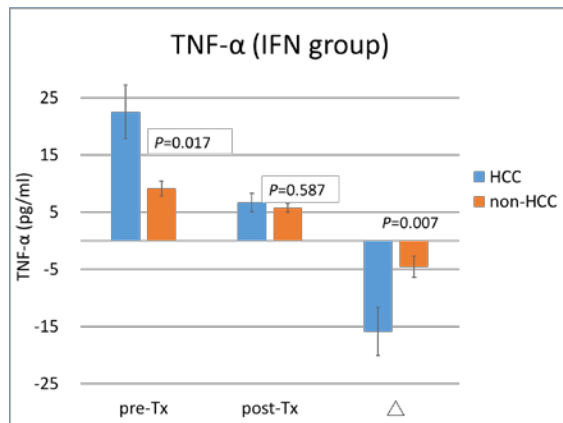
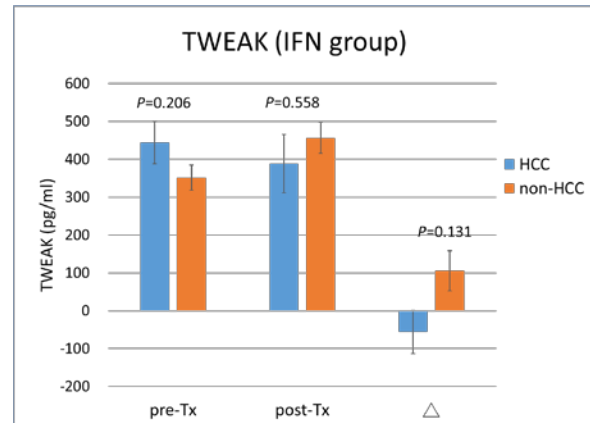
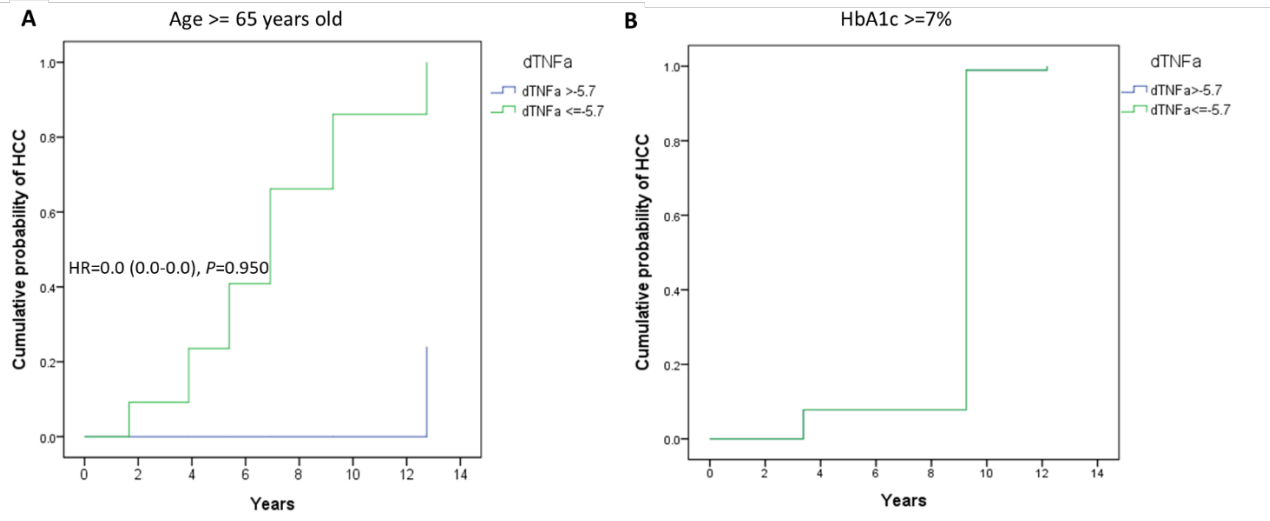


A**B**

Supplementary Figure 1 Cytokine expression between the hepatocellular carcinoma and non-hepatocellular carcinoma groups in the interferon group. The bar represents mean $\pm$ standard error. Δ = (posttreatment cytokine level)–(pretreatment cytokine level). The *P* value was tested by the Mann-Whitney U test. HCC: Hepatocellular carcinoma; TNF- α : Tumor necrosis factor- α ; TWEAK: TNF-like weak inducer of apoptosis; IFN: Interferon; pre-Tx: Pretreatment; post-Tx: Posttreatment.



Supplementary Figure 2 Multivariate Cox regression analysis of tumor necrosis factor- α associated with hepatocellular carcinoma in subgroups. Comparison of the cumulative probability of hepatocellular carcinoma development divided by the tumor necrosis factor- α (TNF- α) with a cutoff value of -5.7pg/mL in patients with (A) age ≥ 65 and (B) hemoglobin A1c (HbA1c) $\geq 7\%$. The P value was adjusted by age, sex, Fibrosis-4 index, and HbA1c.

Supplementary Table 1 Cytokine expression between the hepatocellular carcinoma and non-hepatocellular carcinoma groups among chronic hepatitis C patients with advanced fibrosis

		HCC (<i>n</i> = 12)		Non-HCC (<i>n</i> = 85)		Mann-Whitney value	<i>P</i>
Cytokine		Mean (pg/mL)	SE	Mean (pg/mL)	SE		
Pretreatment	FGF-2	43.66	6.06	52.17	6.85	0.733	
	Eotaxin	65.12	12.30	68.66	5.26	0.857	
	G-CSF	24.80	5.13	19.59	2.98	0.081	
	GM-CSF	5.98	0.69	7.56	1.24	0.150	
	Fractalkine	62.90	13.43	60.17	9.63	0.285	
	IFN- α 2	20.94	2.96	20.68	3.91	0.034	
	IFN- γ	2.78	0.43	4.88	1.71	0.514	
	GRO	552.96	114.10	614.70	69.27	0.784	
	IL-10	11.25	3.61	8.60	0.78	0.818	
	MCP-3	34.77	23.28	21.66	5.06	0.775	
	IL-12p40	2.10	0.54	6.57	1.91	0.089	
	MDC	585.12	71.70	582.16	30.48	0.852	
	IL-12p70	6.43	2.25	6.26	1.83	0.026	
	IL-13	24.73	23.32	11.20	8.39	0.051	
	IL-15	3.05	0.19	3.53	0.34	0.399	
	sCD40L	1987.10	1132.49	2913.13	397.44	0.239	
	IL-17A	2.26	0.18	7.06	1.65	0.439	
	IL-1 α	12.10	6.94	13.88	6.24	0.164	

IL-9	1.13	0.23	0.96	0.08	0.195
IL-1 β	2.86	1.19	6.22	3.94	0.354
IL-2	0.91	0.06	1.42	0.26	0.270
IL-3	0.66	0.04	0.59	0.03	0.034
IL-4	152.28	66.05	190.13	32.68	0.822
IL-6	107.98	63.34	38.95	27.36	0.018
IL-7	4.47	1.67	4.54	0.52	0.846
IL-8	942.19	842.88	166.05	90.26	0.072
IP-10	961.26	167.05	1127.48	87.16	0.701
MCP-1	854.12	102.19	1050.03	93.53	0.818
MIP-1 α	179.29	142.04	190.28	182.33	0.293
MIP-1 β	112.86	46.65	59.45	12.68	0.188
TNF- α	22.22	4.33	12.53	1.03	0.036
TNF- β	36.06	34.48	14.54	11.05	0.182
VEGF	139.66	44.52	130.95	13.39	1.000
IL-22	0.15	0.03	0.16	0.01	0.965
IL-18	12.39	1.17	13.10	0.80	0.952
IL-17E/IL-25	0.02	0.01	0.03	0.00	0.958
IL-27	0.77	0.05	0.84	0.05	0.705
IL-31	0.15	0.04	0.13	0.01	0.705
Eotaxin-2	1084.73	108.96	988.16	53.17	0.329
MCP-2	110.23	16.46	87.35	5.74	0.177
IL-16	100.75	99.12	67.34	28.13	0.464
Eotaxin-3	51.86	13.06	64.10	10.68	0.860
LIF	13.30	1.81	17.14	3.07	0.754

	SCF	37.81	10.65	37.29	5.83	0.332
	TSLP	15.41	8.91	15.79	5.70	0.618
	IL-20	59.60	47.08	88.94	32.87	0.095
	IL-21	11.40	1.12	15.97	3.22	0.784
	TRAIL	465.00	53.33	443.51	21.82	0.965
	ENA-78	885.13	111.84	1060.37	88.92	0.375
	GLP-1 total	311.39	50.87	370.01	19.59	0.164
	Glucagon	98.10	32.64	77.76	14.17	0.229
	Insulin	3266.63	1381.79	2086.89	369.49	0.504
	Leptin	13307.33	2975.77	12659.57	1075.16	0.844
	I-TAC	209.16	54.82	268.77	31.92	0.689
	MIP-3 α	43.73	5.31	55.55	6.48	0.439
	MIG	3706.20	1061.45	3441.25	522.91	0.618
	M-CSF	645.31	219.81	1948.82	607.01	0.599
	OPG	836.06	42.60	954.60	30.30	0.198
	TWEAK	506.60	80.49	517.84	25.66	0.536
	MIF	39.01	6.38	55.02	4.86	0.245
	sICAM-1	163549.58	48446.47	152499.99	16559.46	0.895
	sFasL	26.60	6.26	31.41	2.59	0.131
	sVCAM-1	475670.42	63629.65	407063.75	24579.26	0.319
	tPAI-1	32116.25	5131.35	34663.21	1439.14	0.355
Posttreatment	FGF-2	18.81	6.43	35.27	5.31	0.334
	Eotaxin	55.37	15.67	70.12	5.80	0.247
	G-CSF	6.75	2.48	10.70	2.00	0.767

GM-CSF	3.67	0.95	4.42	0.68	0.683
Fractalkine	43.00	12.84	32.89	4.45	0.210
IFN- α 2	8.50	2.57	11.21	1.80	0.675
IFN- γ	1.66	0.25	3.22	0.79	0.296
GRO	484.51	102.54	664.20	45.13	0.142
IL-10	2.03	0.72	1.88	0.12	0.383
MCP-3	29.60	21.69	16.55	4.08	0.631
IL-12p40	0.37	0.08	2.49	1.18	0.982
MDC	546.58	89.28	562.79	26.26	0.827
IL-12p70	2.70	0.69	9.64	5.79	0.745
IL-13	23.21	22.21	8.38	5.79	0.908
IL-15	1.75	0.18	1.96	0.13	0.606
sCD40L	1622.49	1034.43	3500.31	405.88	0.030
IL-17A	1.45	0.12	4.22	1.15	0.092
IL-1 α	3.81	2.66	8.70	3.94	0.978
IL-9	0.67	0.09	0.77	0.05	0.754
IL-1 β	1.34	0.31	5.09	3.69	0.617
IL-2	0.60	0.06	0.86	0.10	0.589
IL-3	0.47	0.04	0.47	0.02	0.422
IL-4	206.96	91.22	119.53	26.10	0.398
IL-6	27.18	25.19	23.20	15.96	0.822
IL-7	1.16	0.44	1.91	0.26	0.401
IL-8	31.28	9.82	247.69	207.29	0.784
IP-10	400.21	97.66	439.42	44.37	0.638
MCP-1	752.58	107.98	797.94	44.87	0.726

MIP-1 α	20.53	13.41	24.17	20.21	0.258
MIP-1 β	30.32	10.73	45.69	14.49	0.433
TNF- α	7.11	1.52	7.91	0.59	0.784
TNF- β	39.87	38.66	10.92	7.61	0.873
VEGF	108.43	38.00	116.13	13.70	0.478
IL-22	0.13	0.04	0.15	0.02	0.587
IL-18	8.26	1.13	8.94	0.61	0.689
IL-17E/IL-25	0.02	0.01	0.02	0.00	0.518
IL-27	0.63	0.07	0.65	0.05	0.763
IL-31	0.14	0.04	0.14	0.03	0.943
Eotaxin-2	1060.25	226.35	991.94	45.46	0.810
MCP-2	78.83	12.79	79.61	3.82	0.738
IL-16	120.31	106.06	73.82	31.11	0.698
Eotaxin-3	53.93	15.13	73.54	8.47	0.337
LIF	11.42	1.23	14.39	1.75	0.956
SCF	38.98	12.10	37.93	6.02	0.887
TSLP	23.09	14.06	26.94	11.62	0.861
IL-20	57.98	44.89	105.08	32.61	0.239
IL-21	10.38	1.11	13.32	2.33	0.673
TRAIL	519.13	77.70	505.14	20.21	0.463
ENA-78	789.86	151.34	1112.56	94.68	0.128
GLP-1 total	335.49	62.12	338.03	20.97	0.917
Glucagon	113.67	36.09	96.52	16.35	0.293
Insulin	1523.17	1273.96	1006.78	331.61	0.781
Leptin	10450.83	3001.83	16451.45	1555.89	0.131

Δ	I-TAC	61.63	19.24	110.80	14.43	0.121
	MIP-3 α	28.38	3.10	36.82	4.47	0.769
	MIG	1186.82	234.14	2128.40	285.44	0.202
	M-CSF	3703.10	2562.08	302.32	190.00	0.386
	OPG	692.22	60.82	761.68	26.59	0.340
	TWEAK	434.82	84.18	660.65	30.34	0.018
	MIF	41.40	3.83	58.20	3.92	0.052
	sICAM-1	95473.66	35358.42	91529.89	11225.48	0.852
	sFasL	44.36	5.95	40.83	1.31	0.921
	sVCAM-1	242422.56	65243.93	338281.21	24686.99	0.125
	tPAI-1	28151.25	4481.71	33516.53	1239.02	0.161
	FGF-2	-24.86	6.12	-16.90	4.23	0.298
	Eotaxin	-9.75	12.43	1.45	4.37	0.220
	G-CSF	-18.05	4.97	-8.88	2.04	0.058
	GM-CSF	-2.31	0.82	-3.14	0.73	0.974
	Fractalkine	-19.90	12.70	-27.28	8.08	0.724
	IFN- α 2	-12.44	3.03	-9.47	2.89	0.034
	IFN- γ	-1.13	0.41	-1.66	1.03	0.248
	GRO	-68.46	91.27	49.50	65.74	0.497
	IL-10	-9.22	3.12	-6.72	0.75	0.576
	MCP-3	-5.17	3.02	-5.11	2.07	0.452
	IL-12p40	-1.73	0.55	-4.07	1.13	0.054
	MDC	-38.54	62.08	-19.37	25.61	0.921
	IL-12p70	-3.74	1.62	3.37	4.47	0.009
	IL-13	-1.52	1.17	-2.82	2.96	0.036

IL-15	-1.30	0.13	-1.56	0.25	0.202
sCD40L	-364.61	1618.04	587.18	289.64	0.518
IL-17A	-0.81	0.22	-2.84	1.16	0.115
IL-1 α	-8.30	4.50	-5.18	3.12	0.100
IL-9	-0.47	0.20	-0.18	0.07	0.044
IL-1 β	-1.52	1.25	-1.13	5.43	0.387
IL-2	-0.31	0.07	-0.56	0.18	0.236
IL-3	-0.19	0.04	-0.12	0.03	0.018
IL-4	54.68	82.84	-70.59	42.58	0.576
IL-6	-80.80	61.18	-15.75	31.15	0.053
IL-7	-3.30	1.36	-2.63	0.44	0.719
IL-8	-910.91	842.92	81.64	226.49	0.181
IP-10	-561.05	136.47	-688.05	77.07	0.734
MCP-1	-101.54	107.86	-252.09	75.51	0.569
MIP-1 α	-158.77	144.33	-166.11	183.71	0.759
MIP-1 β	-82.54	47.35	-13.77	18.73	0.369
TNF- α	-15.11	3.93	-3.78	1.16	0.001
TNF- β	3.82	4.19	-3.61	3.66	0.310
VEGF	-31.23	30.60	-14.83	12.35	0.805
IL-22	-0.02	0.01	-0.01	0.01	0.908
IL-18	-4.13	1.27	-4.16	0.68	0.657
IL-17E/IL25	0.00	0.00	0.00	0.00	0.880
IL-27	-0.13	0.07	-0.19	0.05	0.751
IL-31	-0.01	0.02	0.00	0.02	0.912
Eotaxin-2	-24.48	174.43	3.78	42.05	0.714

MCP-2	-31.40	11.08	-7.73	4.30	0.086
IL-16	19.56	15.30	6.48	26.52	0.527
Eotaxin-3	2.08	13.66	9.44	10.39	0.730
LIF	-1.88	1.27	-2.75	2.41	0.311
SCF	1.17	11.01	0.64	3.79	0.908
TSLP	7.68	5.32	11.15	10.04	0.080
IL-20	-1.63	13.53	16.13	28.04	0.035
IL-21	-1.02	0.67	-2.65	1.89	0.572
TRAIL	54.13	56.39	61.63	24.38	0.844
ENA-78	-95.27	99.25	52.19	64.89	0.329
GLP-1 total	24.10	37.41	-31.99	17.29	0.113
Glucagon	15.56	28.25	18.76	14.18	0.722
Insulin	-1743.46	1182.48	-1080.11	392.41	0.965
Leptin	-2856.50	1933.50	3791.88	1132.66	0.038
I-TAC	-147.53	49.33	-157.97	27.60	0.673
MIP-3 α	-15.35	3.43	-18.73	6.82	0.126
MIG	-2519.38	1056.33	-1312.85	510.51	0.092
M-CSF	3057.80	2593.59	-1646.50	643.43	0.718
OPG	-143.84	64.62	-192.91	29.63	0.861
TWEAK	-71.78	54.56	142.81	27.69	0.004
MIF	2.39	7.25	3.18	5.25	0.831
sICAM-1	-68075.93	17744.31	-60970.09	11680.70	0.483
sFasL	17.77	2.67	9.42	1.77	0.057
sVCAM-1	-233247.85	63791.88	-68782.54	25106.38	0.046
tPAI-1	-3965.00	3317.48	-1146.68	1344.96	0.298

HCC: Hepatocellular carcinoma; SE: Standard error.

Supplementary Table 2 Factors associated with the onset of hepatocellular carcinoma in the interferon group: univariate and multivariate Cox regression models

Variables	Univariate	Cox	Multivariate Cox regression		
	Crude HR (95%CI)	<i>P</i> value	Adjusted (95%CI)	HR	Adjusted <i>P</i> value
Age (yr)	1.10 (0.99-1.22)	0.071	-	-	-
Sex (male vs female)	3.83 (1.01-14.53)	0.049	-	-	-
HCV genotype	1.03 (0.48-2.24)	0.939	-	-	-
HCV RNA (log IU/ml)	0.65 (0.34-1.23)	0.183	-	-	-
FIB-4	1.11 (0.94-1.32)	0.207	-	-	-
FIB-4 (≥ 9 vs <9)	3.61 (1.05-12.41)	0.041	-	-	-
Platelet(k/ μ L)	0.99 (0.98-1.01)	0.539	-	-	-
AFP (ng/ml)	1.00 (0.98-1.02)	0.742	-	-	-
HbA1c (%)	1.29 (1.01-1.63)	0.039	-	-	-
HbA1c (≥ 7 vs <7)	5.83 (1.44-23.54)	0.013	-	-	-
BMI (kg/m ²)	0.96 (0.78-1.18)	0.662	-	-	-
TNF-α (pg/mL)					
Pre-Tx TNF- $\alpha \geq 18$	4.60 (1.35-15.67)	0.015	-	-	-
Post-Tx TNF- $\alpha \geq 6$	0.73 (0.22-2.41)	0.607	-	-	-
Δ TNF- $\alpha \leq -5.7$	9.77 (1.95-48.96)	0.006	9.98 (1.88-52.87)		0.007
TWEAK (pg/mL)					

Pre-Tx TWEAK $\geq$ 500	2.29 (0.65-8.14)	0.199	-	-
Post-Tx TWEAK $\geq$ 600	0.85 (0.18-3.95)	0.835	-	-
Δ TWEAK $\leq$ -70	2.99 (0.87-10.24)	0.081	-	-

The forward stepwise Cox regression model was adjusted by age, sex, HCV genotypes, viral load, FIB-4, platelet, AFP, HbA1c, BMI, TNF- α , and TWEAK (pretreatment, posttreatment, Δ). The cut-off value for each cytokine and FIB-4 was determined by the Youden index of the receiver operating characteristic curve. HCV: Hepatitis C virus; FIB-4: Fibrosis-4 index; AFP: Alpha-fetoprotein; HbA1c: Hemoglobin A1c; BMI: Body mass index; TNF- α : Tumor necrosis factor- α ; TWEAK: TNF-like weak inducer of apoptosis; pre-Tx: Pretreatment; post-Tx: Posttreatment; HR: Hazard ratio; CI: Confidence interval.

Supplementary Table 3 Appendix of the gene symbols

Gene symbol	Gene name
FGF-2	Fibroblast growth factors-2
Eotaxin	Eosinophil chemotactic protein
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
fractalkine/CX3CL1	Fractalkine/ chemokine (C-X3-C motif) ligand 1
IFN- α 2	Interferon alpha-2
IFN- γ	Interferon-gamma
GRO	Growth-related oncogene
IL-10	Interleukin 10
MCP-3	Monocyte chemotactic protein-3
IL-12p40	Interleukin-12 p40
MDC	Macrophage-derived chemokine
IL-12p70	Interleukin-12 p70
IL-13	Interleukin 13
IL-15	Interleukin 15
sCD40L	Soluble CD40 ligand
IL-17A	Interleukin 17A
IL-1 α	Interleukin 1 alpha
IL-9	Interleukin 9
IL-1 β	Interleukin 1 beta
IL-2	Interleukin 2
IL-3	Interleukin 3
IL-4	Interleukin 4

IL-6	Interleukin 6
IL-7	Interleukin 7
IL-8	Interleukin 8
IP-10	IFN- γ inducible protein-10
MCP-1	Monocyte chemoattractant protein-1
MIP-1 α	Macrophage inflammatory protein 1-alpha
MIP-1 β	Macrophage inflammatory protein 1 beta
TNF- α	Tumor Necrosis Factor Alpha
TNF- β	Tumor necrosis factor b
VEGF	Vascular endothelial growth factor
IL-22	Interleukin-22
IL-18	Interleukin-18
IL-17E/IL-25	Interleukin-17E
IL-27	Interleukin-27
IL-31	Interleukin-31
Eotaxin-2/CCL24	Eosinophil chemotactic protein 2
MCP-2/CCL8	Monocyte chemoattractant protein 2
IL-16	Interleukin-16
eotaxin-3/CCL26	Eosinophil chemotactic protein 3
LIF	Leukemia inhibitory factor
SCF	Stem cell factor
TSLP	Thymic stromal lymphopoietin
IL-20	Interleukin-20
IL-21	Interleukin-21
TRAIL	Tumor necrosis factor (TNF)-related apoptosis-inducing ligand

CXCL5 / ENA78	Epithelial neutrophil-activating protein 78
C-Peptide	C-Peptide
GLP-1 total	Glucagon-like peptide 1
Glucagon	Glucagon
Insulin	Insulin
Leptin	Leptin
I-TAC/ CXCL11	Interferon-inducible T-cell alpha chemoattractant
MIP-3a/ CCL20	Macrophage Inflammatory Protein-3
MIG/CXCL9	Monokine induced by gamma interferon
M-CSF	Macrophage colony-stimulating factor
OPG	Osteoprotegerin
TWEAK	Tumor necrosis factor-like weak inducer of apoptosis
MIF	Macrophage migration inhibitory factor
sICAM-1	Soluble intercellular adhesion molecule-1
sFasL	Serum soluble Fas ligand
sVCAM-1	Soluble vascular cell adhesion molecule-1
tPAI-1	Total plasminogen activator inhibitor type 1
