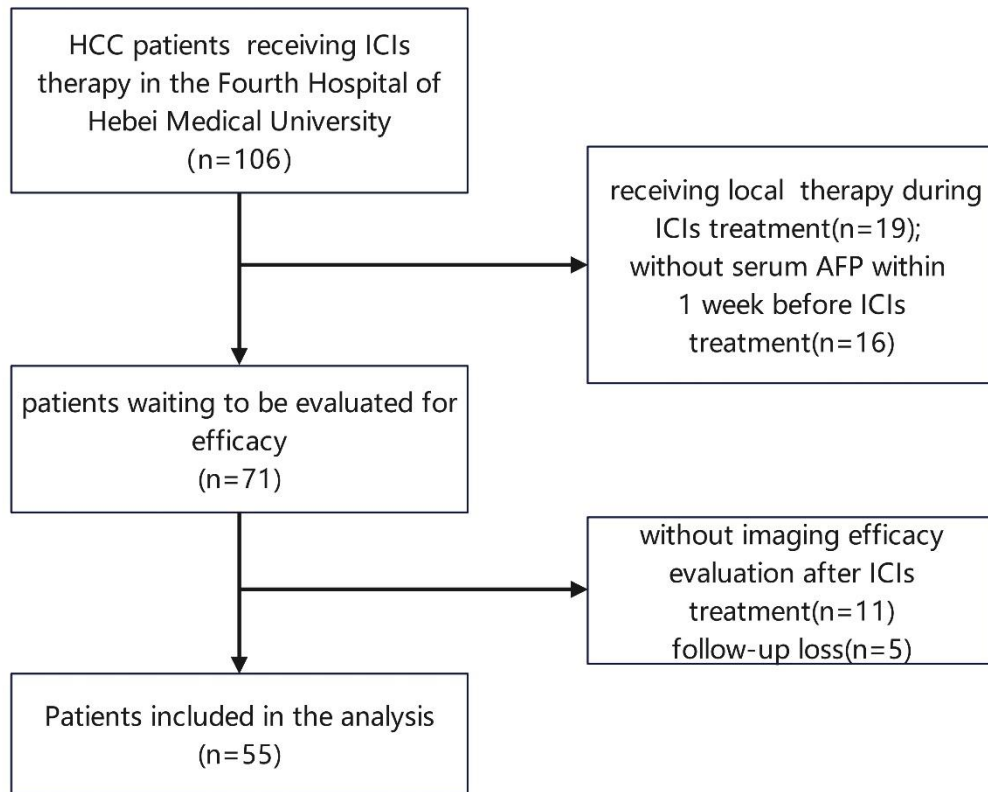
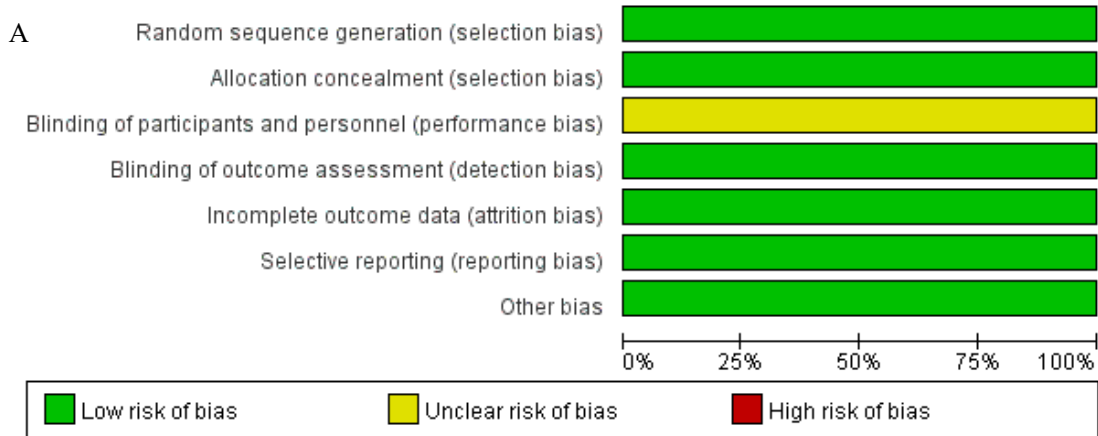


Appendix 1. Flow diagram of the patient selection.



Appendix 2. Quality assessment. A: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. B: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



B

	CheckMate459 2021	IMbrave150 2022	ORIENT-32 2021	
	+	+	+	Random sequence generation (selection bias)
	+	+	+	Allocation concealment (selection bias)
	?	?	?	Blinding of participants and personnel (performance bias)
	+	+	+	Blinding of outcome assessment (detection bias)
	+	+	+	Incomplete outcome data (attrition bias)
	+	+	+	Selective reporting (reporting bias)
	+	+	+	Other bias

Appendix 3. Quality assessment: The 15 cohort studies were assessed by the Newcastle Ottawa scale. Abbreviations: NOS, Newcastle Ottawa scale.

Authors	selection	comparability	outcome	NOS score
Yu - Yun Shao et al.	4	1	3	8
David J. Pinato et al.	4	0	3	7
Kennedy Yao Yi Ng et al.	4	2	2	8
Yiyang Zhang et al.	4	1	2	7
Dailong Li et al.	4	2	2	8
Guosheng Yuan et al.	4	1	2	7
Man Zhao et al.	4	1	2	7
Haonan Liu et al.	4	1	2	7
Rui Huang et al.	4	1	1	6
Shida Pan et al.	4	1	2	7
Yiyang Zhang et al.	4	1	2	7
Dailong Li et al.	4	2	2	8
Man Zhao et al.	4	2	2	8
ChiJung Wu et al.	4	2	2	8
Wei Teng et al.	4	2	2	8

Appendix 4. Characteristics of patients in the retrospective cohort study.

	Total No. (%)	High AFP (%)	Low AFP (%)	p
Total	55	28(50.9)	27(49.0)	
Gender				
Male	49(89.0)	27(96.4)	22(81.4)	0.101
Female	6(10.9)	1(3.5)	5(18.5)	
Age				
≥60	25(45.4)	13(46.4)	12(44.4)	0.883
<60	30(54.5)	15(53.5)	15(55.5)	
ECOG PS				
≥2	23(41.8)	11(39.2)	12(44.4)	0.698
<2	32(58.1)	17(60.7)	15(55.5)	
Hepatitis B status				
Positive	46(83.6)	26(92.8)	20(74.0)	0.078
Negative	9(16.3)	2(7.1)	7(25.9)	
HBV-DNA.copies/ml				
≥500	22(40.0)	16(57.1)	6(22.2)	0.008
<500	33(60.0)	12(42.8)	21(77.7)	
Child-Pugh Score				
A	37(67.2)	17(60.7)	20(74.0)	0.379
B	18(32.7)	10(39.2)	7(25.9)	
Portal vein thrombosis				
Yes	22(40.0)	14(50.0)	8(29.6)	0.123
No	33(60.0)	14(50.0)	19(70.3)	
Number of intrahepatic lesions				
≥3	27(49.0)	15(53.5)	15(55.5)	0.883
<3	28(50.9)	13(46.4)	12(44.4)	
Maximum size of intrahepatic lesions				
≥10cm	18(32.7)	13(46.4)	5(18.5)	0.027
<10cm	37(67.2)	15(53.5)	22(81.4)	
Extrahepatic spread				
Yes	35(63.6)	17(60.7)	18(66.6)	0.646
No	20(36.3)	11(39.2)	9(33.3)	
BCLC stage				
C+D	46(83.6)	23(82.1)	23(85.1)	0.760
A+B	9(16.3)	5(17.8)	4(14.8)	
Previous treatment				
Surgery	6(10.9)	2(7.1)	4(14.8)	
Interventional therapy	15(27.3)	8(28.5)	7(25.9)	
Both	8(14.5)	2(7.1)	6(22.2)	
Neither	26(47.3)	16(57.1)	10(37.0)	0.135
Treatment line				
1	48(87.2)	24(85.7)	24(88.8)	1.000
2	7(12.7)	4(14.2)	3(11.1)	
irAE				
Yes	19(34.5)	5(17.8)	14(51.8)	0.008
No	36(65.4)	23(82.1)	13(48.1)	
Treatment regimen				
ICIs monotherapy	4(7.3)	2(7.1)	2(7.4)	1.000
ICIs+Targeted therapy	51(92.7)	26(92.8)	25(92.6)	

Appendix 5. Prognostic factors for progression-free survival.

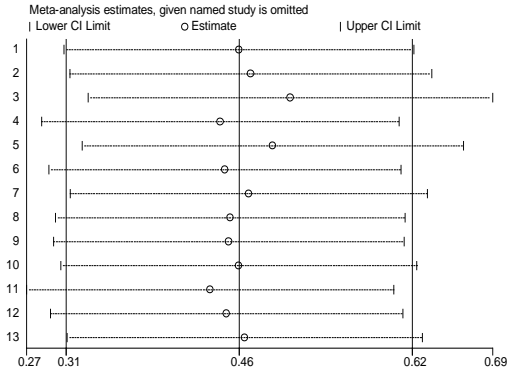
Covariate	PFS			
	Univariate		Multivariate	
	HR(95%CI)	p	HR(95%CI)	p
AFP $\geq$ 400ng/mL vs <400ng/mL	2.034 (1.010-4.096)	0.047	1.822 (0.866-3.832)	0.114
Gender Male vs Female	0.575 (0.237-1.395)	0.221	—	—
Age $\geq$ 60 vs <60	0.960 (0.484-1.907)	0.908	—	—
ECOG PS $\geq$ 2 vs <2	1.950 (0.981-3.878)	0.057	1.971 (0.923-4.209)	0.080
HBV Positive vs Negative	0.651 (0.282-1.505)	0.316	—	—
HBV-DNA $\geq$ 500 vs <500	1.302 (0.645-2.629)	0.462	—	—
Child-Pugh Score B vs A	2.411 (1.173-4.957)	0.017	1.967 (0.858-4.506)	0.110
Portal vein thrombosis Yes vs No	2.055 (1.006-4.195)	0.048	1.093 (0.458-2.607)	0.841
Number of intrahepatic lesions $\geq$ 3 vs <3	2.227 (1.071-4.629)	0.032	—	—
Maximum size of intrahepatic lesions $\geq$ 10cm vs <10cm	2.020 (1.000-4.078)	0.050	3.581 (1.478-8.672)	0.005
Extrahepatic spread Yes vs No	1.013 (0.497-2.064)	0.971	—	—
BCLC stage C+D vs A+B	1.683 (0.591-4.794)	0.330	—	—
Previous treatment Yes vs No	0.543 (0.272-1.084)	0.084	1.075 (0.456-2.533)	0.868
Treatment line 2 vs 1	0.874(0.306-2.495)	0.801	—	—
irAE Yes vs No	0.884(0.437-1.785)	0.730	—	—
Treatment regimen ICIs monotherapy vs ICIs+Targeted therapy	0.706 (0.168-2.954)	0.633	—	—

Appendix 6. Prognostic factors for overall survival.

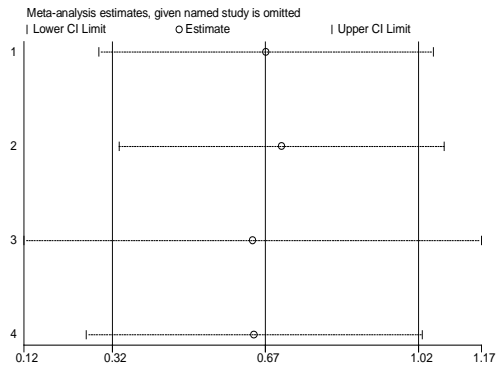
Covariate	OS			
	Univariate		Multivariate	
	HR (95%CI)	p	HR (95%CI)	p
AFP $\geq$ 400ng/mL vs <400ng/mL	2.119(0.988-4.544)	0.054	3.584(1.466-8.762)	0.005
Gender Male vs Female	1.447(0.427-4.898)	0.553	—	—
Age $\geq$ 60 vs <60	1.365(0.648-2.876)	0.413	—	—
ECOG PS $\geq$ 2 vs <2	3.235(1.501-6.975)	0.003	3.159(1.340-7.446)	0.009
HBV Positive vs Negative	0.403(0.176-0.920)	0.031	0.445(0.173-1.146)	0.093
HBV-DNA $\geq$ 500 vs <500	1.258(0.604-2.622)	0.540	—	—
Child-Pugh Score B vs A	5.933(2.508-14.031)	<0.001	2.968(1.132-7.781)	0.027
Portal vein thrombosis Yes vs No	3.488(1.562-7.788)	0.002	1.365(0.530-3.514)	0.519
Number of intrahepatic lesions $\geq$ 3 vs <3	2.798(1.257-6.227)	0.012	1.987(0.787-5.017)	0.146
Maximum size of intrahepatic lesions $\geq$ 10cm vs <10cm	1.405(0.646-3.055)	0.391	—	—
Extrahepatic spread Yes vs No	1.439(0.629-3.294)	0.389	—	—
BCLC stage C+D vs A+B	3.002(0.711-12.678)	0.135	—	—
Previous treatment Yes vs No	0.459(0.215-0.980)	0.044	0.842(0.367-1.935)	0.686
Treatment line 2 vs 1	1.149(0.398-3.321)	0.797	—	—
irAE Yes vs No	0.562(0.250-1.264)	0.163	—	—
Treatment regimen ICIs monotherapy vs ICIs+Targeted therapy	0.895(0.212-3.782)	0.880	—	—

Appendix 7. Sensitivity analysis diagram. A: 13 cohort studies that provided HRs for OS on univariate analysis. B: 4 cohort studies that provided HRs for OS on multivariate analysis. C: 6 cohort studies that provided HRs for PFS on univariate analysis.

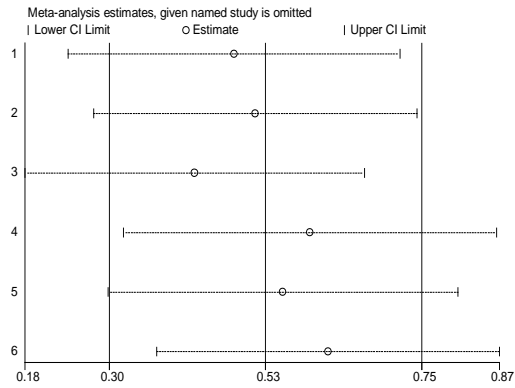
A



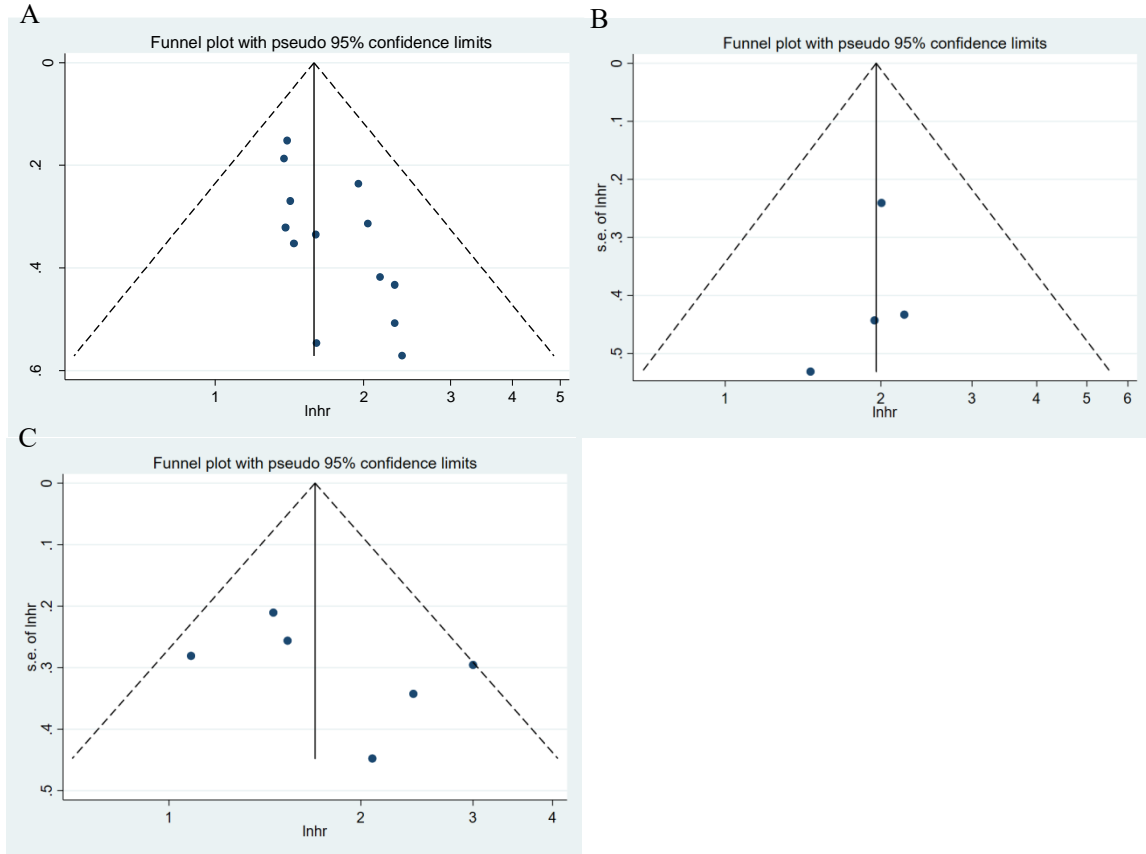
B



C



Appendix 8. Funnel plots. A:13 cohort studies that provided HRs for OS on univariate analysis. B:4 cohort studies that provided HRs for OS on multivariate analysis. C:6 cohort studies that provided HRs for PFS on univariate analysis.





Appendix 9. Symmetry test of funnel plots. A:13 cohort studies that provided HRs for OS on univariate analysis. B: 4 cohort studies that provided HRs for OS on multivariate analysis. C: 6 cohort studies that provided HRs for PFS on univariate analysis.

	A	B	B
Begg's test	0.161	0.308	0.452
Egger's test	0.014	0.547	0.345

Appendix 10. The association of AFP on the prognosis of HCC patients.A: The Kaplan–Meier curve of PFS. B: The Kaplan–Meier curve of OS.

