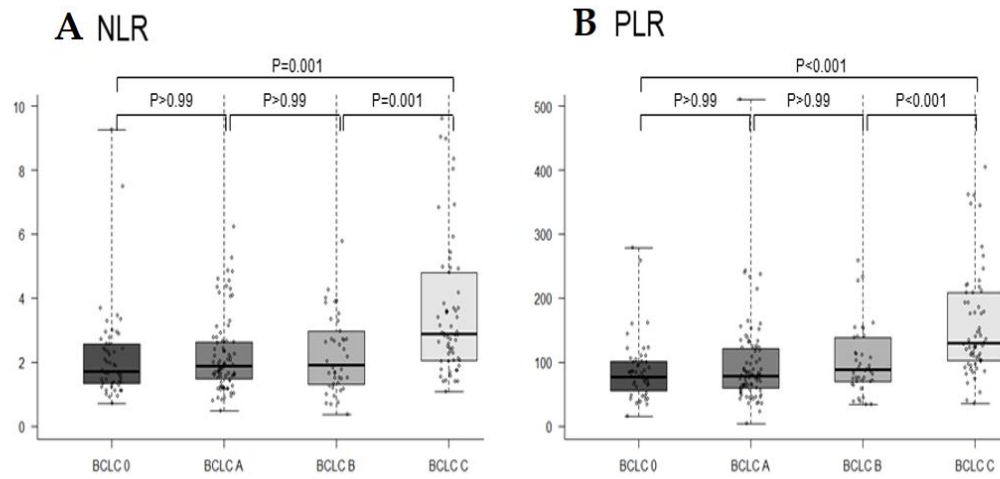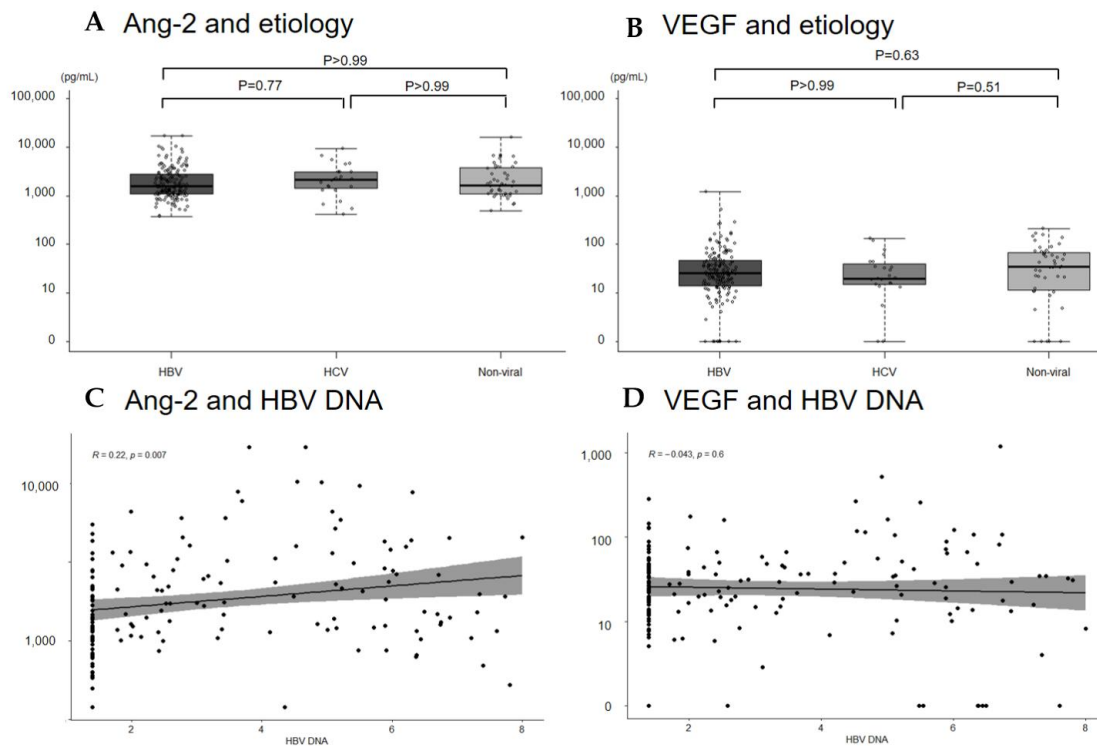HCC patiets group

Supplementary Figure 1 Patient flow diagrams. ALT: Alanine aminotransferase; HCC: Hepatocellular carcinoma; HBsAg: Hepatitis B virus surface antigen; SNUBH: Seoul National University Bundang Hospital; ULN: Upper limit of normal.
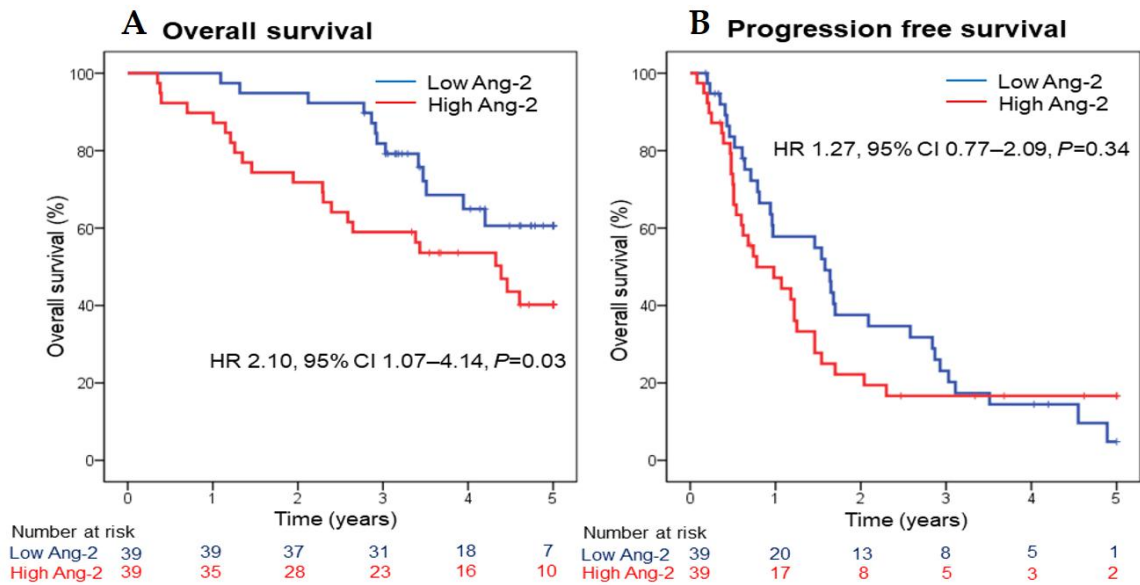
Supplementary Figure 2 Plasma levels of angiopoietin-1, angiopoietin-2, vascular endothelial growth factor, and alpha fetoprotein in the hepatocellular carcinoma patients according to TNM stage. AFP: Alpha-fetoprotein; Ang-1: Angiopoietin-1; Ang-2: Angiopoietin-2; VEGF: Vascular endothelial growth factor; TNM: Tumor-Node-Metastasis.

Supplementary Figure 3 Plasma levels of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in the hepatocellular carcinoma patients according to tumor stage. BCLC: Barcelona Clinic Liver Cancer; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.

A Ang-2 and etiology

B VEGF and etiology

C Ang-2 and HBV DNA

D VEGF and HBV DNA

Supplementary Figure 4 Plasma levels of angiopoietin-1 and angiopoietin-2 according to etiology and hepatitis B virus DNA level. Ang-2: Angiopoietin-1; VEGF: Vascular endothelial growth factor; HBV: Hepatitis B virus.

A Overall survival / **B** Progression free survival

HR 2.10, 95% CI 1.07–4.14, *P*=0.03

HR 1.27, 95% CI 0.77–2.09, *P*=0.34

Number at risk

Low Ang-2	39	39	37	31	18	7
High Ang-2	39	35	28	23	16	10

Number at risk

Low Ang-2	39	20	13	8	5	1
High Ang-2	39	17	8	5	3	2

Supplementary Figure 5 Kaplan-Meire curve for progression free and overall survival after propensity score matching. Ang-2: Angiopoietin-2; HR: Hazard ratio; CI: Confidence interval.

Supplementary Table 1 Baseline characteristics of hepatocellular carcinoma patients according to angiopoietin-2 and vascular endothelial growth factor level

Characteristic	Low Ang-2 group (*n* = 121)	High Ang-2 group (*n* = 119)	*P* value	Low VEGF group (*n* = 121)	High VEGF group (*n* = 119)	*P* value
Age, year	62.1 ± 10.9	59.7 ± 11.4	0.10	60.0 ± 10.8	61.9 ± 11.5	0.18
Male sex	95 (78.5)	98 (82.4)	0.45	96 (79.3)	97 (81.5)	0.67
Etiology			0.45			0.37
HBV	87 (71.9)	80 (67.2)		88 (72.7)	79 (66.4)	
HCV	9 (7.4)	15 (12.6)		14 (11.6)	10 (8.4)	
Alcohol	12 (9.9)	16 (13.4)		12 (9.9)	16 (13.4)	
HBV + HCV	1 (0.8)	1 (0.8)		1 (0.8)	1 (0.8)	
Others	12 (9.9)	7 (5.9)		6 (5.0)	13 (10.9)	
ECOG performance			0.001			0.006
0	94 (77.7)	62 (52.1)		88 (72.7)	68 (57.1)	
1–2	27 (22.3)	53 (44.5)		33 (27.3)	47 (39.5)	
3	0 (0)	4 (3.4)		0 (0)	4 (3.4)	
Presence of cirrhosis	89 (73.6)	95 (79.8)	0.25	100 (82.6)	84 (70.6)	0.03
Child-Pugh class			< 0.001			0.68
A	116 (95.9)	88 (73.9)		104 (86.0)	100 (84.0)	
B	5 (4.1)	30 (25.3)		17 (14.0)	18 (15.2)	
C	0 (0)	1 (0.8)		0 (0)	1 (0.8)	
MELD	4.1 ± 5.4	5.3 ± 4.4	0.08	5.6 ± 5.0	3.8 ± 4.8	0.01
Multi-nodularity	37 (30.6)	68 (57.1)	< 0.001	47 (38.8)	58 (48.7)	0.15
Diffuse infiltrative type	4 (3.3)	37 (31.1)	< 0.001	12 (9.9)	29 (24.4)	0.003

Maximal tumor size	2.7 (1.8–4.1)	6.6 (2.7–11.0)	< 0.001	3.0 (1.8–5.3)	5.3 (2.2–10.9)	< 0.001
Bilobal involvement	22 (18.2)	52 (43.7)	< 0.001	28 (23.1)	46 (38.7)	0.009
Vascular invasion	2 (1.7)	40 (33.6)	< 0.001	15 (12.4)	27 (22.5)	0.04
Distant metastasis	1 (0.8)	16 (13.4)	< 0.001	4 (3.3)	13 (10.9)	0.02
TNM stage			< 0.001			0.04
IA	38 (31.4)	14 (11.8)		32 (26.4)	20 (16.8)	
IB	45 (37.2)	18 (15.1)		35 (28.9)	28 (23.5)	
II	23 (19.0)	19 (16.0)		23 (19.0)	19 (16.0)	
IIIA	14 (11.6)	24 (20.2)		17 (14.0)	21 (17.6)	
IIIB	0 (0)	27 (22.7)		10 (8.3)	17 (14.3)	
D	1 (0.8)	17 (14.3)		4 (3.3)	14 (11.8)	
BCLC stage			< 0.001			0.01
0	38 (31.4)	14 (11.8)		32 (26.4)	20 (16.8)	
A	55 (45.5)	26 (21.8)		46 (38.0)	35 (29.4)	
B	20 (16.5)	23 (19.3)		21 (17.4)	22 (18.5)	
C	8 (6.6)	51 (42.9)		22 (18.2)	37 (31.1)	
D	0 (0)	5 (4.2)		0 (0)	5 (4.2)	
BMI, kg/m^2	24.5 ± 3.2	23.6 ± 2.8	0.02	24.2 ± 2.9	24.0 ± 3.1	0.58
AFP, ng/mL	7.7 (3.6–77.8)	73.3 (8.2–10315)	< 0.001	10.8 (3.8–89.8)	57.6 (4.2–3068.0)	0.01
PIVKA-II, mAU/mL	37 (20–136)	25 (451–10000)	< 0.001	42 (16–459)	196 (24–5899)	0.03
Ang-1, pg/mL	3002 (1680–6917)	3453 (1298–	0.93	1916 (1238–3136)	5266 (3332–9668)	< 0.001

		5898)				
Ang-2, pg/mL	1132 (868–1313)	3072 (2167–4553)	< 0.001	1552 (1142–2408)	1916 (1077–3658)	0.01
VEGF, pg/mL	23.8 (14.5–48.5)	29.4 (13.6–55.7)	0.08	14.0 (10.8–19.8)	51.8 (36.3–85.7)	< 0.001
WBC, x10^3/uL	5.0 (4.0–6.5)	5.6 (3.9–6.8)	0.22	4.8 (3.7–5.9)	5.6 (4.5–7.3)	< 0.001
Hemoglobin, g/dL	14.1 (12.9–15.0)	12.7 (11.3–14.3)	< 0.001	13.6 (12.0–14.7)	13.6 (11.8–14.9)	0.64
Platelet count, ×10^9/uL	131 (96–170)	128 (80–211)	0.22	105 (74–150)	151 (111–208)	< 0.001
NLR	2.2 ± 1.5	3.5 ± 4.7	0.007	2.9 ± 4.5	2.8 ± 2.1	0.92
PLR	98.5 ± 62.8	138.3 ± 155.6	0.01	108.2 ± 140.6	128.4 ± 93.3	0.19
Prothrombin time, INR	1.09 (1.03–1.15)	1.12 (1.05–1.23)	0.02	1.12 (1.06–1.24)	1.08 (1.02–1.13)	0.001
AST, IU/mL	38 (27–47)	69 (41–116)	< 0.001	41 (31–58)	55 (36–95)	0.003
ALT, IU/mL	33 (21–53)	44 (26–74)	0.002	34 (22–52)	44 (26–79)	0.001
Albumin, g/dL	4.1 (3.9–4.4)	3.7 (3.2–4.0)	< 0.001	4.0 (3.5–4.2)	3.9 (3.5–4.3)	0.97
Total bilirubin, mg/dL	0.7 (0.4–0.9)	0.9 (0.6–1.3)	0.07	0.8 (0.6–1.2)	0.7 (0.5–1.1)	0.86
Creatinine, mg/dL	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.57	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.06
Diabetes mellitus	23 (19.0)	30 (25.2)	0.25	23 (19.0)	30 (25.2)	0.25

Hypertension	35 (28.9)	35 (29.4)	0.93	31 (25.6)	39 (32.8)	0.22
Initial treatment			< 0.001			0.03
Resection	25 (20.7)	9 (7.6)		18 (14.9)	16 (13.4)	
RFA	21 (17.4)	6 (5.0)		16 (13.2)	11 (9.2)	
TACE	74 (61.2)	92 (77.3)		86 (71.1)	80 (67.2)	
Sorafenib	0 (0)	2 (1.7)		0 (0)	2 (1.7)	
BSC	1 (0.8)	10 (8.4)		1 (0.8)	10 (8.4)	

Data presented as mean and standard deviation or median and interquartile range or frequency (*n*) and percentage where appropriate. AFP: α-feto protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BSC: Best supportive care; ECOG: Eastern Cooperative Oncology Group; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; IQR: Interquartile range; MELD: Model for End-stage Liver Disease; PIVKA-II: Prothrombin-induced by vitamin K absence or antagonist-II; RFA: Radiofrequency ablation; SD: Standard deviation; TACE: Transarterial chemoembolization; VEGF: Vascular endothelial growth factor; WBC: White blood cell.

Supplementary Table 2 Baseline characteristics of hepatocellular carcinoma patients between low- and high-angiopoietin-2 groups before and after the propensity score-matching

Characteristic	Crude			After PS matching		
	Low Ang-2 group (*n* = 121)	High Ang-2 group (*n* = 119)	SMD	Low Ang-2 group (*n* = 39)	High Ang-2 group (*n* = 39)	SMD
Age, year	62.1 ± 10.9	59.7 ± 11.4	0.22	62.7 ± 10.5	61.0 ± 12.6	0.15
Male sex	95 (78.5)	98 (82.4)	0.10	30 (76.9)	33 (84.6)	0.19
ECOG performance			0.50			0.27
0	95 (78.5)	67 (56.3)		26 (66.7)	29 (74.4)	
1 – 2	26 (21.5)	50 (42.0)		12 (30.8)	10 (25.6)	
3	0 (0)	2 (1.7)		1 (2.6)	0 (06)	
Child-Pugh class			0.64			0.11
A	116 (95.9)	88 (73.9)		36 (92.3)	37 (94.9)	
B or C	5 (4.1)	31 (26.2)		3 (7.7)	2 (5.1)	
Maximal tumor size	2.6 (1.8–4.1)	6.7 (2.7–11.0)	1.04	3.5 (2.0–6.1)	3.0 (2.2–5.5)	0.05
Multiple tumors	37 (30.3)	68 (56.7)	0.55	18 (46.2)	18 (46.2)	< 0.01
Bilobal involvement	22 (18.0)	52 (43.3)	0.57	12 (30.8)	12 (30.8)	< 0.01
Vascular invasion	2 (1.6)	40 (33.3)	0.92	2 (5.1)	3 (7.7)	0.11
Distant metastasis	1 (0.8)	16 (13.3)	0.51	1 (2.6)	1 (2.6)	< 0.01
TNM stage			1.13			< 0.01
I / II	83 (68.6)/23 (19.0)	32 (26.9)/19 (16.0)		20 (51.3)/8 (20.5)	20 (51.3)/8 (20.5)	
III / IV	14 (11.6)/1	24 (20.2)/44		10	10 (25.6)/1(2.6)	

			p			p
	(0.8)	(36.9		(25.6)/1(2.6)		
BMI, kg/m^2	24.5 ± 3.2	23.6 ± 2.8	0.30	24.2 ± 3.2	24.1 ± 2.7	0.04
AFP, ng/mL	7.7 (3.6–77.8)	73.3 (8.2–10315)	0.66	20.9 (4.4–244.5)	12.0 (4.1–118.7)	0.03
Angiopoietin-1, pg/mL	3002 (1680–6917)	3453 (1298–5898)	0.01	4070 (1570–7950)	2751 (1238–4983)	0.26
Angiopoietin-2, pg/mL	1132 (868–1313)	3072 (2167–4553)	1.42	1204 (1021–1315)	2125(1898–3107)	1.88
VEGF, pg/mL	37 (20–136)	25 (451–10000)	0.23	22.1 (6.3–56.9)	19.9 (11.4–39.7)	0.05
Hemoglobin, g/dL	14.1 (12.9–15.0)	12.7 (11.3–14.3)	0.50	13.6 (11.5–14.3)	13.6 (12.2–14.7)	0.14
Platelet count, x10^9/uL	131 (96–170)	128 (80–211)	0.16	110 (76–149)	93 (71–144)	0.02
Prothrombin time, INR	1.09 (1.03–1.15)	1.12 (1.05–1.23)	0.31	1.12 (1.07–1.25)	1.12 (1.06–1.22)	0.12
ALT, IU/mL	33 (21–53)	44 (26–74)	0.42	40 (24–65)	38 (24–55)	0.21
Albumin, g/dL	4.1 (3.9–4.4)	3.7 (3.2–4.0)	0.98	3.9 (3.5–4.1)	4.0 (3.6–4.1)	0.25
Total bilirubin, mg/dL	0.7 (0.4–0.9)	0.9 (0.6–1.3)	0.24	0.8 (0.4–1.0)	0.7 (0.6–1.0)	0.01
Creatinine, mg/dL	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.07	0.9 (0.7–0.9)	0.8 (0.7–1.0)	0.08
NLR	2.2 ± 1.5	3.5 ± 4.7	0.35	2.5 ± 1.6	2.3 ± 1.9	0.11
PLR	98.5 ± 62.8	138.3 ± 155.6	0.34	95.0 ± 55.5	85.3 ± 45.9	0.19
Initial treatment			0.71			0.05
Resection	25 (20.7)	9 (7.6)		3 (7.7)	4 (2.6)	
RFA	21 (17.4)	6 (5.0)		5 (12.8)	5 (12.8)	
TACE	74 (61.2)	92 (77.3)		30 (76.9)	30 (76.9)	

| Sorafenib or BSC | 1 (0.8) | 12 (10.1) | 1 (2.6) | 0 (0) |

Data presented as mean and standard deviation or median and interquartile range or frequency (*n*) and percentage where appropriate. AFP: α-feto protein; ALT: Alanine aminotransferase; BMI: Body mass index; BSC: Base supportive care; ECOG: Eastern Cooperative Oncology Group; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; VEGF: Vascular endothelial growth factor; WBC: White blood cell.