

Table S1 The search strategy summary

Items	Specification
Date of search	August 2024
Databases and other sources searched	PubMed
Search terms used	('lung cancer' 'biomarker' 'metabolite') AND ('blood' OR 'urine' OR 'sputum' OR 'bronchoalveolar lavage fluid' OR 'pleural effusion')
Timeframe	2014 to 2024
Inclusion and exclusion criteria	Full-text English articles were included. Articles were excluded if they focused on non-metabolite biomarkers, including tissue-based markers, circulating tumor cells, DNA, RNA, proteins, and extracellular vesicles.
Selection process	Initial selection was conducted by S.M.K. and J.Y., and verified by the other authors

DNA, deoxyribonucleic acid; RNA, ribonucleic acid.

Table S2 Metabolites upregulated/downregulated in lung cancer

Upregulated in LC		Downregulated in LC	
Metabolite	Comparison	Metabolite	Comparison
3-phosphoglyceric acid	NSCLC > healthy	2,4-dihydroxybenzoic acid	NSCLC < healthy
4-oxoproline	LC > healthy	16-hydroxyhexadecanoic acid	NSCLC < healthy
11,12-epoxy-icosatrienoic acid	NSCLC > healthy	Allyl laurate	NSCLC < healthy
Acetate	NSCLC > healthy	C(18:2)CE	NSCLC < healthy
Alanine	NSCLC > healthy	Choline	NSCLC < healthy
Arginine	NSCLC > healthy	Choline	NSCLC < healthy
Benzaldehyde	NSCLC > healthy	Ethylmalonic acid	NSCLC < healthy
β -hydroxybutyric acid	NSCLC > healthy	Gluconic acid	NSCLC < healthy
Bisphenol A	LC > healthy	Glucose	NSCLC < healthy
Cholesterol	NSCLC > healthy	Glutamine	NSCLC < healthy
Cholic acid	NSCLC > healthy	Glutamine	NSCLC < healthy
Citric acid	NSCLC > healthy	Glycerol	NSCLC < healthy
D-arabinose	NSCLC > healthy	Glycine	NSCLC < healthy
ePE(40:4)	NSCLC > healthy	Glycolic acid	NSCLC < healthy
Fumaric acid	NSCLC > healthy	Glycolic acid	NSCLC < healthy
Glucose	NSCLC > healthy	Heptadecanoic acid	LC < healthy
Glutamate	NSCLC > healthy	L-isoleucine	NSCLC < healthy
Glutamic acid	NSCLC > healthy	L-phenylalanine	NSCLC < healthy
Glycoprotein	NSCLC > healthy	L-proline	LC < healthy
Glycoursodeoxycholic acid	NSCLC > healthy	Linoleic acid	NSCLC < healthy
GpAEA	LC > healthy	Lactone	NSCLC < healthy
Hydroxypyruvic acid	NSCLC > healthy	Linolenic acid	NSCLC < healthy
Hypoxanthine	NSCLC > healthy	LPC 16:0	NSCLC < healthy
Lactate	NSCLC > healthy	LPC 18:0	NSCLC < healthy
LPC 20:3	NSCLC > healthy	LPC 18:1	NSCLC < healthy
LPE(18:1)	NSCLC > healthy	LPC 18:2	NSCLC < healthy
Maltose	NSCLC > healthy	Palmitic acid	LC < healthy
Methanol	NSCLC > healthy	PC ae C40:6	NSCLC < healthy
Methionine	NSCLC > healthy	Phosphocreatine	NSCLC < healthy
Ornithine	LC > healthy	Piperine	NSCLC < healthy
Palmitic acid	NSCLC > healthy	Retinol	LC < healthy
Phenylalanine	NSCLC > healthy	SM(22:0)	NSCLC < healthy
Proline	NSCLC > healthy	Sphingosine	LC < healthy
Pyruvate	NSCLC > healthy	Taurine	NSCLC < healthy
Taurine	NSCLC > healthy	Testosterone sulfate	NSCLC < healthy
Tryptophan	NSCLC > healthy	Threonine	NSCLC < healthy
Tryptophan	NSCLC > healthy	Threonine	NSCLC < healthy
Tyrosine	NSCLC > healthy	Tridecanoic acid	LC < healthy
Tyrosine	NSCLC > healthy		

LC, lung cancer; NSCLC, non-small cell lung cancer; ePE, phosphatidyl ethanolamine with one ether-linked; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; ae, acyl ether; LPC, lysophosphatidylcholines; SM, sphingomyelin; CE, cholesterol esters; GpAEA, glycerophospho-N-arachidonoyl ethanolamine.

Table S3 Significant metabolic pathway identified in lung cancer using MetaboAnalyst

Upregulated metabolic pathway	Expected value	P value	Associated metabolites
Arginine and proline metabolism	0.538	0.000131	Arginine, proline, ornithine, 4-oxoproline
Phenylalanine, tyrosine and tryptophan biosynthesis	0.0598	0.00126	Phenylalanine, tyrosine, tryptophan, benzaldehyde
Citrate cycle (TCA cycle)	0.299	0.00282	Citric acid, fumaric acid, pyruvate, glutamate/glutamic acid, lactate
Pyruvate metabolism	0.344	0.00425	Pyruvate, lactate, alanine, hydroxypyruvic acid
Phenylalanine metabolism	0.12	0.00567	Phenylalanine, tyrosine, benzaldehyde
Butanoate metabolism	0.224	0.0199	β -hydroxybutyric acid, acetate
Tyrosine metabolism	0.628	0.0229	Tyrosine, taurine
Starch and sucrose metabolism	0.269	0.0283	Glucose, maltose, D-arabinose
Primary bile acid biosynthesis	0.687	0.0291	Cholic acid, glyoursodeoxycholic acid, cholesterol
Neomycin, kanamycin and gentamicin biosynthesis	0.0299	0.0297	Glucose, glutamate/glutamic acid, pyruvate (indirectly related to this metabolic pathway)
Downregulated metabolic pathway	Expected value	P value	Associated metabolites
Valine, leucine and isoleucine biosynthesis	0.0936	0.00347	L-isoleucine, ethylmalonic acid, glutamine, threonine
Glycine, serine and threonine metabolism	0.386	0.00589	Glycine, threonine, glutamine, glycolic acid, phosphocreatine
Biosynthesis of unsaturated fatty acids	0.421	0.00754	Linoleic acid, linolenic acid, palmitic acid, 16-hydroxyhexadecanoic acid
Neomycin, kanamycin and gentamicin biosynthesis	0.0234	0.0233	Glucose, glutamine (indirectly related to this metabolic pathway)
Galactose metabolism	0.316	0.0382	Glucose, gluconic acid, glycerol
Phenylalanine, tyrosine and tryptophan biosynthesis	0.0468	0.046	L-phenylalanine, retinol, taurine
Glyoxylate and dicarboxylate metabolism	0.363	0.0492	Glycine, glycolic acid, palmitic acid

TCA, tricarboxylic acid cycle.