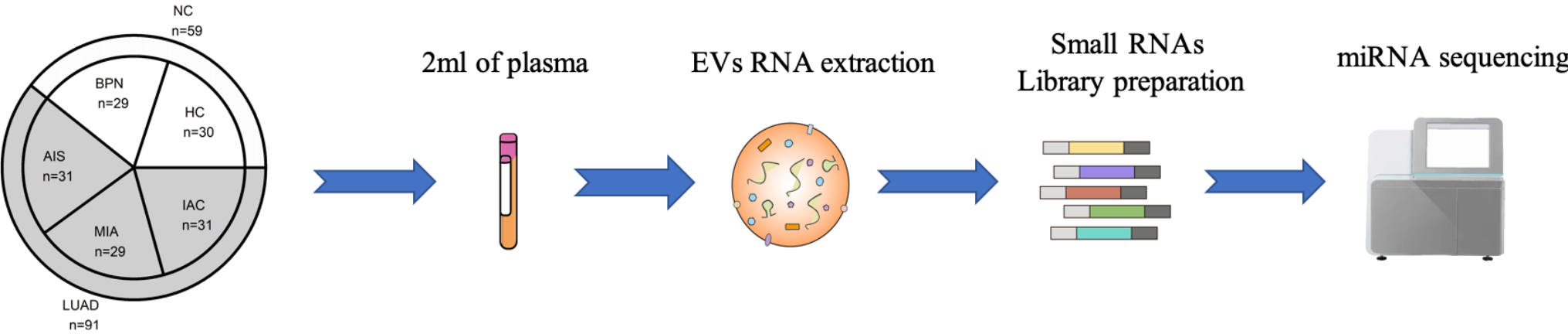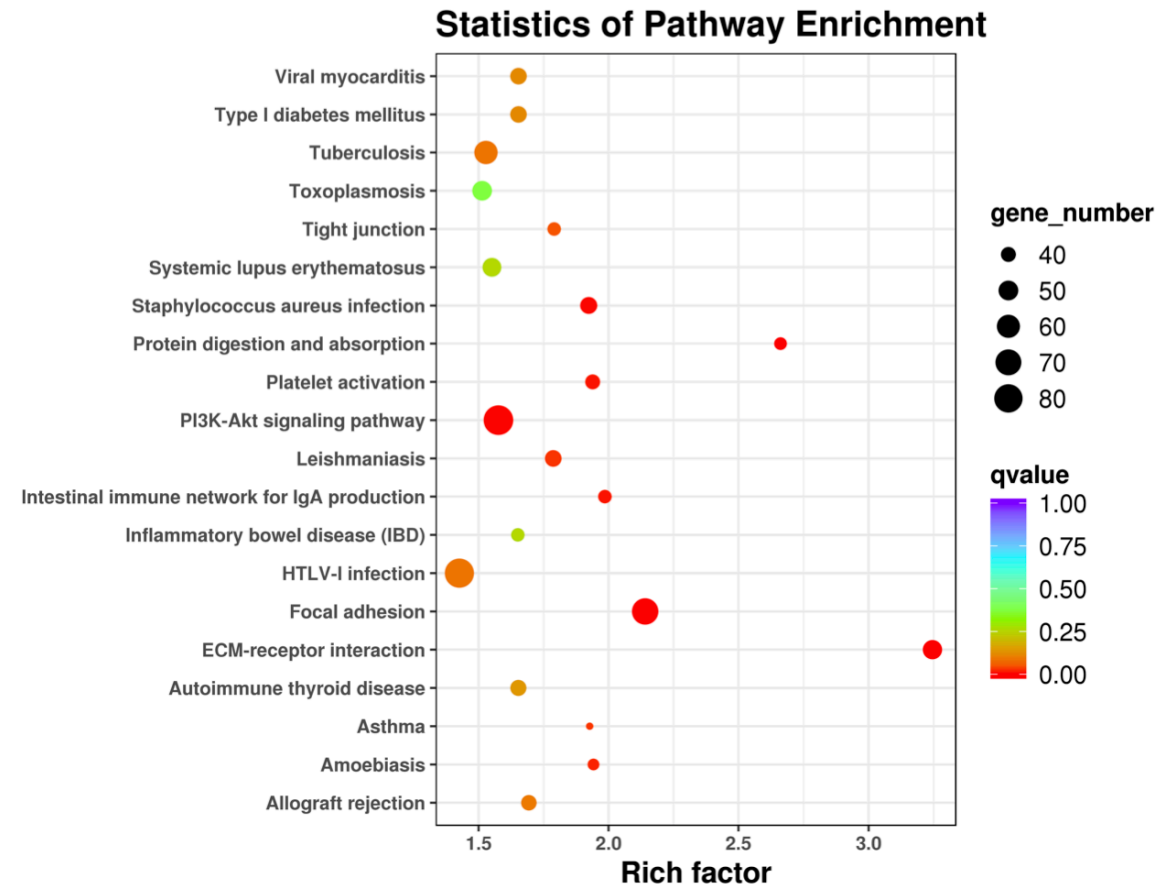# Figure S1 Work flow of exLR-seq of human plasma.

Figure S2 KEGG pathway analysis of the DEmiRs between LUAD patients and NCs.

Statistics of Pathway Enrichment

Figure S3 GO analysis of the DEmiRs between LUAD patients and NC. (A) Biological part; (B) Cellular part; (C) Molecular part.
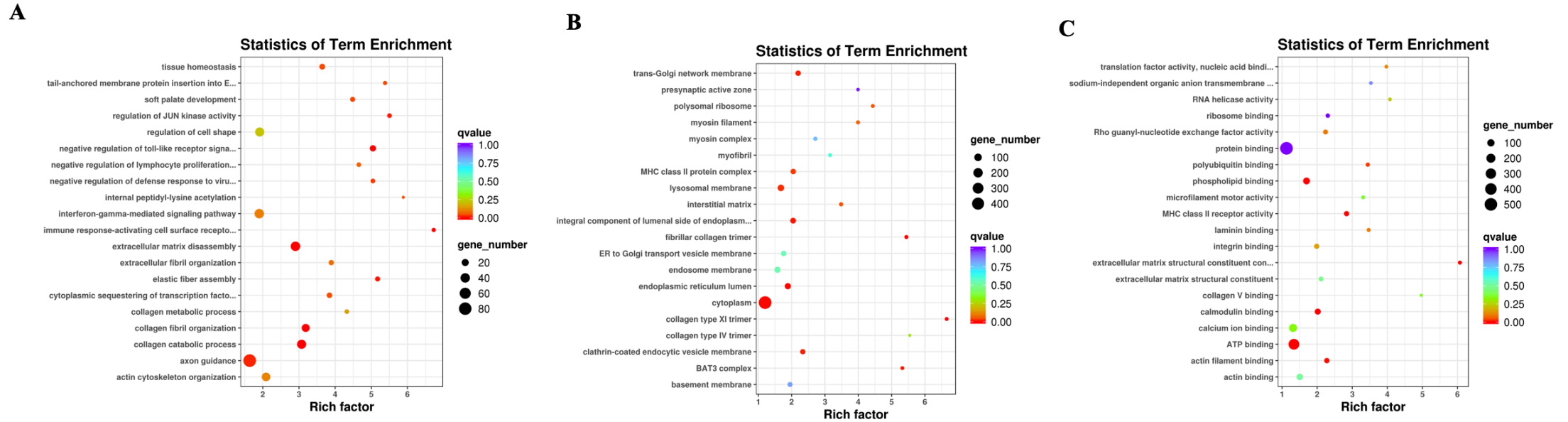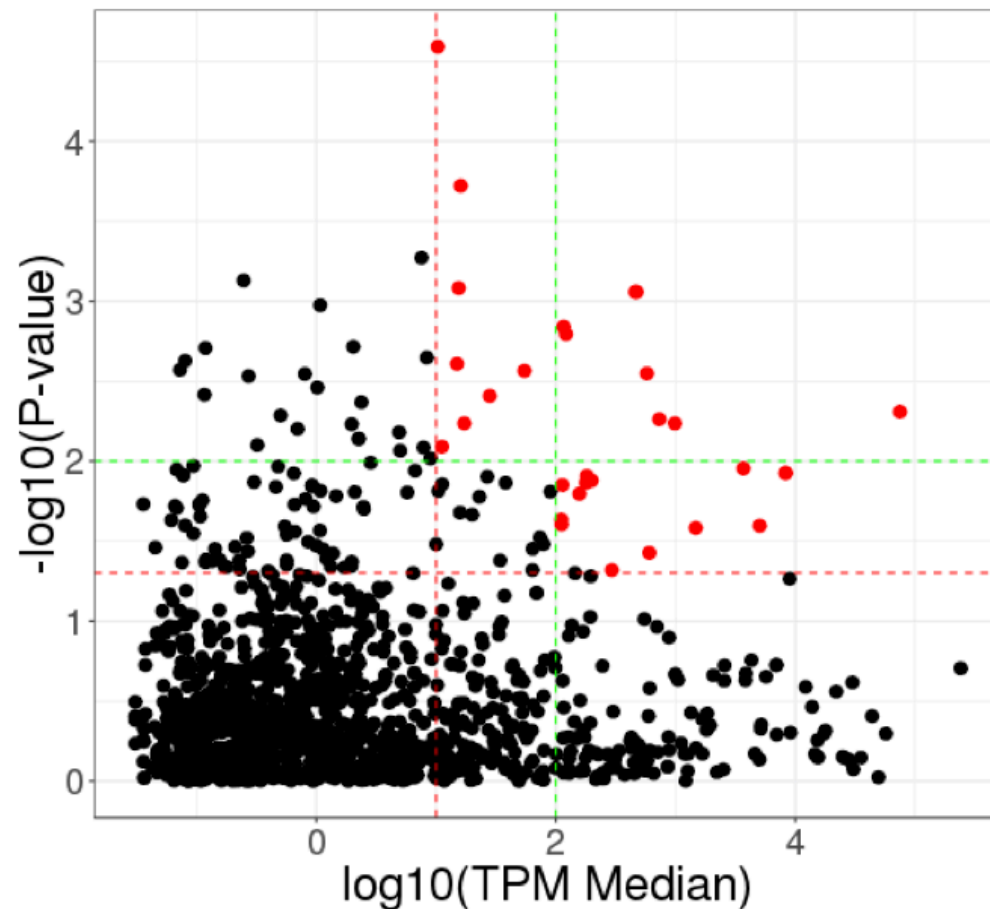
Figure S4 Candidate miRNAs selection from discovery cohort. Thirty miRNAs were chosen for further analysis based on differentially expressed gene analysis (Mann-Whitney U test , P < 0.01, mean TPM > 100).

Figure S5 KEGG pathway analysis of the DEmiRs between AIS, MIA, and IAC groups and the NC group.
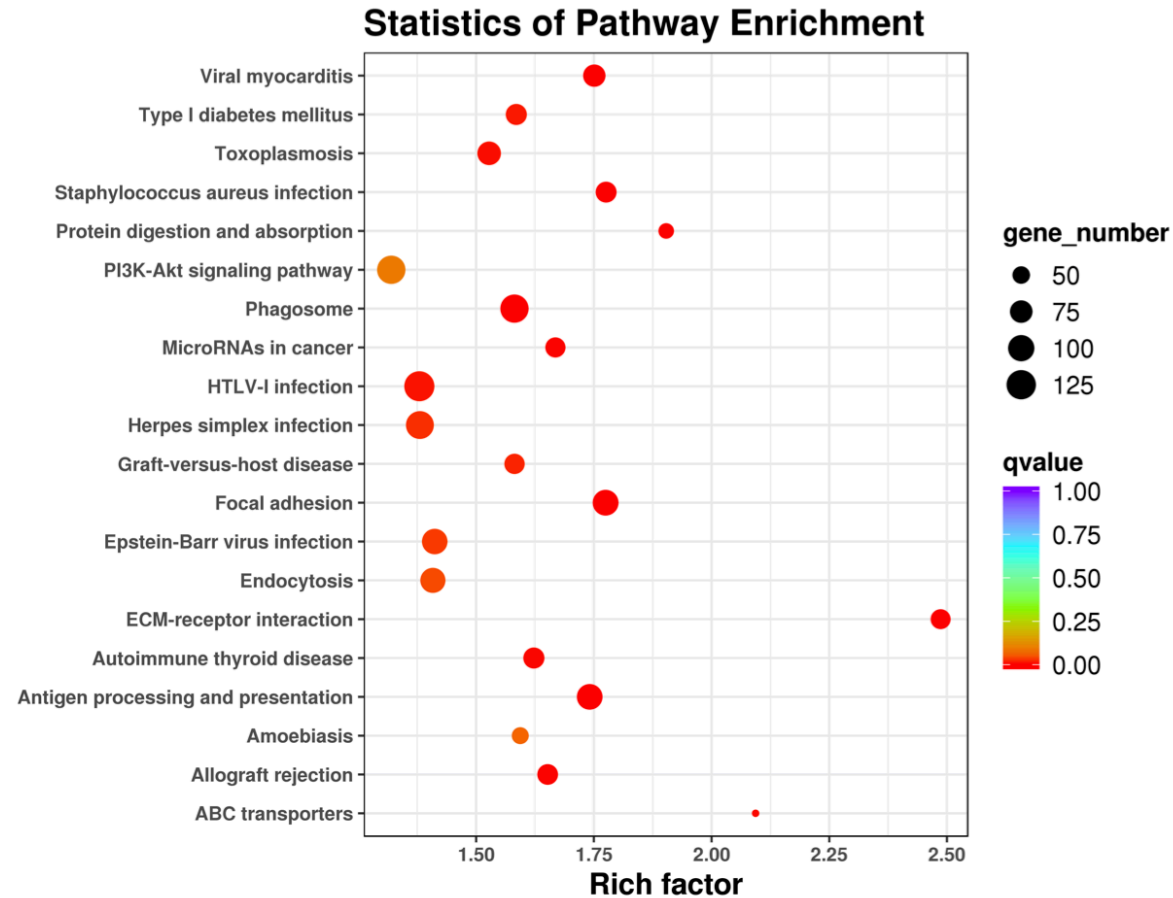
Figure S6 Candidate miRNAs selection from screen cohort. From these 30 miRNAs, eight targets (has-let-7b-3p, has-let-7d-3p, has-let-7f-2-3p, has-miR-501-3p, has-miR-500a-3p, has-miR-10b-5p, has-miR-19b-3p, and has-miR-29c-3p) were eliminated because of sequence similarity.
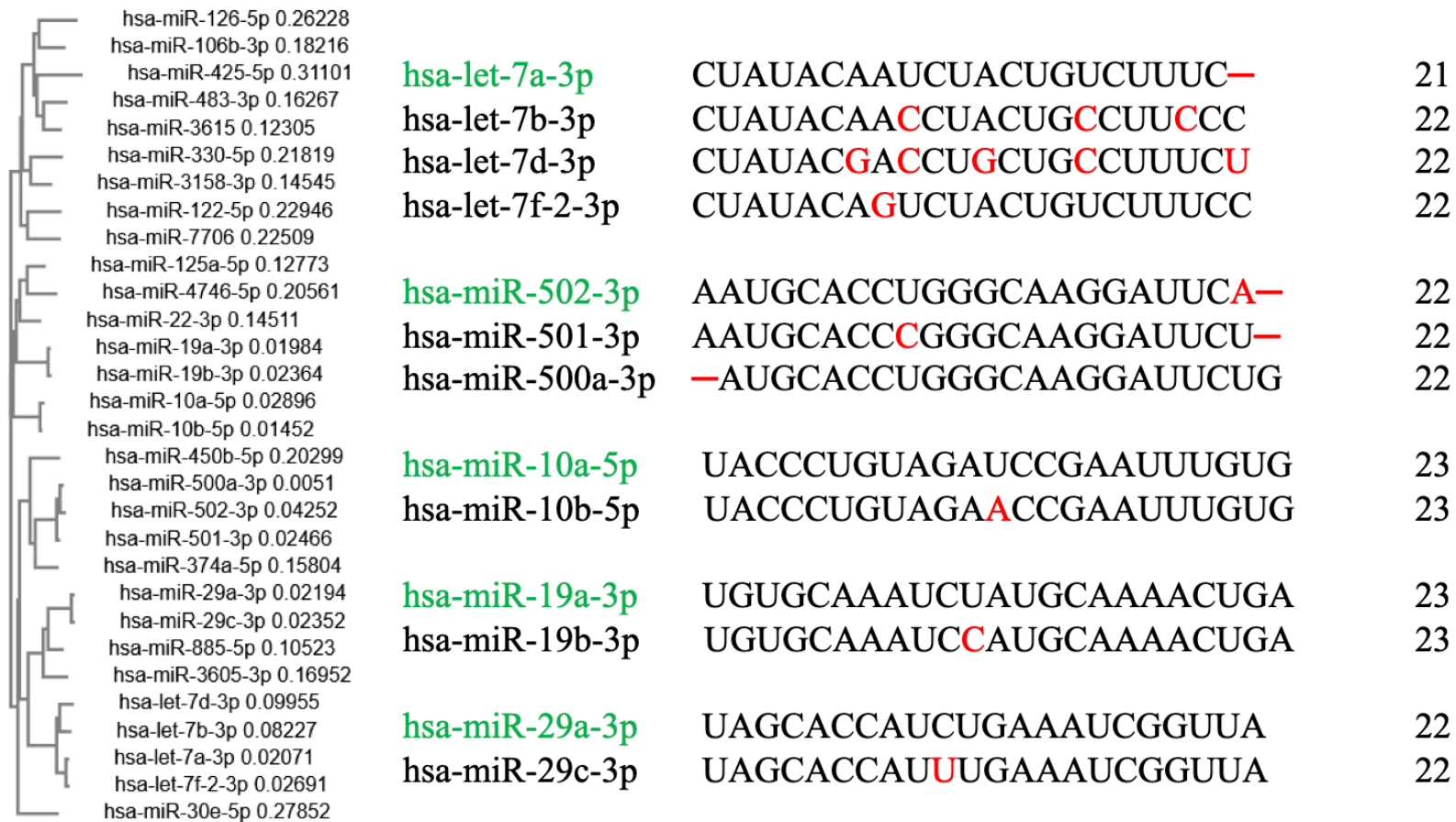
Figure S7

Workflow of the data generation and analysis. Diagnostic marker selection: Step-wise logistic regression was applied to a training cohort of 80 LUAD patients, 22 BPN patients, and 48 healthy subjects, leading to a final selection of 4 markers. These 4 markers were applied to a validation cohort of 53 LUAD patients, 15 BPN patients, and 32 healthy subjects.
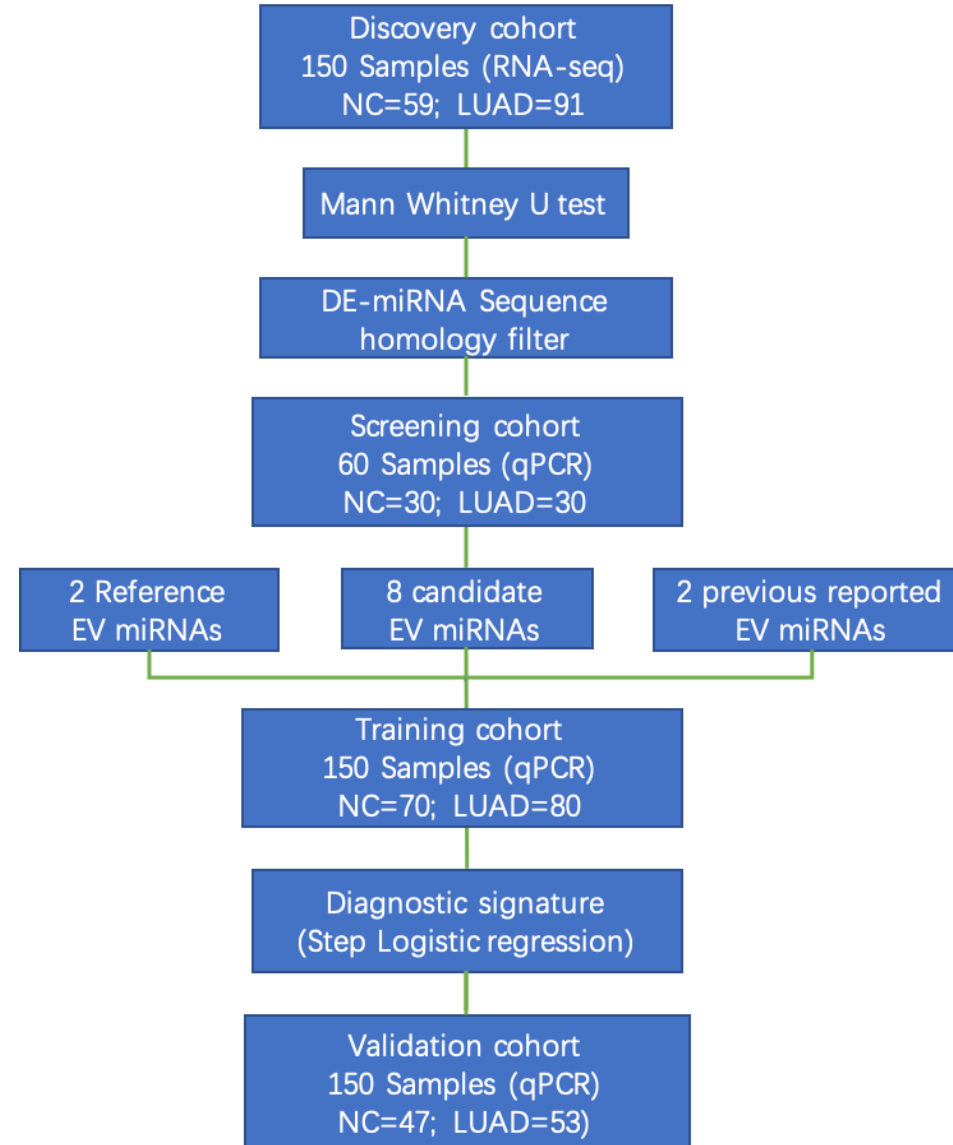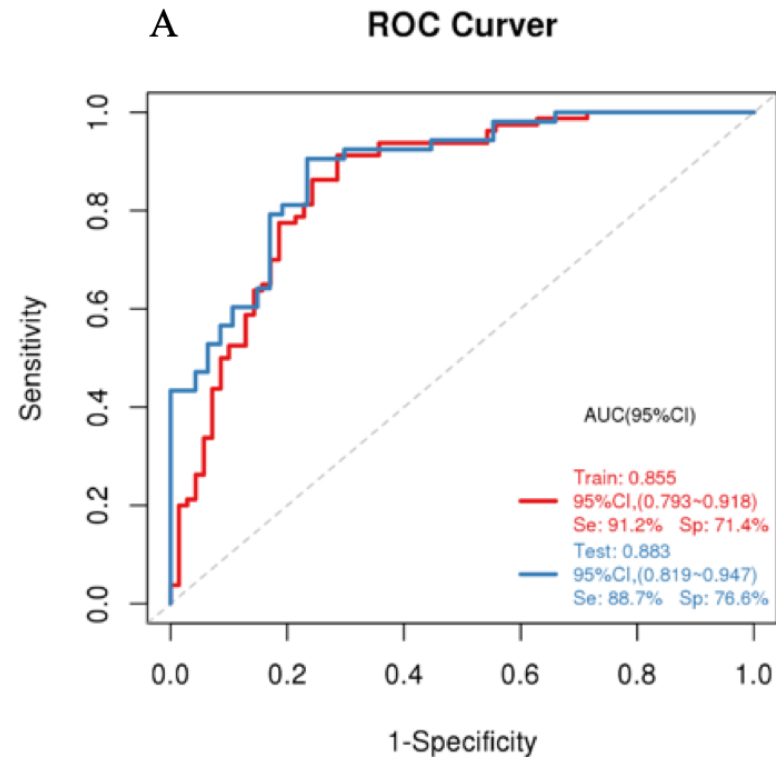
Figure S8 Establishment and validation of the EV miRNA d-signature for LUAD (miR-142-5p as reference gene).
(A) ROC analysis for performance of the EV miRNA d-signature in the training cohort, and validation cohort. (B) Confusion table for performance of the EV miRNA d-signature in the training cohort, and validation cohort.
LUAD, lung adenocarcinoma; ROC, receiver operating characteristic; EV, extracellular vesicle.

A ROC Curver

AUC(95%CI)

Train: 0.855
95%CI,(0.793~0.918)
Se: 91.2% Sp: 71.4%
Test: 0.883
95%CI,(0.819~0.947)
Se: 88.7% Sp: 76.6%

B miR-142-5p

	Trianning data set		Validation data set	
	Real LUAD	Real NC	Real LUAD	Real NC
Predict LUAD	73	20	47	11
Predict NC	7	50	6	36
Totals	80	70	53	47
Correct	73	50	47	36
Sensitivity	91.25%		88.68%	
Specificity		71.43%		76.60%

Figure S9 Gene targeting analysis.
(A) Gene ontology analysis of the 4 candidate EV miRNAs identified 2396 gene targets.
(B) Gene ontology analysis of these 2396 genes according to biological process (B), cellular component (C), and molecular function (D), and KEGG pathway analysis (E).