

Supplementary materials

Supplementary table 1. Comparison of baseline characteristics and clinic features of patients with normal and elevated levels of AFP, CEA and CA 19-9

	AFP			CEA			CA 19-9		
	< 20 ng/ml (n = 99)	≥ 20 ng/ml (n = 402)	p-value	< 5.0 ng/ml (n=130)	≥ 5.0ng/ml (n = 42)	p-value	< 37 U/ml (n = 81)	≥ 37 U/ml (n = 120)	p - value
Age (years) (mean ± SD)	54.32±12.80	49.43±15.05	0.001**	52.61±14.97	54.76±12.16	0.199**	51.74±14.31	52.66±14.92	0.332**
Male/female	72(72.73%)	296(73.63%)	0.855	94(72.31%)	21(50.00%)	0.202	57(70.37%)	81(67.50%)	0.667
Female	27(27.27%)	106(26.37%)	0.855	36(27.69%)	21(50.00%)	0.202	24(29.63%)	39(32.50%)	0.667
WHO/ECOG PS Performance Status (PS)	97(97.98%)	394(98.01%)		130(100%)	41(97.62%)		81(100%)	119(99.17%)	
0	8(8.25%)	29(7.36%)	0.768	15(11.54%)	2(4.88%)	0.249*	12(14.81%)	7(5.88%)	0.033
1	43(43.33%)	156(39.59%)	0.399	58(44.62%)	18(43.90%)	0.040	38(46.91%)	45(37.82%)	0.184
2	29(29.90%)	98(24.87%)	0.314	29(22.31%)	11(26.83%)	0.605	18(22.22%)	34(28.57%)	0.332
3	15(15.46%)	88(22.34%)	0.137	23(17.69%)	9(21.95%)	0.589	12(14.81%)	26(21.84%)	0.224
4	2(2.06%)	23(5.84%)	0.195*	5(3.85%)	1(2.44%)	1*	1(1.23%)	7(5.88%)	0.147*
Comorbidities									
Chronic HBV infection	34(34.34%)	265(65.92%)	< 0.001	83(63.85%)	20(47.62%)	0.062	48(59.26%)	73(60.83%)	0.823
Chronic HCV infection	6(6.06%)	22(5.47%)	0.820	5(3.85%)	0(0.00%)	0.336*	2(2.47%)	5(4.17%)	0.704*
Diabetes mellitus	18(18.18%)	47(11.69%)	0.085	15(11.54%)	9(21.43%)	0.108	13(16.05%)	15(12.50%)	0.476
Hypertension	29(29.29%)	88(21.89%)	0.119	33(25.38%)	14(33.33%)	0.315	19(23.46%)	27(22.50%)	0.874
Ischaemic heart disease	3(3.03%)	8(1.99%)	0.461*	4(3.08%)	2(4.76%)	0.635*	3(3.70%)	2(1.67%)	0.394*

Human immunodeficiency virus (HIV)	10(10.10%)	66(16.41%)	0.117	14(10.77%)	7(16.67%)	0.310	11(13.58%)	14(11.67%)	0.687
Bilharzia	2(2.02%)	12(2.99%)	1*	2(1.54%)	1(2.38%)	0.571*	0(0.00%)	2(1.67%)	0.516*
Smoking	37(37.37%)	111(27.61%)	0.057	40(30.77%)	18(42.86%)	0.150	24(29.63%)	47(39.17%)	0.165
Alcohol intake (any)	37(37.37%)	133(33.08%)	0.419	43(33.08%)	13(30.95%)	0.798	20(24.69%)	46(38.33%)	0.043
Symptomatic presentation	91(91.91%)	395(98.26%)	< 0.001	127(97.69%)	40(95.24%)	0.410	74(91.36%)	119(99.17%)	0.005
Duration of symptoms (days)	90.31±112.69	82.15±90.15	0.238**	110.07±154.78	110.81±133.36	0.490**	78.08±71.43	116.58±167.44	0.039**
Detailed symptoms									
Pain	61(61.62%)	295(73.38%)	0.021	99(76.15%)	32(76.19%)	0.996	58(71.60%)	95(79.17%)	0.217
Weight loss	48(48.48%)	245(60.95%)	0.024	84(64.62%)	29(69.05%)	0.599	42(51.85%)	87(72.50%)	0.002
Anorexia	27(27.27%)	95(23.63%)	0.450	32(24.62%)	11(26.19%)	0.838	21(25.93%)	34(28.33%)	0.707
Nausea	21(21.21%)	69(17.16%)	0.347	29(22.31%)	7(16.67%)	0.435	18(22.22%)	28(23.33%)	0.854
Vomiting	18(18.18%)	73(18.16%)	0.996	27(20.77%)	10(23.81%)	0.677	17(20.99%)	28(23.33%)	0.696
Variceal bleed	6(6.06%)	21(5.22%)	0.741	5(3.85%)	0(0.00%)	0.336*	1(1.23%)	4(3.33%)	0.650*
Peritonitis	1(1.01%)	3(0.75%)	0.587*	0(0.00%)	0(0.00%)	1*	0(0.00%)	0(0.00%)	1*
Fever	4(4.04%)	15(3.73%)	0.776*	3(2.31%)	1(2.38%)	1*	1(1.23%)	1(0.83%)	1*
Signs									
Jaundice	15(15.15%)	61(15.17%)	0.996	15(11.54%)	7(16.67%)	0.387	10(12.35%)	25(20.83%)	0.120
Ascites	26(26.26%)	129(32.01%)	0.261	34(26.15%)	14(33.33%)	0.367	15(18.52%)	46(38.33%)	0.003
Palpable mass	30(30.30%)	142(35.32%)	0.346	64(49.23%)	18(42.86%)	0.472	32(39.51%)	51(42.50)	0.672
Hepatomegaly	28(28.28%)	198(49.25%)	< 0.001	54(41.54%)	22(52.38%)	0.219	32(39.51%)	62(51.67%)	0.091
Encephalopathy	2(2.02%)	5(1.24%)	0.629*	3(2.31%)	1(2.38%)	1*	0(0.00%)	7(5.83%)	0.043*

*Exact-Fischer Test

**Paired Samples T-test

WHO/ECOG PS refers to the World Health Organization/Eastern Cooperative Oncology Group Performance Status; and Chronic HBV and HCV infections indicate chronic hepatitis B and C infections, respectively.

Supplementary table 2. Comparison of disease severity, tumour burden, metastatic profile and treatment in patients with normal and elevated levels of AFP, CEA and CA 19-9

	AFP			CEA			CA 19-9		
	< 20 ng/ml (n = 99)	≥ 20 ng/ml (n = 402)	p-value	< 5.0 ng/ml (n=130)	≥ 5.0ng/ml (n = 42)	p-value	< 37 U/ml (n = 81)	≥ 37 U/ml (n = 120)	p - value
Scoring/Grading									
Child Pugh Grade	99(100%)	402(100%)		130(100%)	40(95.24%)		79(97.53%)	118(98.33%)	
A	52(52.53%)	185(46.02%)	0.246	78(60.00%)	20(50.00%)	0.159	54(68.35%)	51(43.22%)	< 0.001
B	33(33.33%)	148(36.82%)	0.518	34(26.15%)	12(30.00%)	0.758	21(26.58%)	39(33.05%)	0.318
C	14(14.14%)	69(17.16%)	0.469	18(13.85%)	8(20.00%)	0.413	4(5.06%)	28(23.73%)	< 0.001*
MELD-Na score	13.70±6.86	14.12±6.44	0.282**	13.01±6.42	14.18±6.17	0.156**	11.78±5.67	14.85±6.49	< 0.001**
Cirrhotic	49(49.49%)	212(52.74%)	0.563	61(46.92%)	16(38.01%)	0.317	31(38.27%)	62(51.67%)	0.062
BCLC stage	95(95.96%)	399(99.25%)		129(99.23%)	41(97.62%)		78(96.30%)	117(97.50%)	
0	2(2.11%)	0(0.00%)	0.039*	0(0.00%)	0(0.00%)	1*	0(0.00%)	0(0.00%)	1*
A	10(10.53%)	18(4.51%)	0.029	10(7.75%)	0(0.00%)	0.121*	8(10.26%)	1(0.85%)	0.003*
B	10(10.53%)	23(5.76%)	0.116	8(6.20%)	1(2.44%)	0.457*	5(6.41%)	5(4.27%)	0.528*
C	49(51.58%)	231(57.89%)	0.153	74(57.36%)	26(63.41%)	0.801	52(66.67%)	64(54.70%)	0.126
D	24(25.26%)	127(31.83%)	0.153	37(28.68%)	14(34.15%)	0.548	13(16.67%)	47	< 0.001
Liver tumours (n) on imaging									
= 1	46(46.46%)	141(35.07%)	0.035	46(35.38%)	10(23.81%)	0.164	33(40.74%)	33(27.5%)	0.0499
> 1	53(53.54%)	261(64.93%)	0.035	84(64.62%)	32(76.19%)	0.164	48(59.26%)	87(72.50%)	0.0499
Metastatic Profile									
Baseline	17(17.17%)	111(27.61%)	0.033	27(20.77%)	10(23.81%)	0.677	17(20.99%)	28(23.33%)	0.696
Lung	8(8.08%)	73(18.16%)	0.015	15(11.54%)	6(14.29%)	0.636	13(16.05%)	18(15.00%)	0.840
Bone	5(5.05%)	18(4.48%)	0.807	5(3.85%)	3(7.14%)	0.406*	3(3.70%)	5(4.17%)	1*

Spine	2(2.02%)	10(2.49%)	1*	3(2.31%)	1(2.38%)	1*	2(2.47%)	0(0.00%)	0.161*
Peritoneal	4(4.04%)	6(1.49%)	0.115*	4(3.08%)	1(2.38%)	1*	1(1.23%)	4(3.33%)	0.650*
Other	3(3.03%)	21(5.22%)	0.443*	3(2.31%)	2(4.76%)	0.597*	1(1.23%)	5(4.17%)	0.405*
Developed	6(6.06%)	17(4.23%)	0.435	7(5.38%)	0(0.00%)	0.197*	7(8.64%)	3(2.50%)	0.093*
Lung	3(3.03%)	10(2.49%)	0.727*	4(3.08%)	0(0.00%)	0.573	3(3.70%)	1(0.83%)	0.305*
Bone	0(0.00%)	1(0.25%)	1*	0(0.00%)	0(0.00%)	1*	0(0.00%)	0(0.00%)	1*
Spine	1(1.01%)	1(0.25%)	0.357*	2(1.54%)	0(0.00%)	1*	1(1.23%)	1(0.83%)	1*
Peritoneal	0(0.00%)	3(0.75%)	1*	0(0.00%)	0(0.00%)	1*	1(1.23%)	0(0.00%)	0.403*
Other	2(2.02%)	3(0.75%)	0.257*	1(0.77%)	0(0.00%)	1*	2(2.47%)	1(0.83%)	0.566*
Treatment									
Ablation	4(4.04%)	12(2.99%)	0.534*	4(3.08%)	2(4.76%)	0.635*	4(4.94%)	3(2.50%)	0.443*
Resection	25(25.25%)	19(4.73%)	< 0.001	13(10.00%)	3(7.14%)	0.764*	17(20.99%)	0(0.00%)	< 0.001*
Liver transplantation	1(1.01%)	0(0.00%)	0.198*	0(0.00%)	0(0.00%)	1*	1(1.23%)	0(0.00%)	0.403*
Trans-arterial therapies	32(32.32%)	96(23.88%)	0.084	42(32.31%)	11(26.19%)	0.455	27(33.33%)	27(22.50%)	0.089
Sorafenib	9(9.09%)	35(8.71%)	0.904	7(5.38%)	11(26.19%)	< 0.001	5(6.17%)	7(5.83%)	1*
Best supportive care	53(53.54%)	280(69.65%)	0.002	80(61.54%)	30(71.43%)	0.246	45(55.56%)	87(72.50%)	0.013

*Exact-Fischer Test

**Paired Samples T-test

MELD-Na is the Model for End-Stage Liver Disease score adjusted for sodium; and BCLC stage refers to the Barcelona Clinic Liver Cancer staging

Supplementary table 3. Effect of tumour marker levels (elevated vs. normal) on haematological parameters, liver function tests, and derived indices

	AFP			CEA			CA 19-9		
	< 20 ng/ml (n = 99)	≥ 20 ng/ml (n = 402)	p value	< 5.0 ng/ml (n=130)	≥ 5.0ng/ml (n = 42)	p value	< 37 U/ml (n = 81)	≥ 37 U/ml (n = 120)	p value
Blood Results									
Haemoglobin	11.34±2.19	11.82±2.56	0.043	11.51±2.43	11.64±2.52	0.388	11.65±2.75	11.69±2.48	0.459
Platelet count	314.69±219.8	305.82±461.11	0.426	322.92±173.88	320.67±195.81	0.472	320.19±186.91	317.42±174.49	0.457
INR	1.33±0.390	1.35±0.360	0.377	1.30±0.310	1.29±0.220	0.469	1.26±0.280	1.36±0.370	0.019
Total bilirubin	34.76±51.96	44.85±71.56	0.093	39.14±79.25	40.29±63.66	0.466	40.12±73.64	45.69±54.11	0.269
Conjugated bilirubin	24.11±43.32	31.53±56.10	0.114	28.21±58.02	30.54±59.47	0.414	26.81±58.13	33.47±44.80	0.184
ALT	65.26±64	85.79±126.42	0.057	82.02±112.16	84.71±165.96	0.453	88.99±149.24	83.79±129.18	0.396
AST	97.36±92.82	222.17±524.40	0.011	198.36±388.84	172.56±218.31	0.347	186.63±477.22	247.46±743.62	0.261
ALP	352.15±547.2 3	313.91±261.83	0.156	345.38±490.61	383.17±338.97	0.322	264.40±204.02	409.80±529.59	0.009
GGT	307.40±357.9 8	416.29±390.55	0.006	399.96±372.73	473.32±433.92	0.147	380.46±467.02	460.18±387.09	0.095 1
Albumin	33.41±10.46	33.25±7.49	0.355	34.38±8.22	32.88±7.57	0.185	36.01±8.59	32.47±7.07	0.002
Hepatic indices									
AST/ALT ratio	2.06±1.96	3.07±3.00	0.324	3.03±2.83	2.76±2.32	0.366	2.60±2.61	3.25±2.83	0.188
GGT/ALT ratio	8.12±10.38	8.42±10.03	0.348	8.95±9.75	14.42±16.91	0.049 5	8.29±11.11	11.47±12.85	0.170
Albumin-bilirubin (ALBI) score	- 1.96±0.92	- 1.92±0.79	0.232	- 2.04±0.74	- 1.95±0.82	0.333	- 2.20±0.70	-1.82±0.77	0.287
AST to Platelet Ratio Index (APRI)	1.25±1.72	2.51±5.67	0.130	1.89±3.37	2.11±2.93	0.310	1.74±3.98	2.57±7.30	0.302

INR refers to the International Normalised Ratio; ALT and AST indicate alanine transaminase and aspartate transaminase, respectively; ALP denotes alkaline phosphatase; and GGT represents gamma-glutamyl transferase.