Figure S1. Residual analysis of correlation analysis of the expression levels of selected miRNAs from the plasma exosomes and corresponding tissue samples from the same patients with lung-metastatic hepatocellular carcinoma. miRNA/miR, microRNA.

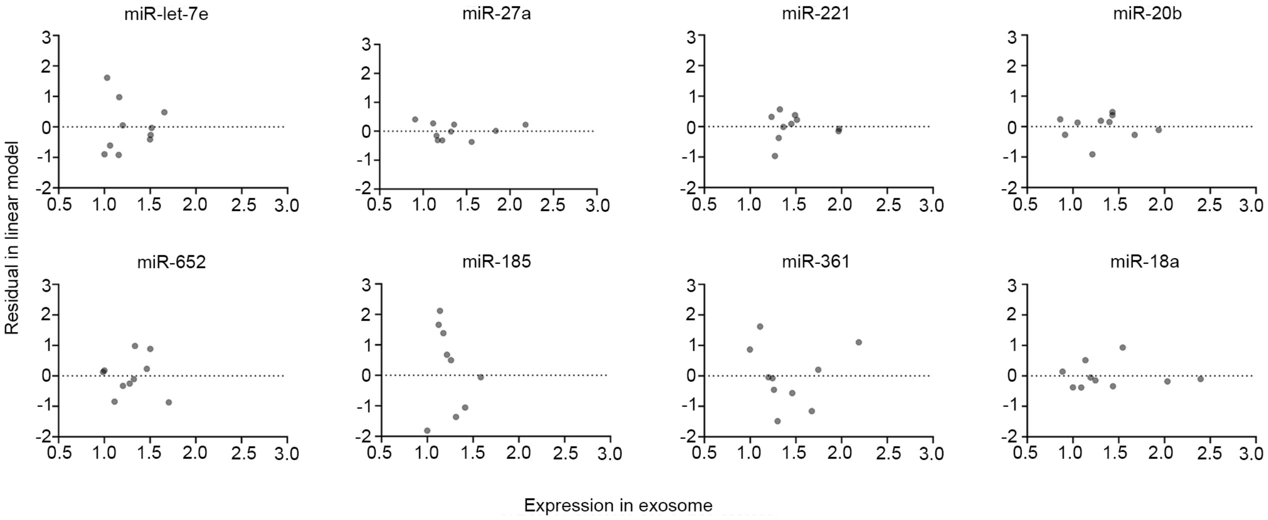

Figure S2. Spline curves of correlation analysis of the expression levels of selected miRNAs from the plasma exosomes and corresponding tissue samples from the same patients with lung-metastatic hepatocellular carcinoma. miRNA/miR, microRNA.

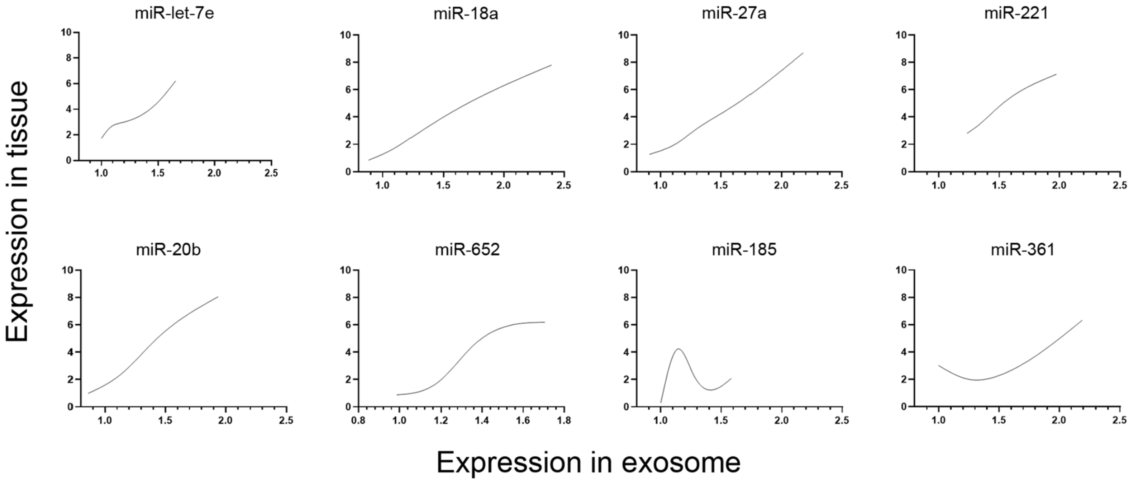

Table SI. AUC comparison of different predictor combinations performed by Delong's test.

Model comparison				
Predictor	AUC (95% CI)	vs.	AUC (95%CI)	P-value
All predictors	0.91 (0.87-0.95)	let-7e	0.61 (0.52-0.69)	<0.001
		miR-18a	0.77 (0.70-0.84)	<0.001
		miR-20b	0.86 (0.81-0.91)	0.012
		miR-221	0.58 (0.49-0.66)	<0.001
		miR-27a	0.82 (0.76-0.88)	<0.001
		miR-652	0.61 (0.52-0.69)	<0.001
		miR-18a + miR-20b + miR-27a	0.87 (0.82-0.92)	0.011
miR-18a + miR-20b + miR-27a	0.87 (0.82-0.92)	miR-18a + miR-20b+ miR-27a + let-7e	0.87 (0.83-0.92)	0.149
		miR-18a + miR-20b+ miR-27a + miR-221	0.91 (0.87-0.95)	0.014
		miR-18a + miR-20b + miR-27a + miR-652	0.88 (0.83-0.93)	0.343
		miR-18a + miR-20b + miR-27a + let-7e + miR-221	0.91 (0.87-0.95)	0.011
		miR-18a + miR-20b + miR-27a + miR-221 + miR-652	0.91 (0.87-0.95)	0.016
		miR-18a + miR-20b + miR-27a + let-7e + miR-652	0.88 (0.83-0.93)	0.249
miR-18a + miR-20b + miR-27a+ miR-221	0.91 (0.87-0.95)	miR-18a + miR-20b + miR-27a + miR-652	0.88 (0.83-0.93)	0.050
miR-18a + miR-20b + miR-27a + let-7e + miR-221	0.91 (0.87-0.95)	miR-18a + miR-20b + miR-27a + let-7e + miR-652	0.88 (0.83-0.93)	0.050
miR-18a + miR-20b + miR-27a	0.87 (0.82-0.92)	miR-18a + miR-20b + miR-221	0.90 (0.86-0.94)	0.048
		miR-18a + miR-221 + miR-27a	0.87 (0.82-0.92)	0.992
		miR-221 + miR-20b + miR-27a	0.90 (0.86-0.94)	0.155
miR-18a + miR-20b + miR-221	0.90 (0.86-0.94)	miR-221 + miR-20b + miR-27a	0.90 (0.86-0.94)	0.878
		miR-18a + miR-20b + miR-27a + miR-221	0.91 (0.87-0.95)	0.336
		All predictors	0.91 (0.87-0.95)	0.292
		miR-20b	0.86 (0.81-0.91)	0.019

95% CI, 95% confidence interval; AUC, area under the curve; miR, microRNA.

Table SII. Functional annotation of the GO and the KEGG pathway analysis of the upregulated exosomal microRNAs.

Category	Term	EnrichScore	P-value
GO_BP	GO:0007179~transforming growth factor beta receptor signaling pathway	1.866516323	$5.98277\text{x}10^{-7}$
GO_BP	GO:0071453~cellular response to oxygen levels	1.857914865	$3.42546\text{x}10^{-8}$
GO_BP	GO:0036294~cellular response to decreased oxygen levels	1.810799418	$4.46878\text{x}10^{-7}$
GO_BP	GO:0071559~response to transforming growth factor beta	1.742081901	$8.39457\text{x}10^{-7}$
GO_BP	GO:0016197~endosomal transport	1.740683762	$8.70854\text{x}10^{-8}$
GO_BP	GO:0070482~response to oxygen levels	1.660243630	$1.37732\text{x}10^{-8}$
GO_BP	GO:0043161~proteasome-mediated ubiquitin-dependent protein catabolic process	1.649479541	$1.12543\text{x}10^{-8}$
GO_BP	GO:0010256~endomembrane system organization	1.626131645	$2.32357\text{x}10^{-8}$
GO_BP	GO:0036293~response to decreased oxygen levels	1.620499845	$1.97134\text{x}10^{-7}$
GO_BP	GO:0001666~response to hypoxia	1.592833578	$8.08599\text{x}10^{-7}$
GO_BP	GO:0001933~negative regulation of protein phosphorylation	1.584778010	$5.66492\text{x}10^{-8}$
GO_BP	GO:0031331~positive regulation of cellular catabolic process	1.583710821	$1.61934\text{x}10^{-7}$
GO_BP	GO:0010498~proteasomal protein catabolic process	1.576074424	$5.43787\text{x}10^{-8}$
GO_BP	GO:0009896~positive regulation of catabolic process	1.515761578	$6.74505\text{x}10^{-7}$
GO_BP	GO:0042326~negative regulation of phosphorylation	1.502909247	$7.99165\text{x}10^{-7}$
GO_CC	GO:0030123~AP-3 adaptor complex	3.994358816	0.000368667
GO_CC	GO:0031519~PcG protein complex	2.480968209	$3.66118\text{x}10^{-5}$
GO_CC	GO:0043657~host cell	2.013962428	0.000336295
GO_CC	GO:0035097~histone methyltransferase complex	2.013962428	0.000336295
GO_CC	GO:0018995~host	2.013962428	0.000336295
GO_CC	GO:1902554~serine/threonine protein kinase complex	1.946830347	0.000168561
GO_CC	GO:1902911~protein kinase complex	1.844436971	0.000249331
GO_CC	GO:0000151~ubiquitin ligase complex	1.594669465	$4.95234\text{x}10^{-6}$
GO_CC	GO:0061695~transferase complex, transferring phosphorus-containing groups	1.540464291	$7.77572\text{x}10^{-5}$
GO_CC	GO:0000790~nuclear chromatin	1.493688801	$3.69842\text{x}10^{-5}$
GO_CC	GO:0005769~early endosome	1.474253145	$8.95858\text{x}10^{-5}$
GO_CC	GO:0005925~focal adhesion	1.404832506	0.000207194
GO_CC	GO:0005924~cell-substrate adherens junction	1.394216643	0.000276041
GO_CC	GO:0010008~endosome membrane	1.36846165	0.000311401
GO_CC	GO:0044440~endosomal part	1.35581837	0.00026152
GO_MF	GO:0001046~core promoter sequence-specific DNA binding	2.191463471	$8.28407\text{x}10^{-8}$
GO_MF	GO:0001047~core promoter binding	1.959035527	$7.06742\text{x}10^{-8}$
GO_MF	GO:0004721~phosphoprotein phosphatase activity	1.67982014	$5.16219\text{x}10^{-5}$
GO_MF	GO:0003924~GTPase activity	1.610627442	$3.45615\text{x}10^{-6}$
GO_MF	GO:0061659~ubiquitin-like protein ligase activity	1.593791615	$4.26056\text{x}10^{-5}$
GO_MF	GO:0045296~cadherin binding	1.578063408	$4.94226\text{x}10^{-6}$
GO_MF	GO:0044389~ubiquitin-like protein ligase binding	1.568331685	$5.05609\text{x}10^{-6}$
GO_MF	GO:0031625~ubiquitin protein ligase binding	1.548483158	$1.55558\text{x}10^{-5}$
GO_MF	GO:0001228~transcriptional activator activity, RNA polymerase II transcription regulatory region sequence-specific binding	1.506540249	$2.60929\text{x}10^{-6}$
GO_MF	GO:0042578~phosphoric ester hydrolase activity	1.456548448	$6.0699\text{x}10^{-5}$
GO_MF	GO:0032549~ribonucleoside binding	1.446218317	$5.75654\text{x}10^{-5}$
GO_MF	GO:0050839~cell adhesion molecule binding	1.433723991	$1.50223\text{x}10^{-5}$
GO_MF	GO:0032550~purine ribonucleoside binding	1.431855569	0.000101729
GO_MF	GO:0019787~ubiquitin-like protein transferase activity	1.430947689	$1.78999\text{x}10^{-5}$
GO_MF	GO:0004842~ubiquitin-protein transferase activity	1.416906276	$4.89833\text{x}10^{-5}$
KEGG_Pathway	hsa05223~Non-small cell lung cancer	2.443842298	$8.53234\text{x}10^{-7}$
KEGG_Pathway	hsa05214~Glioma	2.428412502	$4.25902\text{x}10^{-7}$
KEGG_Pathway	hsa05211~Renal cell carcinoma	2.337588285	$2.59082\text{x}10^{-6}$
KEGG_Pathway	hsa05210~Colorectal cancer	2.263542786	$6.16121\text{x}10^{-7}$
KEGG_Pathway	hsa04933~AGE-RAGE signaling pathway in diabetic complications	2.191031026	$3.91409\text{x}10^{-7}$
KEGG_Pathway	hsa01521~EGFR tyrosine kinase inhibitor resistance	2.182497312	$6.64357\text{x}10^{-6}$
KEGG_Pathway	hsa05215~Prostate cancer	2.121529645	$1.95378\text{x}10^{-6}$
KEGG_Pathway	hsa04068~FoxO signaling pathway	1.980354965	$8.79729\text{x}10^{-7}$

Table SII. Continued.

Category	Term	EnrichScore	P-value
KEGG_Pathway	hsa04722~Neurotrophin signaling pathway	1.963005172	$4.32136\text{x}10^{-6}$
KEGG_Pathway	hsa04919~Thyroid hormone signaling pathway	1.917878617	$1.37947\text{x}10^{-5}$
KEGG_Pathway	hsa04218~Cellular senescence	1.772839046	$1.24224\text{x}10^{-5}$
KEGG_Pathway	hsa05205~Proteoglycans in cancer	1.770936673	$1.03423\text{x}10^{-6}$
KEGG_Pathway	hsa04141~Protein processing in endoplasmic reticulum	1.75282482	$1.46388\text{x}10^{-5}$
KEGG_Pathway	hsa04014~Ras signaling pathway	1.702117272	$1.41014\text{x}10^{-6}$
KEGG_Pathway	hsa04010~MAPK signaling pathway	1.583712647	$4.14117\text{x}10^{-6}$

GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological process; CC, cellular component; MF, molecular function.

Table SIII. Functional annotation of the GO and KEGG pathway analysis of the downregulated exosomal microRNAs.

Category	Term	EnrichScore	P-value
GO_BP	GO:0060368~regulation of Fc receptor mediated stimulatory signaling pathway	9.505605688	0.000322024
GO_BP	GO:0035280~miRNA loading onto RISC involved in gene silencing by miRNA	8.147662018	0.000709555
GO_BP	GO:0034135~regulation of toll-like receptor 2 signaling pathway	7.921338073	0.000167021
GO_BP	GO:0060213~positive regulation of nuclear-transcribed mRNA poly(A) tail shortening	6.481094787	0.000543706
GO_BP	GO:0060211~regulation of nuclear-transcribed mRNA poly(A) tail shortening	6.481094787	0.000543706
GO_BP	GO:0035791~platelet-derived growth factor receptor-beta signaling pathway	5.484003281	0.001345298
GO_BP	GO:0034134~toll-like receptor 2 signaling pathway	5.092288761	0.001972595
GO_BP	GO:0007223~Wnt signaling pathway, calcium modulating pathway	3.752212771	0.000213971
GO_BP	GO:0061014~positive regulation of mRNA catabolic process	3.376991494	0.001014865
GO_BP	GO:0070534~protein K63-linked ubiquitination	3.240547394	0.000764375
GO_BP	GO:0045739~positive regulation of DNA repair	3.033703943	0.001316845
GO_BP	GO:1903313~positive regulation of mRNA metabolic process	2.632321575	0.001681368
GO_BP	GO:2001020~regulation of response to DNA damage stimulus	1.933343532	0.001416778
GO_BP	GO:0006839~mitochondrial transport	1.671995789	0.001681752
GO_BP	GO:0010256~endomembrane system organization	1.620273697	0.000931164
GO_CC	GO:0098826~endoplasmic reticulum tubular network membrane	8.643268482	0.003000706
GO_CC	GO:0016442~RISC complex	8.643268482	$1.82167x10^{-5}$
GO_CC	GO:0031332~RNAi effector complex	7.857516802	$3.77133x10^{-5}$
GO_CC	GO:0070578~RISC-loading complex	6.402421098	0.002194285
GO_CC	GO:0035068~micro-ribonucleoprotein complex	6.402421098	0.002194285
GO_CC	GO:0070822~Sin3-type complex	4.501702335	0.003659919
GO_CC	GO:0000118~histone deacetylase complex	3.361271077	$4.74245x10^{-5}$
GO_CC	GO:0010494~cytoplasmic stress granule	2.946568801	0.002821387
GO_CC	GO:0017053~transcriptional repressor complex	2.776953729	0.000162963
GO_CC	GO:0005758~mitochondrial intermembrane space	2.585593136	0.000868033
GO_CC	GO:0031970~organelle envelope lumen	2.512578047	0.000786499
GO_CC	GO:0033116~endoplasmic reticulum-Golgi intermediate compartment membrane	2.330292973	0.006825256
GO_CC	GO:1904949~ATPase complex	2.145492177	0.005264245
GO_CC	GO:0005681~spliceosomal complex	1.878971409	0.002106866
GO_CC	GO:0000790~nuclear chromatin	1.525282673	0.007603835
GO_MF	GO:0015057~thrombin-activated receptor activity	8.437925446	0.003216346
GO_MF	GO:0070566~adenylyltransferase activity	4.101769314	0.001067008
GO_MF	GO:0035198~miRNA binding	4.101769314	0.001067008
GO_MF	GO:0004435~phosphatidylinositol phospholipase C activity	3.646017168	0.002269119
GO_MF	GO:0004629~phospholipase C activity	3.281415451	0.004314745
GO_MF	GO:0016409~palmitoyltransferase activity	2.960675595	0.004583709
GO_MF	GO:0030145~manganese ion binding	2.757491976	0.002784942
GO_MF	GO:0003727~single-stranded RNA binding	2.604297977	0.000523409
GO_MF	GO:0003725~double-stranded RNA binding	2.556947105	0.002162669
GO_MF	GO:0016779~nucleotidyltransferase activity	2.378336829	$8.54568x10^{-5}$
GO_MF	GO:0004620~phospholipase activity	2.296034135	0.001436734
GO_MF	GO:0061659~ubiquitin-like protein ligase activity	1.704631403	0.003951937
GO_MF	GO:0003714~transcription corepressor activity	1.702720381	0.004667508
GO_MF	GO:0019787~ubiquitin-like protein transferase activity	1.559181876	0.001050444
GO_MF	GO:0004842~ubiquitin-protein transferase activity	1.512519054	0.002965973
KEGG_Pathway	hsa04710~Circadian rhythm	3.384376215	0.003638013
KEGG_Pathway	hsa01040~Biosynthesis of unsaturated fatty acids	3.330655957	0.007593651
KEGG_Pathway	hsa04392~Hippo signaling pathway-multiple species	3.100955546	0.010882844
KEGG_Pathway	hsa00062~Fatty acid elongation	2.997590361	0.012857403
KEGG_Pathway	hsa03410~Base excision repair	2.725082147	0.020260061

Table SIII. Continued.

Category	Term	EnrichScore	P-value
KEGG_Pathway	hsa04962~Vasopressin-regulated water reabsorption	2.725082147	0.007788216
KEGG_Pathway	hsa00071~Fatty acid degradation	2.384446878	0.025119712
KEGG_Pathway	hsa05230~Central carbon metabolism in cancer	2.305838747	0.010316542
KEGG_Pathway	hsa01212~Fatty acid metabolism	2.262332348	0.023085505
KEGG_Pathway	hsa00562~Inositol phosphate metabolism	2.227938782	0.009450481
KEGG_Pathway	hsa05214~Glioma	2.110979128	0.018647127
KEGG_Pathway	hsa04115~ p53-signaling pathway	2.081659973	0.020412253
KEGG_Pathway	hsa04137~Mitophagy-animal	2.075254866	0.027583436
KEGG_Pathway	hsa03015~mRNA surveillance pathway	1.976433205	0.017235498
KEGG_Pathway	hsa05133~Pertussis	1.972098922	0.028702765

GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological process; CC, cellular component; MF, molecular function.