ORIGINAL ARTICLE

Metabolomic profiling highlights the metabolic bases of acute-on-chronic and post-hepatectomy liver failure

Francois Faitot[1,2], Elisa Ruhland[3], Constantin Oncioiu[1], Camille Besch[1], Pietro Addeo[1,2], A. Ercument Cicek[4,5], Philippe Bachellier[1] & Izzie-Jacques Namer[2,3]

[1]Hepatobiliopancreatic Surgery and Transplantation Department, Hopital de Hautepierre, Hopitaux Universitaires de Strasbourg, [2]Laboratoire ICube, UMR7357, University of Strasbourg, [3]Biophysics and Nuclear Medicine Department, Hopital de Hautepierre, Hopitaux Universitaires de Strasbourg, France, [4]Lane Center of Computational Biology, School of Computer Science, Carnegie Mellon University, Pittsburgh, USA, and [5]Computer Engineering Department, Bilkent University, Ankara, Turkey

Abstract

Background: Posthepatectomy liver failure (PHLF) is the main limitation to extending liver resection but its pathophysiology is not yet fully understood. The aim of the study was to describe the metabolic adaptations that occur with PHLF.

Methods: A retrospective study of 82 patients using nuclear magnetic resonance metabolomics to identify and quantify intra-hepatic metabolites was performed. The metabolite levels were compared using metabolic network analysis ADEMA between fatal PHLF (FLF) and non fatal PHLF and according to PHLF/ACLF grading.

Results: Metabolomic profiles were significantly different between patients presenting FLF and non FLF or grade 3 ACLF versus < grade 3 ACLF. In the patients undergoing hepatectomy, valine, alanine and glycerophosphocholine were identified as powerful biomarkers to predict FLF (AUROC 0.806, 0.802 and 0.856 respectively). Network analysis showed an activation of aerobic glycolysis with glutaminolysis as observed in highly proliferating systems. Inversely, ACLF3 showed deprivation of glucose and lactate compared to lower ACLF grade.

Conclusion: Clinical andbiological severity of ACLF and PHLF correlate with specific metabolic adaptations. Metabolomics can predict fatal liver failure after hepatectomy and underline significant differences in the metabolic patterns of ACLF and PHLF.

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Correspondence

François Faitot, Hepatobiliopancreatic Surgery and Transplantation Department, Hopitaux Universitaires de Strasbourg, Hôpital de Hautepierre, 1, avenue Molière, 67000 Strasbourg, France. E-mail: francois.faitot@chru-strasbourg.fr

Introduction

Liver failure is the main cause of mortality after major hepatectomy (PHLF).[1] It represents a major limitation to curative treatment of primary and secondary liver cancers. In cirrhotic patients, liver failure is associated to a significant mortality as described by the entity of acute-on-chronic liver failure (ACLF).[2]

The mechanisms underlying these 2 types of liver failure are not entirely known. These entities share common biological and clinical features such as ascites, encephalopathy, hyperbilirubinemia, thrombopenia and coagulopathy along with associated extrahepatic dysfunction. Taking in consideration hepatic and extrahepatic dysfunctions, ACLF have been graded and ACLF grading correlates to short-term outcomes, ACLF grade 3 being associated to a 90% 1-month mortality rate.[3] PHLF has been classified according to the impact on outcome from biological-only diagnosis to fatal liver failure.[4] In both cases, additional events such as sepsis or hemorrhage may trigger multiorgan failure and subsequent death.

Studies have underlined the disparities in liver regeneration mechanisms between chronic versus acute or after resection versus hepatitis. Different cells are implicated in these different entities that are now more or less considered as distinct one from

the other. In the setting of PHLF, there is a consistent body of data showing a potential negative impact of inadequately important liver regeneration after major hepatectomy due to asynchronic proliferation of parenchymal and endothelial cells.[5]

In ACLF and cirrhotic patients, metabolic changes have been well studied and correlate with the stage of cirrhosis. Particular metabolic patterns among which accelerated aerobic and anaerobic glycolysis, lactate production have been described and, at the last stage, metabolic exhaustion with impossibility to use lactate for further energy production occurs.[6] The metabolic derangements in PHLF are only partially described. Given the central role in metabolic control of the liver, the interactions between inflammation and both liver metabolism and liver regeneration, ACLF and PHLF stages could be correlated to specific metabolic patterns that could therefore predict outcomes in liver failure.

Metabolomics is a new field of research looking at the entire set of metabolites from a given solid or liquid sample. In the field of liver regeneration some metabolomic data exist focusing on specific metabolic pathways that may be up or downregulated. More generally proliferating systems such as cancer cells[7] and its environment,[8] activated immune cells[9] or reprogrammed progenitor cells[10] have shown to be associated to specific metabolomic profiles among which are decreased oxidative phosphorylation, neoglucogenesis activation and lipid accumulation – with a more specifically increased liver triglycerides. Among the tools of metabolomics, high-resolution magic-angle-spinning nuclear magnetic resonance (HR-MAS-NMR) is an interesting tool as it enables solid tissue analysis of the metabolome within a time compatible with the clinical situation of liver resection and liver failure.

The aim of this was to describe the metabolic patterns associated to liver failure according to the grade of liver failure after hepatectomy and in decompensated cirrhotic patients using network analysis. Its main goal was to evaluate the capacity of HR-MAS-NMR metabolomics to predict the severity and outcome of liver failure, establishing a correlation between metabolic pattern and liver failure grade.

Methods

Over a 2 year period (Jan 2015–Dec 2016), patients undergoing hepatectomy for benign or malignant liver disease were included if they fulfilled the following criteria: liver biopsy snap-frozen within less than 5 min after sample harvesting, patients undergoing major hepatectomy and/or hepatectomy on injured liver (chemotherapy induced toxicity at histology, stage 3/4 fibrosis) or liver transplantation for a histologically proven cirrhosis (excluding fulminant hepatitis). The sample was obtained from the remnant liver at the end of hepatectomy taking care to select a non-ischemic or non-congestive area in the hepatectomy group. In the cirrhotic group, the sample was obtained from the native liver just after portal clamping in order to avoid both ischemia and hemorrhage. Histological analysis of the analyzed sample was realized to exclude the presence of cancer or necrosis in the sample. A signed informed consent for biological and genetic analysis in the setting of an authorized biobank and ethical approval from the CPP Grand Est (registration number 1970 390v0) was obtained for all patients.

Patient selection and preparation for surgery

Patients were selected for hepatectomy according to liver function tests and liver volumetry. Ascites and portal hypertension were assessed by imaging and endoscopic examination whenever suspected. Portal hypertension was generally considered a contraindication except when the indocyanine clearance test was normal (retention at 15min < 10%). Biliary drainage was performed in all cases of patients with biliary obstruction before hepatectomy. Portal vein embolization was indicated systematically in case of concomitant extrahepatic resection, histologically proven cirrhosis or in case of bilobar lesions necessitating a resection leaving less than 30% remnant liver or <0.5% remnant liver to body weight ratio.

Liver transplantation was indicated according to the current international guidelines. For patients with HCC, the Duvoux score was used to exclude patients with a score >2 after a downstaging treatment. There was no general contraindications for liver transplantation in ACLF patients except for non-controlled active infection, ARDS (defined by the PaO_2/FiO_2 ratio < 200) or ineffective intensive care with persistent elevated lactate >5 mmol/L.

Metabolomic study

HRMAS analysis was achieved on a Brucker Avance III 500 spectrometer operating at a proton frequency of 500.13 MHz. The detailed procedure and statistical analysis has been previously reported.[11]

Statistical analysis for metabolomics study – Network analysis

The time needed for sample preparation and spectrometric analysis was 20 min. In-house statistical model was used to quantify the metabolites (5–15 min according to the number of quantified metabolites) enabling a complete analysis and interpretation of the results of the metabolomics analysis of one sample within 25–35 min.

PLDS-DA (Partial Least Squares-Discriminant Analysis) was employed to check for the validity of the model and explore potential confounding factors. OPLS-DA was used to take in consideration the potential confounding effect. The 2 measurements of model quality were $R^2\gamma$ and Q^2 representing the accuracy of fit (i.e. data variation) and accuracy of prediction respectively. $Q^2 \geq 0.5$ was considered as a good predictor.

Algorithm to Determine Expected Metabolite Level Alterations Using Mutual Information (ADEMA) has been applied on

metabolite quantification values.[12] ADEMA includes information on the metabolic pathway in a unidirectional or bidirectional manner. Using the metabolic network topology, the ADEMA algorithm evaluates the change in groups of metabolites between concentration data from two experimental groups instead of analyzing metabolite concentrations one by one. Based on mutual information, the algorithm determines whether some metabolites are biomarkers when considered together, and it can predict the direction of the expected change per metabolite depending on the metabolic network topology considered. This statistical analysis ensures strong results in small samples as reported in the original paper.[12] ADEMA analysis strengthens the conclusions as it provides strong evidence even in very small sample size. The original report using ADEMA used a 2 versus 2 population. It ensures a valuable multivariate analysis in small sample populations while considering interactions between all the variables analyzed at once. This analysis was conducted after checking that the model was actually discriminant by PLS-DA and OPLS-DA analyses.

The network was constructed using Kyoto Encyclopedia of Genes and Genomes[13] and Selway's work.[14] The following pathways were used for the analysis: glucose/lactate; glucose/ascorbate/glutathione/glutamate; glucose/alanine/valine/isoleucine; choline/glycerophosphocholine/phosphocholine/total choline.

Endpoint definition

Grading of PHLF was adapted from the definition of the ISGLS group. Fatal liver failure (FLF) was defined as PHLF as defined by the 50-50 criteria or bilirubin >119 μmol/L during the first 5 days that led to death within the first 90 days.[6] It was termed grade C in parallel to grade 3 ACLF.

Acute-on-chronic liver failure (ACLF) was defined according to the CANONIC study group for the cirrhotic patients.[15] Grading was adapted by evaluating together grade 1 and grade 2 ACLF (termed grade B).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median according to their distribution. Student t-test or Mann–Whitney U test were used as appropriate. Categorical variables are expressed as number and percentage. Chi-2 test was used to compare the distribution of categorical variables between groups. Spearman's test was performed to determine correlation between variables. A retrospective evaluation of the number of patients to be included was realized using the mean values and standard deviation (α risk = 0.05; power 1-β = 0.9). Given the number of metabolites analyzed, even though the results are issued from the network analysis ADEMA, a Bonferroni correction was performed using a familywise error rate of 0.05 and identified p value for significant difference <0.003. These statistical analyses were performed using Statview (USA) and SPSS softwares.

Receiving Operating Characteristics (ROC) curves were constructed to evaluate the value of identified metabolic biomarkers and to identify the best cutoff for these variables. SPSS software was used for this analysis.

Results

Among 325 patients undergoing hepatectomy during the study period among whom 112 (34%) underwent major hepatectomy or hepatectomy on diseased parenchyma, there were 45 (14%) patients who fulfilled the inclusion criteria. The main reason for exclusion was lack of samples with short ischemia time. Among the 162 patients transplanted during the same period, 37 (23%) patients met the inclusion criteria after excluding non cirrhotic livers and available biopsy at the time of portal clamping.

In the hepatectomy group, the main indication for hepatectomy was colorectal liver metastases (n = 22) followed by hepatocellular carcinoma (n = 5), endocrine tumor liver metastases (n = 5) and hilar cholangiocarcinoma (n = 5). Thirty patients underwent major hepatectomy. In patients with colorectal liver metastases, 21 patients received neoadjuvant chemotherapy. Patients with hepatocellular carcinoma had advanced fibrosis (n = 3) or Child A cirrhosis (n = 2). PHLF occurred in 7 patients, 6 of whom eventually died (PHLF grade C).

In the cirrhotic group, the main indication for liver transplantation was alcoholic cirrhosis (n = 24) followed by hepatitis C (n = 4). The median uncapped MELD score and mean CLIF-SOFA were 25 (6–51) and 8.5 (2–27) respectively. The number of patients with grade 3 ACLF was 8.

The characteristics of patients with grade C liver failure in the hepatectomy and the liver transplantation group are described in Table 1.

Metabolomic profile in posthepatectomy livers predicts mortality due to PHLF

When comparing fatal PHLF versus non-fatal PHLF, the metabolic profile was significantly different according to PLS-DA and OPLS-DA analysis (Q^2 = 0.516; $R^2\gamma$ = 0.85) (Fig. 1a).

Network analysis (Fig. 1b) showed that FLF livers were richer in glucose, lactate, isoleucine, glutamine and glutamate regarding energy metabolism. There was a significantly lower level of antioxidant such as ascorbate and glutathione. Choline metabolism was significantly altered with higher choline level and lower glycerophosphocholine level.

Metabolite quantification showed that there was a significantly higher level of alanine, valine, isoleucine and glutamine and lower level of glycerophosphocholine (Table 2). When analyzing quantification of the identified metabolites, valine and alanine were significantly higher in livers exerting fatal PHLF (AUROC = 0.806 and 0.802 respectively). The most powerful metabolite predicting PHLF was low glycerophosphocholine.

Table 1 Demographic and clinical characteristics of the studied population in the hepatectomy and transplantation groups according to the occurrence of grade C liver failure

	Hepatectomy; n = 45			Transplantation; n = 37		
	PHLF C n = 6	PHLF A-B n = 39	p value	ACLF C n = 8	ACLF A-B n = 29	p value
Age	69 ± 6	62 ± 12	0.243	58 ± 9	55 ± 9	0.459
Male gender	4	16	0.239	6	21	0.884
BMI (kg/m^2)	26 ± 4	25 ± 4	0.624	27.9 ± 2	27.3 ± 5	0.799
Obesity	1	5	0.245	2	9	0.611
Diabetes	3	5	0.027	3	16	0.376
Insulin	0	1		1	7	
Metformin	3	3	0.043	1	7	0.208
Arterial hypertension	3	15	0.591	3	10	0.874
Statin use	1	4	0.642	0	4	0.451
Metabolic syndrome	1	8	0.826	3	11	0.999
Major hepatectomy	6	24	0.063	NA	NA	
Portal vein embolization	2	8	0.079	NA	NA	
Portal triad clamping	4	13	0.608	NA	NA	
Parenchymal injury						
Steatosis	1	21	0.090	2	8	0.956
Fibrosis > F3	2	2	0.024	8	29	0.214
Sinusoidal obstruction	1	11	0.552	NA	NA	
Preoperative bilirubin (μmol/L)	82 ± 46	10 ± 8	0.020	422 ± 246	88 ± 102	<0.001
Preoperative INR	1.17 ± 0.2	1.06 ± 0.2	0.349	3.84 ± 1.7	2.64 ± 1.6	0.074
Preoperative creatinine (μmol/L)	64 ± 14	68 ± 19	0.657	84 ± 11	67 ± 4	0.099
Preoperative ASAT (IU)	173 ± 165	24 ± 23	0.001	294 ± 166	75 ± 47	0.015
Preoperative platelets (10^3/mm^3)	285 ± 84	255 ± 95	0.423	67 ± 30	113 ± 86	0.141
Preoperative NLR	4.65 ± 2	2.97 ± 2	0.105	16.2 ± 7	5 ± 4	<0.001
Preoperative ICG clearance (%)	15 ± 10	9 ± 6	0.312	NA	NA	
Preoperative MELD score	9 ± 4	7 ± 3	0.463	42.5 ± 6	20 ± 10	<0.001
Preoperative APRI score	0.42 ± 0.2	0.41 ± 0.5	0.245	15.7 ± 11	2.8 ± 1	0.033

INR: international normalized ration; ASAT: aspartate aminotransferase; NLR: neutrophil to lymphocyte ratio; ICG: indocyanine green clearance.

ROC curve identified a 1.16 mmol/g threshold which predicted fatal PHLF with a 73% sensitivity and a 100% specificity (AUROC = 0.856; IC 95% 0.738–0.974).

When further analyzing choline metabolism, there was a significant difference in choline/glycerophosphocholine and phosphocholine/glycerophosphocholine ratio.

In order to check for potential confounders, a comparison of the whole metabolic profile using PLS-DA analysis between patients presenting significantly well recognized predicting factors was realized. It showed that the metabolic profile differed neither due to extension of the resection, preoperative chemotherapy, age or portal triad clamping. The only difference in metabolic profile was observed within diabetic patients between those treated by metformin versus insulin with a beneficial impact of metformin.

Metabolic score to predict post-hepatectomy liver failure

Using the identified optimal threshold for alanine, valine and glycerophosphocholine, a simple metabolic risk score for FLF was designed and showed a powerful predictive value with a 100% sensibility, specificity, positive predictive value and negative predictive value for a score $\geq$1 (Fig. 2).

Metabolomic profile in ACLF cirrhotic patients correlates with ACLF grading

Network analysis was conducted to compare metabolomic profile among cirrhotic patients according to ACLF grade (Supplemental Figure). Quantification of the metabolites did not enable to identify a valuable predictive biomarker in this population with low AUROC for all metabolites.

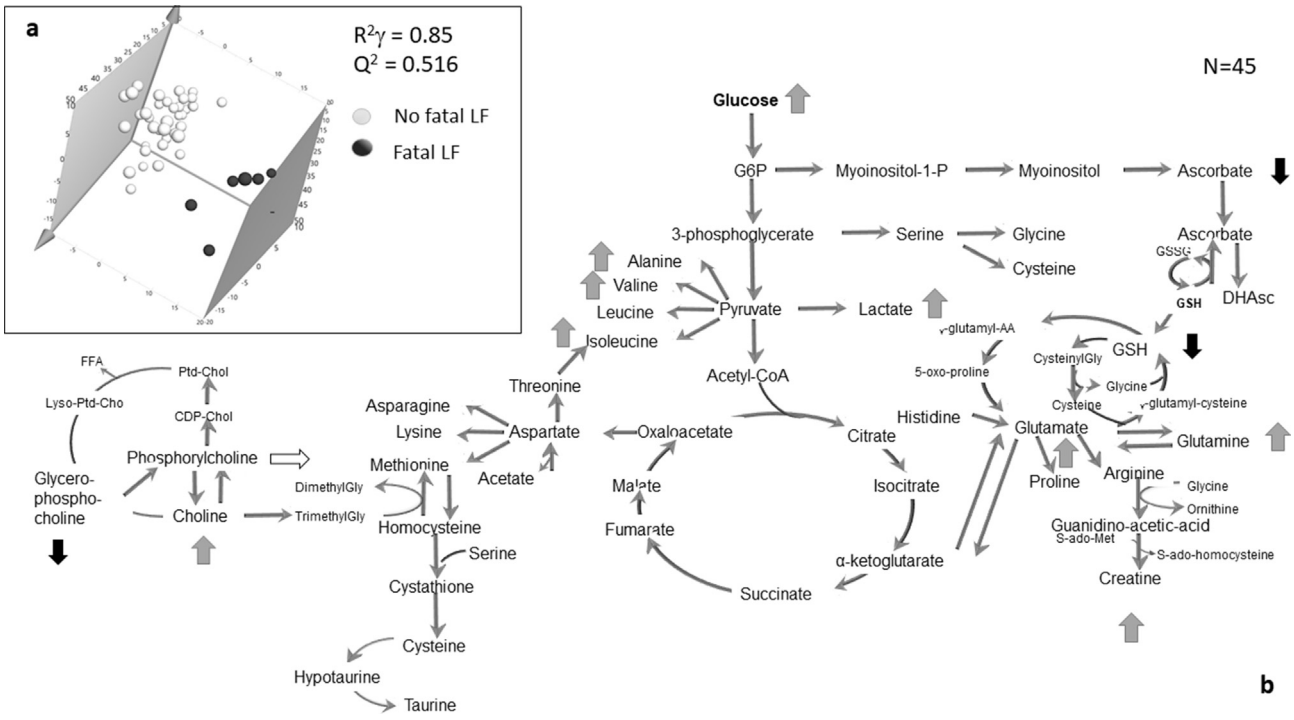

Figure 1 a – OPLS-DA analysis showing the difference in metabolic profiles between fatal and non fatal PHLF; b-**metabolic map with pathways analyzed through ADEMA network analysis with metabolites level in fatal PHLF compared to non fatal PHLF in end-hepatectomy liver biopsy**. The analysis shows a significantly higher level of glucose, lactate and neoglucogenic amino acids. The level of antioxidants and glycerophosphocholine are lower in case of fatal PHLF. Together these data are in accordance with endoplasmic reticulum stress and glycolysis activation

Table 2 Metabolite quantification according to the occurrence of a fatal post-hepatectomy liver failure

	Fatal PHLF	No fatal PHLF	p value
Glucose	6.69 (1.74–10.43)	4.27 (1.96–22.32)	0.564
Lactate	6.86 (3.15–15.65)	5.78 (1.11–15.59)	0.053
Alanine	2.69 (0.65–6.18)	0.96 (0.29–2.96)	<0.0001
Valine	0.49 (0.06–0.88)	0.12 (0.01–0.44)	<0.0001
Isoleucine	0.31 (0.02–0.93)	0.08 (0.01–0.29)	<0.0001
Glutamine	1.18 (0.52–1.55)	0.87 (0.25–1.47)	0.049
Glutamate	2.06 (1.14–4.69)	1.8 (0.84–3.78)	0.063
GABA	0.64 (0.01–1.41)	0.4 (0.01–2.26)	0.157
Ascorbate	0.1 (0.01–0.48)	0.22 (0.04–0.6)	0.120
GSH	0.43 (0.01–0.87)	0.75 (0.01–1.45)	0.092
Choline	1.18 (0.2–1.99)	0.7 (0.25–2.89)	0.255
Phosphocholine	0.45 (0.17–0.58)	0.59 (0.25–2.68)	0.060
Glycerophosphocholine	0.81 (0.01–1.12)	1.67 (0.33–3.45)	0.005
PC/GPC	0.51 (0.39–24)	0.32 (0.16–1.82)	0.011
Choline/GPC	1.69 (0.83–22)	0.52 (0.18–8.71)	0.006
Ethanolamine	0.68 (0.01–1.25)	0.33 (0.01–1.72)	0.072
Taurine	4.85 (0.95–11.63)	4.72 (1.71–9.04)	0.757

Expressed in mmol/g.
Median.

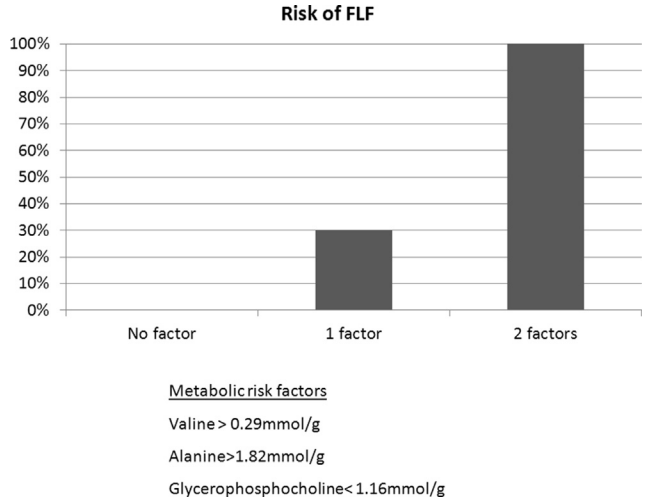

Figure 2 **Predicted rate of fatal liver failure** according to the number of metabolic risk factors (alanine>1.82 mmol/g, valine >0.29 mmol/g and glycerophosphocholine<1.16 mmol/g)

Liver failure translates in significantly different metabolic patterns according to type and grade

PHLF grade B differed from grade A by lower levels of glucose, lactate and neoglucogenic amino acids. There were higher levels of antioxidant, glutamine and glutamate as well as higher levels of all choline derivatives.

ACLF grade B differed from grade A by higher level of lactate, alanine, valine, isoleucine and glutamate whereas there was no change in glucose or glutamine among neoglucogenic pathway. There was a lower level of glycerophosphocholine, total choline. No changes were observed in antioxydants between these 2 grades.

Table 3 summarizes the way in which the metabolites predict ACLF and PHLF grading.

Table 3 Metabolite quantification and respective evolution of metabolites according to the grade of ACLF and PHLF

	PHLF C vs A+B	ACLF C vs A+B	PHLF B vs A	ACLF B vs A	PHLF C vs B	ACLF C vs B
Glucose	↑	↓	↓	→	↑	↓
Lactate	↑	↓	↓	↑	↑	↓
Alanine	↑	↑	↓	↑	↑	↑
Valine	↑	↑	→	↑	↑	↑
Isoleucine	↑	↑	↓	↑	↑	↑
Ascorbate	↓	↓	↑	→	↓	↓
Glutathion	→	→	↑	→	↓	→
Glutamate	↑	↑	↑	↑	→	→
Glutamine	↑	↑	↑	→	→	↑
Gaba	↑	↑	↑	↑	↑	↑
Choline	↑	→	↑	→	↑	→
GPC	↓	↓	↑	↑	↓	↓
PC	→	↓	↑	→	→	↓
EthanolA	↑	↑	↑	↑	↑	↓
Taurine	↑	↓	↑	↑	→	↓

Discussion

Metabolomic profiling may be a powerful tool in the field of hepatology as it enables to underline the strong correlation between the clinical and biological grading and metabolic derangements in liver failure. This is the first-in-man study showing the value of HR-MAS-NMR to predict post-hepatectomy liver failure.

In the case of ACLF, HR-MAS-NMR shows comparable results as other works published regarding metabolic modifications in advanced cirrhosis.[8] Low hepatic lactate and glucose seem to be a hallmark of severe liver dysfunction on diseased liver. As a biomarker of terminal liver failure, it could be further investigated as a marker of utility or futility in transplantation. In this setting, HR-MAS-NMR metabolomics present the major interest of being clinically applicable.

In the case of PHLF, the most striking finding is that these metabolic derangements are similar to those observed in rapidly proliferating systems such as cancer or activated immune cells. The early timing of these metabolic derangements may precede many of the reported mechanisms leading to overt regeneration and then liver failure. The metabolic profile of failing livers is compatible with that of proliferating systems reinforcing the hypothesis of a negative impact of early regenerative boost. Indeed the elevation of glucose and lactate with high levels of neoglucogenic amino acids (known as Warburg effect) is also described in cancer cells and iPS cells.[16] Whether the metabolic profile is a cause or a consequence of liver failure is beyond the scope of this research. The significant derangements in choline metabolism are original findings. Increased choline/phosphocholine, choline/GPC and phosphocholine/GPC indicate a significant impairment in choline handling by endoplasmic reticulum.[17] Apart from ER stress, the alteration in choline metabolism may be seen as stigmata of lipid metabolism derangements during liver regeneration. Lipid droplets accumulation is well described in the early stages of the process. The characterization of differential lipid constitution of this post-operative steatosis may be an important aspect for future studies[18] as confirmed by metabolically different lipid profiling between lean and obese patients with fat accumulation.[19]

This study has limitations mainly given to its retrospective aspect. A first limitation of this study may be the selection biases leading to the observed rate of PHLF which is higher than in current published data. It should be underlined that, in order to focus on high risk patients, the study only included patients with injured livers or major hepatectomy. This may explain the 14%

rate of fatal PHLF. The strict inclusion criteria enable to draw valuable conclusions as it analyzes a homogeneous population. The clinical impact of the timing of the biopsy may seem poor at first view. The earliness of metabolic derangements observed may be considered as the sign of altered liver parenchyma that should lead to decline hepatectomy. However the analysis of native cirrhotic livers from transplanted patients showed that the metabolic profiles are not similar between failing livers and decompensated cirrhotic livers and compensated livers do not exert significantly different metabolic profile. In order to take in consideration intraoperative events, tolerance to hepatectomy should be evaluated at the end of the hepatectomy. Pre-hepatectomy biopsies may be of interest, mainly in a perspective of evaluating dynamic changes in metabolites and identifying pathways that are regulated during hepatectomy. This may help to identify specific actions or times during hepatectomy for convenient metabolic intervention. Whether a percutaneous pre- or post hepatectomy biopsy may bring further information is an important question to be answered in future studies. In the setting of liver transplantation, graft metabolomic analysis during backtable preparation has shown to be effective.[11] Metabolic matching between donor and recipient may be achieved and studies will probably evaluate the benefit of liver resuscitation on machine perfusion in the near future. A last limitation could be the sensibility of HR-MAS-NMR that limits the capacity to identify and quantify metabolites that are present in very small quantity. It is counterbalanced by its relevance in the operative theater as the metabolic profile and metabolite quantifications can be achieved in 30 min. A specific point to be raised here is the unique situation of a spectrometer within the hospital, enabling such extemporaneous analysis. Whether tertiary expert centers should acquire the technology in this view requires much more powerful studies.

Metabolic intervention may be an elegant way of research for the prevention of liver failure. Metabolic intervention is under investigation in many domains of medical research. Prevention or treatment of hepatocellular carcinoma by the use of metformin is being studied since a decade and the results of randomized trials will help better delineate the place of this therapy. Metformin is much used as an AMP kinase inhibitor. In rodent models, it has shown: preventive effect on allograft rejection by targeting T cell metabolism,[20] beneficial impact on the outcome in severely burned patients associated to antilipolytic action.[21] Another metabolic intervention would regard the endoplasmic reticulum stress. Intermittent selective clamping has recently been shown to improve ER stress.[22] The effect of octreotide on metabolomic profile after hepatectomy showed significant modifications in the methionine cycle with concomitant inhibition of early hepatocyte regeneration after massive hepatectomy.[23]

In conclusion, metabolic profiling of failing livers correlates with the grade of liver failure in the case of PHLF as well as in the case of ACLF. In comparable grades, the profiles differ between the 2 types of liver failure, therefore validating, in a metabolic point of view, the distinction between these entities and their respective grading. Extemporaneous HR-MAS-NMR metabolomics allows accurate and early prediction of fatal liver failure after hepatectomy. Although there is currently no efficient treatment for PHLF, metabolic intervention may be a future way of research.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2019.02.008.