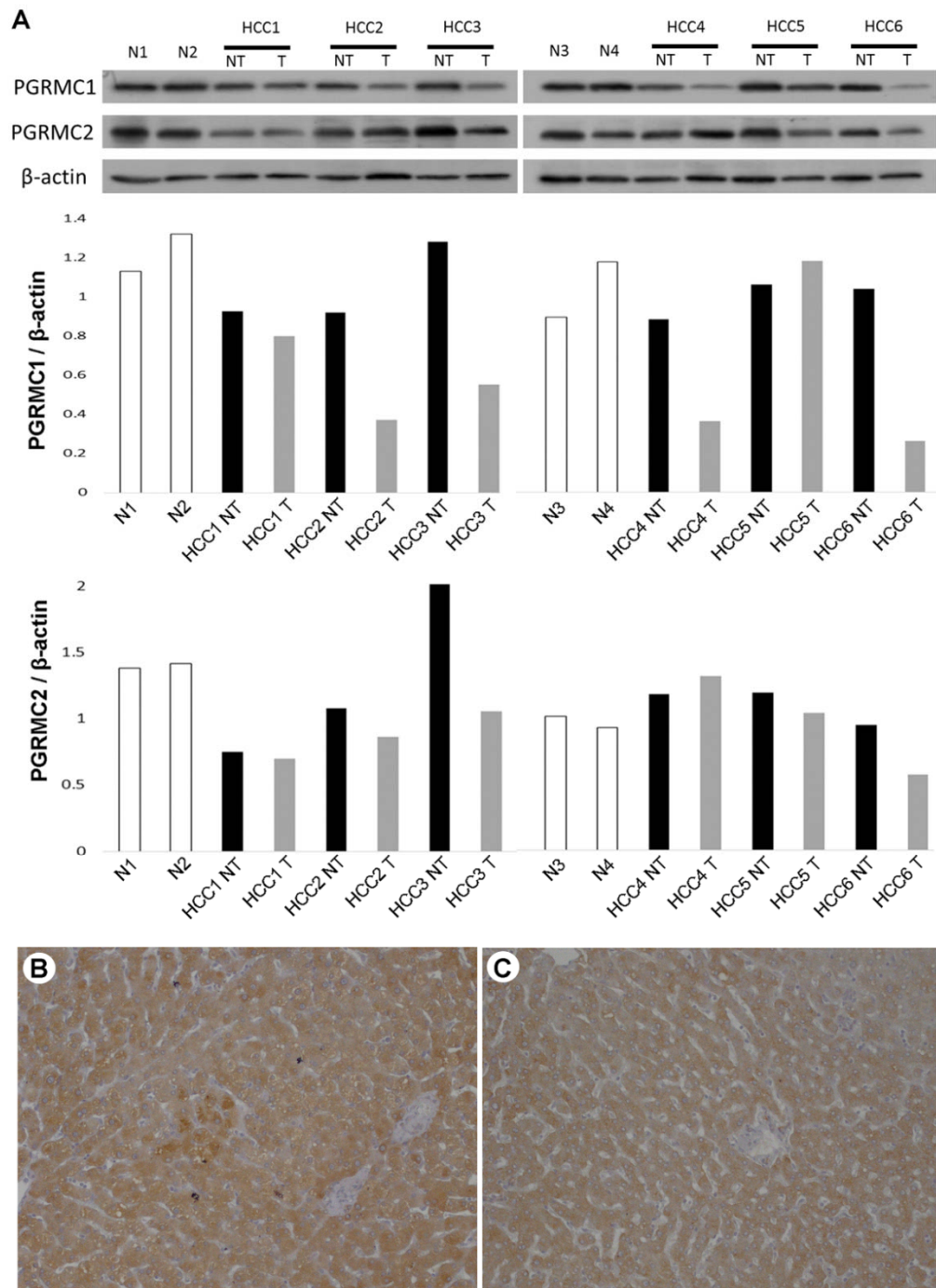
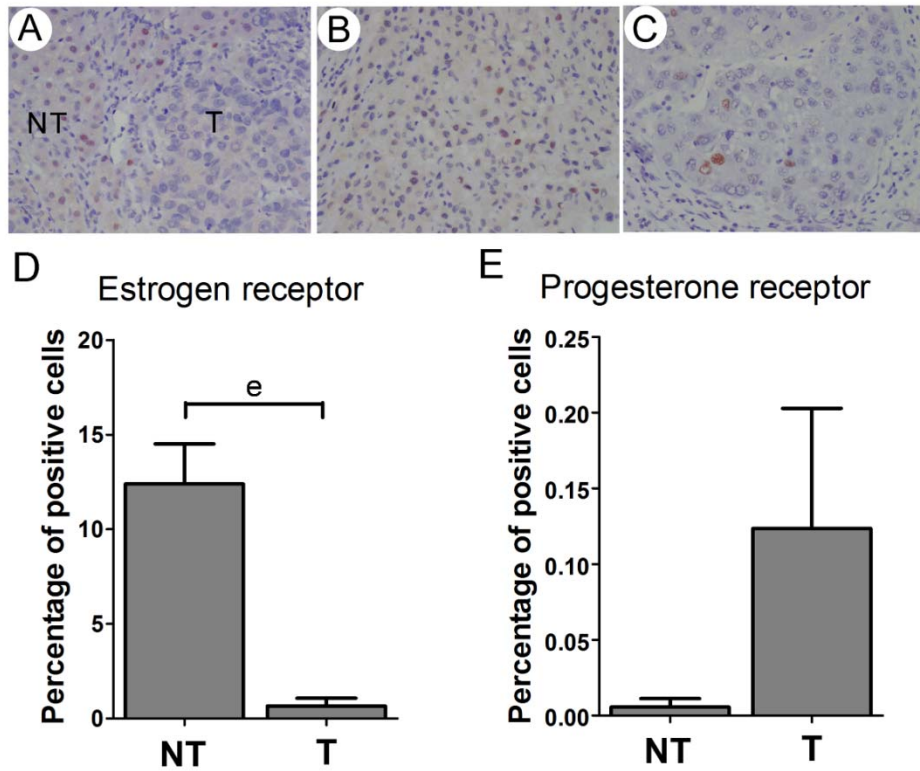


## Supplementary Figure 1



**Supplementary Figure 1 Western blot analysis of PGRMC1 and PGRMC2 expression in four normal liver samples (N1~N4) in comparison with 6 pairs of HCC tumor (T)/non-tumor liver (NT) samples (A). (B and C) Representative images of PGRMC1 and PGRMC2 immunohistochemical staining in normal liver tissue. Both PGRMC1 (B) and PGRMC2 (C) showed diffuse staining.**

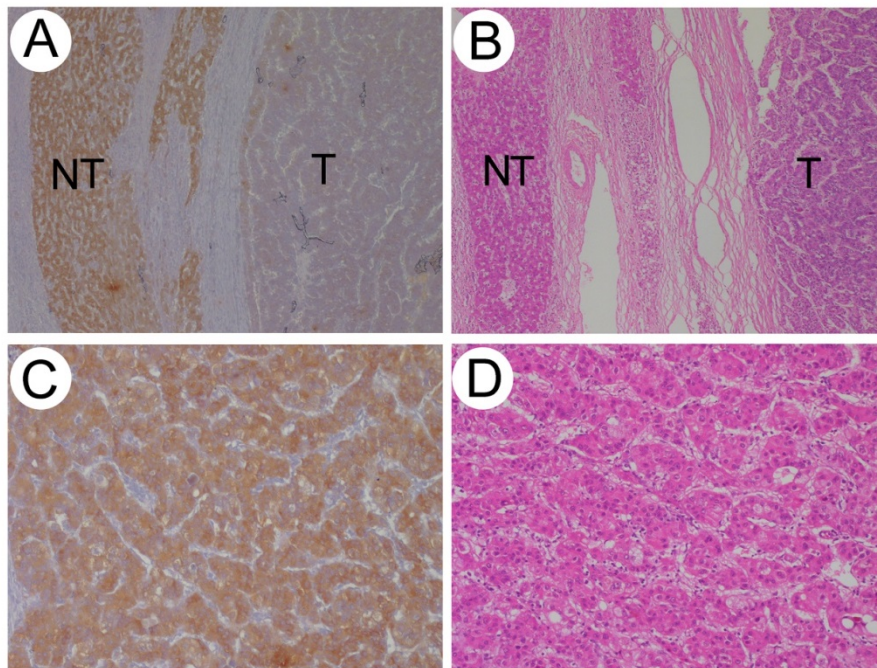
## Supplementary Figure 2



### Supplementary Figure 2 ER and PR immunohistochemical staining in HCC.

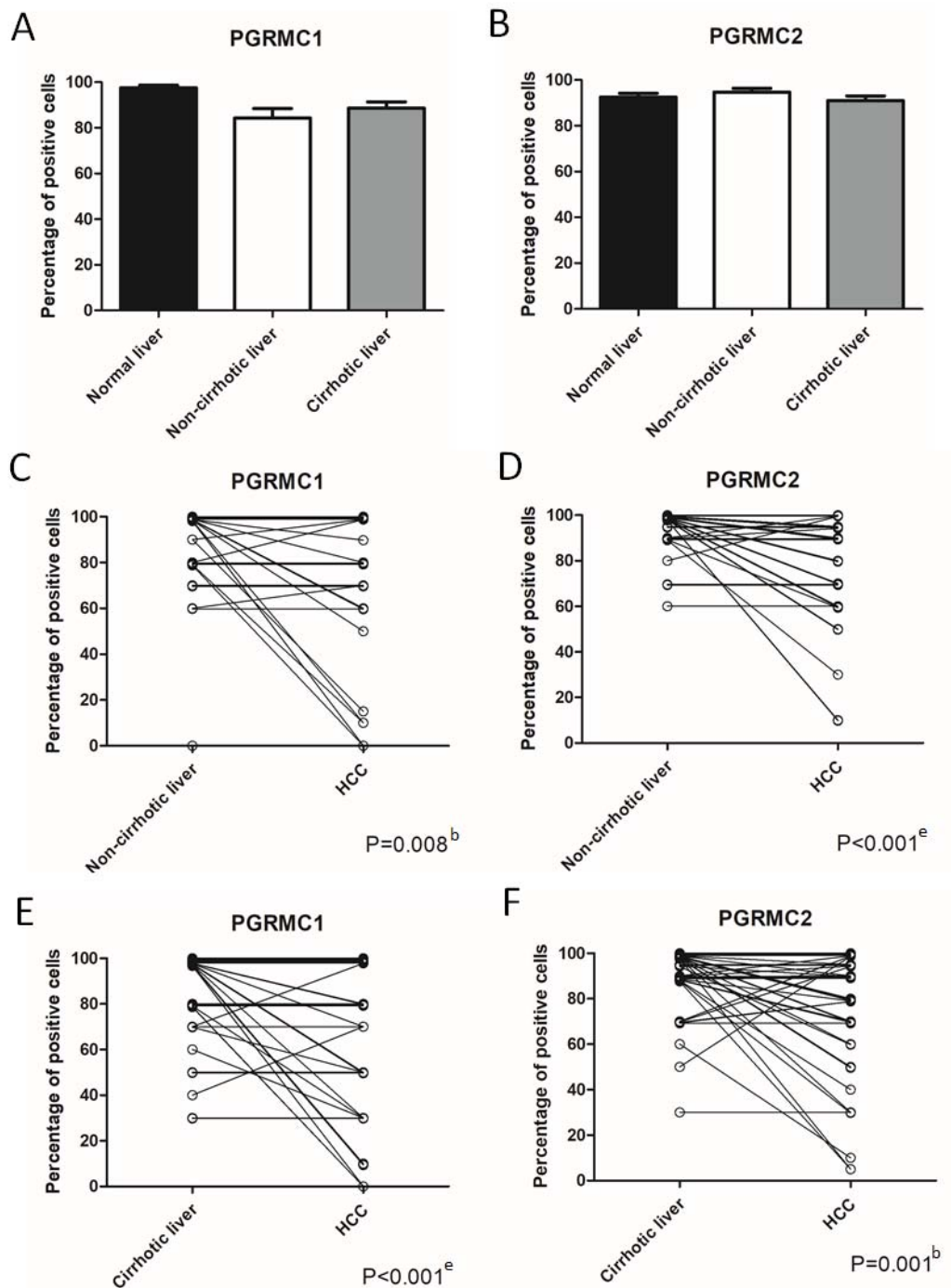
(A) A representative picture of an HCC case showing ER nuclear expression in a non-tumor liver (NT) but no expression in HCC (T) (200X). (B) Another HCC case showing ER nuclear expression in HCC (200X). (C) A representative picture of an HCC case with PR nuclear expression. (D) A comparison of ER staining in HCC (T) and non-tumor liver (NT) tissue samples. (E) A comparison of PR staining in HCC (T) and non-tumor liver (NT) tissue samples.  $^eP < 0.001$ .

Supplementary Figure 3



Supplementary Figure 3 Representative images of PGRMC2 immunohistochemical staining. **(A)** Lower PGRMC2 expression was noted in HCC tissue samples (T) than in the non-tumor liver-tissue samples (NT) (40X). **(B)** Corresponding H&E stain of (A). **(C)** Another image showing high PGRMC2 expression in HCC tissue samples (100X). **(D)** Corresponding H&E stain of (C).

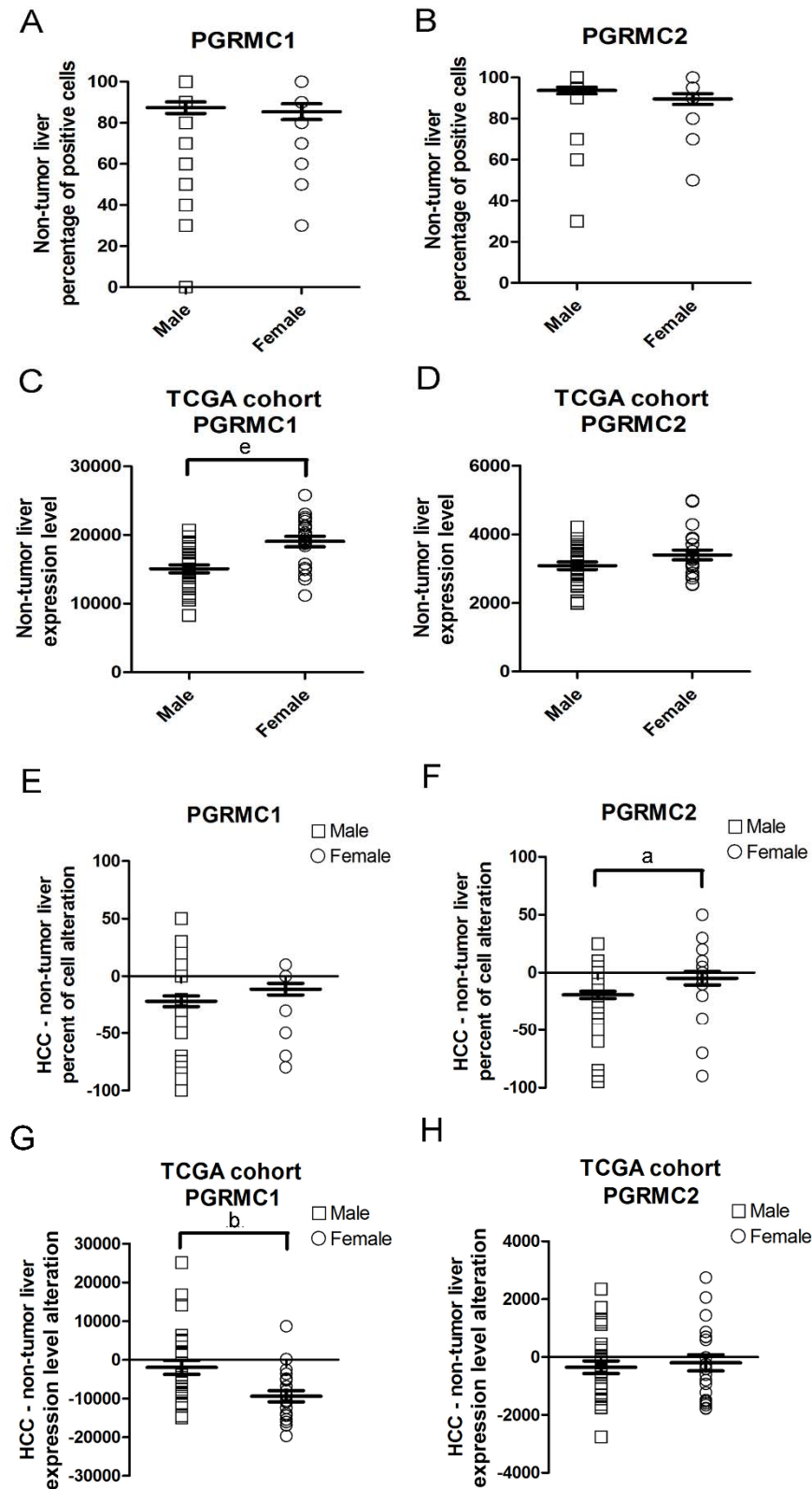
Supplementary Figure 4



Supplementary Figure 4 PGRMC1 and PGRMC2 expression levels in normal liver tissue from healthy persons, non-cirrhotic livers, cirrhotic livers and HCC tissue. A comparison of PGRMC1 and PGRMC2 expression levels among normal liver tissue from healthy persons, non-cirrhotic liver tissue and cirrhotic liver tissue from HCC patients (A and B). A comparison of PGRMC1 (C) and PGRMC2 (D) expression levels in non-cirrhotic liver and in

HCC in the same patient. A comparison of PGRMC1 (E) and PGRMC2 (F) expression levels in cirrhotic liver and in HCC in the same patient.

Supplementary Figure 5

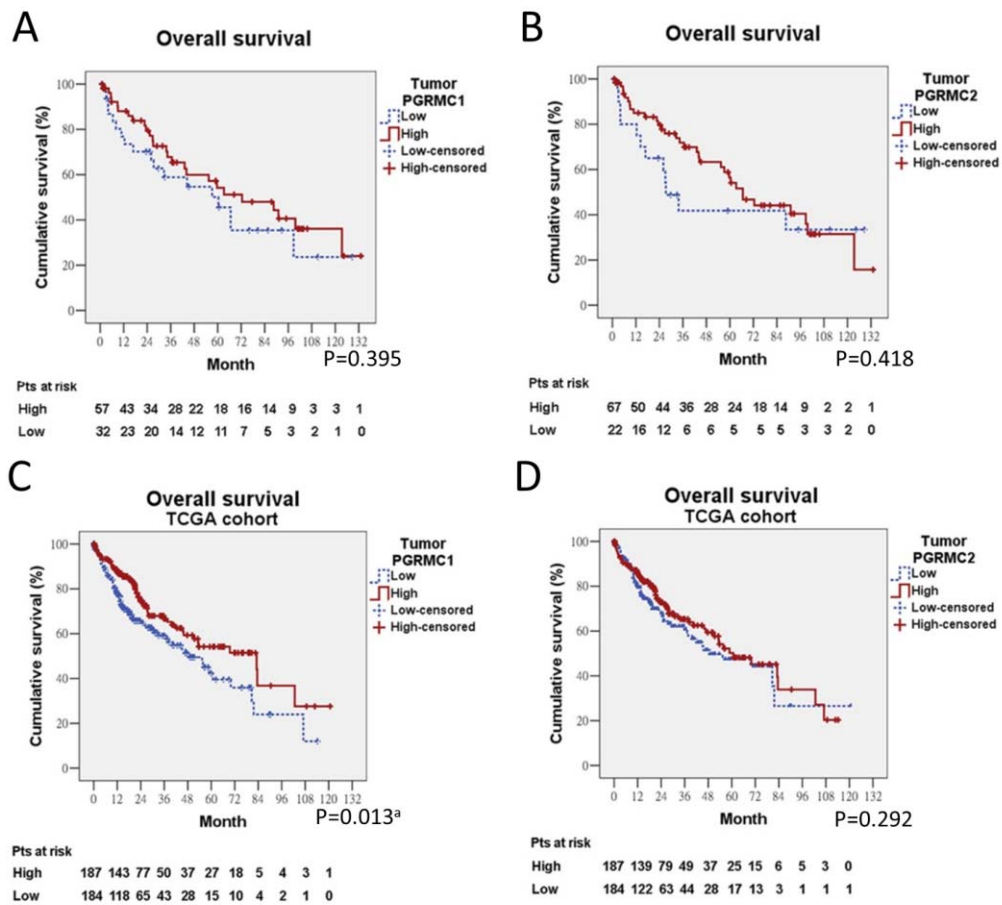


Supplementary Figure 5 Gender differences in PGRMC1 and PGRMC2 expression in background non-tumor liver-tissue samples in the clinical

**cohort (A and B) and TCGA cohort (C and D).** Gender differences in PGRMC1 and PGRMC2 expression alterations in HCC in the clinical cohort **(E and F)** and TCGA cohort **(G and H)**. These alterations were calculated as the expression level in the HCC tissue sample minus that in the reference non-tumor liver-tissue sample. <sup>a</sup>*P* < 0.05, <sup>b</sup>*P* < 0.01, <sup>e</sup>*P* < 0.001.



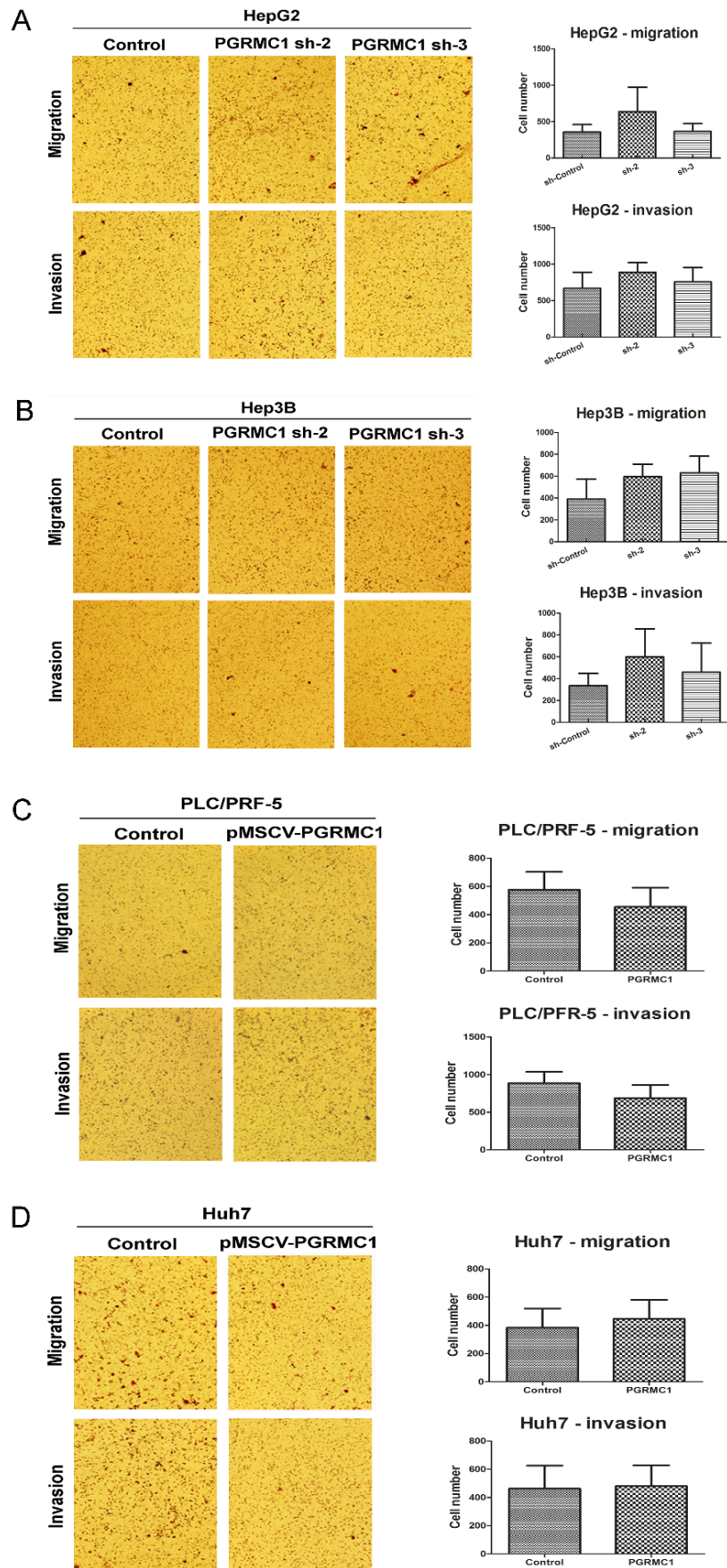
## Supplementary Figure 6



Supplementary Figure 6 Kaplan-Meier analysis of the relationships of PGRMC1 and PGRMC2 expression with overall survival in the clinical cohort (A and B) and TCGA cohort (C and D). <sup>a</sup> $P < 0.05$ .

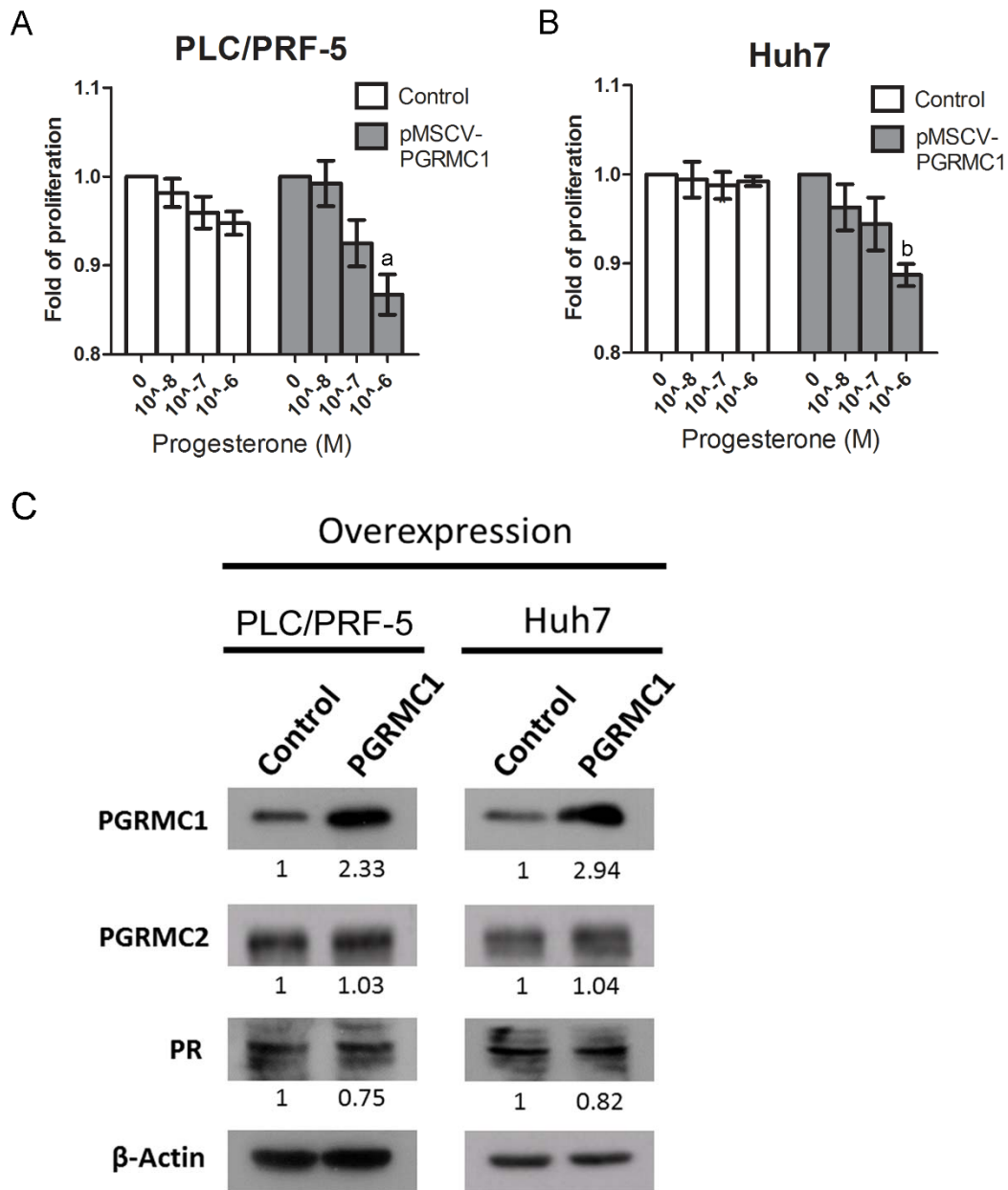


Supplementary Figure 7



**Supplementary Figure 7 Migration assay and invasion assay of PGRMC1-knockdown HepG2 (A) and Hep3B cells (B) and PGRMC1-overexpressing PLC/PRE/5 (C) and Huh7 cells (D). Each experiment was performed in triplicate.**

Supplementary Figure 8



**Supplementary Figure 8 The effects of progesterone on PGRMC1-overexpressing PLC/PRF-5 (A) and Huh7 cell proliferation (B).** <sup>a</sup>*P* < 0.05, <sup>b</sup>*P* < 0.01. Each experiment was performed in triplicate. Western blot analysis of PR and PGRMC2 in PGRMC1-overexpressing PLC/PRF/5 and Huh7 cells (C).

**Supplementary Table 1 Protein identification using MS with database search**

<b>Protein accession</b>	<b>Precursor m/z</b>	<b>Miss cleavage</b>	<b>Charge</b>	<b>Ion score</b>	<b>Expected value</b>	<b>Peptide sequence</b>
K1C9	530.8016	0	2	48.72	1.1E-3	TLLDIDNTR
	616.8279	0	2	77.62	1.2E-6	SGGGGGGGLSGGSIR
	618.2925	0	2	75.42	1.8E-6	FSSSSGYGGGSSR
	793.9092	0	2	85.42	1.4E-7	VQALEEANNDLENK
	896.4001	0	2	120.02	4.0E-11	GGSGGSYGGGGSGGGYGGGSGSR
	919.4992	0	2	85.06	1.2E-7	HGVQELEIELQSQLSK
	1088.8617	0	3	78.52	1.9E-7	DIENQYETQITQIEHEVSSSGQEVQSSAK
K2C1	487.2851	0	2	49.51	9.8E-4	IEISELNR
	517.2841	0	2	49.81	8.3E-4	TLLEGEESR
	563.2958	0	2	45.57	1.8E-3	AEAESLYQSK
	576.8014	1	2	44.81	2.1E-3	NKYEDEINK
	590.3247	0	2	55.21	2.0E-4	YEELQITAGR
	633.3425	0	2	52.89	3.0E-4	TNAENEFVTIK
	651.8882	0	2	69.03	6.9E-6	SLDLDSEIAEVK
	738.4208	0	2	21.73	3.5E-1	FLEQQNQVLQTK

	1192.5234	0	2	101.36	1.5E-9	GGGGGGYGSGGSSYSGGGSYSGGGGGGGR
SODM	872.5423	0	1	29.9	9.0E-2	GELLEAIK
	502.8002	0	2	26.08	1.9E-1	NVRPDYLK
	872.4744	0	2	77.1	7.9E-7	AIWNVINWENVTER
LGUL	489.2894	1	2	28.49	1.1E-1	RFEELGVK
	1152.1147	0	2	70.97	2.0E-6	GLAFIQDPDGYWIEILNPNK
K1C10	498.2769	1	2	27.97	1.0E-1	IKEWYEK
	1018.2327	1	3	66.57	2.5E-6	TIDDLKNQILNLTTDNANILLQIDNAR
GSTA2	436.2798	0	2	47.40	1.3E-3	ISNLPTVK
	609.3198	0	2	38.82	8.9E-3	SHGQDYLGVNK
KCY	884.9597	0	2	62.46	2.2E-5	SVDEVFDEVVQIFDK
K2C6A	576.8014	1	2	44.80	2.1E-3	NKYEDEINK
RL17	541.9750	0	3	43.32	2.0E-3	EQIVPKPEEEVAQK
<b>PGRC1</b>	<b>1208.5767</b>	<b>1</b>	<b>3</b>	<b>39.32</b>	<b>1.2E-3</b>	<b>EALKDEYDDLSDLTAAQQETLSDWESQFTFK</b>

Abbreviation: m/z: mass-to-charge ratio.

Protein names: GSTA2, glutathione S-transferase A2; K1C9, Keratin, type I cytoskeletal 9; K1C10 Keratin, type I cytoskeletal 10; K2C1, Keratin, type II cytoskeletal 1; K2C6A Keratin, type II cytoskeletal 6A; KCY, cytidine/Uridine monophosphate kinase 1; LGUL, lactoylglutathione lyase; PGRC1, progesterone receptor membrane component 1; RL17, ribosomal protein L17; SODM,

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superoxide dismutase mitochondrial precursor.

**Supplementary Table 2 Patient profiles of the clinical cohort**

Variables	Value
Age: mean, range (years)	55.2, 26~82
Sex: male/female (cases)	65/24
Hepatitis virus: B/C/B + C (cases)	45/37/7
AFP: mean, range (ng/ml)	9038.20, 0.1-210300
Differentiation: well/moderate/poor (cases)	20/49/20
Multifocal tumor: no/yes (cases)	74/15
Satellite nodule: no/yes (cases)	61/28
Size: mean, range (cm)	5.14, 0.3~25
Tumor capsular invasion: no/yes (cases)	18/71
Vascular invasion: no/yes (cases)	49/40
Liver capsule penetration: no/yes (cases)	81/8
Margin: $\geq 1$ mm / $< 1$ mm (cases)	72/17
Child-Pugh score: 5/6/7/8 (cases)	67/17/3/2
Cirrhosis: no/yes (cases)	37/52
AJCC stage: I/II/IIIA~IIIC (cases)	35/27 /27
Tumor differentiation according to the WHO system; AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer 2010.	



**Supplementary Table 3 Patient profiles of the TCGA cohort**

<b>Variables</b>	<b>Value</b>
Age: mean, range (yr)	59.5, 16-90
Sex: male/female (cases)	252/121
HCC risk factors: HBV/HCV/HBV+HCV/ Alcohol/NAFLD	85/39/3/126 /14
AFP: mean, range (ng/mL)	13937.10, 1~2035400
Tumor grade: 1/2/3/4 (cases)	55/178/123/12
Vascular invasion: no/yes (cases)	207/110
Residual tumor: no/yes (cases)	326/18
Child-Pugh score: A/B/C (cases)	218/21/1
Cirrhosis: no/yes (cases)	134/80
AJCC stage: I/II/III/IV (cases)	172/87/85/5

NAFLD, non-alcoholic fatty liver disease; AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer.

**Supplementary Table 4 Association between tumor PGRMC expression and clinicopathological indicators in the clinical cohort**

Factors	Group	PGRMC1 % (mean ± SD)	<i>P</i>	PGRMC2% (mean ± SD)	<i>P</i>
Age	< 60 yr	59.90 ± 37.37	0.016 <sup>a</sup>	78.13±24.40	0.819
	≥ 60 yr	77.32 ± 32.33		76.34±27.17	
Sex	Male	65.62 ± 37.52	0.400	74.54±26.10	0.040 <sup>a</sup>
	Female	74.17 ± 31.47		84.79±22.96	
Virus infection	HBV	69.44 ± 36.15	0.863	77.44±25.75	0.482
	HCV	65.14 ± 38.49		78.78±25.31	
	IBV+HCV	72.86 ± 21.38		68.57±27.95	
Cirrhosis	Absent	67.16 ± 36.68	0.742	77.57±24.20	0.746
	Present	68.46 ± 35.89		77.12±26.74	
Serum AFP (ng/ml)	< 150	76.39 ± 32.57	0.004 <sup>a</sup>	80.28±22.14	0.271
	≥ 150	54.86 ± 37.60		72.71±29.89	
Tumor differentiation	W	81.75 ± 26.91	0.045 <sup>a</sup>	83.00±21.18	0.304
	M-P	63.91 ± 37.46		75.65±26.62	
Multifocal tumors	Absent	67.57 ± 35.57	0.632	76.28±25.91	0.471
	Present	69.67 ± 39.39		82.33±24.04	
Satellite nodule	Absent	69.75 ± 33.62	0.734	79.18±22.66	0.580
	Present	63.93 ± 41.13		73.21±31.07	
Tumor size	< 5 cm	71.10 ± 35.27	0.163	77.54±23.95	0.598
	≥ 5 cm	61.67 ± 37.24		76.83±28.93	
Tumor capsular invasion	Absent	73.89 ± 34.49	0.444	87.22±18.25	0.048 <sup>a</sup>
	Present	66.41 ± 36.47		74.79±26.64	
Vascular invasion	Absent	71.33 ± 34.80	0.326	78.88±24.11	0.388
	Present	63.75 ± 37.46		75.38±27.44	

Liver capsule	Absent	70.19 ± 35.31	0.038 <sup>a</sup>	79.38±23.91	0.035 <sup>a</sup>
penetration	Present	45.00 ± 37.42		56.25±33.67	
Bile duct	Absent	68.78 ± 35.48	0.387	78.55±24.59	0.032 <sup>a</sup>
invasion	Present	43.33 ± 51.32		41.67±33.29	
Margin status	≥1mm	68.82 ± 35.61	0.629	77.36±23.29	0.438
	<1mm	64.12 ± 38.58		77.06±34.51	
AJCC stage	I~II	70.40 ± 34.22	0.360	79.92±22.04	0.446
	IIIA~C	62.22 ± 39.94		71.30±31.94	

<sup>a</sup> $P < 0.05$ . Tumor differentiation according to the WHO system; AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer 2010.

**Supplementary Table 5 Association between tumor PGRMC expression and clinicopathological indicators in the TCGA cohort**

Factors	Group	<i>PGRMC1</i>	<i>P</i>	<i>PGRMC2</i>	<i>P</i>
		Normalized count (mean ± SD)		Normalized count (mean ± SD)	
Age	<55 years	9869.9 ± 6871.8	0.014 <sup>a</sup>	2537.5±1022.3	0.006 <sup>a</sup>
	≥55 years	11832.7 ± 7674.4		2811.5±1021.7	
Sex	Male	11796.0±7695.3	0.015 <sup>a</sup>	2695.4±998.8	0.540
	Female	9934.0±6877.1		2781.2±1087.9	
Virus infection	HBV	9915.8±4702.9	0.062	2610.1±957.8	0.925
	HCV	13263.6±10826.3		2594.8±872.2	
	NAFLD	14979.5±5077.4		2683.9±609.0	
	Alcohol	11456.1±7584.5		2704.7±1104.8	
Cirrhosis	Absent	11486.6±6999.6	0.288	2902.2±1111.8	0.491
	Present	12798.3±8290.5		2758.9±912.2	
Serum AFP (ng/ml)	<100	12405.5±7088.5	<0.001 <sup>a</sup>	2799.2±1055.0	0.150
	≥100	8206.2±5380.1		2622.7±1025.0	
Tumor grade	1	14294.0±7628.6	<0.001 <sup>a</sup>	2974.4±1057.4	0.022 <sup>a</sup>
	2~4	10589.4±7094.5		2678.1±1022.4	
Vascular invasion	Absent	11934.5±7308.2	0.007 <sup>a</sup>	2841.4±1101.7	0.062
	Present	9866.6±6630.3		2564.9±894.7	
Residual tumor	Absent	11329.3±7472.8	0.050	2720.9±1048.2	0.724
	Present	8373.9±6659.8		2741.9±753.5	
AJCC stage	I~II	11620.9±7498.9	0.002 <sup>a</sup>	2766.0±1027.6	0.183
	III~VI	9116.4±6316.7		2616.0±1084.5	

<sup>a</sup>*P* < 0.05. NAFLD, non-alcoholic fatty liver disease; AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer.

**Supplementary Table 6 Prognostic significance of clinicopathological indicators, *PGRMC1* and *PGRMC2* for overall survival in the TCGA cohort (*n* = 373)**

Factor	Group	OS univariate			OS multivariate		
		HR	95%CI	<i>P</i>	HR	95%CI	<i>P</i>
Age	<60/≥60 years	1.186	(0.836-1.683)	0.339			
Sex	Male/female	1.249	(0.877-1.780)	0.218			
HCC factors	risk			0.092			
	B/NAFLD	1.411	(0.415-4.801)	0.582			
	B/Alcohol	1.963	(1.121-3.440)	0.018			
	B/C	2.164	(1.011-4.634)	0.047			
Child-Pugh score	A/B~C	1.630	(0.804-3.303)	0.175			
Cirrhosis	-/+	0.815	(0.475-1.400)	0.459			
Serum AFP	<100/≥100 ng/ml	1.160	(0.737-1.824)	0.521			
Tumor grade	1/2~4	1.197	(0.726-1.973)	0.480			
Vascular invasion	-/+	1.330	(0.878-2.014)	0.178			
Residual tumor	-/+	1.591	(0.805-3.143)	0.182			
AJCC stage	I~II/ III~IV	2.485	(1.714-3.603)	<0.001 <sup>a</sup>	2.430	(1.675-3.526)	<0.001 <sup>a</sup>
<i>PGRMC1</i>	H/L	1.545	(1.092-2.186)	0.014 <sup>a</sup>	1.556	(1.072-2.260)	0.020 <sup>a</sup>
<i>PGRMC2</i>	H/L	1.204	(0.852-1.701)	0.293			

<sup>a</sup>*P* < 0.05. OS: Overall survival; NAFLD: Non-alcoholic fatty liver disease; AFP: Alpha-fetoprotein; AJCC: American Joint Committee on Cancer; H: High expression; L: Low expression.