# Supplementary materials

**Table S1.** Demographic characteristics and clinical factors for each subgroup.

| Subgroup | | Stage I (n=47) | | Stage II (n=86) | | Stage III (n=64) | |
|---|---|---|---|---|---|---|---|
| | | RCC (n=22) | LCC (n=25) | RCC (n=44) | LCC (n=42) | RCC (n=32) | LCC (n=32) |
| **Sex, n** | Males | 10 | 15 | 23 | 25 | 15 | 14 |
| | Females | 12 | 10 | 21 | 17 | 17 | 18 |
| **Age, y, mean (SD)** | Males | 73.9 (6.5) | 69.3 (5.8) | 72.9 (7.8) | 72.2 (8.5) | 73.5 (7.8) | 63.7 (5.8) |
| | Females | 72.1 (6.2) | 69.6 (7.6) | 73.5 (9.8) | 69.1 (7.8) | 72.2 (6.6) | 71.1 (6.0) |
| **Race/Ethnicity, n** | NHWs | 20 | 22 | 40 | 37 | 26 | 25 |
| | Hispanic | 2 | 3 | 2 | 3 | 4 | 2 |
| | AA | 0 | 0 | 1 | 0 | 1 | 4 |
| | API | 0 | 0 | 1 | 2 | 1 | 1 |
| ***KRAS* mutation, n** | Wild type | 7 | 14 | 24 | 21 | 16 | 19 |
| | Mutant | 8 | 8 | 12 | 13 | 10 | 9 |
| | Unknown | 7 | 3 | 8 | 8 | 6 | 4 |
| ***BRAF* mutation, n** | Wild type | 13 | 19 | 20 | 30 | 18 | 27 |
| | Mutant | 0 | 0 | 9 | 1 | 8 | 0 |
| | Unknown | 9 | 6 | 15 | 11 | 6 | 5 |
| **Microsatellite instability status, n** | MSS | 10 | 16 | 17 | 27 | 15 | 17 |
| | MSI | 5 | 4 | 17 | 4 | 10 | 8 |
| | Unknown | 7 | 5 | 10 | 11 | 7 | 7 |
| **5-year Overall survival rate, %[a]** | Males | 87.5 | 85.1 | 76.5 | 74.1 | 47.1 | 78.6 |
| | Females | 100 | 100 | 82.9 | 100 | 65.2 | 61.8 |
| **5-year Recurrence-free survival rate, %[a]** | Males | 90.0 | 78.3 | 86.8 | 67.6 | 82.1 | 70.1 |
| | Females | 90.9 | 100.0 | 87.5 | 87.4 | 76.0 | 68.8 |

RCC: right-sided colon cancer, LCC: left-sided colon cancer, NHWs: non-Hispanic whites, AA: African-Americans, API: Asian-Pacific Islander, MSI; microsatellite instable, MSS; microsatellite stable. [a] The survival rates were calculated using the Kaplan-Meier estimation method.

**Table S2.** Prognosis of patients in early stage (Stage I and II) vs late stage (Stage III).

| 5-year Overall Survival (OS) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Subgroup** | **RCC males** | | **RCC females** | | **LCC males** | | **LCC females** | |
| **Event[a]** | **0** | **1** | 0 | 1 | 0 | 1 | 0 | 1 |
| **Early stage[b]** | 28 | 5 | 30 | 3 | 32 | 8 | 27 | 0 |
| **Late stage[c]** | 8 | 7 | 12 | 5 | 11 | 3 | 12 | 6 |
| **Total** | 36 | 12 | 42 | 8 | 43 | 11 | 39 | 6 |
| **5-year Recurrence-free Survival (RFS)** | | | | | | | | |
| **Subgroup** | **RCC males** | | **RCC females** | | **LCC males** | | **LCC females** | |
| **Event[d]** | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 |
| **Early stage[b]** | 30 | 3 | 30 | 3 | 32 | 8 | 25 | 2 |
| **Late stage[c]** | 13 | 2 | 14 | 3 | 10 | 4 | 13 | 5 |
| **Total** | 43 | 5 | 44 | 6 | 42 | 12 | 38 | 7 |

[a] Event = death. Event =1 represents that death occurred within 5 years of follow-up, and event = 0 indicates the event did not occur within 5 years of follow-up (survived or scored as censored). [b] Early stage combines stage I and II together. [c] Late stage refers to stage III. [d] Event = recurrence. Event = 1 indicates that recurrence occurred within 5 years of follow-up, event = 0 indicates that recurrence did not occur within 5 years of follow-up. If a patient died before CRC recurrence occurred, it is counted towards a death event.

Notes:

If a patient died for any reason without recurrence within 5 years of follow-up, it is only counted toward a death event in OS.

If a patient experienced recurrence but did not die within 5 years of follow-up, it is only counted toward a recurrence event in RFS.

If a patient experienced recurrence and then died within 5 years of follow-up, it is counted toward a recurrence event in RFS and a death event in OS.

If a patient experienced neither recurrence nor death within 5 years of follow-up, the event is 0 for both OS and RFS.

Due to the absence of death events in females of clinical stage I, we regarded stage I and II as early stage, and stage III as late stage.

**Table S3.** Multivariate analyses of the associations between individual metabolites and 5-year OS by sex, adjusted for anatomic location, chemotherapy history, clinical stages, and age.

| Metabolite name | Females | | | Males | | | Int. Sex *P* value[b] |
|---|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* value[a] | HR | 95% CI | *P* value[a] | |
| **Acetyl-lysine** | 0.97 | 0.75–1.25 | 0.809 | 0.82 | 0.71–0.96 | 0.012 | 0.298 |
| Adenosine | 0.90 | 0.69–1.17 | 0.421 | 1.29 | 1.03–1.62 | 0.026 | 0.038 |
| Alanine | 1.06 | 0.78–1.44 | 0.705 | 0.77 | 0.61–0.98 | 0.034 | 0.092 |
| Argininosuccinic acid | 0.93 | 0.71–1.23 | 0.629 | 0.74 | 0.58–0.93 | 0.010 | 0.151 |
| Asparagine | 1.51 | 0.89–2.57 | 0.127 | 0.72 | 0.54–0.96 | 0.025 | 0.026 |
| Carnitine | 0.61 | 0.04–9.10 | 0.717 | 0.53 | 0.30–0.94 | 0.031 | 0.897 |
| Citrulline | 1.66 | 0.97–2.83 | 0.065 | 0.65 | 0.46–0.92 | 0.014 | 0.002 |
| Glycerol 3-phosphate | 3.64 | 1.26–10.49 | 0.017 | 0.91 | 0.47–1.77 | 0.777 | 0.018 |
| Hypoxanthine | 1.05 | 0.35–3.14 | 0.929 | 0.65 | 0.44–0.95 | 0.027 | 0.441 |
| LysoPC(16:0) | 1.52 | 1.03–2.25 | 0.035 | 0.85 | 0.65–1.11 | 0.242 | 0.009 |
| Ornithine | 0.97 | 0.56–1.66 | 0.904 | 0.68 | 0.47–0.97 | 0.035 | 0.310 |
| Serine | 1.25 | 0.65–2.41 | 0.497 | 0.55 | 0.37–0.81 | 0.002 | 0.035 |
| Spermine | 1.49 | 1.04–2.13 | 0.031 | 1.03 | 0.83–1.27 | 0.811 | 0.073 |
| Succinate | 0.35 | 0.12–0.99 | 0.047 | 1.91 | 1.23–2.96 | 0.004 | 0.004 |
| Threonine | 1.12 | 0.67–1.87 | 0.670 | 0.61 | 0.44–0.85 | 0.004 | 0.035 |
| UDP-D-Glucose | 0.81 | 0.67–0.97 | 0.025 | 1.16 | 0.95–1.41 | 0.152 | 0.010 |
| Uracil | 1.24 | 0.56–2.76 | 0.599 | 0.42 | 0.26–0.69 | 0.001 | 0.024 |
| Xanthosine | 1.22 | 0.86–1.73 | 0.266 | 0.71 | 0.54–0.94 | 0.016 | 0.028 |

[a] *P* values for the association between individual metabolites and 5-year OS calculated by multivariate Cox PH regression models, adjusted for anatomic location, clinical stages, chemotherapy history and age (before FDR adjustment). The abundance of each metabolite was treated as a continuous variable and was $log_2$ transformed. A metabolite with HR < 1 was associated with better OS; a metabolite with HR > 1 was associated with worse OS. [b] *P* value of the interaction between the metabolite and sex. Int. Sex *P* value < .05 indicate a significant sex interaction.

**Table S4.** Multivariate analyses of the associations between individual metabolites and 5-year RFS by sex, adjusted for anatomic location, chemotherapy history, clinical stages, and age.

| Metabolite name | Females | | | Males | | | Int. Sex *P* value[b] |
|---|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* value[a] | HR | 95% CI | *P* value[a] | |
| **Acetyl-lysine** | 0.98 | 0.76–1.26 | 0.855 | 0.78 | 0.67–0.92 | 0.002 | 0.076 |
| Alanine | 1.12 | 0.81–1.55 | 0.495 | 0.74 | 0.58–0.94 | 0.013 | 0.053 |
| AMP | 1.10 | 0.69–1.77 | 0.689 | 0.69 | 0.51–0.95 | 0.021 | 0.124 |
| Argininosuccinic acid | 1.03 | 0.79–1.35 | 0.825 | 0.70 | 0.54–0.92 | 0.011 | 0.036 |
| Asparagine | 1.54 | 0.93–2.56 | 0.093 | 0.74 | 0.56–0.97 | 0.031 | 0.007 |
| Carnitine | 3.52 | 0.25–50.41 | 0.354 | 0.37 | 0.20–0.66 | 0.001 | 0.117 |
| CMP | 0.97 | 0.57–1.65 | 0.906 | 0.70 | 0.50–0.96 | 0.029 | 0.287 |
| Creatinine | 0.75 | 0.42–1.32 | 0.317 | 1.70 | 1.15–2.51 | 0.008 | 0.040 |
| Cytidine | 0.46 | 0.28–0.75 | 0.002 | 0.75 | 0.49–1.16 | 0.194 | 0.134 |
| Fructose 6-phosphate | 0.84 | 0.55–1.28 | 0.414 | 0.68 | 0.49–0.95 | 0.026 | 0.534 |
| Glutamine | 0.77 | 0.26–2.30 | 0.642 | 0.47 | 0.23–0.97 | 0.041 | 0.338 |
| Glutathione | 0.73 | 0.56–0.95 | 0.019 | 0.92 | 0.79–1.06 | 0.246 | 0.302 |
| Glutathione disulfide | 0.72 | 0.57–0.91 | 0.006 | 0.81 | 0.67–0.98 | 0.034 | 0.092 |
| GMP | 1.04 | 0.69–1.58 | 0.838 | 0.74 | 0.57–0.96 | 0.024 | 0.169 |
| Hypoxanthine | 1.95 | 0.59–6.45 | 0.276 | 0.32 | 0.20–0.51 | <0.001 | 0.008 |
| LysoPC(16:1) | 1.06 | 0.76–1.49 | 0.729 | 0.77 | 0.61–0.97 | 0.025 | 0.106 |
| LysoPE(18:2) | 1.07 | 0.70–1.65 | 0.750 | 0.72 | 0.55–0.96 | 0.023 | 0.127 |
| LysoPE(20:1) | 0.98 | 0.77–1.24 | 0.856 | 0.83 | 0.70–0.98 | 0.031 | 0.225 |
| LysoPE(22:5) | 1.09 | 0.70–1.70 | 0.701 | 0.70 | 0.53–0.92 | 0.010 | 0.072 |
| Serine | 1.45 | 0.74–2.84 | 0.282 | 0.57 | 0.40–0.83 | 0.003 | 0.010 |
| Sphinganine-1-phosphate | 0.94 | 0.60–1.47 | 0.777 | 0.66 | 0.45–0.95 | 0.026 | 0.216 |
| Stearamide | 0.92 | 0.63–1.36 | 0.674 | 0.70 | 0.53–0.92 | 0.012 | 0.211 |
| Threonine | 0.98 | 0.58–1.64 | 0.929 | 0.64 | 0.46–0.89 | 0.007 | 0.074 |
| Xanthine | 0.62 | 0.38–1.01 | 0.053 | 0.69 | 0.48–0.98 | 0.036 | 0.869 |
| Xanthosine | 1.01 | 0.72–1.40 | 0.973 | 0.71 | 0.52–0.98 | 0.040 | 0.112 |

[a] *P* values for the association between individual metabolites and 5-year RFS calculated by multivariate Cox PH regression models, adjusted for anatomic location, clinical stages, chemotherapy history and age (before FDR adjustment). The abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed. A metabolite with HR < 1 was associated with better RFS; a metabolite with HR > 1 was associated with worse RFS. [b] *P* value of the interaction between the metabolite and sex. Int. Sex *P* value < .05 indicate a significant sex interaction.

**Table S5.** Multivariate analysis of association between metabolites in ASNS-catalyzed asparagine synthesis pathway and OS and RFS for all patients .

| Variable[a] | OS | | | | RFS | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* value | Int. Sex *P* value[b] | HR | 95% CI | *P* value | Int. Sex *P* value[b] |
| **Asparagine** | **0.89** | **0.61–1.29** | **0.535** | **0.021** | **1.27** | **0.84–1.92** | **0.251** | 0.003 |
| Aspartate | 1.25 | 0.85–1.84 | 0.257 | 0.639 | 1.31 | 0.86–2.00 | 0.202 | 0.237 |
| Glutamate | 0.93 | 0.45–1.90 | 0.837 | 0.808 | 0.93 | 0.44–1.97 | 0.841 | 0.064 |
| Glutamine | 0.86 | 0.35–2.08 | 0.734 | 0.974 | 0.37 | 0.16–0.87 | 0.023 | 0.285 |
| AMP | 0.83 | 0.64–1.06 | 0.135 | 0.860 | 0.75 | 0.57–0.98 | 0.034 | 0.295 |
| Sex = Male (ref: Female) | 2.01 | 1.00–4.05 | 0.051 | – | 1.12 | 0.53–2.38 | 0.761 | – |
| Anatomic location = RCC (ref: LCC) | 0.87 | 0.43–1.77 | 0.710 | – | 0.67 | 0.31–1.44 | 0.300 | – |
| Clinical stage = late (ref: early) | 4.48 | 2.26–9.24 | 0.003 | – | 1.91 | 0.63–5.79 | 0.252 | – |
| Chemotherapy = Yes (ref: No) | 1.03 | 0.38–2.76 | 0.956 | – | 1.26 | 0.41–3.86 | 0.685 | – |
| Age | 1.10 | 1.05–1.15 | <0.001 | – | 0.97 | 0.92–1.03 | 0.304 | – |

[a] All the variables listed were included in one multivariate Cox PH model where the abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed. [b] *P* value of the interaction between the metabolite and sex.

**Table S6.** Multivariate analysis of association between metabolites in ASNS-catalyzed asparagine synthesis metabolic pathway and OS and RFS by sex.

| **Variable**[a] | **OS** | | | | | | **RFS** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Females** | | | **Males** | | | **Females** | | | **Males** | | |
| | **HR** | **95% CI** | ***P* value** | **HR** | **95% CI** | ***P* value** | **HR** | **95% CI** | ***P* value** | **HR** | **95% CI** | ***P* value** |
| Asparagine | 6.39 | 1.78–22.91 | 0.004 | 0.57 | 0.36–0.91 | 0.018 | 4.36 | 1.39–13.68 | 0.012 | 0.96 | 0.61–1.50 | 0.856 |
| Aspartate | 1.47 | 0.64–3.40 | 0.365 | 1.32 | 0.75–2.32 | 0.339 | 1.60 | 0.71–4.05 | 0.239 | 1.40 | 0.79–2.50 | 0.252 |
| Glutamate | 0.24 | 0.06–0.95 | 0.042 | 1.28 | 0.48–3.38 | 0.618 | 0.76 | 0.19–3.11 | 0.705 | 0.75 | 0.28–2.02 | 0.573 |
| Glutamine | 0.16 | 0.03–1.06 | 0.057 | 1.18 | 0.39–3.54 | 0.772 | 0.10 | 0.02–0.57 | 0.010 | 0.52 | 0.17–1.63 | 0.266 |
| AMP | 0.65 | 0.31–1.37 | 0.252 | 0.89 | 0.65–1.22 | 0.476 | 0.59 | 0.25–1.36 | 0.214 | 0.70 | 0.49–1.00 | 0.049 |
| Anatomic location = RCC (ref: LCC) | 1.63 | 0.47–5.65 | 0.438 | 0.80 | 0.31–2.10 | 0.653 | 0.78 | 0.23–2.65 | 0.692 | 0.61 | 0.20–1.84 | 0.380 |
| Clinical stage = late (ref: early) | 14.90 | 2.19–101.43 | 0.006 | 6.02 | 1.39–26.06 | 0.016 | 1.92 | 0.34–10.99 | 0.462 | 1.29 | 0.23–7.09 | 0.771 |
| Chemotherapy = Yes (ref: No) | 1.78 | 0.39–8.23 | 0.458 | 0.74 | 0.18–2.99 | 0.676 | 2.34 | 0.38–14.29 | 0.358 | 1.01 | 0.19–5.24 | 0.991 |
| Age | 1.09 | 1.00–1.19 | 0.037 | 1.15 | 1.07–1.23 | <0.001 | 1.01 | 0.91–1.11 | 0.905 | 0.94 | 0.87–1.01 | 0.112 |

[a] All the variables listed were included in one multivariate Cox PH model. The abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed.

**Table S7.** Multivariate analysis of association between metabolites in PPP and glycolysis metabolic pathway and OS and RFS for all patients .

| Variable[a] | OS | | | | RFS | | | |
|---|---|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | ***P* value[a]** | **Int. Sex *P* value[b]** | **HR** | **95% CI** | ***P* value[a]** | **Int. Sex *P* value[b]** |
| **Ribulose 5-phosphate** | **1.18** | **0.84–1.65** | **0.354** | **0.934** | **1.33** | **0.89–1.99** | **0.164** | 0.263 |
| Lactate | 1.49 | 0.81–2.75 | 0.203 | 0.601 | 1.21 | 0.51–2.85 | 0.660 | 0.472 |
| DHAPorG3P | 1.21 | 0.72–2.03 | 0.479 | 0.214 | 0.99 | 0.57–1.71 | 0.975 | 0.137 |
| Glucose 6-phosphate | 0.95 | 0.67–1.35 | 0.775 | 0.817 | 1.30 | 0.90–1.87 | 0.156 | 0.110 |
| Fructose 6-phosphate | 0.68 | 0.42–1.10 | 0.114 | 0.899 | 0.46 | 0.27–0.78 | 0.004 | 0.615 |
| Glycerol 3-phosphate | 1.44 | 0.80–2.59 | 0.222 | 0.046 | 0.53 | 0.25–1.12 | 0.097 | 0.253 |
| Phosphoenolpyruvate | 1.05 | 0.83–1.35 | 0.670 | 0.241 | 1.17 | 0.84–1.61 | 0.358 | 0.418 |
| Sex = Male (ref: Female) | 1.95 | 0.97–3.90 | 0.060 | – | 1.33 | 0.64–2.78 | 0.442 | – |
| Anatomic location = RCC (ref: LCC) | 0.65 | 0.29–1.42 | 0.279 | – | 0.83 | 0.36–1.93 | 0.665 | – |
| Clinical stage = late (ref: early) | 4.24 | 1.58–11.42 | 0.004 | – | 1.53 | 0.46–5.14 | 0.491 | – |
| Chemotherapy = Yes (ref: No) | 1.01 | 0.36–2.85 | 0.980 | – | 1.63 | 0.47–5.72 | 0.442 | – |
| Age | 1.11 | 1.06–1.16 | <0.001 | – | 0.99 | 0.93–1.04 | 0.596 | – |

[a] All the variables listed were included in one multivariate Cox PH model where the abundance of each metabolite was treated as a continuous variable and was $log_2$ transformed. [b] *P* value of the interaction between the metabolite and sex.

**Table S8.** Multivariate analysis of association between metabolites in PPP and glycolysis metabolic pathway and OS and RFS by sex.

| Variable[a] | OS | | | | RFS | | | |
|---|---|---|---|---|---|---|---|---|
| | Females | | Males | | Females | | Males | |
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Ribulose 5-phosphate | 1.30 (0.72–2.35) | 0.388 | 1.09 (0.70–1.69) | 0.700 | 1.87 (0.96–3.65) | 0.068 | 1.13 (0.63–2.03) | 0.673 |
| Lactate | 1.63 (0.45–5.98) | 0.460 | 1.02 (0.45–2.34) | 0.960 | 1.17 (0.26–5.18) | 0.839 | 0.92 (0.28–3.00) | 0.885 |
| DHAPorG3P | 2.20 (0.75–6.48) | 0.153 | 0.91 (0.48–1.75) | 0.785 | 1.35 (0.51–3.56) | 0.550 | 0.94 (0.45–1.98) | 0.879 |
| Glucose 6-phosphate | 0.93 (0.48–1.81) | 0.842 | 0.86 (0.51–1.43) | 0.553 | 1.90 (1.00–3.58) | 0.048 | 0.74 (0.44–1.24) | 0.254 |
| Fructose 6-phosphate | 0.77 (0.32–1.87) | 0.570 | 0.96 (0.50–1.82) | 0.890 | 0.26 (0.11–0.64) | 0.003 | 0.72 (0.37–1.42) | 0.344 |
| Glycerol 3-phosphate | 2.94 (0.86–9.99) | 0.084 | 0.89 (0.42–1.88) | 0.760 | 0.79 (0.27–2.28) | 0.664 | 0.27 (0.08–0.88) | 0.029 |
| Phosphoenolpyruvate | 1.16 (0.69–1.93) | 0.572 | 0.96 (0.70–1.33) | 0.817 | 1.54 (0.85–2.77) | 0.154 | 0.98 (0.63–1.53) | 0.940 |
| Anatomic location = RCC (ref: LCC) | 1.01 (0.27–3.80) | 0.993 | 0.58 (0.17–1.91) | 0.367 | 1.03 (0.27–3.94) | 0.968 | 0.80 (0.23–2.78) | 0.728 |
| Clinical stage = late (ref: early) | 13.00 (1.96–86.35) | 0.008 | 3.36 (0.87–13.02) | 0.080 | 2.00 (0.20–19.67) | 0.551 | 0.99 (0.18–5.34) | 0.994 |
| Chemotherapy = Yes (ref: No) | 0.75 (0.13–4.43) | 0.753 | 0.99 (0.23–4.20) | 0.987 | 1.65 (0.16–16.89) | 0.675 | 1.21 (0.24–6.12) | 0.816 |
| Age | 1.08 (0.98–1.20) | 0.132 | 1.12 (1.05–1.19) | 0.001 | 1.01 (0.92–1.10) | 0.832 | 0.92 (0.84–1.00) | 0.064 |

[a] All the variables listed were included in one multivariate Cox PH model. The abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed.

**Table S9.** Multivariate analysis of association between metabolites in lysophospholipids synthesis and OS and RFS for all patients .

| Variable[a] | OS | | | RFS | | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* value[a] | Int. Sex *P* value[b] | HR (95% CI) | *P* value[a] | Int. Sex *P* value[b] |
| **Oleic acid** | **1.13 (0.82–1.56)** | **0.457** | **0.271** | **1.33 (0.94–1.89)** | **0.107** | 0.472 |
| L-Palmitoylcarnitine | 1.25 (0.76–2.06) | 0.378 | 0.784 | 2.64 (1.43–4.86) | 0.002 | 0.481 |
| Stearoylcarnitine | 0.84 (0.64–1.09) | 0.190 | 0.900 | 0.76 (0.56–1.04) | 0.089 | 0.595 |
| Carnitine | 0.52 (0.22–1.23) | 0.137 | 0.681 | 0.29 (0.11–0.78) | 0.014 | 0.098 |
| LysoPC(16:0) | 1.22 (0.83–1.80) | 0.306 | 0.002 | 0.87 (0.44–1.72) | 0.691 | 0.233 |
| LysoPC(16:1) | 0.68 (0.39–1.20) | 0.183 | 0.153 | 1.18 (0.61–2.28) | 0.626 | 0.376 |
| LysoPC(18:1) | 0.75 (0.40–1.41) | 0.364 | 0.018 | 1.07 (0.53–2.14) | 0.854 | 0.447 |
| LysoPE(16:0) | 1.66 (0.69–3.99) | 0.253 | 0.088 | 4.38 (1.75–10.97) | 0.002 | 0.443 |
| LysoPE(16:1) | 0.98 (0.56–1.72) | 0.940 | 0.675 | 0.70 (0.33–1.49) | 0.358 | 0.720 |
| LysoPE(18:0) | 0.84 (0.37–1.90) | 0.674 | 0.027 | 1.04 (0.47–2.29) | 0.924 | 0.283 |
| LysoPE(18:1) | 0.88 (0.31–2.50) | 0.817 | 0.275 | 0.36 (0.13–1.00) | 0.051 | 0.595 |
| LysoPE(20:1) | 1.08 (0.70–1.65) | 0.740 | 0.205 | 1.04 (0.64–1.69) | 0.875 | 0.334 |
| LysoPE(22:5) | 0.88 (0.41–1.93) | 0.758 | 0.042 | 0.50 (0.24–1.07) | 0.073 | 0.052 |
| LysoPE(18:2) | 1.52 (0.84–2.77) | 0.167 | 0.467 | 0.99 (0.49–1.98) | 0.970 | 0.395 |
| Sex = Male (ref: Female) | 2.30 (1.07–4.92) | 0.032 | – | 1.58 (0.73–3.43) | 0.250 | – |
| Anatomic location = RCC (ref: LCC) | 0.59 (0.26–1.35) | 0.213 | – | 0.74 (0.28–1.92) | 0.532 | – |
| Clinical stage = late (ref: early) | 4.02 (1.42–11.38) | 0.009 | – | 3.70 (1.26–10.84) | 0.017 | – |
| Chemotherapy = Yes (ref: No) | 1.42 (0.48–4.16) | 0.523 | – | 0.91 (0.30–2.72) | 0.862 | – |
| Age | 1.11 (1.06–1.16) | <0.001 | – | 0.96 (0.90–1.02) | 0.174 | – |

Abbreviation: LysoPC, lysophosphatidylcholine; LysoPE, lysophosphatidylethanolamine. [a] All the variables listed were included in one multivariate Cox PH model where the abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed. [b] *P* value of the interaction between the metabolite and sex.

**Table S10.** Multivariate analysis of association between metabolites in lysophospholipids synthesis and OS and RFS by sex.

| Variable[a] | OS | | | | RFS | | | |
|---|---|---|---|---|---|---|---|---|
| | Females | | Males | | Females | | Males | |
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Oleic acid | 1.05 (0.50–2.20) | 0.905 | 1.66 (1.02–2.69) | 0.041 | 2.27 (0.95–5.44) | 0.065 | 0.91 (0.53–1.57) | 0.728 |
| L-Palmitoylcarnitine | 1.55 (0.61–3.89) | 0.355 | 2.99 (1.03–8.69) | 0.044 | 3.93 (1.29–12.04) | 0.016 | 1.79 (0.57–5.64) | 0.323 |
| Stearoylcarnitine | 0.65 (0.41–1.05) | 0.076 | 0.60 (0.34–1.05) | 0.074 | 0.60 (0.37–0.99) | 0.047 | 0.75 (0.42–1.34) | 0.329 |
| Carnitine | 6.83 (0.11–431.17) | 0.363 | 0.19 (0.06–0.67) | 0.009 | 5.84 (0.08–435.95) | 0.422 | 0.19 (0.03–1.03) | 0.054 |
| LysoPC(16:0) | 2.07 (1.06–4.07) | 0.034 | 0.64 (0.27–1.54) | 0.319 | 1.06 (0.37–3.04) | 0.920 | 0.43 (0.08–2.21) | 0.313 |
| LysoPC(16:1) | 0.39 (0.11–1.37) | 0.144 | 0.52 (0.22–1.27) | 0.151 | 2.71 (0.66–11.17) | 0.169 | 0.86 (0.27–2.70) | 0.798 |
| LysoPC(18:1) | 1.56 (0.43–5.75) | 0.501 | 0.29 (0.08–1.00) | 0.050 | 0.41 (0.10–1.65) | 0.210 | 7.82 (1.30–47.16) | 0.025 |
| LysoPE(16:0) | 1.66 (0.35–7.95) | 0.524 | 12.72 (2.20–73.55) | 0.005 | 1.52 (0.34–6.83) | 0.588 | 6.58 (0.99–43.95) | 0.052 |
| LysoPE(16:1) | 1.27 (0.38–4.30) | 0.695 | 1.16 (0.50–2.73) | 0.726 | 1.07 (0.26–4.45) | 0.927 | 0.70 (0.18–2.73) | 0.604 |
| LysoPE(18:0) | 2.56 (0.65–10.11) | 0.179 | 0.10 (0.02–0.44) | 0.002 | 4.21 (0.79–22.39) | 0.092 | 2.64 (0.36–19.31) | 0.338 |
| LysoPE(18:1) | 0.57 (0.06–5.17) | 0.618 | 0.80 (0.14–4.63) | 0.806 | 0.07 (0.01–0.63) | 0.017 | 0.30 (0.04–2.19) | 0.233 |
| LysoPE(20:1) | 0.71 (0.25–2.04) | 0.521 | 1.14 (0.62–2.11) | 0.679 | 0.33 (0.07–1.47) | 0.147 | 1.37 (0.61–3.06) | 0.444 |
| LysoPE(22:5) | 0.78 (0.21–2.93) | 0.714 | 2.47 (0.66–9.16) | 0.179 | 5.38 (1.02–28.42) | 0.048 | 0.10 (0.02–0.62) | 0.013 |
| LysoPE(18:2) | 1.06 (0.20–5.45) | 0.948 | 2.41 (1.12–5.20) | 0.024 | 1.59 (0.31–8.26) | 0.580 | 0.50 (0.14–1.77) | 0.286 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Anatomic location = RCC (ref: LCC) | 1.05 (0.29–3.79) | 0.941 | 0.09 (0.02–0.43) | 0.002 | 1.11 (0.19–6.58) | 0.909 | 1.00 (0.14–6.97) | 1.000 |
| Clinical stage = late (ref: early) | 18.99 (2.31–155.90) | 0.006 | 15.45 (2.48–96.39) | 0.003 | 4.40 (0.24–79.55) | 0.316 | 2.49 (0.36–17.33) | 0.355 |
| Chemotherapy = Yes (ref: No) | 0.84 (0.13–5.37) | 0.853 | 0.83 (0.16–4.37) | 0.827 | 2.24 (0.14–36.07) | 0.570 | 0.51 (0.08–3.33) | 0.485 |
| Age | 1.10 (1.01–1.21) | 0.038 | 1.30 (1.16–1.45) | <0.001 | 1.05 (0.96–1.16) | 0.278 | 0.86 (0.76–0.97) | 0.018 |

Abbreviation: LysoPC, lysophosphatidylcholine; LysoPE, lysophosphatidylethanolamine. [a] All the variables listed were included in one multivariate Cox PH model. The abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed.

**Table S11.** Multivariate analysis of association between metabolites in methionine metabolism and OS and RFS for all patients .

| **Variable**[a] | **OS** | | | **RFS** | | |
|---|---|---|---|---|---|---|
| | **HR (95% CI)** | ***P* value**[a] | **Int. Sex *P* value**[b] | **HR (95% CI)** | ***P* value**[a] | **Int. Sex *P* value**[b] |
| **Dimethylglycine** | **0.99 (0.64–1.52)** | **0.955** | **0.390** | **0.74 (0.46–1.20)** | **0.228** | 0.555 |
| Methionine | 1.26 (0.73–2.19) | 0.408 | 0.045 | 1.90 (1.01–3.57) | 0.045 | 0.022 |
| S-adenosylhomocysteine (SAH) | 0.96 (0.75–1.23) | 0.751 | 0.078 | 0.96 (0.72–1.27) | 0.753 | 0.931 |
| S-adenosylmethionine (SAM) | 1.08 (0.88–1.31) | 0.467 | 0.355 | 1.07 (0.86–1.32) | 0.541 | 0.765 |
| Serine | 0.56 (0.34–0.92) | 0.023 | 0.039 | 0.49 (0.29–0.83) | 0.008 | 0.045 |
| Sex = Male (ref: Female) | 2.02 (0.99–4.13) | 0.054 | – | 1.14 (0.53–2.44) | 0.740 | – |
| Anatomic location = RCC (ref: LCC) | 0.77 (0.38–1.58) | 0.483 | – | 0.62 (0.28–1.37) | 0.235 | – |
| Clinical stage = late (ref: early) | 5.32 (2.01–14.11) | 0.001 | – | 1.88 (0.60–5.85) | 0.277 | – |
| Chemotherapy = Yes (ref: No) | 1.02 (0.40–2.61) | 0.962 | – | 1.24 (0.41–3.77) | 0.703 | – |
| Age | 1.10 (1.05–1.15) | <0.001 | – | 0.96 (0.91–1.02) | 0.189 | – |

[a] All the variables listed were included in one multivariate Cox PH model where the abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed. [b] *P* value of the interaction between the metabolite and sex.

**Table S12.** Multivariate analysis of association between metabolites in methionine metabolism and OS and RFS by sex.

| Variable[a] | OS | | | | RFS | | | |
|---|---|---|---|---|---|---|---|---|
| | Females | | Males | | Females | | Males | |
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Dimethylglycine | 0.69 (0.33–1.42) | 0.308 | 1.45 (0.77–2.74) | 0.250 | 0.63 (0.29–1.36) | 0.239 | 0.69 (0.33–1.46) | 0.331 |
| Methionine | 2.52 (0.27–23.62) | 0.419 | 1.30 (0.64–2.65) | 0.465 | 5.49 (0.49–61.80) | 0.168 | 1.39 (0.62–3.10) | 0.423 |
| S-adenosylhomocysteine (SAH) | 0.87 (0.56–1.36) | 0.545 | 1.09 (0.76–1.58) | 0.631 | 1.07 (0.67–1.72) | 0.776 | 0.81 (0.54–1.21) | 0.304 |
| S-adenosylmethionine (SAM) | 1.18 (0.78–1.78) | 0.426 | 1.04 (0.80–1.36) | 0.757 | 1.08 (0.72–1.62) | 0.709 | 1.20 (0.90–1.60) | 0.211 |
| Serine | 0.48 (0.05–4.59) | 0.527 | 0.37 (0.19–0.72) | 0.004 | 0.31 (0.03–3.13) | 0.322 | 0.49 (0.24–0.98) | 0.044 |
| Anatomic location = RCC (ref: LCC) | 1.32 (0.42–4.17) | 0.636 | 0.58 (0.22–1.58) | 0.289 | 0.81 (0.26–2.53) | 0.714 | 0.43 (0.12–1.50) | 0.184 |
| Clinical stage = late (ref: early) | 9.44 (1.44–61.68) | 0.019 | 9.11 (2.22–37.39) | 0.002 | 2.25 (0.42–12.14) | 0.345 | 0.76 (0.13–4.39) | 0.764 |
| Chemotherapy = Yes (ref: No) | 1.12 (0.24–5.18) | 0.886 | 0.81 (0.23–2.82) | 0.742 | 2.04 (0.39–10.71) | 0.398 | 1.67 (0.34–8.30) | 0.529 |
| Age | 1.06 (0.98–1.14) | 0.134 | 1.16 (1.08–1.25) | <0.001 | 0.97 (0.90–1.06) | 0.541 | 0.93 (0.86–1.01) | 0.076 |

[a] All the variables listed were included in one multivariate Cox PH model. The abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed.

**Table S13.** Multivariate analysis of association between metabolites in polyamine synthesis and OS and RFS for all patients .

| Variable[a] | OS | | | RFS | | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* value[a] | Int. Sex *P* value[b] | HR (95% CI) | *P* value[a] | Int. Sex *P* value[b] |
| ***N*[1], *N*[12]-diacetylspermine (DAS)** | **0.87 (0.62–1.23)** | **0.439** | **0.356** | **1.01 (0.68–1.50)** | **0.954** | 0.336 |
| Spermidine | 1.30 (0.64–2.63) | 0.465 | 0.594 | 0.72 (0.34–1.53) | 0.396 | 0.329 |
| Spermine | 1.16 (0.83–1.62) | 0.386 | 0.082 | 1.06 (0.76–1.49) | 0.719 | 0.933 |
| N[1]-acetylspermine | 1.07 (0.78–1.48) | 0.675 | 0.887 | 1.24 (0.89–1.74) | 0.203 | 0.109 |
| Ornithine | 0.97 (0.54–1.74) | 0.927 | 0.105 | 0.84 (0.51–1.39) | 0.503 | 0.206 |
| Arginine | 1.38 (0.83–2.27) | 0.210 | 0.070 | 2.03 (1.14–3.60) | 0.016 | 0.037 |
| Citrulline | 0.96 (0.69–1.34) | 0.818 | 0.002 | 1.05 (0.73–1.51) | 0.801 | 0.023 |
| Argininosuccinic acid | 0.69 (0.48–0.98) | 0.039 | 0.123 | 0.72 (0.49–1.04) | 0.081 | 0.055 |
| Sex = Male (ref: Female) | 2.15 (1.08–4.29) | 0.030 | – | 1.17 (0.54–2.56) | 0.690 | – |
| Anatomic location = RCC (ref: LCC) | 0.81 (0.39–1.71) | 0.584 | – | 0.65 (0.29–1.48) | 0.306 | – |
| Clinical stage = late (ref: early) | 6.11 (1.91–19.57) | 0.002 | – | 1.93 (0.64–5.81) | 0.242 | – |
| Chemotherapy = Yes (ref: No) | 0.92 (0.28–2.95) | 0.882 | – | 1.14 (0.36–3.63) | 0.824 | – |
| Age | 1.10 (1.05–1.15) | <0.001 | – | 0.96 (0.90–1.01) | 0.120 | – |

[a] All the variables listed were included in one multivariate Cox PH model where the abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed. [b] *P* value of the interaction between the metabolite and sex.

**Table S14.** Multivariate analysis of association between metabolites in polyamine synthesis and OS and RFS by sex.

| Variable[a] | OS | | | | RFS | | | |
|---|---|---|---|---|---|---|---|---|
| | Females | | Males | | Females | | Males | |
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| $N^1$, $N^{12}$-diacetylspermine (DAS) | 2.45 (0.96–6.22) | 0.059 | 0.66 (0.42–1.02) | 0.060 | 1.10 (0.50–2.42) | 0.813 | 1.07 (0.61–1.90) | 0.812 |
| Spermidine | 0.51 (0.15–1.67) | 0.264 | 3.21 (1.04–9.93) | 0.043 | 0.28 (0.09–0.91) | 0.034 | 4.18 (1.03–16.96) | 0.045 |
| Spermine | 3.88 (1.50–10.06) | 0.005 | 0.71 (0.43–1.18) | 0.184 | 1.61 (0.90–2.88) | 0.106 | 0.56 (0.32–1.00) | 0.048 |
| $N^1$-acetylspermine | 0.37 (0.16–0.86) | 0.020 | 1.14 (0.74–1.75) | 0.557 | 0.92 (0.46–1.83) | 0.816 | 1.62 (0.99–2.63) | 0.054 |
| Ornithine | 0.64 (0.10–4.28) | 0.646 | 0.78 (0.40–1.55) | 0.481 | 0.41 (0.10–1.67) | 0.213 | 0.86 (0.45–1.67) | 0.660 |
| Arginine | 5.63 (1.33–23.78) | 0.019 | 1.06 (0.54–2.08) | 0.869 | 3.22 (1.14–9.13) | 0.028 | 1.57 (0.74–3.34) | 0.237 |
| Citrulline | 2.57 (1.04–6.33) | 0.040 | 0.73 (0.47–1.15) | 0.178 | 1.24 (0.60–2.59) | 0.561 | 0.88 (0.51–1.50) | 0.630 |
| Argininosuccinic acid | 0.57 (0.23–1.38) | 0.212 | 0.74 (0.47–1.19) | 0.214 | 1.20 (0.53–2.73) | 0.667 | 0.43 (0.24–0.78) | 0.005 |
| Anatomic location = RCC (ref: LCC) | 0.33 (0.06–1.69) | 0.182 | 0.80 (0.31–2.08) | 0.648 | 0.55 (0.14–2.08) | 0.375 | 0.50 (0.15–1.69) | 0.265 |
| Clinical stage = late (ref: early) | 119.96 (4.62–3116.09) | 0.004 | 3.56 (0.94–13.45) | 0.061 | 1.27 (0.19–8.70) | 0.805 | 0.95 (0.20–4.60) | 0.947 |
| Chemotherapy = Yes (ref: No) | 0.10 (0.01–1.50) | 0.096 | 2.20 (0.56–8.66) | 0.258 | 4.54 (0.59–34.72) | 0.145 | 1.14 (0.21–6.14) | 0.878 |
| Age | 1.18 (1.05–1.33) | 0.007 | 1.15 (1.07–1.23) | <0.001 | 0.97 (0.87–1.08) | 0.625 | 0.90 (0.82–0.98) | 0.014 |

[a] All the variables listed were included in one multivariate Cox PH model. The abundance of each metabolite was treated as a continuous variable and was $\log_2$ transformed.