Supplementary Figure S1

Spearman correlation matrix of measured metabolites from 318 samples with complete measurements of all 13 metabolites. Cis-aconitate (CisAC) and isocitrate (IsoCA) correlate with citrate (CA), malate (MAL) correlates with fumarate (FUM). Cis-aconitate, isocitrate, and malate were not used for further analyses.

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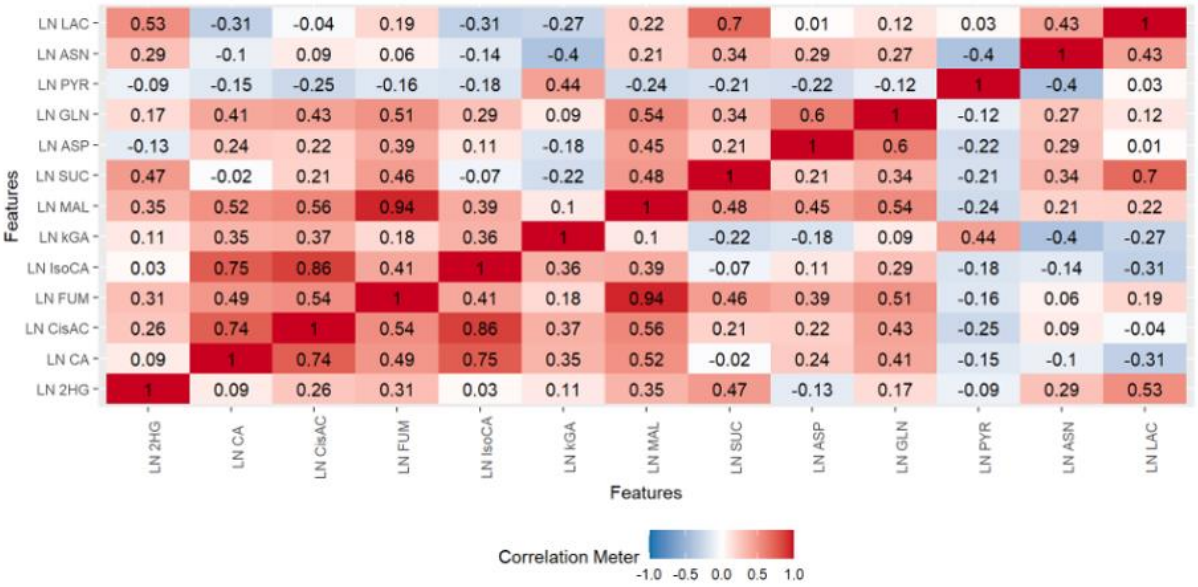

Supplementary Figure S2

Significantly different metabolites between lower (pT1/2) and higher (pT3/4) primary pathological tumour stage across the entire sample set, n = 419, except for pyruvate n = 399 and lactate n = 338. Significance was assessed by Mann-Whitney U test.

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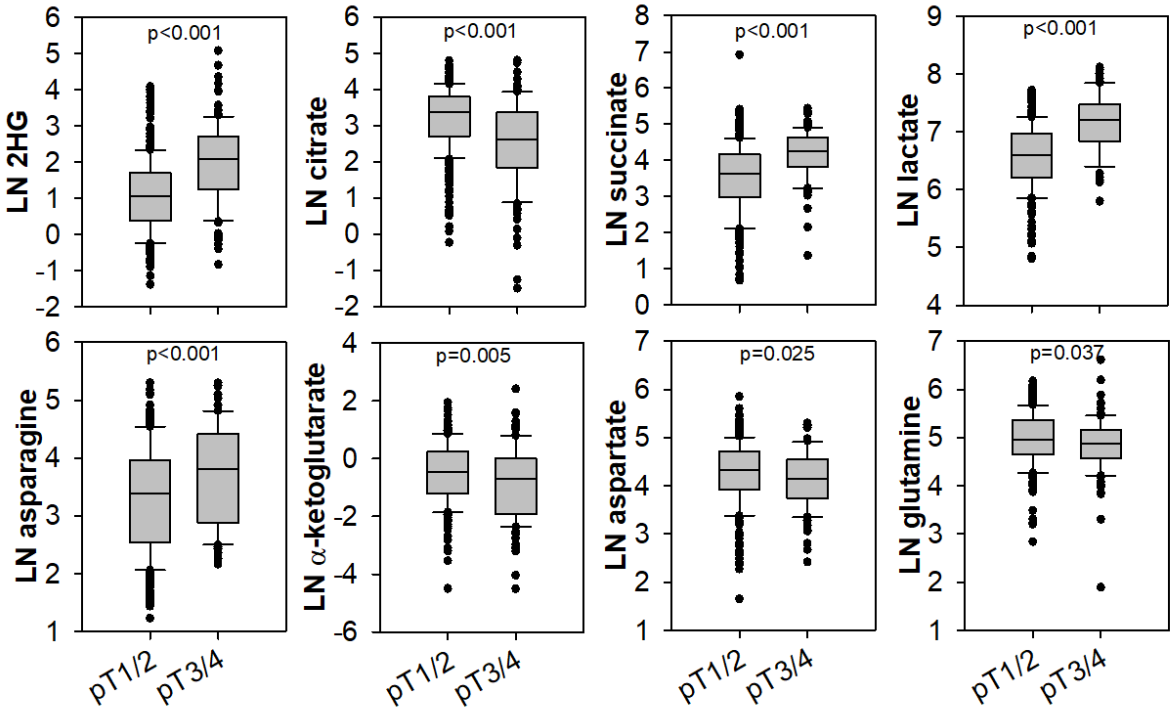

Supplementary Figure S3

Significantly different metabolites between lower (I/II) and higher (III/IV) TNM stage in RCCs across the entire sample set, n = 405, except for pyruvate n = 385 and lactate n = 328. Significance was assessed by Mann-Whitney U test.

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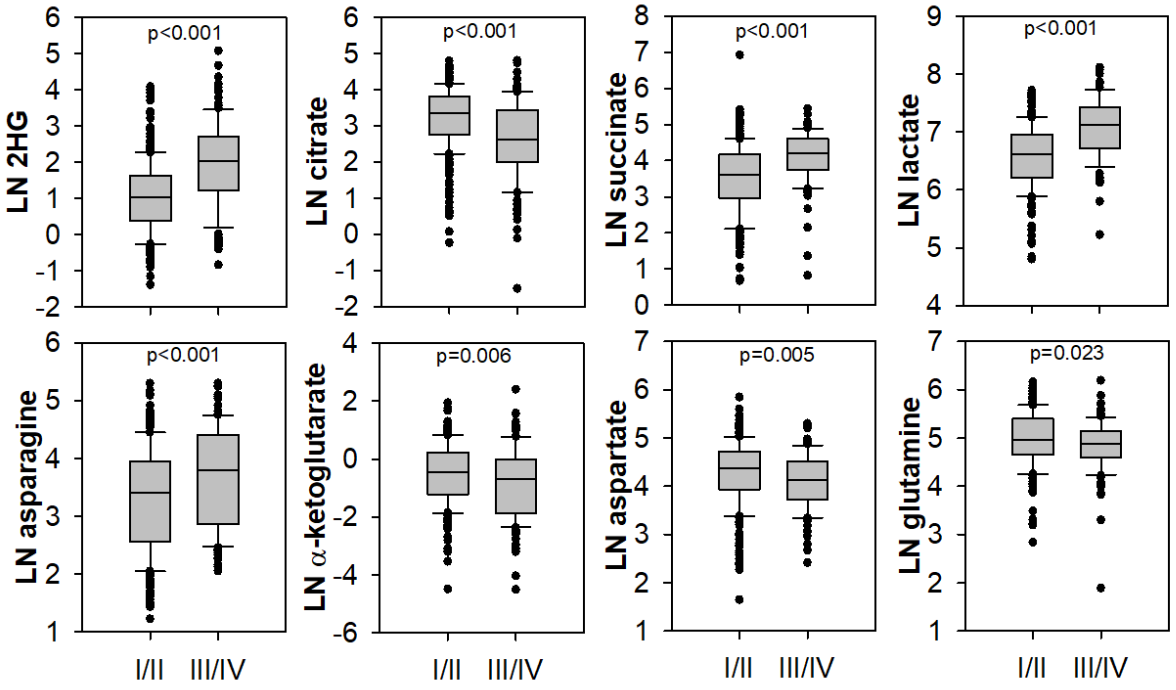

Supplementary Figure S4

Metabolite changes in necrotic (YES) versus non-necrotic (NO) RCC tissue. Significance was assessed by Mann-Whitney U test, n = 419, except for lactate n = 338.

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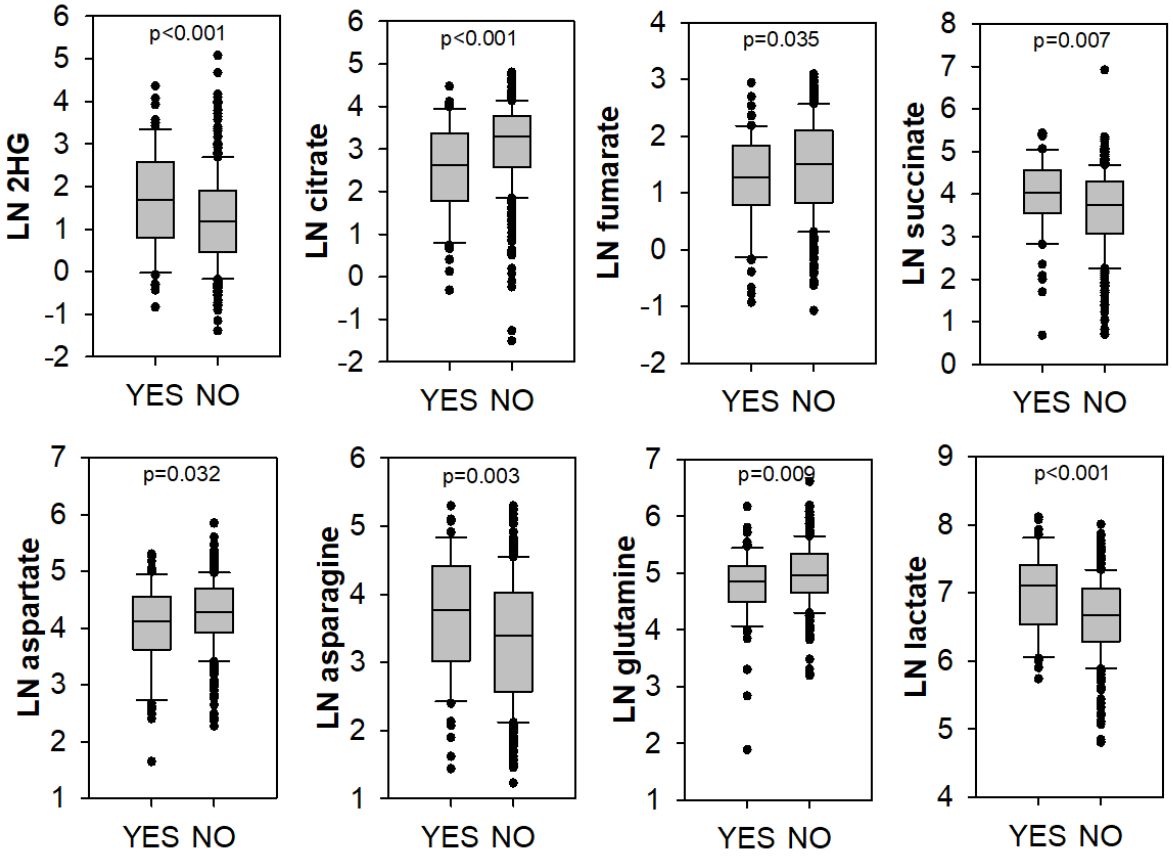

Supplementary Figure S5

Mosaic plot depicting the proportion of primary tumour stages in necrotic and non-necrotic samples. The difference between the necrotic and non-necrotic group is significant by chi-square test, $p<0.001$.

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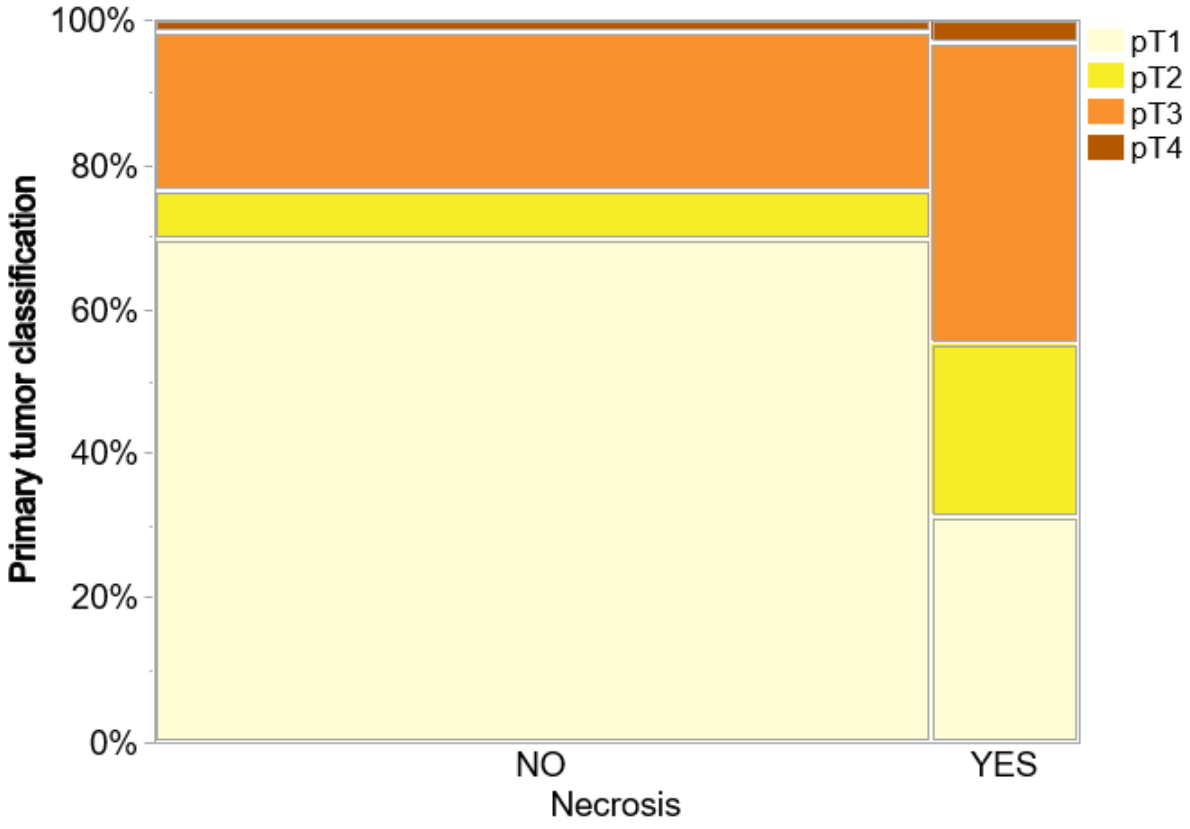

Supplementary Figure S6

Unsupervised hierarchical clustering of metabolites excluding necrotic samples. Colour coding: Necrosis – yes (black), no (grey); Primary tumour stage (pT) and TNM stage – darker is a higher stage; Type – CC (light green), P (dark green), CHR (olive), mixed type (grey).

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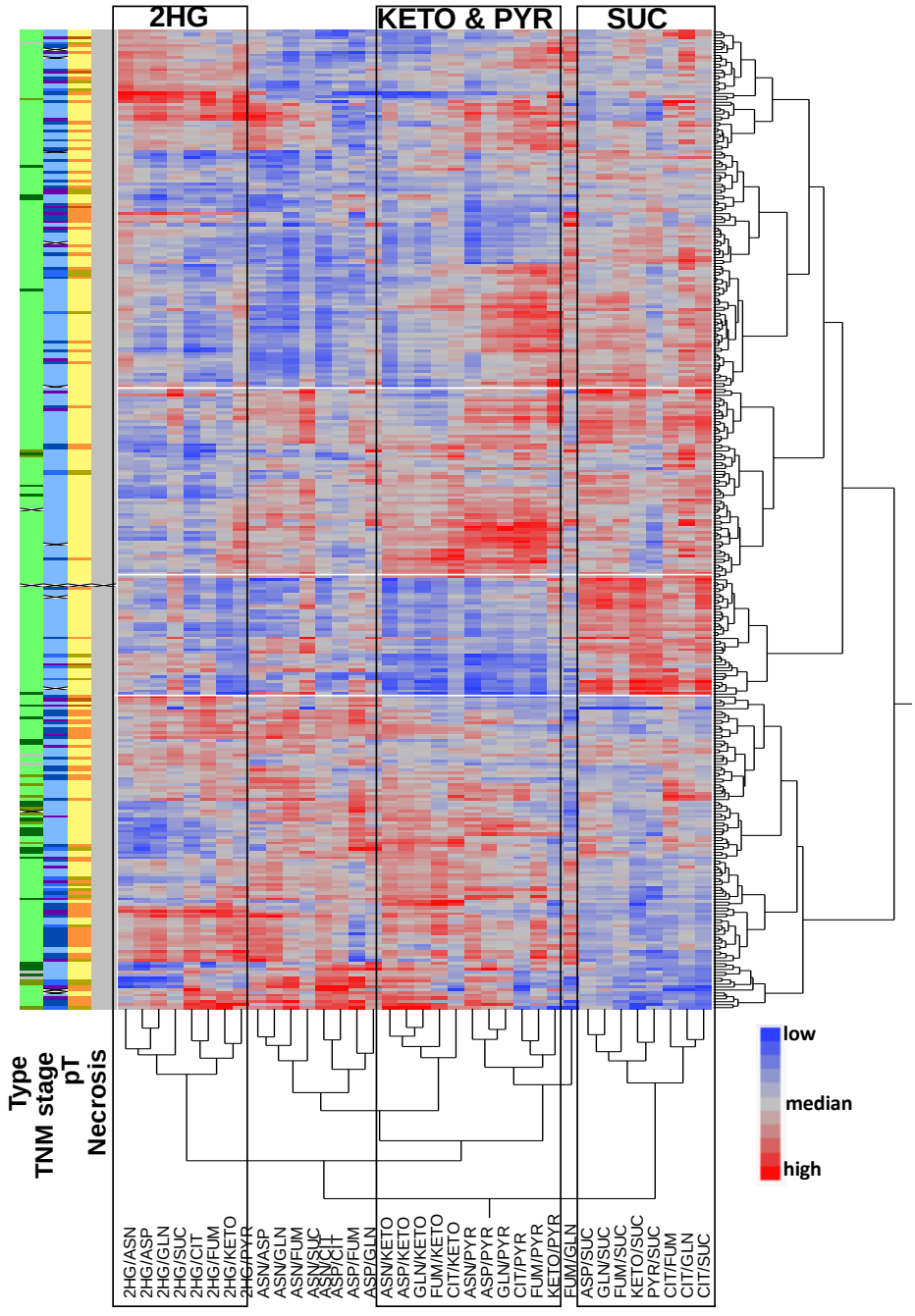

Supplementary Figure S7

Internal validation receiver operating characteristics (ROC) curves for all analytes' classification with the bootstrap forest algorithm between low-TNM-tumours (red lines) and high-TNM-tumours (blue lines). Area under the curve (AUC) score is displayed for all analytes within plots. Training and validation sets were split randomly by 70% and 30% of the original dataset using weighted cross validation.

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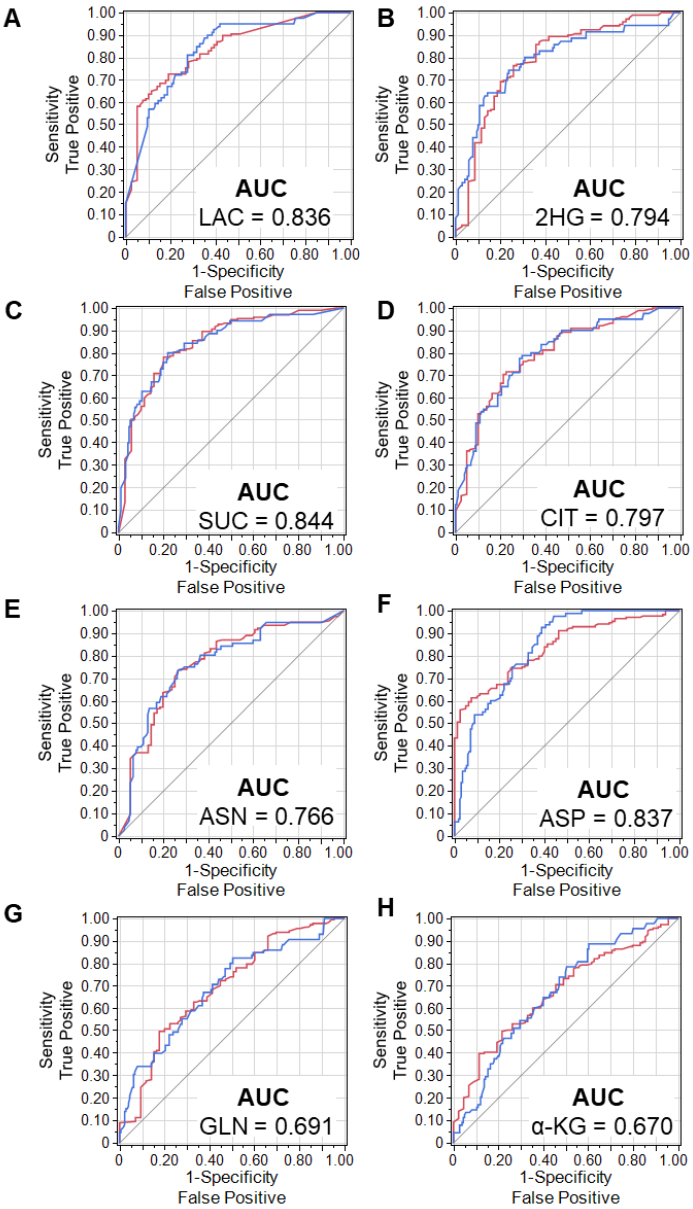

Supplementary Figure S8

Survival analyses for risk assessment based on tumour metabolite levels of lactate (A), succinate (B), 2HG (C), and citrate (D). The figures show probability of disease-specific deaths (which does not include relapse) over time. Metabolite-based predictions were made by the bootstrap forest algorithm, and CSS (n=266) was plotted. Univariable Cox proportional hazards models were used for calculation of hazard ratios (HR) with significance levels at *p<0.05 and **p<0.001.

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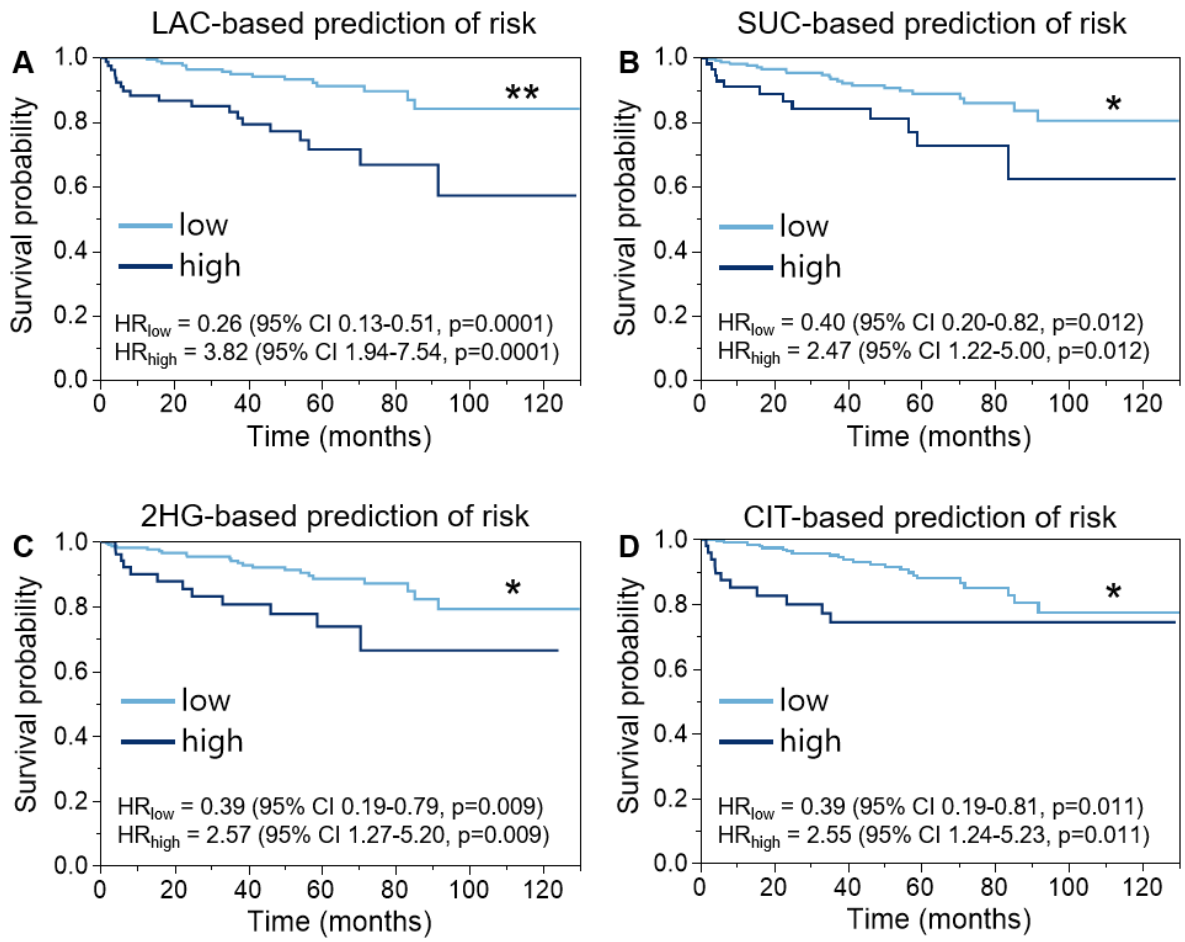

Supplementary Figure S9

ROC curves with areas under the curve (AUC) for the bootstrap forest models predicting risk based on tissue metabolites (n = 405). A'-D'. These predictions for a high or low risk tumour were analysed in respect to CSS (lower panels, n=266); aspartate (ASP, A, A'), asparagine (ASN, B, B'), glutamine (GLN, C, C'), and α-ketoglutarate (α-KG, D, D'). Statistical difference was assessed by log rank test, and significance was considered at *p<0.05. HR – hazard ratios according to Cox proportional hazards model.

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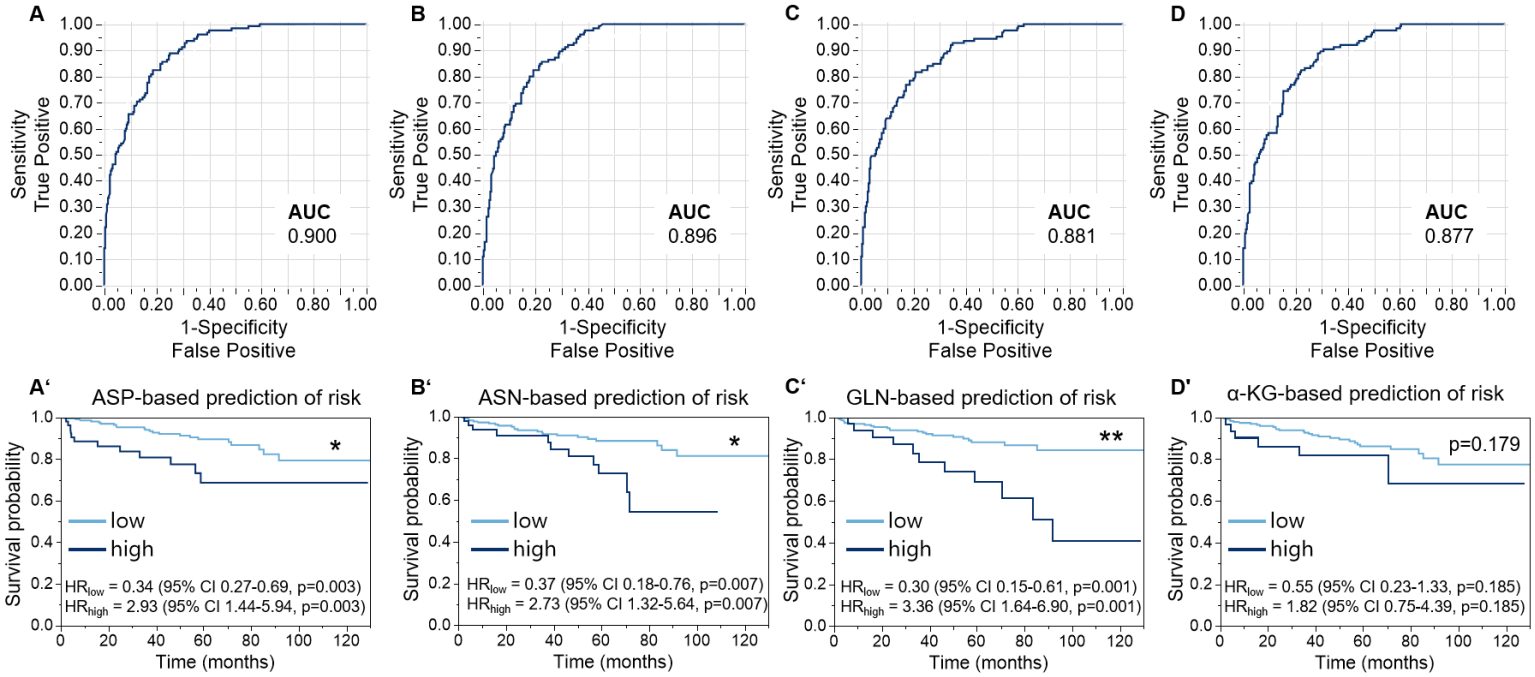

Supplementary Figure S10

Succinate (A) and α-ketoglutarate (B) levels in papRCC type 1 (P1, n=18) versus type 2 (P2, n=15). In five papRCC the type was not differentiated. Statistical significance was assessed by rank sum test.

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