Supplementary Figure Legends

Supplementary Figure 1. Histogram of nuclear area of mononuclear hepatocytes for one HCC patient (A). The shape of the histogram shows a clear trimodal distribution (peaks), which are positioned proportionally. The first, second and third peaks are representative of diploid, tetraploid and octoploid nucleus, respectively (nuclear ploidy). Nuclei with area < 200 or > 4000 pixel^2 were excluded from analysis (non-hepatocytes population and incorrect DAPI segmentation). Immunochemistry analysis of positive (left panel) and negative (right panel) PD-L1 expressions on tumoral cells (B) and immune stroma (C). Upper panel, 200× magnification, scale bar = 200 μm; lower panel, 400× magnification, scale bar = 50 μm. PD-L1 showed a membrane staining. PD-L1, programmed death-ligand 1.

Supplementary Figure 2. Recurrence-free survival and HCC-specific survival stratified by the Milan criteria (A), AFP model (B) and Metroticket 2.0 criteria (C), and compared using the log-rank test in the derivation cohort. HCC, hepatocellular carcinoma. HMP–HCC, highly mononuclear polyploid hepatocellular carcinoma; PMP–HCC, poorly mononuclear polyploid hepatocellular carcinoma.

Supplementary Figure 3. Recurrence-free survival and HCC-specific survival according to the Milan criteria (A), AFP model (B), and Metroticket 2.0 criteria (C) in the validation cohort, and compared using the log-rank test. HCC, hepatocellular carcinoma. HMP–HCC, highly mononuclear polyploid hepatocellular carcinoma; PMP–HCC, poorly mononuclear polyploid hepatocellular carcinoma.

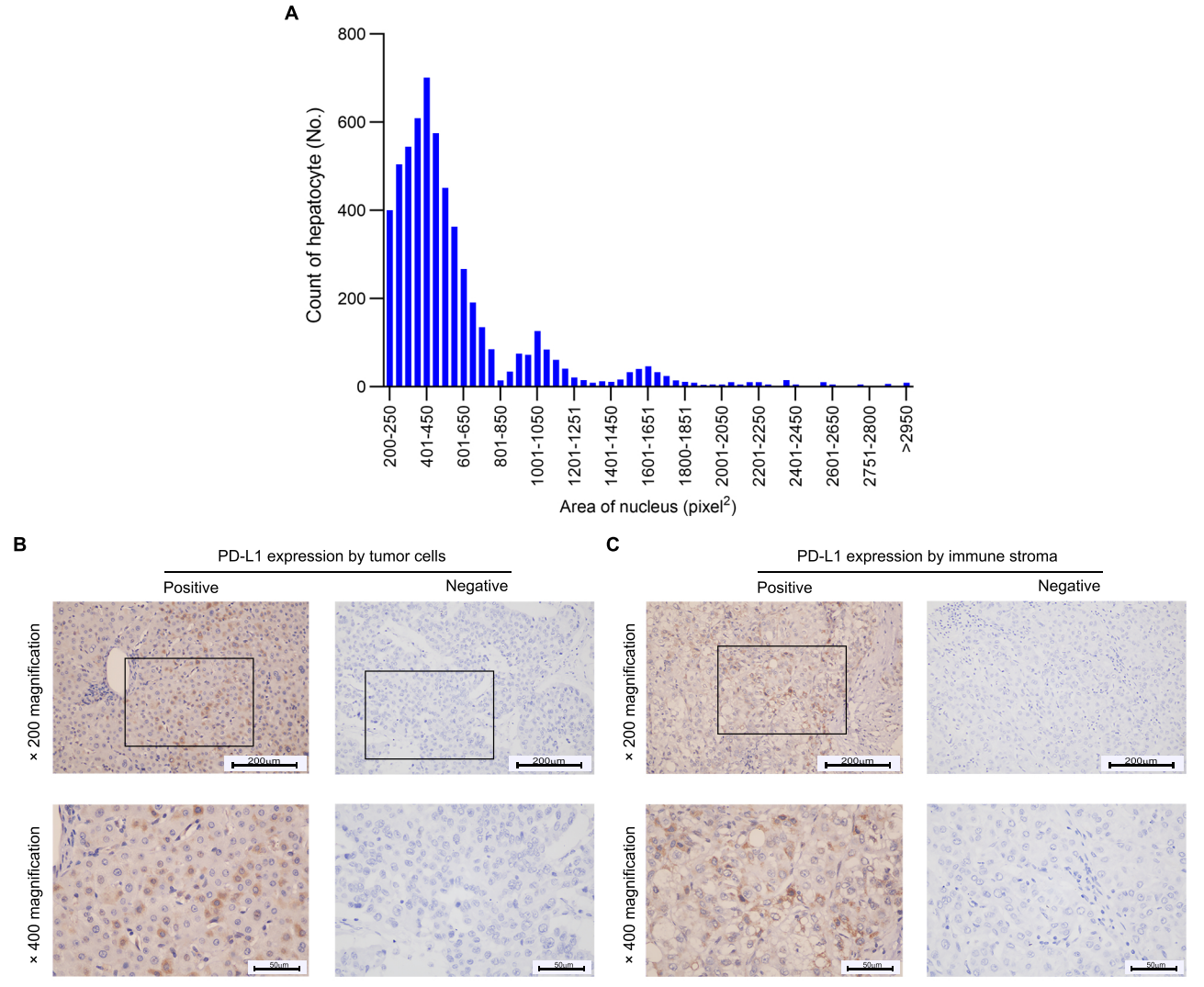
Supplementary Figure 4. HCC-specific survival curves according to the ploidy distribution (A), and the Milan criteria (B), AFP model (C), and Metroticket 2.0 criteria (D) in the derivation set. HCC, hepatocellular carcinoma. HMP–HCC, highly mononuclear polyploid hepatocellular carcinoma; PMP–HCC, poorly mononuclear polyploid hepatocellular carcinoma.

Supplementary Figure 5. Distributions of density of FoxP3$^+$ Treg cells (A) and CD8$^+$ cytotoxic T cells (B) between HMP–HCC and PMP–HCC. Similar distribution of density of CD4$^+$ Th cells

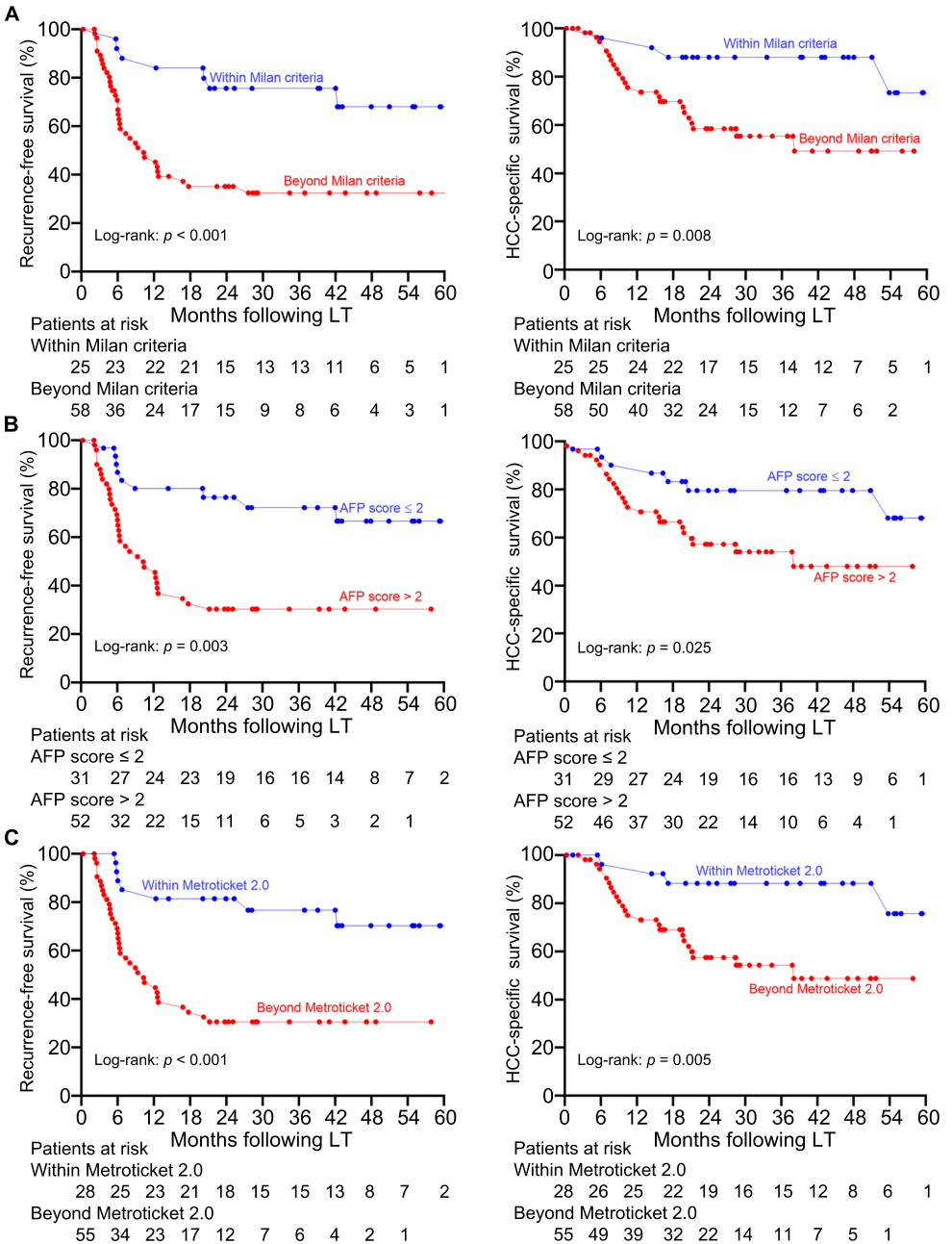
between HMP–HCC and PMP–HCC (C). No significant correlation between density of $CD4^+$ Th cells and the fraction of mononuclear polyploidy (D). FoxP3, forkhead box P3; HMP–HCC, highly mononuclear polyploid hepatocellular carcinoma; PMP–HCC, poorly mononuclear polyploid hepatocellular carcinoma.

Supplementary Figure 6. Recurrence-free survival stratified according to the ploidy distribution (A), and with the combinations of the Milan criteria (B), AFP model (C), and Metroticket 2.0 criteria (D) in the validation set. HCC, hepatocellular carcinoma. HMP–HCC, highly mononuclear polyploid hepatocellular carcinoma; PMP–HCC, poorly mononuclear polyploid hepatocellular carcinoma.

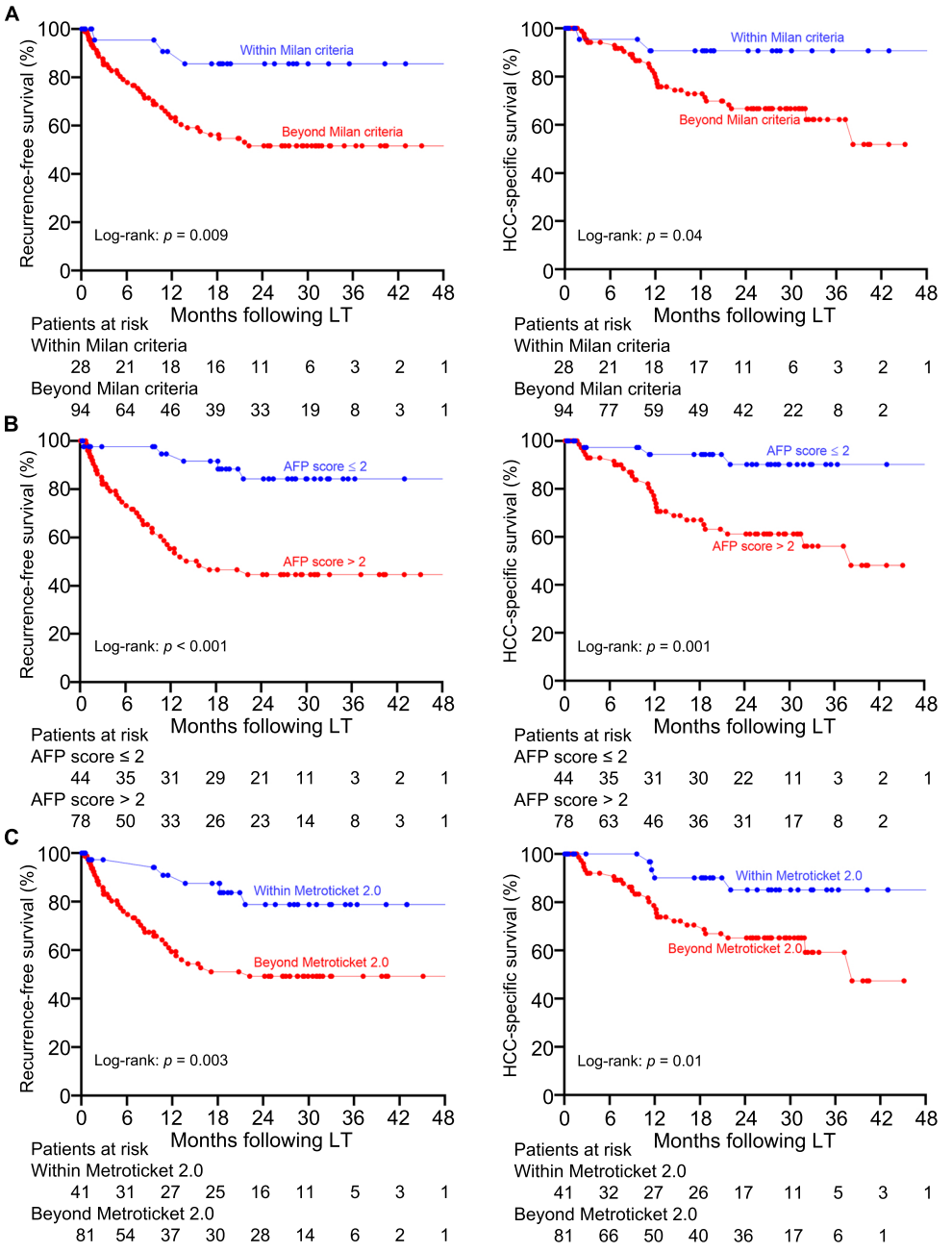
Supplementary Figure 7. HCC-specific survival according to the ploidy distribution (A), and with the combinations of the Milan criteria (B), AFP model (C), and Metroticket 2.0 criteria (D) in the validation set. HCC, hepatocellular carcinoma. HMP–HCC, highly mononuclear polyploid hepatocellular carcinoma; PMP–HCC, poorly mononuclear polyploid hepatocellular carcinoma.



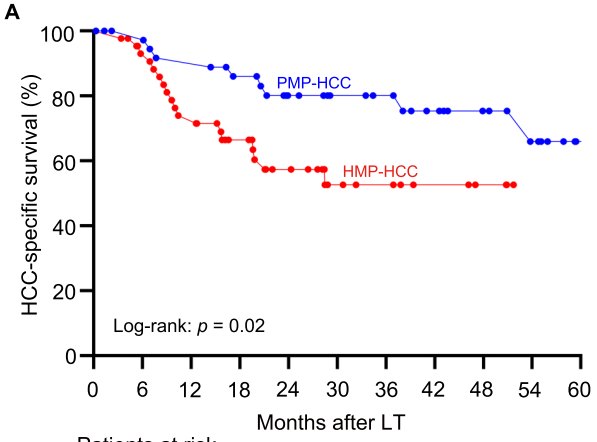
Zhang et al Supplementary Figure 1

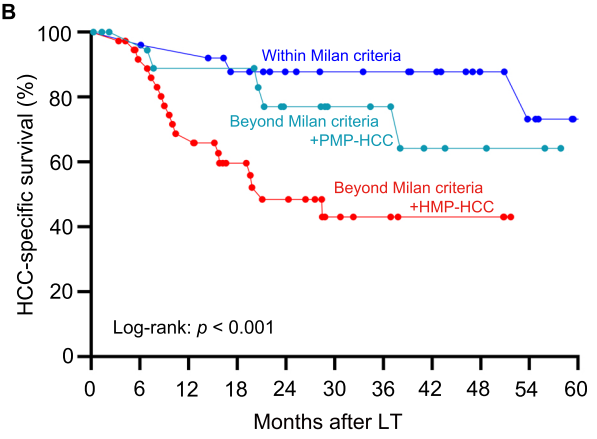


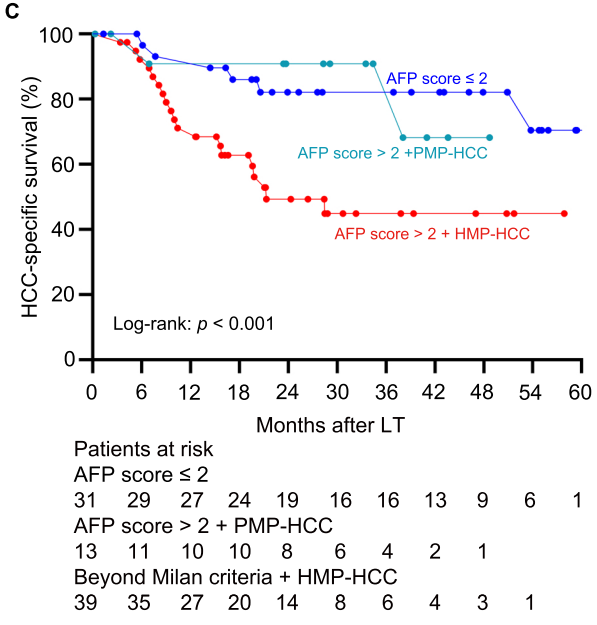
Zhang et al Supplementary Figure 2

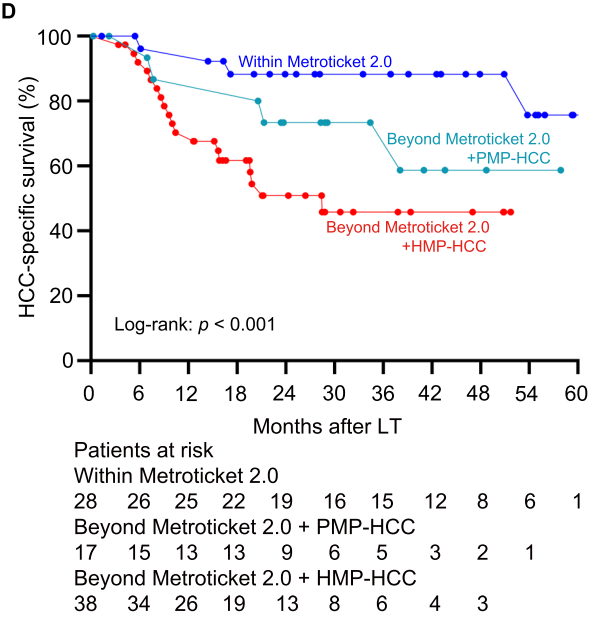


Zhang et al Supplementary Figure 3

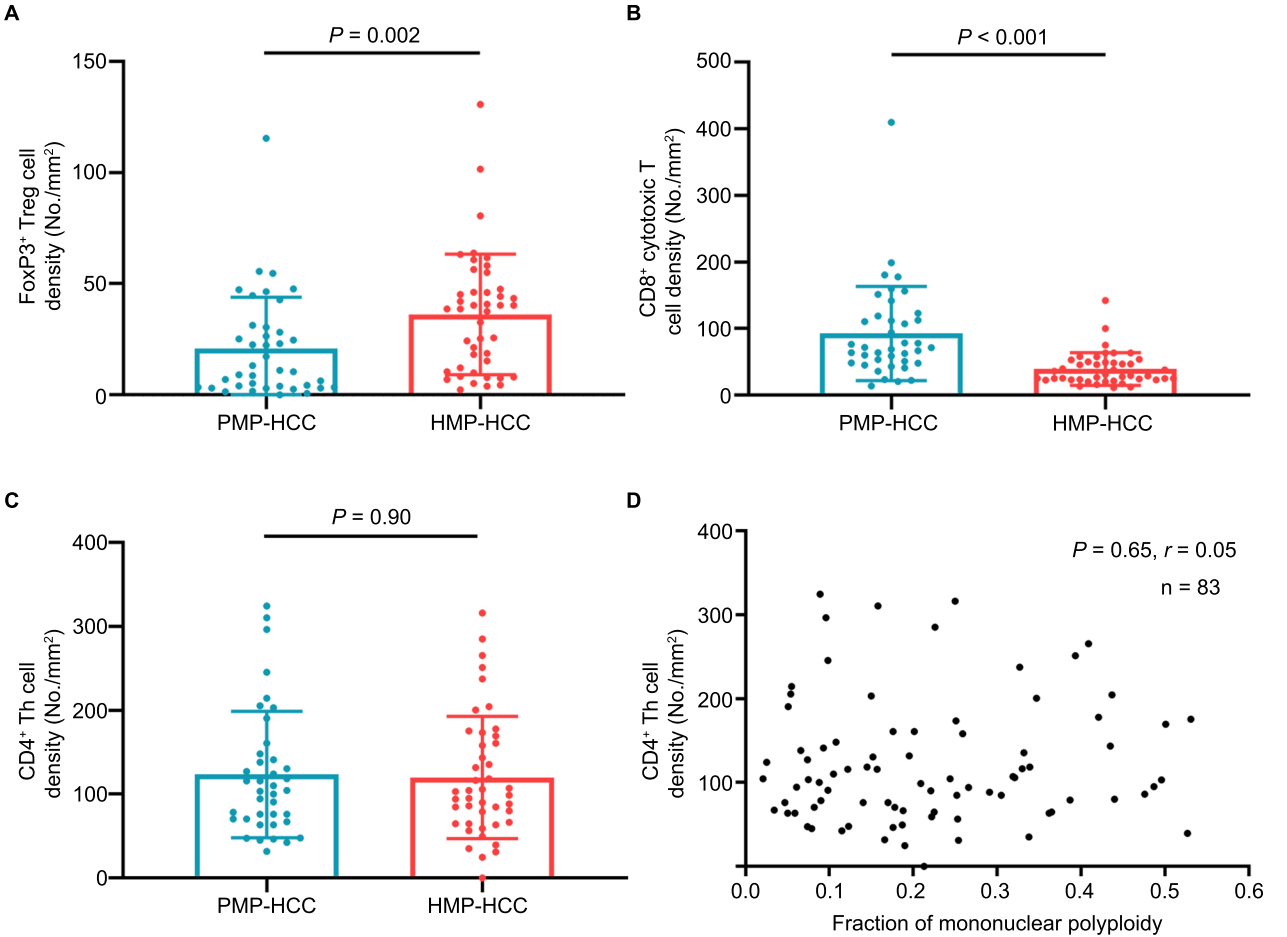




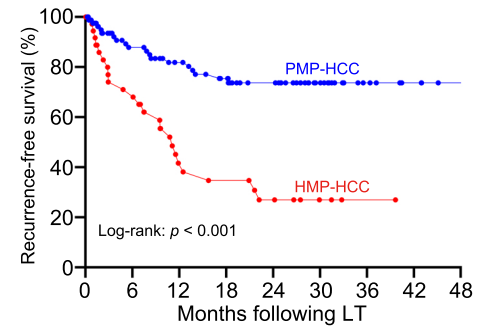




Zhang et al Supplementary Figure 4

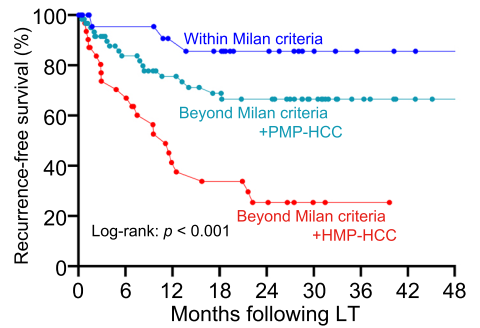


Zhang et al Supplementary Figure 5



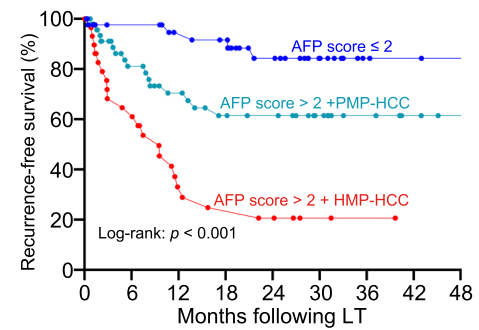
Patients at risk

PMP-HCC								
85	61	52	45	37	22	10	5	2
HMP-HCC								
37	24	12	10	7	3	1		



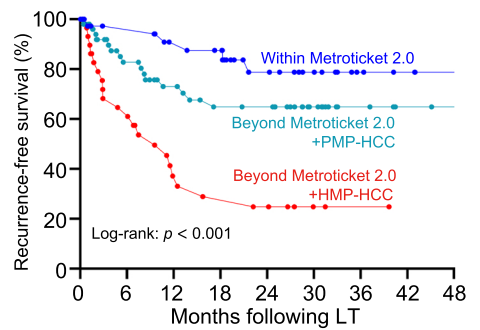
Patients at risk

Within Milan criteria								
28	21	18	16	11	6	3	2	1
Beyond Milan criteria + PMP-HCC								
63	43	35	30	27	17	7	3	1
Beyond Milan criteria + HMP-HCC								
31	21	11	9	6	2	1		



Patients at risk

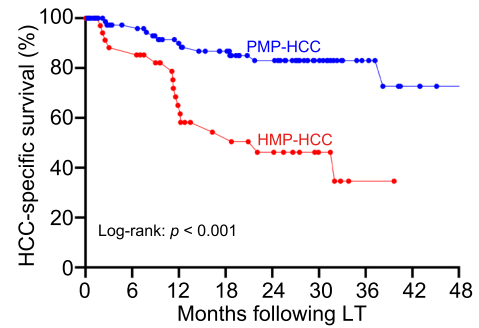
AFP score ≤ 2								
44	35	31	29	21	11	3	2	1
AFP score > 2 + PMP-HCC								
48	32	25	20	18	12	7	3	1
AFP score > 2 + HMP-HCC								
30	18	8	6	5	2	1		



Patients at risk

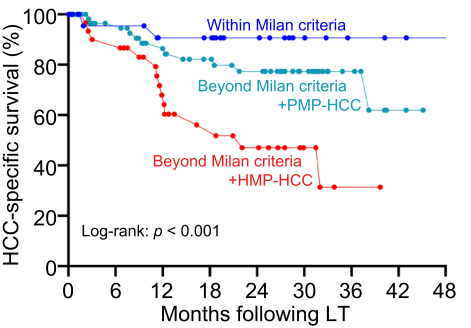
Within Metroticket 2.0								
41	31	27	25	16	11	5	3	1
Beyond Metroticket 2.0 + PMP-HCC								
52	36	28	23	22	12	5	2	1
Beyond Metroticket 2.0 + HMP-HCC								
29	18	9	7	6	2	1		

Zhang et al Supplementary Figure 6



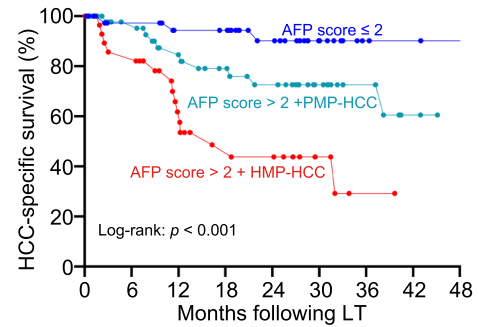
Patients at risk

PMP-HCC								
85	68	58	52	42	23	10	4	1
HMP-HCC								
37	30	19	14	11	5	1		



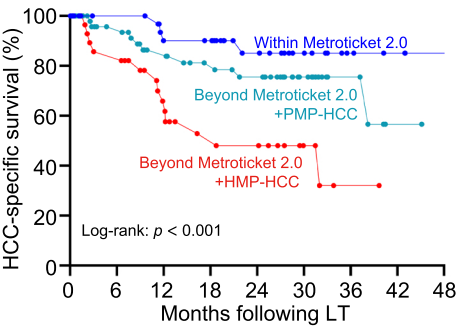
Patients at risk

Within Milan criteria								
28	21	18	17	11	6	3	2	1
Beyond Milan criteria + PMP-HCC								
63	50	41	36	32	18	7	2	
Beyond Milan criteria + HMP-HCC								
31	27	18	13	10	4	1		



Patients at risk

AFP score ≤ 2								
44	35	31	30	22	11	3	2	1
AFP score > 2 + PMP-HCC								
48	39	31	26	22	13	7	2	
AFP score > 2 + HMP-HCC								
30	24	15	10	9	4	1		



Patients at risk

Within Metroticket 2.0								
41	32	27	26	17	11	5	3	1
Beyond Metroticket 2.0 + PMP-HCC								
52	42	34	29	26	13	5	1	
Beyond Metroticket 2.0 + HMP-HCC								
29	24	16	11	10	4	1		

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