Original Article

Plasma GLP-1 and metabolic dynamics during human liver regeneration and their association with posthepatectomy liver failure

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Background: Metabolic regulation is critical during liver regeneration in rodents, but human data are limited. We investigated perioperative dynamics of circulating metabolites and plasma levels of glucagon-like peptide-1 (GLP-1) and GLP-2, in patients undergoing liver resections, exploring their associations with the histological phenotype of metabolic dysfunction-associated steatotic liver disease (MASLD) and posthepatectomy liver failure (PHLF).

Methods: Eighty-one and 75 patients from two centers between 2012 and 2023 were studied. Targeted quantitative metabolomic assay of 180 circulating metabolites, perioperative GLP-1, GLP-2, and standard lipid parameter level evaluation was employed. An exploratory PHLF prediction model was developed, including GLP-1 as a metabolic parameter.

Results: Significant alterations of 44 metabolites by postoperative day (POD) 1 and 40 by POD5 were observed, mainly among phospholipid species. Unsupervised clustering identified two metabolic clusters, with one encompassing 93% of PHLF patients by POD5 (P<0.001). Standard plasma lipid parameters displayed consistent decrease after hepatectomy, independent from MASLD phenotype, with the lowest levels in PHLF patients. Postoperative GLP-1 and GLP-2 dynamics displayed a reciprocal pattern, indicating adaptive change in secretion. Preoperative GLP-1 levels were significantly increased in PHLF (P=0.02). Furthermore, incorporation of GLP-1 into the established aspartate aminotransferase to platelet ratio index (APRI) + albumin-bilirubin (ALBI) score, improved PHLF prediction [area under the curve (AUC): 0.833, 95% confidence interval (CI): 0.660–0.964].

Conclusions: Significant metabolic changes occur during human liver resection, particularly in phospholipid metabolism, along with distinct perioperative dynamics of GLP-1 and GLP-2, closely linked

to PHLF and independent of the histological phenotype of MASLD. Additionally, we provide exploratory results on the predictive value of GLP-1 for PHLF, emphasizing a holistic model of liver function assessment highlighting the metabolic component of human liver regeneration.

Keywords: Liver regeneration; posthepatectomy liver failure (PHLF); lipid metabolism; glucagon-like peptide-1 (GLP-1); metabolic dysfunction-associated steatotic liver disease (MASLD)

Submitted Aug 23, 2024. Accepted for publication Nov 30, 2024. Published online Jan 17, 2025.
doi: 10.21037/hbsn-24-464
View this article at: https://dx.doi.org/10.21037/hbsn-24-464

Introduction

The liver's ability to regenerate after substantial tissue loss is the foundation of oncologic liver surgery. Understanding the limits of how much tissue loss the remaining liver can compensate for maintaining homeostasis, and accurately estimating its regenerative capacity preoperatively, is critical to identify patients eligible for major liver surgery. Posthepatectomy liver failure (PHLF) still remains the leading cause of short-term mortality following major hepatectomy (1-3). Underlying liver diseases, increasingly prevalent in patients, critically impact hepatic functional reserve and regenerative capacity (4,5). Additionally, accumulating evidence suggests that alterations in intermediary metabolism significantly impact hepatic regeneration (6,7). In this context, lipid metabolism, providing for the increased energy demands and structural components necessary for membrane synthesis, is of utmost importance (7). Rodent models have demonstrated significant changes in lipid metabolism after induction of liver regeneration, involving not only hepatic de-novo synthesis, hepatic fatty acid trafficking and lipid oxidation, but also affecting peripheral lipid mobilization (7-9). Increased flux of lipids and fatty acids to the liver result in transient liver steatosis, crucially required for sufficient liver regeneration and disruption or delay of this process has been proven detrimental (10,11).

Although extensively studied in murine models, little is known about regulators of such and post-operative dynamics of lipid metabolism in humans following hepatectomy. In the context of hepatic regeneration, to our knowledge, these have never been reported. Previously, we suggested an association of the enteroendocrine L-cell derived incretin hormones glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2) in regulating lipid metabolism (6). In particular, both have been attributed to opposing effects on lipid and (apo)lipoprotein mobilization and metabolism. While GLP-1 exerts a decreasing effect on lipid absorption, plasma levels and hepatic fatty content, GLP-2 has pro-lipidemic effects and is critically regulated during liver regeneration (6). In rodent partial hepatectomy models, GLP-1 administration was reported to be detrimental (12), while GLP-2 administration has shown to improve liver regeneration (13).

Acknowledging that therapeutic targets for treating PHLF have not yet been identified, preoperative risk stratification remains paramount (14). Importantly, the majority of approaches for preoperative liver function assessment primarily focus on the liver's excretory or synthetic functions, neglecting the metabolic aspects of hepatic regeneration.

We aimed to investigate perioperative dynamics of circulating metabolites in functional and dysfunctional liver regeneration in patients undergoing partial hepatectomy by utilizing an unbiased metabolomic approach. Furthermore, given the fact that little is known about regulators critically affecting alterations in lipid metabolism during liver regeneration, we evaluated plasma level dynamics of GLP-1 and GLP-2 in relation to the histologic phenotype of metabolic dysfunction-associated steatotic liver disease (MASLD) and PHLF. We further assessed the predictive potential of baseline GLP-1 plasma levels, aiming to reflect the metabolic component of hepatic regeneration and ultimately compared it to established predictors of PHLF (15-18). We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-464/rc) (19).

Methods

Study populations

This study included 156 patients from two institutions. Eighty-one patients underwent liver resection at the

Clinicum Landstrasse, Vienna from January 2012 to January 2018 (cohort 1) and 75 patients had liver resections at State Hospital Wiener Neustadt, Austria between July 2018 and December 2023 (cohort 2). Patient selection for inclusion was conducted according to plasma sample availability in our prospectively maintained biobank. All patients underwent liver resections for colorectal liver metastasis (CRLM), hepatocellular carcinoma (HCC), intrahepatic or perihilar cholangiocarcinoma carcinoma (iCCA/pCCA), other secondary liver tumors or benign liver lesions. None of the patients had a documented history of chronic excessive alcohol consumption. Patients with type II diabetes mellitus did not take any antidiabetic drugs within 24 hours prior to surgery (except short-acting insulin for immediate blood glucose correction), and none of the patients had used GLP-1 analogs. Resections were classified as minor (<3 anatomical segments) or major (≥3 anatomical segments) resections according to the Brisbane 2000 nomenclature (20). Good Scientific Practice in accordance with guidelines and principles of the Declaration of Helsinki (as revised in 2013) were followed. Blood collection was conducted after obtaining written informed consent of patients and approval by the institutional ethics committees (Ethics Committee of the Medical University of Vienna: EK 16-253-0117 and Ethics Committee Niederösterreich: GS-1-EK-4/568-2018).

Highlight box

Key findings

- Lipid metabolism is significantly altered during human liver regeneration, especially in cases of impaired regeneration. Glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2), regulators of hepatic lipid metabolism, show altered perioperative plasma levels in patients who develop posthepatectomy liver failure (PHLF), independent of the metabolic dysfunction-associated steatotic liver disease (MASLD) histologic phenotype. Elevated preoperative GLP-1 levels were linked to PHLF risk and may serve as a predictive tool.

What is known and what is new?

- Lipid metabolism is tightly regulated during liver regeneration in rodents, involving reduced hepatic lipid synthesis and export, alongside increased lipid uptake for energy and cell proliferation. GLP-1 and GLP-2 plasma levels have been reported to adjust during hepatic regeneration. However, human data on these dynamics and their association with PHLF are lacking, and the metabolic perspective for PHLF risk stratification has not yet been explored.
- This study identified significant perioperative changes in lipid metabolism, including alterations in circulating phospholipids, standard plasma lipids, GLP-1, and GLP-2, with no association to advanced steatosis or the MASLD histologic phenotype. Preoperative GLP-1 levels were linked to PHLF risk and incorporated into a combined stratification tool.

What is the implication, and what should change now?

- Maintaining lipid homeostasis is crucial for effective liver regeneration. Given the strong association between preoperative GLP-1 levels and PHLF, along with its role in lipid homeostasis during liver regeneration, the perioperative use of GLP-1 analogs may pose a risk for patients undergoing hepatic resection. Larger studies are needed to confirm GLP-1 as a predictive marker for integration into risk stratification tools.

Definition of outcome parameters

PHLF according to the definition of the International Study Group of Liver Surgery (ISGLS) was defined as clinical endpoint. In brief, elevation of serum bilirubin (SB) level exceeding the ULON and a prolonged prothrombin time (PT) on POD5 or beyond was classified as PHLF. If SB or PT were preoperatively elevated, any further increase until POD5 or beyond was considered for PHLF classification. Patients who were discharged before POD5 due to excellent clinical presentation were classified as not having PHLF (21).

Postoperative morbidity was graded according to the Dindo *et al.* classification. Severe morbidity was noted if invasive complication management was required, with the most severe complication taken as the reference (22).

Blood collection and processing

For the first cohort, blood was collected into prechilled citrate, theophylline, adenosine and dipyridamole (CTAD) tubes prior to surgery (PRE), on POD1 and POD5 and immediately placed on ice. In the second cohort, blood was collected following the same protocol as in cohort 1 and drawn into EDTA tubes additionally containing a DPP4-inhibitor (10 µmol/L, Sigma Aldrich, St. Louis, MO, USA) and aprotinin (500 KIU/mL, Sigma Aldrich, St. Louis, MO, USA) for protease inhibition, according to established protocols (23). Blood was drawn after a minimum of 8 hours of fasting, consistently at the same time each morning at the specified timepoints. For both cohorts, plasma preparation was carried out as previously described (24). In brief, drawn blood samples were chilled on ice and further processed by two immediate centrifugation steps within 20 min after acquisition, including 10 min, 1,000 g at 4 ℃ and 10,000 g for 10 min at 4 ℃ for further purification from cell detritus and platelets. Plasma was stored in aliquots at –80 ℃ until further use.

Metabolomic analysis

Metabolites were analyzed using a targeted quantitative metabolomics assay with internal quality control (Biocrates Absolute IDQ p180 kit from Biocrates Life Science, Innsbruck, Austria). This independently validated kit includes analyses of 76 phosphatidylcholines (PCs), 14 lysophosphatidylcholines, 15 sphingomyelins (SMs), 40 acylcarnitines, 21 amino acids, and 19 biogenic amines (25). Sample preparation and quality control were conducted according to the vendor's manual (Archimed Life Science, Vienna, Austria).

GLP-1, GLP-2 and standard plasma lipid parameters

Commercially available ELISA kits were used to determine plasma concentrations of total GLP-1 (7–36 and 9–36) (ALPCO, Salem, NH, USA) and total GLP-2 (1–33 and 3–33) (Merck Millipore, Burlington, MA) following the manufacturers' instructions. Routine laboratory parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (γ-GT), alkaline phosphatase (AP), bilirubin, PT, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB), were measured perioperatively in fasting plasma.

Histological analysis

The histological phenotype of MASLD was evaluated in tumor distant liver tissue from resection specimens. Two trained clinical pathologists, blinded for patient's clinical outcome analyzed hematoxylin/eosin dyed formalin-fixed paraffin-embedded (FFPE) tissue slices by employing the NAFLD activity score (NAS) (26). Briefly, by allocating points for histological findings of steatosis, hepatocyte ballooning and inflammation activity, groups were stratified and named according to the Delphi consensus nomenclature noMASLD (0–2 patients) and MASLD (≥3 patients). Fibrosis was assessed employing the Kleiner *et al.* classification (27).

Statistical analysis

The analysis was based on non-parametric tests due to the small sample sizes in rare clinical outcome groups and to increase robustness regarding outliers. Partial least squares discriminant analysis (PLS-DA) was used to identify the most relevant postoperatively changed metabolites and their association with PHLF. Metabolic profiles were hierarchically clustered based on Euclidean distance with average linkage using Genesis (TU Graz, Austria, version 1.8.1, 2017). The Mann-Whitney *U* test or Kruskal-Wallis test was applied for the comparison of means. The chi-square and Fisher exact test were used to analyze group differences regarding metabolic clusters and histological phenotypes. Associations between variables were evaluated using Spearman correlation. The odds ratios of variables potentially associated with PHLF were calculated using univariate binary regression modeling. Sensitivity and specificity for PHLF risk prediction were calculated using receiver operating characteristic (ROC) and in order to avoid overfitting, leave-one-out cross validation (LOOCV) was performed. Total GLP-1 values were $\log_2$ transformed to approximate normal distribution. The optimal cutoffs for PHLF prediction were determined by calculating the Youden index (J). Collinearity between the evaluated models was assessed and ruled out, as indicated by a variance inflation factor (VIF) of 1. Model goodness of fit was evaluated based on minimal Akaike information criterion (AIC). A P-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS® version 20 (IBM, Armonk, NY, USA), GraphPad Prism 8.0.2 (GraphPad Software Inc., San Diego, CA, USA), and R (R Foundation for Statistical Computing, Vienna, Austria, version 3.6.1, 2019).

Results

Patient demographics

In this study, a total of 156 patients were included and evaluated according to technical considerations in two separate cohorts of 81 and 75 patients. The median age of the total cohort was 64.9 years at the time of surgery and 69% were men. Severe underlying fibrosis was observed in 19% of patients in cohort 1 and 16% in cohort 2, with higher prevalence in patients with HCC, at 42% and 56%, respectively. Patient characteristics are displayed in *Table 1*. Our first cohort was stratified for their alterations of their metabolic profile until the first and fifth postoperative day (POD) (Cluster A and Cluster B). The second cohort was stratified in subgroups according to the presence of MASLD histologic phenotype and PHLF. Both cohorts were comparable to each other, except major liver resections

Table 1 Patient characteristics of both cohorts

Characteristics	Cluster A		Cluster B		P	noMASLD		MASLD		P
	n	%/M [IQR]	n	%/M [IQR]		n	%/M [IQR]	n	%/M [IQR]	
Age (years)†	31	65.3 [57.3–71.7]	50	63.9 [56.3–72.7]	0.89	44	65.3 [60.7–75.9]	31	65.1 [55.3–74.7]	0.69
Sex					0.27					0.39
Male	20	65	38	76		27	61	22	71	
Female	11	35	12	24		17	39	9	29	
Entity					0.33					0.057
CRCLM	15	48	28	56		21	48	12	39	
HCC	6	19	13	26		6	14	10	32	
CCA	10	33	9	18		15	34	4	13	
Others	0	0	0	0		1	2	2	6	
Benign	0	0	0	0		1	2	3	10	
PHLF					0.003					0.75
Yes	12	39	5	10		8	18	4	13	
No	19	61	45	90		36	82	27	87	
Steatosis†					0.31					<0.001
≤33%	22	96	29	74		41	93	10	32	
>33%	1	4	10	26		3	7	21	68	
MASLD†	9	40	8	24	0.31					
noMASLD†	13	60	25	76						
Fibrosis†					0.41					0.21
Mild (f0–2)	20	72	37	82		41	93	23	74	
Severe (f3+4)	7	28	8	18		3	7	8	26	
Major resection	25	81	32	64	0.11	21	48	7	23	0.03
Minor resection	6	19	18	36		23	52	24	77	
Severe morbidity (CD ≥3)					0.20					0.73
Yes	8	26	7	14		10	23	6	19	
No	23	74	43	86		34	77	25	81	
Preoperative chemotherapy					0.90					>0.99
Yes	11	35	17	34		17	39	12	39	
No	20	65	33	66		27	61	19	61	
Oxaliplatin based‡	8	73	15	88	0.35	13	76	9	75	>0.99
Irinotecan based‡	5	45	2	12	0.08	3	18	2	17	>0.99
BMI (kg/m^2)						44	25.2 [23.2–27.5]	31	27.5 [23.8–32.2]	0.02
Diabetes					0.52					0.94
Yes	5	16	11	22		11	25	8	26	
No	26	84	39	78		33	75	23	74	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Cluster A		Cluster B		P	noMASLD		MASLD		P
	n	%/M [IQR]	n	%/M [IQR]		n	%/M [IQR]	n	%/M [IQR]	
Metformin					0.69					0.26
Yes	4	15	5	10		3	7	5	16	
No	27	85	45	90		41	93	26	84	
DPP-4 inhibitor					–					0.73
Yes	0	0	0	0		5	12	5	16	
No	31	100	50	100		39	88	26	84	
Statin[†]					0.15					0.96
Yes	0	0	5	10		13	30	9	29	
No	29	100	43	90		31	70	22	71	
Laboratory parameters										
Triglycerides (mg/dL)						41	114 [98–162]	31	170 [113–238]	0.009
Total cholesterol (mg/dL)						41	184 [137–218]	31	184 [152–220]	0.38
HDLc (mg/dL)						41	49 [36–64]	29	43 [36–56]	0.53
LDLc (mg/dL)						41	97 [57.5–139.5]	29	105 [73–123]	0.86
ApoA1 (g/L)						38	1.32 [1.06–1.60]	31	1.35 [1.17–1.54]	0.71
ApoB (g/L)						38	0.77 [0.77–1.14]	31	1.02 [0.72–1.13]	0.11
Total GLP-1 (pg/mL)						21	7.26 [6.10–15.83]	23	11.87 [6.10–50.79]	0.23
Total GLP-2 (pg/mL)						21	2.81 [1.85–3.92]	23	3.82 [2.49–4.20]	0.16
Bilirubin (mg/dL)	31	1.1 [0.8–1.6]	48	1.0 [0.7–1.5]	0.44	42	0.6 [0.4–0.8]	31	0.6 [0.4–0.8]	0.76
Platelets (T/L)	31	187 [142–298]	49	190 [160–228]	0.78	42	192 [147–242]	30	236 [187–310]	0.055
PT (%)	31	80 [70–90]	48	89 [74–98]	0.08	42	95 [86–103]	31	96 [84–108]	0.60
Albumin (mg/mL)	13	28.5 [27.7–31.1]	31	32.8 [30.2–34.8]	0.006	40	41.2 [37.8–42.7]	27	42.6 [39.5–44.3]	0.11
AST (U)	30	340 [260–539]	48	319 [202–477]	0.36	42	29 [23–47]	31	33 [23–49]	0.89
ALT (U)	31	295 [133–440]	48	240 [148–413]	0.60	42	24 [16–41]	31	28 [19–56]	0.29
GammaGT (U)	31	64 [40–112]	47	61 [34–106]	0.96	42	69 [27–186]	31	66 [32–162]	0.79
Alkaline phosphatase (U)	23	60 [49–86]	32	77 [57–86]	0.31	42	98 [64–161]	31	86 [73–111]	0.33
Cholinesterase (U/mL)	14	4.15 [3.16–5.37]	32	4.99 [4.04–6.55]	0.12	41	7.01 [5.42–8.01]	28	8.49 [6.03–9.46]	0.07

[†], group comparisons with missing patient details. [‡], patients that received both, oxaliplatin and irinotecan based chemotherapy were accounted for in both groups. MASLD, metabolic dysfunction-associated steatotic liver disease; CRCLM, colorectal cancer liver metastasis; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; PHLF, posthepatectomy liver failure; CD, Clavien-Dindo classification; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GammaGT, γ-glutamyltransferase; M, median; IQR, interquartile range.

were more often performed in the first cohort than in the second (70% *vs.* 37%; P<0.001). PHLF occurred in 27% in cohort 1 and in 16% in cohort 2 (P=0.42).

Alterations of circulating metabolites during liver regeneration

By analyzing postoperative changes of 180 circulating metabolites in 81 patients, we were able to delineate 44 metabolites that changed significantly during liver regeneration. Among those, we found 12 proteinogenic amino acids and 23 phospholipid species significantly altered within the first POD (all P<0.05). Utilizing an unsupervised hierarchical clustering approach, we identified 2 metabolomic clusters displaying most similar variance, including 31 patients in cluster A and 50 patients in cluster B. Cluster A was associated with an increase in circulating amino acids, while phospholipids were markedly decreased compared to baseline level. Among the decreased ten identified PC species, 80% had polyunsaturated primary acyl chains, while only 17% of the 12 SM metabolites had 2 or more double bounds. Interestingly, the incidence of PHLF was significantly higher in cluster A compared to cluster B (39% *vs.* 10%; P=0.004). When assessing PHLF incidence in the subgroups of major resections, 48% of patients in cluster A and 9% in cluster B developed PHLF (P=0.01). Additionally, the incidence of steatosis >33% was lower (4%) in cluster A than in cluster B (26%, P=0.04) and histologic phenotype of MASLD was present in histological specimens of tumor distant liver tissue in 40% and 24%, respectively (P=0.31) (*Figure 1*).

Differences in lipid metabolism aggravate till POD5

When evaluating changes of circulating metabolites until POD5 in 38 patients (samples available for patients that had not left the hospital), 40 metabolites remained significantly altered. Thirty-five of these were lipid species, including 20 PCs, 9 SMs and 6 Acyl-carnitines (ACs). Interestingly, 15 PCs were polyunsaturated with 12 PCs having 4 or more double bounds. Except for PCaaC36:5, all other phospholipids were decreased in cluster A. On the contrary, all 6 ACs were increased in Cluster A. Two were medium-chain length ACs (6–12 carbon acyl-residues) and 3 had >12 carbon acyl-residues (long-chain). Of note, 93% of all PHLFs in this cohort (P<0.001) were associated with the metabolic profile of Cluster A. Again, intriguingly, cluster A showed a lower rate of baseline >33% steatosis (6% in cluster A *vs.* 37% in cluster B; P=0.04) and a similar rate of MASLD (21% cluster A *vs.* 38% cluster B; P=0.44) (*Figure 2*).

Perioperative dynamics of standard plasma lipid parameters

We further aimed to confirm, if the observed alterations of lipid metabolites would be reflected standard blood lipid parameters during liver regeneration. Accordingly, we investigated perioperative triglyceride, total cholesterol, HDLc, LDLc, apolipoprotein A1 and apolipoprotein B trajectories in patients stratified for their histological phenotype of MASLD and PHLF perioperatively during liver regeneration. We observed a consistent postoperative decrease in all parameters until the first POD. While triglyceride levels tended to increase again until POD5 in all patients, this recovery was delayed in PHLF (*Figure 3A*). Plasma total cholesterol, HDLc, LDLc, apolipoprotein A1 and apolipoprotein B further decreased, with significant differences between groups at certain time points (as illustrated in *Figure 3*). Except of triglycerides, PHLF was associated with the lowest circulating levels of total cholesterol, HDLc, LDLc, apolipoprotein A1 and apolipoprotein B, already present at baseline level preoperatively (*Figure 3B-3F*).

When summarizing patients who did not develop PHLF and compare baseline lipid levels to PHLF patients, HDLc and apoA1 level were already preoperatively significantly decreased in PHLF (P=0.01 and P=0.005, respectively). PHLF development was not related to patients BMI, MASLD histology, preoperative chemotherapy, but related to diabetes [odds ratio (OR) 3.85, 95% CI: 1.06–13.91; P=0.04] (Table S1).

GLP-1 and GLP-2 are linked to circulating lipid dynamics during liver regeneration

Given the suggested involvement of GLP-1 and GLP-2 in regulating lipid mobilization and trafficking during liver regeneration, we further evaluated perioperative GLP-1 and GLP-2 plasma concentrations in patients stratified according to their histological phenotype of tumor distant liver tissue and PHLF. In PHLF patients, GLP-1 was already preoperatively 3-fold elevated compared to patients without the histological phenotype of MASLD (noMASLD) (P=0.009, *Figure 4A*) and 2.3 times increased compared to MASLD patients, although statistically not significant (P=0.19, *Figure 4A*). In all patients GLP-1 level

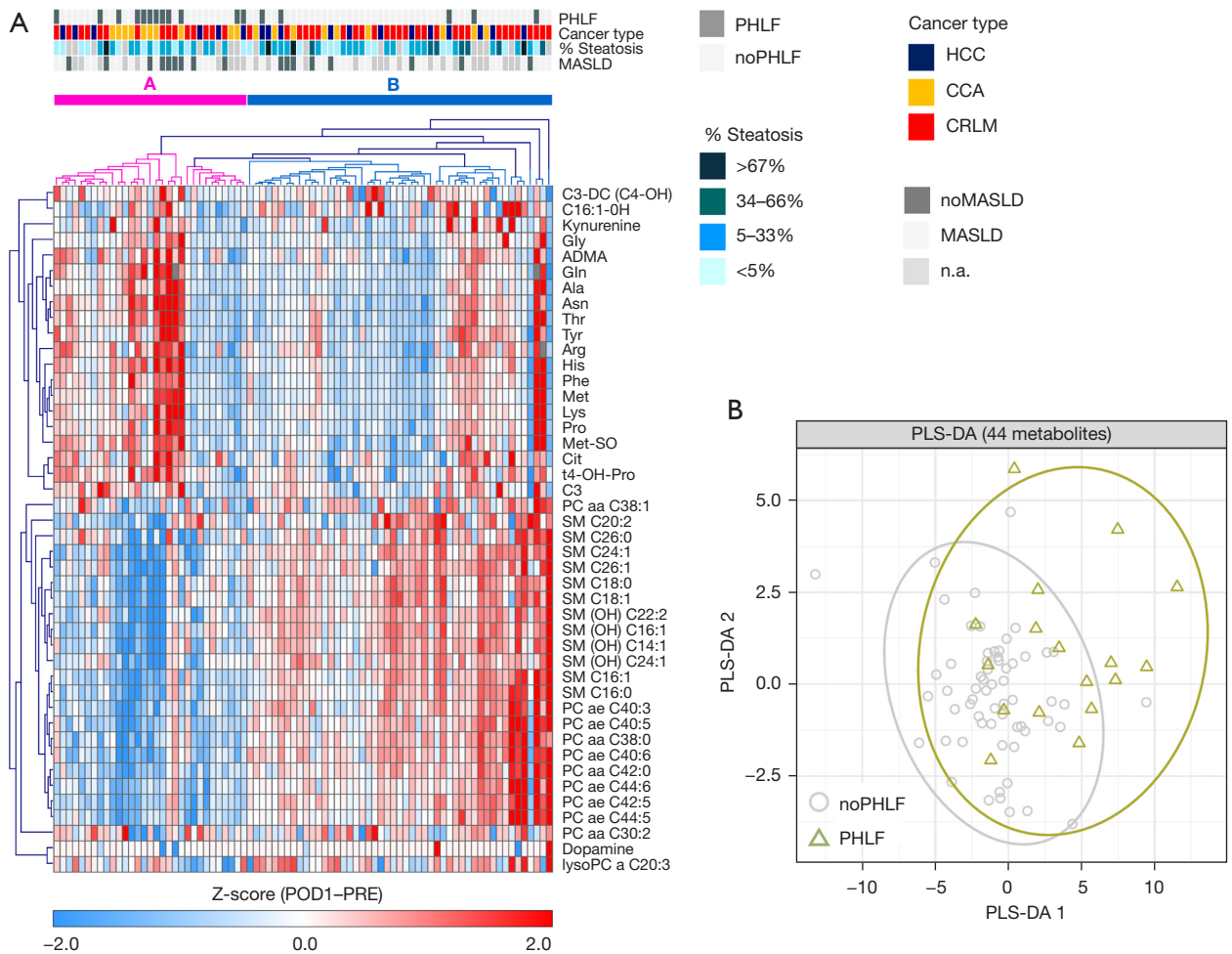

Figure 1 Changes in circulating metabolites until POD1. (A) Heatmap of 44 significantly changed metabolites from baseline until POD1. (B) Partial least squares-discriminant analysis indicates the distribution of the 44 metabolites according to PHLF development. PHLF, posthepatectomy liver failure; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; CRLM, colorectal cancer liver metastasis; MASLD, metabolic dysfunction-associated steatotic liver disease; n.a., detail not available; POD1, postoperative day 1; PRE, prior to surgery; PLS-DA, partial least squares discriminant analysis.

decreased until the first POD and further reached baseline level until POD5. The magnitude of change between groups were similar (right panel of *Figure 4A*). On the other hand, baseline GLP-2 concentrations were not elevated in PHLF patients, but differed between noMASLD and MASLD (P=0.03). Postoperatively, GLP-2 level increased markedly when PHLF occurred (2.1-fold in PHLF *vs.* 1.1-fold in noMASLD *vs.* 1.0-fold in MASLD, P=0.002 and P=0.10, respectively), most prominent upon POD5 (2.5-fold in PHLF *vs.* 1.6-fold in noMASLD *vs.* 1.2-fold in MASLD, P=0.02 and P=0.005, respectively) (*Figure 4*).

When correlating total GLP-1 and -2 plasma levels with standard plasma lipid parameters in the entire cohort 2, our data surprisingly revealed an inverse correlation of lipid parameters with GLPs. Our findings depicted a positive correlation of triglycerides with total GLP-1 and an inverse correlation of total GLP-2 with total cholesterol, HDLc, LDLc, apolipoprotein A1 and apolipoprotein B. This relation was even stronger in the cohort that developed PHLF (Table S2).

Preoperative GLP-1 level predict risk for PHLF

We further compared baseline GLP-1 in patients that did

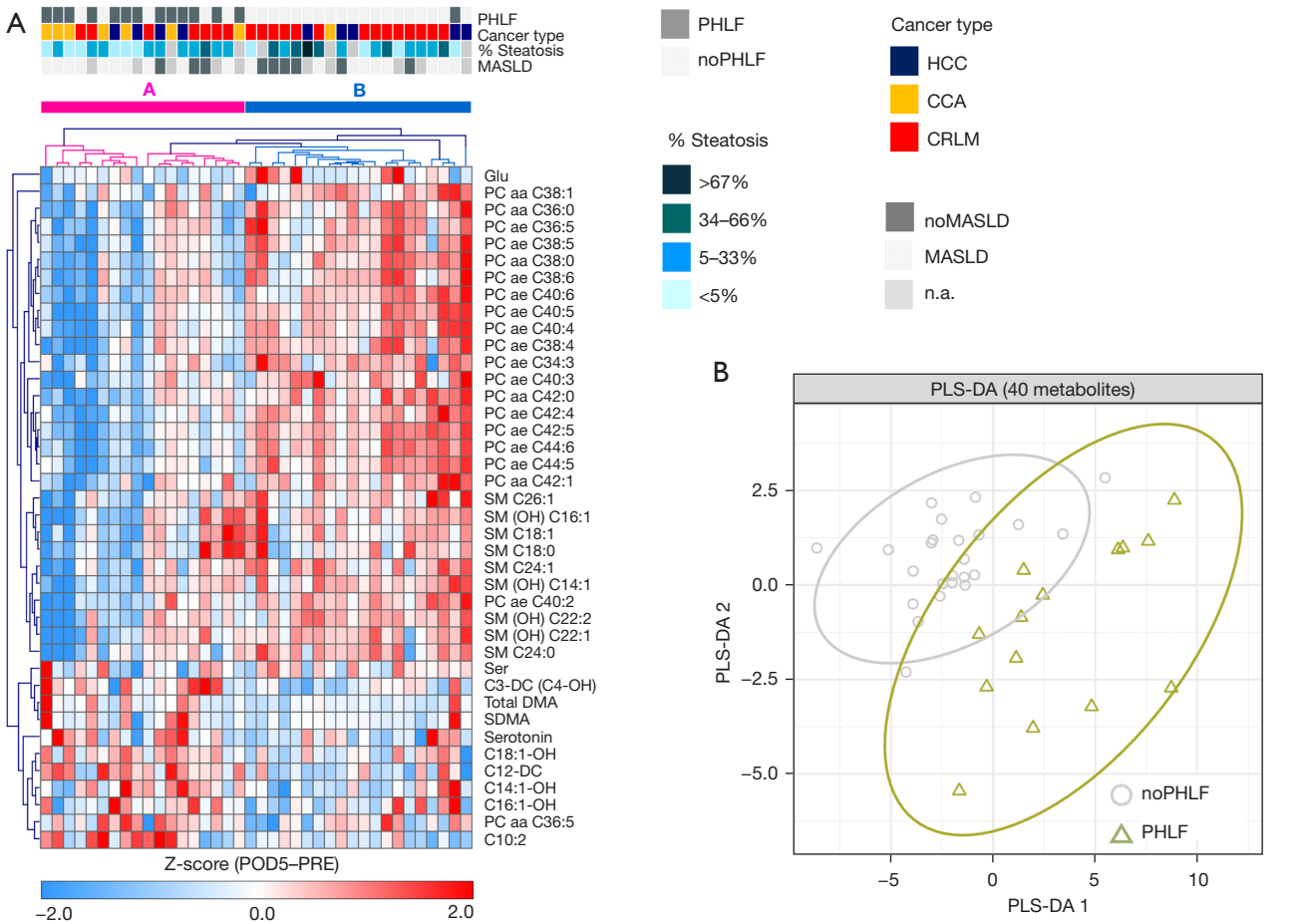

Figure 2 Changes in circulating metabolites until POD5. (A) Heatmap of the 40 unsupervised hierarchical clustered metabolites according to their significant changes in 38 patients with accessible plasma samples until POD5. (B) Partial least squares-discriminant analysis of the 40 metabolites in PHLF. PHLF, posthepatectomy liver failure; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; CRLM, colorectal cancer liver metastasis; MASLD, metabolic dysfunction-associated steatotic liver disease; n.a., detail not available; POD, postoperative day; PRE, prior to surgery; PLS-DA, partial least squares discriminant analysis.

and did not develop PHLF. We found a significant elevation of GLP-1 levels already preoperatively in patients with PHLF (P=0.02) (*Figure 5*). Of note, preoperative GLP-1 level did not appear to be associated with diabetes, steatosis, fibrosis or MASLD (Figure S1).

We further assessed baseline GLP-1 level for its PHLF predictive potential and compared it to the combined APRI + ALBI score, that we previously identified as strong preoperative predictor for PHLF.

ROC analysis confirmed the predictive potential of the APRI + ALBI score [area under the curve (AUC): 0.804, 95% confidence interval (CI): 0.614–0.961, bootstrap]. Furthermore, we evaluated $\log_2$(GLP-1): AUC: 0.753 (95% CI: 0.614–0.961, bootstrap) and integrated it into the APRI + ALBI | $\log_2$(GLP-1) model, observing an improved prediction for PHLF [AUC: 0.833 (0.660–0.964, bootstrap)] reaching a superior sensitivity of 67%, specificity of 91% with a PPV of 67% and a NPV of 91% (*Figure 6*, *Table 2*).

Discussion

This study highlights the role of lipid metabolism homeostasis in human liver regeneration across two independent cohorts. We identified significant alterations in circulating lipid species during hepatic regeneration in all patients, but also striking differences between patients with and without PHLF. Importantly, we found these processes to be independent from advanced hepatic steatosis or the

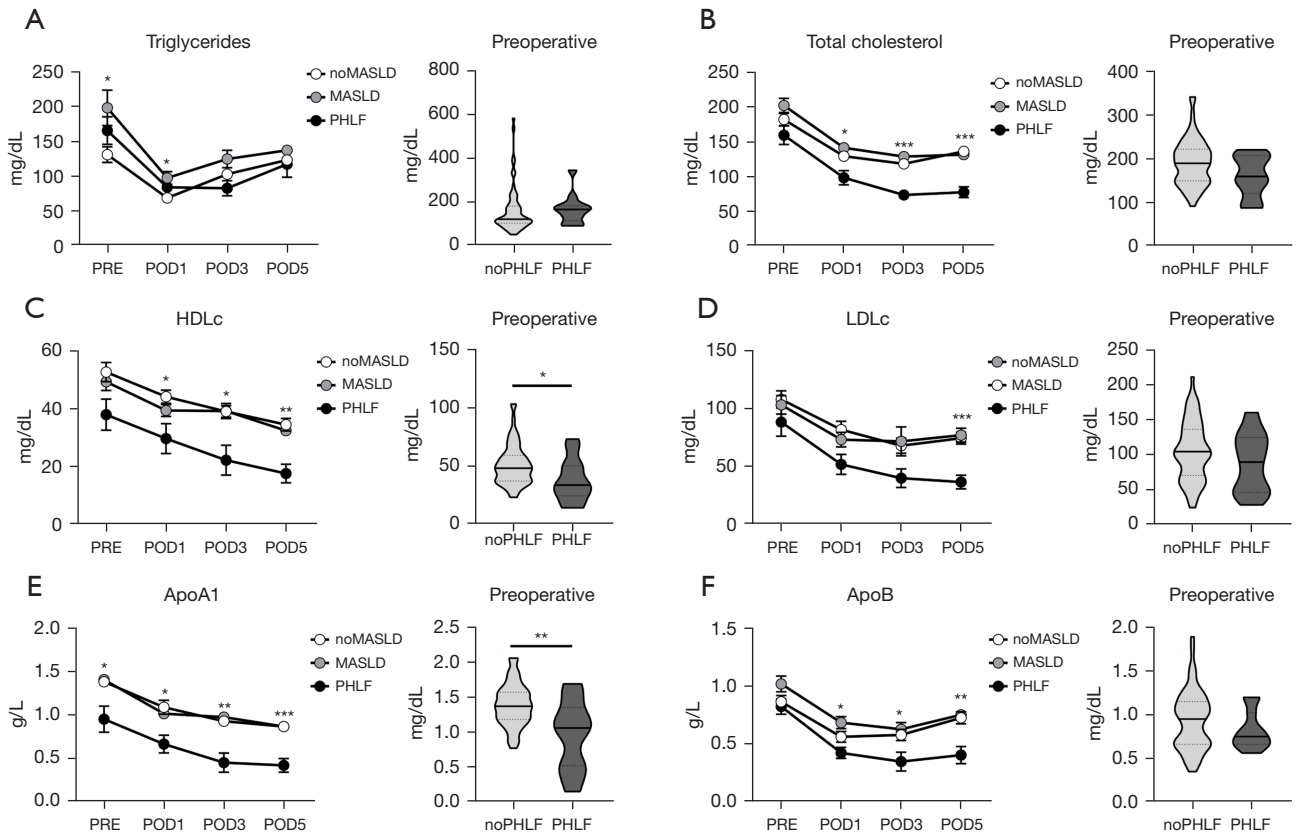

Figure 3 Perioperative standard plasma lipid parameter dynamics stratified for histologic MASLD phenotype and PHLF. (A-F, left panels) Postoperative dynamics of plasma triglycerides, total cholesterol, HDLc, ApoA1, LDLc and ApoB. (A-F, right panels) Preoperative differences of indicated lipid parameters according to PHLF development. *, P<0.05; **, P<0.005; ***, P<0.0005. MASLD, metabolic dysfunction-associated steatotic liver disease; PHLF, posthepatectomy liver failure; PRE, preoperative; POD, postoperative day; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B.

histologic phenotype of MASLD. Additionally, we found correlations with metabolic regulators GLP-1 and GLP-2, which are crucial for and affected by hepatic regeneration. Recognizing the link between PHLF development and lipid homeostasis, we identified significant preoperative differences in GLP-1, HDLc, and ApoA1. We found GLP-1 plasma levels to be a strong predictor of PHLF in our exploratory analyses, highlighting the metabolic aspect of liver function. Integrating GLP-1 levels into the APRI + ALBI score, a strongly validated prediction model that does not include metabolic parameters, we were able to improve predictive performance and offer a more holistic model for PHLF risk stratification.

Rodent studies show significant metabolic changes in lipid homeostasis during liver regeneration, including lipid mobilization from peripheral storage and fatty acid flux into hepatocytes. These changes provide metabolites for beta-oxidation and structural components. Importantly, these adaptations are global and occur independently of the liver injury model used (7-11). Our metabolomic data of human samples closely mirrored these observations, revealing a significant decrease in circulating PCs, especially those with polyunsaturated acyl-chains (PUFA-PCs), in cases of delayed or impaired liver regeneration. PCs, crucial for cell homeostasis and viability, are synthesized via the Kennedy (CDP-choline) pathway and the Lands cycle ubiquitously across all cell types (28-30). However, hepatocytes specifically use the phosphatidylethanolamine N-methyltransferase (PEMT) pathway, accounting for about 30% of liver PC synthesis and the primary source of circulating PUFA-PCs (31,32). Liver derived lipids, including SMs, must be packaged into very-low-density

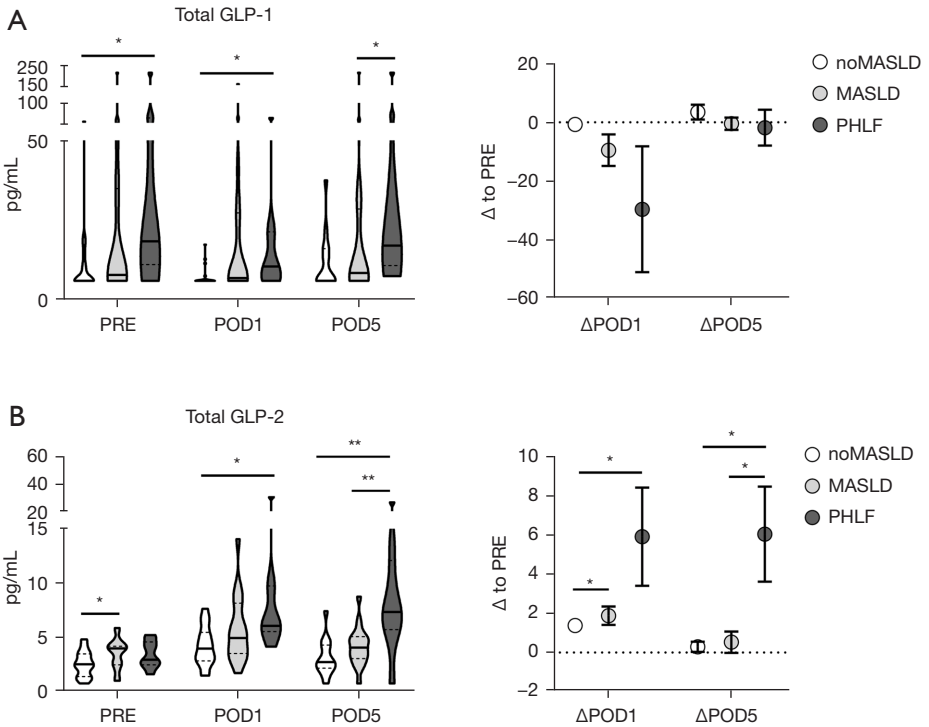

Figure 4 Perioperative total GLP-1 and total GLP-2 dynamics. (A, left) Total GLP-1 and (B, left) total GLP-2 concentrations at baseline, on POD1 and POD5 according to the histological phenotype of MASLD and PHLF. (A + B, right) Comparison of absolute magnitude of total GLP-1 and total GLP-2 change until POD1 and POD5. *, P<0.05; **, P<0.005. GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; PRE, preoperative; MASLD, metabolic dysfunction-associated steatotic liver disease; PHLF, posthepatectomy liver failure; POD, postoperative day.

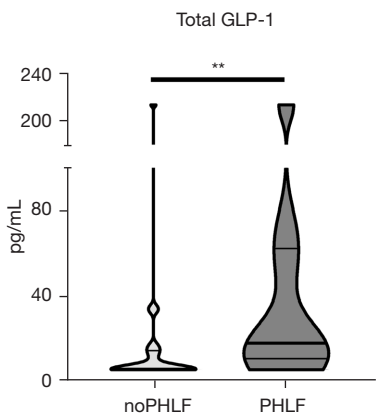

Figure 5 Preoperative total GLP-1 plasma level. Baseline total GLP-1 plasma level in patients who did and did not develop PHLF. **, P<0.005. GLP-1, glucagon-like peptide-1; PHLF, posthepatectomy liver failure.

lipoproteins (VLDL) to enter circulation and are exchanged between HDL and LDL particles for liver recycling, a process critically dependent on PC synthesis (33). Common rodent liver injury models often disrupt PC synthesis by dietary choline depletion, underscoring the importance of PC homeostasis (34-36). Our data showed decreased perioperative HDLc and ApoA1 level in PHLF patients, potentially reflecting compromised liver function associated with impaired liver regeneration.

Previous reports have shown down-regulation of the PEMT pathway during liver regeneration, reducing hepatic PUFA-PC content and secretion (37). Our data indicated a postoperative decrease in circulating PUFA-PCs and SMs, along with decreased levels of ApoA1, HDLc, and total cholesterol, especially in patients with insufficient liver regeneration, reflecting a shift of plasmatic lipids

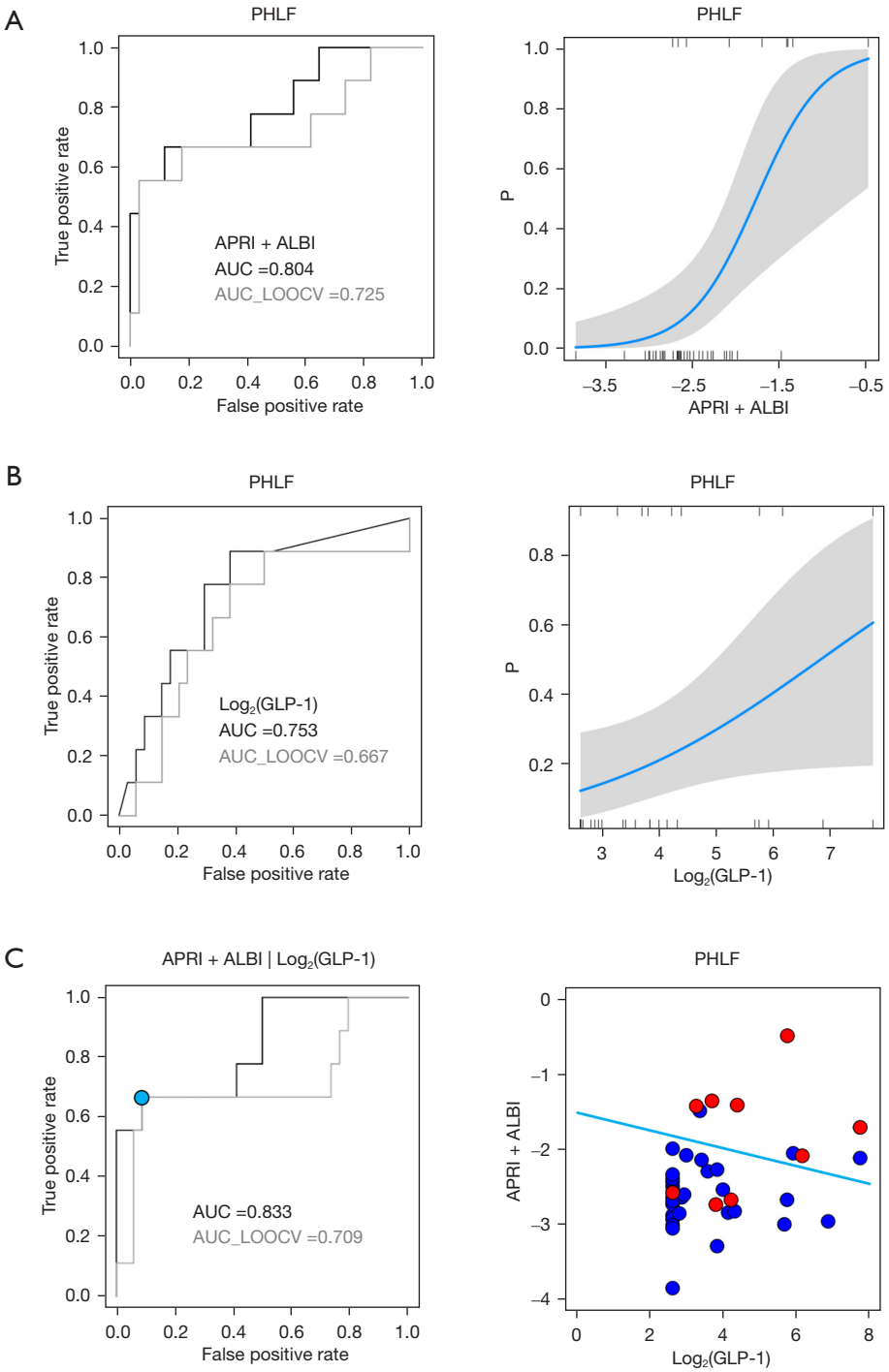

Figure 6 Prediction of PHLF. (A) ROC evaluation of the combined APRI + ALBI score, and regression curve of the logistic regression model's P-score illustrating the relationship of PHLF and the APRI + ALBI score (B) and log_2(GLP-1). (C) ROC analysis of the integrated APRI + ALBI | log_2(GLP-1) model; light blue dot indicating cut-off according to the Youden index (left panel); scatter blot of the combined APRI + ALBI | log_2(GLP-1) model, light blue line indicating model's cut-off for identification of PHLF patients (red dots). PHLF, posthepatectomy liver failure; APRI, aspartate aminotransferase to platelet ratio index; ALBI, albumin-bilirubin score; AUC, area under the curve; LOOCV, leave one out cross validation; Log_2(GLP-1), log_2 transformation of non-normal distributed GLP-1 plasma values; ROC, receiver operating characteristic.

Table 2 Evaluation of APRI + ALBI, log_2(GLP-1) and combined model to predict PHLF

Prediction model	AUC (95% CI, bootstrap)	AIC	J	SN (%)	SP (%)	PPV (%)	NPV (%)
APRI + ALBI	0.804 (0.614–0.961)	35.44	0.549	67	88	60	91
Log_2 (GLP-1)	0.753 (0.614–0.961)	44.24	0.507	89	62	38	96
APRI + ALBI	log_2(GLP-1)	0.833 (0.660–0.964)	36.41	0.578	67	91	67	91

APRI, aspartate aminotransferase to platelet ratio index; ALBI, albumin-bilirubin score; log_2(GLP-1), log_2 transformation of non-normal distributed GLP-1 plasma values; PHLF, posthepatectomy liver failure; AUC, area under the curve; CI, confidence interval; AIC, Akaike information criterion; J, Youden Index; SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value.

into hepatocytes and decreased de novo synthesis during regeneration (9).

Although the baseline metabolomic profile was not distinctly associated with PHLF development, our observation of differences in preoperative standard plasma lipid parameters in the second cohort suggests a disruption of underlying metabolic homeostasis that predisposes to impaired liver regeneration. Of note, we did not observe alterations of circulating metabolites associated with the histological phenotype of MASLD or advanced steatosis, which were even less prevalent in patients who developed PHLF.

While a number of cellular regulators are known to influence hepatocyte lipid metabolism during liver regeneration, little is known about the systemic effectors that orchestrate lipid mobilization and trafficking during this process (7). GLP-1 and GLP-2 have been extensively studied in the context of metabolic disorders, particularly in diabetes and short bowel syndrome, respectively (38,39). Their roles in liver regeneration on multiple levels have been discussed, including their metabolism-regulating effects across various models and in humans (6,12,13). Briefly, as effectors of the gut-liver axis, GLP-1 and GLP-2 secretion from enteroendocrine L-cells is regulated not only by luminal nutrient exposure, but also during fasting via bile acids and interleukin-6, both of which are altered during liver regeneration after hepatectomy (6). Physiologically, GLP-1 and GLP-2 have opposing effects on plasma and hepatic lipid metabolism. GLP-1 decreases plasma lipid levels and hepatic lipid content (40,41), while GLP-2 mobilizes lipids from peripheral stores (42), upregulates lipid mobilization via chylomicron and VLDL synthesis, thereby increasing plasma lipid levels and ultimately hepatic lipid content, both in rodents and humans (40,43-45). Interestingly, in rodents, perioperative GLP-1 supplementation has been reported to negatively affect hepatocyte proliferation, potentially by reducing postoperative hepatic lipid accumulation, a process repeatedly shown to be critical for effective liver regeneration (12). Mechanistically, GLP-1 increases protein kinase A (PKA) activity, leading to phosphorylation of Akt and AMP-activated protein kinase (AMPK), the master regulator of cellular energy homeostasis. This promotes fatty acid β-oxidation, lipid breakdown, and inhibition of hepatic lipogenesis, ultimately reducing hepatic lipid content (46-49). In contrast, GLP-2 supplementation has been shown to support liver regeneration in rodents (13), potentially through additional mechanisms beyond its lipogenic effects, including immunological regulation within the gut-liver axis and improved mesenteric perfusion, as we have discussed in more detail elsewhere (6).

Our data further elucidate the relationship between GLP-1 and GLP-2 levels and standard lipid parameter dynamics during liver regeneration. Interestingly, the plasma concentrations of GLP-1 and GLP-2 exhibited an inverse relationship with plasma lipid levels, which is contrary to their expected physiological effects. This suggests an adaptive postoperative downregulation of GLP-1 and upregulation of GLP-2 secretion, most prominent in PHLF, independent of the liver tissue's histological phenotype.

Maintaining lipid homeostasis is a critical aspect of overall liver function, and its adaptive capacity is essential for effective liver regeneration. Established preoperative liver function assessments to predict PHLF risk have been largely neglecting lipid metabolic processes. Our observation of elevated baseline GLP-1 levels in patients who developed PHLF, independent of severe fibrosis, diabetes, hepatic steatosis or histological MASLD phenotype, suggests an unfavorable preoperative homeostatic state. This is particularly intriguing, as GLP-1 levels are typically decreased in type 2 diabetes and obesity, both key features of metabolic syndrome, frequently associated hepatic steatosis/MASLD (50,51). Given this

preoperative association, along with previously reported detrimental effects of GLP-1 on liver regeneration in rodent models, the perioperative use of GLP-1 analogs, which are widely used for weight reduction in obesity (52) and are highly effective at reducing hepatic lipid content (53), raises concerns about their safety in the context of liver surgery.

Leveraging baseline GLP-1 levels as a predictive marker from the metabolic component of liver health and integrating it into the combined APRI + ALBI score, which we previously have documented to represent the most comprehensive stratifier for assessing global liver function and PHLF risk (16,17), demonstrated a superior model to predict PHLF.

In interpreting these study results, several limitations must be acknowledged. First, it is important to acknowledge that our study population is quite heterogeneous in terms of tumor type, multimodal therapies, and the extent of resection, all of which must be considered when interpreting our results. Additionally, potential pharmacological side effects that may influence metabolism should also be taken into account as a confounding factor. Secondly, we did evaluate two separate cohorts, one with detailed metabolic profiling and one with detailed routine lipid parameter profile. While it might be perceived as strength of the study that we observed similar processes in these two independent cohorts, we are unable to directly correlate metabolic assessments with lipid profiles. Thirdly, while our GLP-1-based PHLF prediction model is the first to reflect the metabolic component of liver regeneration, it is important to emphasize that this analysis is exploratory in nature. The findings are constrained by the small cohort size, highlighting the need for validation and further investigation in larger-scale studies. Moreover, whether GLP-1 is causatively involved in the pathophysiology of PHLF or merely reflects the metabolic steady state requires further clarification.

Conclusions

In summary, our data provide evidence that significant alterations in lipid metabolism occur during human liver regeneration, as reflected by changes in circulating plasma lipids, most distinct in cases of impaired liver regeneration. We identified an association between the dynamics of plasma GLP-1, GLP-2 and plasma lipid levels, as well as with PHLF, which was not associated with the histological liver tissue phenotypes of severe steatosis or MASLD. Preoperative GLP-1 levels were vital to predict PHLF, highlighting the necessity of including lipid metabolism parameters in global liver function and PHLF risk assessments.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-464/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-464/dss

Peer Review File: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-464/prf

Funding: This study was supported by the Austrian government "Bürgermeisterfonds, Vienna, Austria" (18129); NIH (R01DK122813); the Austrian Science Fund (FWF) (P-32064); and "City of Vienna Fund for Innovative Interdisciplinary Cancer Research" (21041). M.A. was personally supported by means of the IHPBA Kenneth Warren Fellowship during conducting this study. The funding organizations had no influence on study design, data management or publication of this article.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-464/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committees (Ethics Committee of the Medical University of Vienna: EK 16-253-0117 and Ethics Committee Niederösterreich: GS-1-EK-4/568-2018) and individual consent for this retrospective analysis was obtained.

References

1. Baumgartner R, Gilg S, Björnsson B, et al. Impact of post-hepatectomy liver failure on morbidity and short- and long-term survival after major hepatectomy. BJS Open 2022;6:zrac097.
2. Gilg S, Sandström P, Rizell M, et al. The impact of post-hepatectomy liver failure on mortality: a population-based study. Scand J Gastroenterol 2018;53:1335-9.
3. Sparrelid E, Olthof PB, Dasari BVM, et al. Current evidence on posthepatectomy liver failure: comprehensive review. BJS Open 2022;6:zrac142.
4. Capussotti L, Muratore A, Amisano M, et al. Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival--a European single center experience. Eur J Surg Oncol 2005;31:986-93.
5. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018-22.
6. Ammann M, Santol J, Pereyra D, et al. Glucagon-like peptide-1 and glucagon-like peptide-2 regulation during human liver regeneration. Sci Rep 2023;13:15980.
7. Rudnick DA, Davidson NO. Functional Relationships between Lipid Metabolism and Liver Regeneration. Int J Hepatol 2012;2012:549241.
8. Zhang L, Li Y, Wang Y, et al. mTORC2 Facilitates Liver Regeneration Through Sphingolipid-Induced PPAR-α-Fatty Acid Oxidation. Cell Mol Gastroenterol Hepatol 2022;14:1311-31.
9. Hall Z, Chiarugi D, Charidemou E, et al. Lipid Remodeling in Hepatocyte Proliferation and Hepatocellular Carcinoma. Hepatology 2021;73:1028-44.
10. Shteyer E, Liao Y, Muglia LJ, et al. Disruption of hepatic adipogenesis is associated with impaired liver regeneration in mice. Hepatology 2004;40:1322-32.
11. Huang J, Rudnick DA. Elucidating the metabolic regulation of liver regeneration. Am J Pathol 2014;184:309-21.
12. Fontana J, Kučera O, Mezera V, et al. Glucagon-like peptide-1 analogues exenatide and liraglutide exert inhibitory effect on the early phase of liver regeneration after partial hepatectomy in rats. Physiol Res 2017;66:833-44.
13. El-Jamal N, Erdual E, Neunlist M, et al. Glugacon-like peptide-2: broad receptor expression, limited therapeutic effect on intestinal inflammation and novel role in liver regeneration. Am J Physiol Gastrointest Liver Physiol 2014;307:G274-85.
14. Søreide JA, Deshpande R. Post hepatectomy liver failure (PHLF) - Recent advances in prevention and clinical management. Eur J Surg Oncol 2021;47:216-24.
15. Pereyra D, Rumpf B, Ammann M, et al. The Combination of APRI and ALBI Facilitates Preoperative Risk Stratification for Patients Undergoing Liver Surgery After Neoadjuvant Chemotherapy. Ann Surg Oncol 2019;26:791-9.
16. Santol J, Ammann M, Reese T, et al. Comparison of the LiMAx test vs. the APRI+ALBI score for clinical utility in preoperative risk assessment in patients undergoing liver surgery - A European multicenter study. Eur J Surg Oncol 2024;50:108048.
17. Santol J, Kim S, Gregory LA, et al. An APRI+ALBI Based Multivariable Model as Preoperative Predictor for Posthepatectomy Liver Failure. Ann Surg 2023. [Epub ahead of print]. doi: 10.1097/SLA.0000000000006127.
18. Starlinger P, Ubl DS, Hackl H, et al. Combined APRI/ALBI score to predict mortality after hepatic resection. BJS Open 2021;5:zraa043.
19. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4:e296.
20. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg 2005;12:351-5.
21. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-24.
22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
23. Ryskjaer J, Deacon CF, Carr RD, et al. Plasma dipeptidyl peptidase-IV activity in patients with type-2 diabetes mellitus correlates positively with HbAlc levels, but is

not acutely affected by food intake. Eur J Endocrinol 2006;155:485-93.
24. Starlinger P, Haegele S, Wanek D, et al. Plasma thrombospondin 1 as a predictor of postoperative liver dysfunction. Br J Surg 2015;102:826-36.
25. Siskos AP, Jain P, Römisch-Margl W, et al. Interlaboratory Reproducibility of a Targeted Metabolomics Platform for Analysis of Human Serum and Plasma. Anal Chem 2017;89:656-65.
26. Brunt EM, Janney CG, Di Bisceglie AM, et al. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 1999;94:2467-74.
27. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-21.
28. Moessinger C, Klizaite K, Steinhagen A, et al. Two different pathways of phosphatidylcholine synthesis, the Kennedy Pathway and the Lands Cycle, differentially regulate cellular triacylglycerol storage. BMC Cell Biol 2014;15:43.
29. Pynn CJ, Henderson NG, Clark H, et al. Specificity and rate of human and mouse liver and plasma phosphatidylcholine synthesis analyzed in vivo. J Lipid Res 2011;52:399-407.
30. WEISS SB, SMITH SW, KENNEDY EP. The enzymatic formation of lecithin from cytidine diphosphate choline and D-1,2-diglyceride. J Biol Chem 1958;231:53-64.
31. Vance DE, Walkey CJ, Cui Z. Phosphatidylethanolamine N-methyltransferase from liver. Biochim Biophys Acta 1997;1348:142-50.
32. Waite KA, Cabilio NR, Vance DE. Choline deficiency-induced liver damage is reversible in Pemt(-/-) mice. J Nutr 2002;132:68-71.
33. Minahk C, Kim KW, Nelson R, et al. Conversion of low density lipoprotein-associated phosphatidylcholine to triacylglycerol by primary hepatocytes. J Biol Chem 2008;283:6449-58.
34. Yao ZM, Vance DE. The active synthesis of phosphatidylcholine is required for very low density lipoprotein secretion from rat hepatocytes. J Biol Chem 1988;263:2998-3004.
35. Itagaki H, Shimizu K, Morikawa S, et al. Morphological and functional characterization of non-alcoholic fatty liver disease induced by a methionine-choline-deficient diet in C57BL/6 mice. Int J Clin Exp Pathol 2013;6:2683-96.
36. Rizki G, Arnaboldi L, Gabrielli B, et al. Mice fed a lipogenic methionine-choline-deficient diet develop hypermetabolism coincident with hepatic suppression of SCD-1. J Lipid Res 2006;47:2280-90.
37. Houweling M, Cui Z, Tessitore L, et al. Induction of hepatocyte proliferation after partial hepatectomy is accompanied by a markedly reduced expression of phosphatidylethanolamine N-methyltransferase-2. Biochim Biophys Acta 1997;1346:1-9.
38. Wong C, Lee MH, Yaow CYL, et al. Glucagon-Like Peptide-1 Receptor Agonists for Non-Alcoholic Fatty Liver Disease in Type 2 Diabetes: A Meta-Analysis. Front Endocrinol (Lausanne) 2021;12:609110.
39. Jeppesen PB, Gilroy R, Pertkiewicz M, et al. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut 2011;60:902-14.
40. Hein GJ, Baker C, Hsieh J, et al. GLP-1 and GLP-2 as yin and yang of intestinal lipoprotein production: evidence for predominance of GLP-2-stimulated postprandial lipemia in normal and insulin-resistant states. Diabetes 2013;62:373-81.
41. Koehler JA, Kain T, Drucker DJ. Glucagon-like peptide-1 receptor activation inhibits growth and augments apoptosis in murine CT26 colon cancer cells. Endocrinology 2011;152:3362-72.
42. Ejarque M, Sabadell-Basallote J, Beiroa D, et al. Adipose tissue is a key organ for the beneficial effects of GLP-2 metabolic function. Br J Pharmacol 2021;178:2131-45.
43. Hsieh J, Longuet C, Maida A, et al. Glucagon-like peptide-2 increases intestinal lipid absorption and chylomicron production via CD36. Gastroenterology 2009;137:997-1005, 1005.e1-4.
44. Dash S, Xiao C, Morgantini C, et al. Glucagon-like peptide-2 regulates release of chylomicrons from the intestine. Gastroenterology 2014;147:1275-1284.e4.
45. Taher J, Baker C, Alvares D, et al. GLP-2 Dysregulates Hepatic Lipoprotein Metabolism, Inducing Fatty Liver and VLDL Overproduction in Male Hamsters and Mice. Endocrinology 2018;159:3340-50.
46. Li R, Sun X, Li P, et al. GLP-1-Induced AMPK Activation Inhibits PARP-1 and Promotes LXR-Mediated ABCA1 Expression to Protect Pancreatic β-Cells Against Cholesterol-Induced Toxicity Through Cholesterol Efflux. Front Cell Dev Biol 2021;9:646113.
47. Ben-Shlomo S, Zvibel I, Shnell M, et al. Glucagon-like peptide-1 reduces hepatic lipogenesis via activation of AMP-activated protein kinase. J Hepatol 2011;54:1214-23.
48. Petrovic A, Igrec D, Rozac K, et al. The Role of GLP1-

RAs in Direct Modulation of Lipid Metabolism in Hepatic Tissue as Determined Using In Vitro Models of NAFLD. Curr Issues Mol Biol 2023;45:4544-56.
49. Svegliati-Baroni G, Saccomanno S, Rychlicki C, et al. Glucagon-like peptide-1 receptor activation stimulates hepatic lipid oxidation and restores hepatic signalling alteration induced by a high-fat diet in nonalcoholic steatohepatitis. Liver Int 2011;31:1285-97.
50. Jędrysik M, Wyszomirski K, Różańska-Walędziak A, et al. The Role of GLP-1, GIP, MCP-1 and IGFBP-7 Biomarkers in the Development of Metabolic Disorders: A Review and Predictive Analysis in the Context of Diabetes and Obesity. Biomedicines 2024;12:159.
51. Rameshrad M, Razavi BM, Lalau JD, et al. An overview of glucagon-like peptide-1 receptor agonists for the treatment of metabolic syndrome: A drug repositioning. Iran J Basic Med Sci 2020;23:556-68.
52. Rosen CJ, Ingelfinger JR. Once-Weekly Semaglutide in Adults with Overweight or Obesity. Reply. N Engl J Med 2021;385:e4.
53. Mantovani A. GLP-1 receptor agonists and reduction of liver fat content in NAFLD patients: Just a question of weight loss? Dig Liver Dis 2021;53:1673-4.

Cite this article as: Ammann M, Jonas JP, Pereyra D, Santol J, Hackl H, Kalchbrenner T, Laengle J, Podrascanin V, Lehner F, Viragos-Toth IL, Hulla W, Ruso V, Smoot R, Laengle F, Gruenberger T, Assinger A, Starlinger PP. Plasma GLP-1 and metabolic dynamics during human liver regeneration and their association with posthepatectomy liver failure. HepatoBiliary Surg Nutr 2025;14(1):49-65. doi: 10.21037/hbsn-24-464

