Supplementary

Table S1 The ultrasound instruments

Ultrasound manufacturers	Ultrasound instrument	probe	Production country	Width × Height
Philips	IU22	C5-1	American	800×600
GE	LOGIQ E9	CI-5 and CI-6	American	960×540
Siemens	Acuson S2000	4C1	Germany	1,024×768
Siemens	Sequoia 512	4C1	Germany	768×576

Table S2 Identification performance of the proposed models in IV and EV cohorts (3-fold CV, Fold1)

	$FS3D^{U}$		$FS3D^{U+H}$		$FS3D^{U+A}$		$FS3D^{U+H+A}$	
	Training	IV and EV	Training	IV and EV	Training	IV and EV	Training	IV and EV
AUC (95% CI)	0.931 (0.883,0.979)	0.710 (0.585.0.835)	0.954 (0.915,0.993)	0.883 (0.797,0.969)	1.000 (1.000,1.000)	0.923 (0.857,0.993)	0.968 (0.935,1.000)	0.931 (0.864,0.998)
ACC (95% CI)	0.867 (0.798,0.919)	0.725 (0.604,0.825)	0.904 (0.841,0.948)	0.841 (0.733,0.918)	1.000 (0.973,1.000)	0.870 (0.767,0.939)	0.933 (0.877,0.965)	0.899 (0.802,0.958)
SEN (95% CI)	0.909 (0.822,0.963)	0.744 (0.579,0.870)	0.948 (0.872,0.986)	0.872 (0.726,0.957)	1.000 (0.953,1.000)	0.897 (0.758,0.971)	0.974 (0.909,0.997)	0.849 (0.827,0.994)
SPE (95% CI)	0.810 (0.686.0.901)	0.700 (0.506,0.853)	0.845 (0.726,0.927)	0.800 (0.614,0.923)	1.000 (0.938,1.000)	0.833 (0.653,0.944)	0.879 (0.767,0.950)	0.833 (0.653,0.944)
PPV (95% CI)	0.864 (0.758,0.922)	0.763 (0.598,0.886)	0.890 (0.802,0.949)	0.850 (0.702,0.943)	1.000 (0.953,1.000)	0.875 (0.732,0.958)	0.915 (0.832,0.965)	0.881 (0.744,0.960)
NPV (95% CI)	0.870 (0.770,0.957)	0.677 (0.486,0.833)	0.925 (0.818,0.979)	0.828 (0.642,0.942)	1.000 (0.938,1.000)	0.862 (0.683,0.961)	0.962 (0.870,0.995)	0.926 (0.757,0.991)
Speed (sec)	10.76	10.76	10.76	10.76	10.76	10.76	10.76	10.76

$FS3D^{U}$= $FS3D^{CEUS}$; $FS3D^{U+A}$ = $FS3D^{CEUS+AFP}$; $FS3D^{U+H}$ = $FS3D^{CEUS+Hepatitis}$; $FS3D^{U+A+H}$ = $FS3D^{CEUS+AFP+Hepatitis}$. IV, internal validation; EV, external validation; CV, cross validation; AUC, the area under the receiver operating characteristic curve; ACC, accuracy; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; 95% CI, confidence interval of 95%; FS3D, Four-Stream three-dimensional.

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Table S3 Identification performance of the proposed models in IV and EV cohorts (3-fold CV, Fold2)

	$FS3D^{U}$		$FS3D^{U+H}$		$FS3D^{U+A}$		$FS3D^{U+H+A}$	
	Training	IV and EV	Training	IV and EV	Training	IV and EV	Training	IV and EV
AUC (95% CI)	0.950 (0.910,0.990)	0.651 (0.517,0.785)	0.969 (0.937,1.000)	0.785 (0.671,0.899)	1.000 (1.000,1.000)	0.725 (0.600,0.850)	0.966 (0.933,0.999)	0.795 (0.671,0.899)
ACC (95% CI)	0.904 (0.842,0.948)	0.706 (0.552,0.785)	0.927 (0.869,0.964)	0.735 (0.614,0.835)	1.000 (0.973,1.000)	0.691 (0.567,0.800)	0.927 (0.869,0.964)	0.750 (0.630,0.847)
SEN (95% CI)	0.987 (0.930,1.000)	0.821 (0.635,0.907)	0.961 (0.890,0.992)	0.821 (0.665,0.925)	1.000 (0.953,1.000)	0.692 (0.524,0.830)	0.922 (0.838,0.971)	0.846 (0.645,0.941)
SPE (95% CI)	0.797 (0.672,0.890)	0.552 (0.325,0.706)	0.881 (0.771,0.951)	0.621 (0.423,0.793)	1.000 (0.939,1.000)	0.690 (0.492,0.847)	0.932 (0.835,0.981)	0.621 (0.423,0.793)
PPV (95% CI)	0.864 (0.774,0.928)	0.711 (0.534,0.818)	0.914 (0.830,0.965)	0.744 (0.588,0.865)	1.000 (0.953,1.000)	0.750 (0.578,0.879)	0.947 (0.869,0.985)	0.750 (0.597,0.868)
NPV (95% CI)	0.979 (0.889,1.000)	0.696 (0.427,0.836)	0.946 (0.849,0.989)	0.720 (0.506,0.879)	1.000 (0.939,1.000)	0.625 (0.437,0.789)	0.902 (0.798,0.963)	0.750 (0.533,0.902)
Speed (sec)	10.76	10.76	10.76	10.76	10.76	10.76	10.76	10.76

$FS3D^{U}$= $FS3D^{CEUS}$; $FS3D^{U+A}$ = $FS3D^{CEUS+AFP}$; $FS3D^{U+H}$ = $FS3D^{CEUS+Hepatitis}$; $FS3D^{U+A+H}$ = $FS3D^{CEUS+AFP+Hepatitis}$. IV, internal validation; EV, external validation; CV, cross validation; ACC, accuracy; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, the area under the receiver operating characteristic curve; 95% CI, confidence interval of 95%; FS3D, Four-Stream three-dimensional.

Table S4 Identification performance of the proposed models in IV and EV cohorts (3-fold CV, Fold3)

	$FS3D^{U}$		$FS3D^{U+H}$		$FS3D^{U+A}$		$FS3D^{U+H+A}$	
	Training	IV and EV	Training	IV and EV	Training	IV and EV	Training	IV and EV
AUC (95% CI)	0.934 (0.888,0.980)	0.795 (0.683,0.907)	0.932 (0.885,0.979)	0.930 (0.862,0.998)	1.000 (1.000,1.000)	0.886 (0.800,0.972)	0.917 (0.865,0.969)	0.924 (0.853,0.995)
ACC (95% CI)	0.876 (0.809,0.926)	0.746 (0.625,0.845)	0.883 (0.817,0.932)	0.851 (0.743,0.926)	1.000 (0.973,1.000)	0.851 (0.743,0.926)	0.876 (0.809,0.919)	0.866 (0.760,0.937)
SEN (95% CI)	0.987 (0.931,1.000)	0.895 (0.752,0.971)	0.962 (0.892,0.992)	0.921 (0.786,0.983)	1.000 (0.954,1.000)	0.895 (0.752,0.971)	0.949 (0.874,0.986)	0.947 (0.823,0.994)
SPE (95% CI)	0.729 (0.597,0.836)	0.552 (0.357,0.736)	0.780 (0.653,0.877)	0.759 (0.565,0.897)	1.000 (0.939,1.000)	0.793 (0.603,0.920)	0.780 (0.653,0.877)	0.759 (0.564,0.897)
PPV (95% CI)	0.828 (0.736,0.898)	0.723 (0.574,0.844)	0.852 (0.761,0.919)	0.833 (0.686,0.930)	1.000 (0.954,1.000)	0.850 (0.702,0.943)	0.851 (0.758,0.918)	0.837 (0.693,0.932)
NPV (95% CI)	0.977 (0.880,0.999)	0.800 (0.563,0.943)	0.939 (0.831,0.987)	0.880 (0.688,0.975)	1.000 (0.939,1.000)	0.852 (0.663,0.958)	0.920 (0.808,0.978)	0.917 (0.730,0.990)
Speed (sec)	10.76	10.76	10.76	10.76	10.76	10.76	10.76	10.76

$FS3D^{U}$= $FS3D^{CEUS}$; $FS3D^{U+A}$ = $FS3D^{CEUS+AFP}$; $FS3D^{U+H}$ = $FS3D^{CEUS+Hepatitis}$; $FS3D^{U+A+H}$ = $FS3D^{CEUS+AFP+Hepatitis}$. IV, internal validation; EV, external validation; CV, cross validation; ACC, accuracy; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, the area under the receiver operating characteristic curve; 95% CI, confidence interval of 95%; FS3D, Four-Stream three-dimensional.

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Table S5 Number of lesion types in training, IV and EV cohorts

		Lesion type	Training cohort (n=203)	IV cohort (n=50)	EV cohort (n=50)
1	Malignant	Hepatocellular carcinoma	87	28	24
2		Cholangiocellular carcinoma	12	5	4
3		Combined hepatocellular-cholangiocarcinoma	1		
4		Metastatic cancers	15	5	1
5		Hepatoblastoma	1		
6		Hepatic neuroendocrine tumors	1		
7		Inflammatory pseudotumor-like follicular dendritic cell tumor	1		
8	Benign	Focal Nodular Hyperplasia	20	2	1
9		Inflammatory lesions	17		
10		Hemangioma	20	6	18
11		Mucinous cystadenomas	1		
12		Angiomyolipoma	24	3	
13		Liver cirrhotic with dysplasia	1		
14		Focal fatty sparing			1
15		Hepatic adenoma		1	
16		Schwannomatosis	1		
17		Granulomatous inflammatory	1		
18		Hepatic cyst			1

IV, internal validation; EV, external validation.

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Table S6 Identification performance of liver cancer using FS3D models and radiologists in the IV and EV cohorts

	IV cohort						EV cohort					
	$FS3D^{U}$	$FS3D^{U+H}$	$FS3D^{U+A}$	$FS3D^{U+H+A}$	R 1	R 2	$FS3D^{U}$	$FS3D^{U+H}$	$FS3D^{U+A}$	$FS3D^{U+H+A}$	R 1	R 2
AUC	0.898*	0.938	0.950	0.969	0.935	0.867*	0.798*	0.849*	0.892	0.957	0.935	0.864*
(95% CI)	(0.780, 1.000)	(0.844, 1.000)	(0.865, 1.000)	(0.901, 1.000)	(0.839, 1.000)	(0.735, 0.999)	(0.668, 0.928)	(0.734, 0.964)	(0.793, 0.991)	(0.894, 1.000)	(0.857, 1.000)	(0.754, 0.974)
ACC	0.840	0.940	0.920	0.960	0.940	0.840	0.800	0.880	0.920	0.940	0.940	0.880
(95% CI)	(0.709, 0.928)	(0.835, 0.988)	(0.808, 0.978)	(0.863, 0.995)	(0.835, 0.988)	(0.709, 0.928)	(0.663, 0.900)	(0.757, 0.955)	(0.808, 0.978)	(0.835, 0.988)	(0.835, 0.988)	(0.757, 0.955)
SEN	0.838	0.946	0.919	0.973	0.946	0.811	0.862	0.966	0.966	0.966	0.966	0.966
(95% CI)	(0.680, 0.938)	(0.818, 0.993)	(0.781, 0.983)	(0.858, 0.999)	(0.818, 0.993)	(0.648, 0.920)	(0.683, 0.961)	(0.822, 0.999)	(0.822, 0.999)	(0.822, 0.999)	(0.822, 0.999)	(0.822, 0.999)
SPE	0.846	0.923	0.923	0.923	0.923	0.923	0.714	0.762	0.857	0.905	0.905	0.762
(95% CI)	(0.546, 0.981)	(0.640, 0.998)	(0.640, 0.998)	(0.640, 0.998)	(0.640, 0.998)	(0.640, 0.998)	(0.478, 0.887)	(0.528, 0.918)	(0.637, 0.970)	(0.696, 0.988)	(0.696, 0.988)	(0.528, 0.918)
PPV	0.939	0.972	0.971	0.973	0.972	0.968	0.806	0.848	0.903	0.933	0.933	0.848
	(0.798, 0.993)	(0.855, 0.999)	(0.851, 0.999)	(0.858, 0.999)	(0.855, 0.999)	(0.833, 0.999)	(0.625, 0.926)	(0.681, 0.949)	(0.743, 0.980)	(0.779, 0.992)	(0.779, 0.992)	(0.681, 0.949)
NPV	0.647	0.857	0.800	0.923	0.857	0.632	0.789	0.941	0.947	0.950	0.950	0.941
	(0.383, 0.858)	(0.572, 0.982)	(0.519, 0.957)	(0.640, 0.998)	(0.572, 0.982)	(0.384, 0.837)	(0.544, 0.940)	(0.713, 0.999)	(0.740, 0.999)	(0.751, 0.999)	(0.751, 0.999)	(0.713, 0.999)
Speed (sec)	10.76	10.76	10.76	10.76	23.74	25.95	10.76	10.76	10.76	10.76	27.75	29.50
P value	0.020	0.143	0.080	0.185	0.126	0.008	0.003	0.020	0.050	0.114	0.080	0.007

$FS3D^{U}$= $FS3D^{CEUS}$, $FS3D^{U+A}$ = $FS3D^{CEUS+AFP}$, $FS3D^{U+H}$ = $FS3D^{CEUS+Hepatitis}$, $FS3D^{U+A+H}$ = $FS3D^{CEUS+AFP+Hepatitis}$. *, comparisons the AUCs of model $FS3D^{U+H+A}$ amongst six subgroups were performed by Delong test. IV, internal validation; EV, external validation; AUC, the area under the receiver operating characteristic curve; ACC, accuracy; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV= negative predictive value; AUC, the area under the receiver operating characteristic curve; 95% CI, confidence interval of 95%; FS3D, Four-Stream three-dimensional.

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Table S7 Stratification analysis among $FS3D^{U+H+A}$ and radiologists in IV and EV cohorts (<20 mm)

	IV cohort(n=13)			EV cohort(n=13)		
	$FS3D^{U+H+A}$	R1	R2	$FS3D^{U+H+A}$	R1	R2
AUC (95% CI)	0.900 (0.783,1.000)	1.000 (1.000,1.000)	0.950 (0.768,1.000)	0.881 (0.778,0.984)	0.929 (0.778,1.000)	0.786 (0.531,1.000)
ACC (95% CI)	0.923 (0.640,0.998)	1.000 (0.753,1.000)	0.923 (0.640,0.998)	0.846 (0.546,0.981)	0.923 (0.640,0.998)	0.769 (0.462,0.950)
SEN (95% CI)	1.000 (0.692,1.000)	1.000 (0.692,1.000)	0.900 (0.555,0.998)	1.000 (0.541,1.000)	1.000 (0.541,1.000)	1.000 (0.541,1.000)
SPE (95% CI)	0.667 (0.094,0.992)	1.000 (0.292,1.000)	1.000 (0.292,1.000)	0.714 (0.290,0.963)	0.857 (0.421,0.996)	0.571 (0.184,0.901)

$FS3D^{U+A+H}$ = $FS3D^{CEUS+AFP+Hepatitis}$. IV, internal validation; EV, external validation; ACC, accuracy; SEN, sensitivity; SPE, specificity; AUC, the area under the receiver operating characteristic curve; 95% CI, confidence interval of 95%; FS3D, Four-Stream three-dimensional.

Table S8 Stratification analysis among $FS3D^{U+H+A}$ and radiologists in IV and EV cohorts (20–50 mm)

	IV cohort (n=13)			EV cohort (n=21)		
	$FS3D^{U+H+A}$	R1	R2	$FS3D^{U+H+A}$	R1	R2
AUC (95% CI)	1.000 (1.000,1.000)	0.900 (0.596,1.000)	0.800 (0.402,1.000)	0.933 (0.854,1.000)	0.899 (0.743,1.000)	0.899 (0.743,1.000)
ACC (95% CI)	1.000 (0.735,1.000)	0.833 (0.516,0.979)	0.667 (0.349,0.901)	0.857 (0.637,0.970)	0.905 (0.696,0.988)	0.905 (0.696,0.988)
SEN (95% CI)	1.000 (0.692,1.000)	0.800 (0.444,0.975)	0.600 (0.262,0.878)	0.923 (0.640,0.998)	0.923 (0.640,0.998)	0.923 (0.640,0.998)
SPE (95% CI)	1.000 (0.158,1.000)	1.000 (0.158,1.000)	1.000 (0.158,1.000)	0.750 (0.349,0.968)	0.875 (0.474,0.997)	0.875 (0.474,0.997)

$FS3D^{U+A+H}$ = $FS3D^{CEUS+AFP+Hepatitis}$. IV, internal validation; EV, external validation; ACC, accuracy; SEN, sensitivity; SPE, specificity; AUC, the area under the receiver operating characteristic curve; 95% CI, confidence interval of 95%; FS3D, Four-Stream three-dimensional.

Table S9 Stratification analysis among $FS3D^{U+H+A}$ and radiologists in IV and EV cohorts (>50 mm)

	IV cohort(n=25)			EV cohort(n=15)		
	$FS3D^{U+H+A}$	R 1	R 2	$FS3D^{U+H+A}$	R 1	R 2
AUC (95% CI)	0.956 (0.852,1.000)	0.938 (0.816,1.000)	0.879 (0.713,1.000)	0.983 (0.943,1.000)	1.000 (1.000,1.000)	0.917 (0.751,1.000)
ACC (95% CI)	0.920 (0.740,0.990)	0.960 (0.797,0.999)	0.880 (0.688,0.975)	0.9375 (0.698,0.998)	1.000 (0.794,1.000)	0.938 (0.698,0.998)
SEN (95% CI)	0.941 (0.713,0.999)	1.000 (0.805,1.000)	0.882 (0.636,0.985)	0.900 (0.555,0.998)	1.000 (0.692,1.000)	1.000 (0.692,1.000)
SPE (95% CI)	0.875 (0.474,0.997)	0.875 (0.474,0.997)	0.875 (0.474,0.997)	1.000 (0.541,1.000)	1.000 (0.541,1.000)	0.833 (0.359,0.996)

$FS3D^{U+A+H}$ = $FS3D^{CEUS+AFP+Hepatitis}$. IV, internal validation; EV, external validation; ACC, accuracy; SEN, sensitivity; SPE, specificity; AUC, the area under the receiver operating characteristic curve; 95% CI, confidence interval of 95%; FS3D, Four-Stream three-dimensional.

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