**Table S1.** Plasma differential metabolites between NSCLC and HC groups.

|  |  |  |  |
| --- | --- | --- | --- |
| Metabolites | NSCLC (n=141) | HC (n=54) | P-value |
| Pyruvate | 5.86±0.42 | 6.09±0.12 | 3.23E-09 |
| Glycolic acid | 4.58±0.18 | 4.52±0.12 | 1.45E-02 |
| 3-Hydroxybutyric acid | 5.28±0.36 | 5.49±0.32 | 2.06E-04 |
| Monomethylphosphate | 5.21±0.15 | 5.27±0.16 | 2.31E-02 |
| Succinate | 4.27±0.18 | 4.38±0.12 | 1.31E-06 |
| Glyceric acid | 4.66±0.31 | 4.56±0.09 | 1.88E-04 |
| Nonanoic acid | 4.29±0.1 | 4.25±0.06 | 1.08E-02 |
| Aspartate | 5.97±0.35 | 5.81±0.16 | 9.78E-06 |
| Cysteine | 5.36±0.33 | 5.59±0.09 | 5.54E-13 |
| 2-Ketoglutaric Acid | 4.35±0.29 | 4.24±0.23 | 1.35E-02 |
| Glutamate | 6.09±0.36 | 5.96±0.18 | 1.13E-02 |
| Lauric acid | 4.46±0.17 | 4.52±0.17 | 1.85E-02 |
| Glycerol-3-phospahte | 4.64±0.23 | 4.53±0.18 | 1.29E-03 |
| Hypoxanthine | 5.02±0.54 | 4.36±0.46 | 1.31E-13 |
| Fructose | 4.92±0.35 | 5±0.11 | 1.91E-02 |
| Glucose | 6.32±0.54 | 6.44±0.06 | 7.70E-03 |
| Xanthine | 4.05±0.31 | 3.95±0.15 | 2.27E-03 |
| Palmitic acid | 6.31±0.11 | 6.35±0.11 | 3.97E-02 |
| Linoleic acid | 5.71±0.15 | 5.76±0.11 | 2.12E-02 |
| Stearic acid | 6.03±0.09 | 6.08±0.11 | 1.59E-03 |
| Alpha-Tocopherol | 5.42±0.58 | 5.76±0.12 | 8.41E-11 |

Values are presented with Mean±SD.

**Table S2**. Serum differential metabolites between NSCLC and HC groups.

|  |  |  |  |
| --- | --- | --- | --- |
| Metabolites | NSCLC (n=131) | HC (n=49) | P-value |
| Lactate | 6.57±0.17 | 6.33±0.12 | 1.46E-19 |
| Glycine | 4.98±0.12 | 4.87±0.10 | 9.95E-08 |
| 3-Hydroxybutyric acid | 4.93±0.30 | 5.12±0.28 | 1.97E-04 |
| Urea | 5.04±0.12 | 4.97±0.10 | 5.50E-05 |
| Leucine | 6.17±0.20 | 6.09±0.10 | 9.62E-03 |
| Isoleucine | 5.83±0.16 | 5.75±0.11 | 9.87E-04 |
| Proline | 5.41±0.43 | 5.15±0.36 | 1.62E-04 |
| Succinate | 4.06±0.14 | 3.93±0.10 | 1.29E-10 |
| Uracil | 3.46±0.22 | 3.38±0.14 | 1.03E-02 |
| Glyceric acid | 4.53±0.16 | 4.44±0.12 | 1.75E-03 |
| Fumarate | 4.33±0.17 | 4.24±0.17 | 1.48E-03 |
| Serine | 5.92±0.19 | 5.83±0.09 | 6.54E-04 |
| Threonine | 5.59±0.18 | 5.51±0.11 | 8.56E-03 |
| Aminomalonic acid | 4.87±0.24 | 4.69±0.29 | 3.30E-05 |
| Malate | 4.00±0.27 | 3.74±0.16 | 1.33E-12 |
| Aspartate | 5.33±0.24 | 5.10±0.09 | 1.14E-17 |
| Methionine | 5.09±0.17 | 5.03±0.11 | 2.64E-02 |
| Pyroglutamate | 6.51±0.09 | 6.43±0.07 | 3.49E-09 |
| Threonic acid | 4.47±0.20 | 4.37±0.23 | 5.29E-03 |
| Creatinine | 4.30±0.21 | 4.21±0.20 | 6.44E-03 |
| Glutamate | 5.81±0.28 | 5.47±0.14 | 8.48E-21 |
| Phenylalanine | 5.71±0.17 | 5.59±0.09 | 2.12E-06 |
| Asparagine | 4.65±0.20 | 4.46±0.18 | 1.13E-08 |
| Lyxose | 4.19±0.40 | 3.74±0.26 | 4.82E-15 |
| Hypoxanthine | 5.21±0.34 | 4.57±0.17 | 9.80E-37 |
| Ornithine | 5.75±0.17 | 5.52±0.18 | 7.32E-13 |
| Histidine | 4.84±0.15 | 4.90±0.06 | 2.54E-04 |
| Glucose | 6.26±0.41 | 6.38±0.06 | 7.99E-04 |
| Tyrosine | 5.87±0.16 | 5.81±0.19 | 3.98E-02 |
| Myo-Inositol | 5.07±0.11 | 4.92±0.09 | 1.50E-14 |
| Fructose-6-Phosphate | 4.07±0.10 | 4.03±0.09 | 1.25E-02 |
| Myo-Inositol-2-phosphate | 4.34±0.13 | 4.28±0.12 | 1.30E-02 |
| Inosine | 3.86±0.62 | 3.27±0.31 | 2.84E-14 |
| Glucopyranose | 4.79±0.27 | 4.90±0.13 | 3.44E-04 |
| 1-Monooleoylglycerol | 4.11±0.17 | 4.22±0.20 | 1.80E-04 |
| 2-Hydroxybutyric acid | 5.52±0.16 | 5.57±0.13 | 3.83E-02 |

Values are presented with Mean±SD.

**Table S3.** ROC analysis results of co-existing metabolites in HC and NSCLC.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sample type | Metabolites | AUROC | 95%CI | Sensitivity | Specificity |
| **Plasma** | 3-Hydroxybutyric acid | 0.68  | 0.60-0.76 | 6.00% | 94.44% |
|  | Succinate | 0.76  | 0.69-0.82 | 4.67% | 96.30% |
|  | Glyceric acid | 0.77  | 0.70-0.83 | 56.67% | 94.44% |
|  | Aspartate | 0.74  | 0.67-0.80 | 62.67% | 90.74% |
|  | Glutamate | 0.73  | 0.66-0.81 | 66.67% | 72.22% |
|  | Hypoxanthine | 0.86  | 0.80-0.92 | 79.33% | 90.74% |
|  | Glucose | 0.54  | 0.46-0.62 | 50.00% | 70.37% |
|  |  |  |  |  |  |
| **Serum** | 3-Hydroxybutyric acid | 0.72  | 0.64-0.81 | 1.83% | 100.00% |
|  | Succinate | 0.80  | 0.73-0.87 | 60.55% | 93.18% |
|  | Glyceric acid | 0.65  | 0.56-0.74 | 44.95% | 84.09% |
|  | Aspartate | 0.93  | 0.89-0.97 | 84.40% | 90.91% |
|  | Glutamate | 0.89  | 0.84-0.94 | 73.39% | 93.18% |
|  | Hypoxanthine | 0.99  | 0.98-1.00 | 92.66% | 97.73% |
|  | Glucose | 0.61  | 0.52-0.70 | 2.75% | 100.00% |

**Table S4.** Plasma differential metabolites in HC, AdC and SqCC.

|  |  |  |  |
| --- | --- | --- | --- |
| Metabolites | HC (n=54) | AdC (n=106) | SqCC (n=35) |
| Alpha-Tocopherolabc | 5.76±0.12 | 5.49±0.54 | 5.11±0.70 |
| Pyruvateab | 6.09±0.12 | 5.88±0.42 | 5.78±0.47 |
| 3-Hydroxybutyric acidab | 5.49±0.32 | 5.29±0.33 | 5.21±0.38 |
| Cysteineab | 5.59±0.09 | 5.37±0.37 | 5.33±0.20 |
| Glutamateab | 5.96±0.18 | 6.07±0.35 | 6.14±0.46 |
| Hypoxanthineab | 4.36±0.46 | 5.00±0.56 | 5.06±0.51 |
| Stearic acidab | 6.08±0.11 | 6.04±0.08 | 6.00±0.12 |
| Glycolic acida | 4.52±0.12 | 4.59±0.16 | 4.59±0.24 |
| Monomethylphosphatea | 5.27±0.16 | 5.20±0.14 | 5.24±0.18 |
| Succinatea | 4.38±0.12 | 4.26±0.17 | 4.31±0.23 |
| Glyceric acida | 4.56±0.09 | 4.67±0.31 | 4.62±0.37 |
| Nonanoic acida | 4.25±0.06 | 4.30±0.11 | 4.28±0.11 |
| Aspartateac | 5.81±0.16 | 6.04±0.28 | 5.86±0.44 |
| 2-Ketoglutaric Acida | 4.24±0.23 | 4.35±0.29 | 4.35±0.30 |
| Glycerol-3-phospahtea | 4.53±0.18 | 4.66±0.22 | 4.59±0.30 |
| Fructosea | 5.00±0.11 | 4.92±0.33 | 4.90±0.43 |
| Glucosea | 6.44±0.06 | 6.31±0.58 | 6.31±0.53 |
| Xanthinea | 3.95±0.15 | 4.06±0.30 | 4.03±0.37 |
| 3-Hydroxyisobutyric acidb | 4.04±0.15 | 4.00±0.20 | 3.95±0.17 |
| 2-keto-3-methylvaleric acidbc | 4.89±0.14 | 4.87±0.23 | 4.77±0.25 |
| Ureab | 5.21±0.10 | 5.24±0.10 | 5.26±0.12 |
| Serineb | 5.07±0.22 | 5.04±0.24 | 4.96±0.21 |
| Aminomalonic acidb | 5.57±0.15 | 5.62±0.28 | 5.65±0.18 |
| Lauric acidbc | 4.52±0.17 | 4.49±0.17 | 4.38±0.13 |
| Glutamineb | 6.65±0.08 | 6.62±0.13 | 6.56±0.18 |
| Citrateb | 6.25±0.11 | 6.22±0.34 | 6.13±0.44 |
| Palmitic acidbc | 6.35±0.11 | 6.32±0.11 | 6.26±0.13 |
| Linoleic acidbc | 5.76±0.11 | 5.73±0.13 | 5.63±0.16 |
| Monopalmitinc | 4.95±0.11 | 4.98±0.11 | 4.93±0.12 |

Values are presented with Mean±SD, a, b, and c respectively represent significant differences in AdC vs. HC, SqCC vs. HC, and AdC vs. SqCC.

**Table S5.** Serum differential metabolites in HC, AdC and SqCC.

|  |  |  |  |
| --- | --- | --- | --- |
| Metabolites | HC (n=49) | AdC (n=107) | SqCC (n=24) |
| 3-Hydroxybutyric acidabc | 5.12±0.28 | 4.96±0.30 | 4.78±0.24 |
| Aspartateabc | 5.10±0.09 | 5.30±0.25 | 5.45±0.16 |
| Cysteineabc | 4.73±0.12 | 4.80±0.24 | 4.65±0.11 |
| Phenylalanineabc | 5.59±0.09 | 5.69±0.17 | 5.78±0.10 |
| Citrateabc | 5.29±0.10 | 5.33±0.14 | 5.23±0.15 |
| Ornithineabc | 5.52±0.18 | 5.74±0.18 | 5.82±0.15 |
| Lactateab | 6.33±0.12 | 6.57±0.17 | 6.60±0.15 |
| Glycineab | 4.87±0.10 | 4.97±0.12 | 4.99±0.12 |
| Ureaab | 4.97±0.10 | 5.04±0.11 | 5.07±0.14 |
| Leucineab | 6.09±0.10 | 6.16±0.22 | 6.20±0.11 |
| Isoleucineab | 5.75±0.11 | 5.82±0.17 | 5.86±0.13 |
| Prolineab | 5.15±0.36 | 5.41±0.44 | 5.43±0.36 |
| Succinateab | 3.93±0.10 | 4.06±0.13 | 4.08±0.14 |
| Serineab | 5.83±0.09 | 5.92±0.20 | 5.93±0.10 |
| Threonineab | 5.51±0.11 | 5.58±0.20 | 5.59±0.09 |
| Malateab | 3.74±0.16 | 4.00±0.28 | 3.98±0.19 |
| Pyroglutamateab | 6.43±0.07 | 6.51±0.09 | 6.52±0.06 |
| Glutamateab | 5.47±0.14 | 5.79±0.29 | 5.91±0.20 |
| Asparagineab | 4.46±0.18 | 4.65±0.21 | 4.65±0.14 |
| Lyxoseab | 3.74±0.26 | 4.17±0.38 | 4.28±0.50 |
| Hypoxanthineab | 4.57±0.17 | 5.21±0.34 | 5.20±0.33 |
| Myo-Inositolab | 4.92±0.09 | 5.07±0.12 | 5.06±0.09 |
| Fructose-6-Phosphateab | 4.03±0.09 | 4.07±0.11 | 4.08±0.08 |
| Inosineab | 3.27±0.31 | 3.85±0.59 | 3.94±0.73 |
| Phosphatea | 5.40±0.13 | 5.49±0.28 | 5.41±0.13 |
| Uracila | 3.38±0.14 | 3.46±0.22 | 3.45±0.20 |
| Glyceric acida | 4.44±0.12 | 4.54±0.15 | 4.48±0.22 |
| Fumarateac | 4.24±0.17 | 4.34±0.17 | 4.26±0.15 |
| Aminomalonic acida | 4.69±0.29 | 4.89±0.23 | 4.78±0.26 |
| Threonic acida | 4.37±0.23 | 4.49±0.21 | 4.40±0.17 |
| Creatininea | 4.21±0.20 | 4.30±0.21 | 4.30±0.19 |
| Histidinea | 4.90±0.06 | 4.84±0.16 | 4.88±0.08 |
| Glucosea | 6.38±0.06 | 6.23±0.45 | 6.36±0.09 |
| Myo-Inositol-2-phosphatea | 4.28±0.12 | 4.34±0.12 | 4.35±0.18 |
| Monopalmitina | 4.88±0.12 | 4.85±0.08 | 4.92±0.35 |
| Glucopyranosea | 4.90±0.13 | 4.77±0.29 | 4.89±0.16 |
| 1-Monooleoylglycerola | 4.22±0.20 | 4.10±0.16 | 4.15±0.20 |
| Valineb | 5.49±0.10 | 5.53±0.25 | 5.55±0.12 |
| Methionineb | 5.03±0.11 | 5.08±0.18 | 5.14±0.08 |
| Lauric acidbc | 4.16±0.24 | 4.17±0.22 | 4.03±0.21 |
| Lysineb | 5.29±0.17 | 5.35±0.23 | 5.40±0.12 |
| Linoleic acidbc | 5.38±0.13 | 5.37±0.14 | 5.29±0.12 |
| Oleic acidc | 5.58±0.15 | 5.58±0.17 | 5.49±0.19 |
| Oleamidec | 4.10±0.76 | 4.21±0.78 | 3.83±0.81 |

Values are presented with Mean±SD, a, b, and c respectively represent significant differences in AdC vs. HC, SqCC vs. HC, and AdC vs. SqCC.