Increase of portal vein pressure gradient after hepatectomy predicts post-operative liver dysfunction

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Research article

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Abstract

Background

Post-hepatectomy liver failure (PHLF) is an important cause of mortality and morbidity. Whether Child–Pugh A patients with varying degrees of cirrhosis are good candidates for hepatectomy is disputed. The purpose of this study was to analyse the impact of portal venous pressure gradient (PVPG) variation during surgery on PHLF.

Methods

PVPG, the pressure gradient between the portal vein and central vein, was measured in consecutive patients before and after liver resection. The optimal cut-off of PVGP to predict PHLF was determined by receiver operating characteristic (ROC) curve analysis. Risk factors for PHLF were subjected to univariable and multivariable analysis.

Results

Sixty Child-Pugh A patients were recruited. The mean PVPG was increased from $5.17 \pm 4.78$ millimeters of Mercury (mmHg) to $6.37 \pm 4.44$ mmHg after liver resection. The optimal cut-off value of PVPG increments to predict PHLF was $1.5$ mmHg. Multivariable analysis showed prothrombin time (PT), post-hepatectomy PVPG increments of $1.5$ mmHg or greater, and resected liver segments of 3 or more to be independent predictors of PHLF.

Conclusions

Acute PVPG increase after hepatectomy is associated with a higher risk of PHLF in Child-Pugh A patients.

Background

Hepatectomy is currently the main treatment for focal liver diseases in patients with Child-Pugh A cirrhosis [1]. Despite progress in surgical techniques over the past decades, post-hepatectomy liver failure (PHLF) is still an important cause of mortality and morbidity, especially in patients with liver cirrhosis [2, 3]. Child–Pugh A patients have various degrees of cirrhosis, which are associated with different levels of risk for PHLF [4]. Thus, it is of great clinical value to identify the predictive factors of PHLF in patients with Child–Pugh A cirrhosis.

Portal hypertension (PHT) is one of the main features of cirrhosis [5]. PHT in patients that have undergone hepatectomy is associated with a higher risk of PHLF [6]. The Barcelona Clinic Liver Cancer classification guidelines for hepatocellular carcinoma (HCC) suggests that a hepatic venous pressure
Gradient greater than 10 mmHg is a contraindication for hepatectomy [1, 6]; however, many doctors do not agree that PHT precludes hepatectomy in all cases [7].

Several studies have shown that increased portal vein pressure (PVP) affects postoperative safety in patients who have undergone hepatectomy [8–11]. However, very few studies have measured the gradient between caval pressure and portal pressure. Many studies have demonstrated that increases of central venous pressure (CVP) are transmitted to PVP [12–18]. Thus, measurement of PVP could be affected by CVP. Portal vein pressure gradient (PVPG) is the gradient between PVP and CVP. This prospective study conducted in Child-Pugh A patients is aimed at exploring the predictive value of acute PVPG change during surgery on post-operative liver dysfunction.

**Methods**

**Patients**

Patients who meets the following criteria are eligible for this study: (1) pre-operative liver function of Child–Pugh A with a future liver remnant > 30%; (2) patient age ≥ 18 and ≤ 75; (3) major resection (defined by removal of 3 or more liver segments) planned, or liver stiffness (LS) higher than 12 kilopascals (kPa) measured before hepatectomy (our previous study showed that patients with LS higher than 12 kPa were more likely to be associated with higher risk of PHLF [19]).

The exclusion criteria were as follows: (1) portal vein tumour thrombus confirmed by preoperative assays; (2) preoperative portal vein embolization or transjugular intrahepatic portosystemic shunt; (3) previous or intraoperative devascularisation and splenectomy.

Clinically significant portal hypertension (CSPH) was defined according to the Barcelona Clinic Liver Cancer group criteria [9]. The spleen diameter was defined as its longest axis. Liver fibrosis was staged using the Scheuer classification [20].

PHLF was defined by the International Study Group of Liver Surgery (ISGLS) [21]. Postoperative complications were recorded according to the modified Clavien–Dindo classification [22]. Perioperative mortality was defined as 90-day mortality.

This study was approved by the Hospital Research Ethics Committee. Written consent was obtained from all patients.

**Surgical procedures and PVPG measurement**

The procedure for hepatectomy has been previously described [23]. Briefly, hepatectomy was conducted using a clamp crushing method with cycles of porta hepatis clamping/unclamping of 15 minutes/5 minutes. The extent of liver resection was defined according to the number of Couinaud liver segments.
removed. Major hepatectomy was defined as resection of 3 liver segments or more; minor hepatectomy was defined as fewer than 3 segments [24].

A central venous catheter was inserted into the jugular or subclavian vein before operation. After exploration of the abdomen and decision to proceed with the hepatectomy, a 16-Fr polyvinyl chloride catheter was inserted into the main portal vein through the right gastroepiploic vein, with all air purged from the extension tubing beforehand. The position of the tip of the tube was verified by intraoperative ultrasonography. PVP was measured electronically using a transducer fixed at the level of the right atrium and set to atmospheric. The readings were standardized to 0 when the transducer was connected to the atmosphere. The PVP and CVP measurements were displayed on a monitor (Dräger, Infinity C700). PVP and CVP were recorded before liver resection and 15 minutes after hepatectomy when hemodynamics were stable. All measurements were performed twice. In cases where the two measurement values diverged greatly, a third measurement was performed. PVPG was defined as the pressure gradient between the portal vein and the central vein.

**Postoperative Management And Follow-up**

Routine blood, liver, and coagulation function tests and serum electrolyte detection were performed once every other day during the first postoperative week. Patients were followed up every 2 months for 1 year after discharge from hospital, and then every 3 months thereafter.

**Statistical analysis**

For PVP and PVPG data, delta values (ΔPVP and ΔPVPG) were generated by subtraction of post-hepatectomy and pre-hepatectomy values. Continuous variables are reported as mean (standard deviation, SD) or median (interquartile range, IQR), and were compared using Student’s t test, Mann–Whitney U test, or one-way ANOVA, Kruskal–Wallis H test, as appropriate. Categorical variables are reported as numbers and percentages, and compared using Pearson’s χ² analysis or Fisher’s exact test. Variables shown to be statistically significant in univariable analysis (P < 0.05) were included in multivariable logistic regression analysis to identify independent predictors of PHLF. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off for PVPG variation predicting PHLF. Calculations were done with SPSS 22.0 (IBM, New York, USA). Graphical illustrations were carried out with GraphPad Prism v7 (GraphPad Software, Inc., La Jolla, USA). A P-value less than 0.05 indicates statistical significance.

**Results**

**Patient demographics**

A total of 60 eligible patients were recruited for the study from April 2018 to March 2019. The characteristics of the patients are listed in Table 1. There were 54 men (90%) and 6 women (10%), with a
mean age of 57.5 years. Two patients were diagnosed with hepatic cyst, 48 patients were diagnosed with hepatocellular carcinoma (HCC), 4 patients were diagnosed with intrahepatic cholangiocarcinoma (ICC) and 6 patients were diagnosed with mixed type (HCC-ICC). None of the patients received preoperative chemotherapy, radiotherapy, or interventional treatment. When patients were grouped by a binary classification of PVPG increment (illustrated by the ROC curve in Fig. 1), all variables were similar between the two groups except for pre-hepatectomy PVPG.
Table 1
Basic characteristics of the study population

| Variable                      | Total n = 60 | ΔPVPG < 1.5 mmHg n = 36 | ΔPVPG ≥ 1.5 mmHg n = 24 | P value |
|-------------------------------|--------------|-------------------------|-------------------------|---------|
| Age, mean (SD), years         | 57.5         | 57.2 (10.7)             | 58.0 (7.8)              | 0.752   |
| Gender, F/M                   | 6/54         | 6/30                    | 0/24                    | 0.072   |
| Diagnosis*, Benign/Malignant   | 2/58         | 1/35                    | 1/23                    | 1.000   |
| HBsAg, -/+                    | 10/50        | 5/31                    | 5/19                    | 0.501   |
| HBeAg, -/+                    | 50/10        | 28/8                    | 22/2                    | 0.289   |
| HBV-DNA, ≤/> 10^3/mL          | 36/24        | 23/13                   | 13/11                   | 0.451   |
| Hb, mean (SD), g/L            | 143.6 (17.8) | 144.9 (16.4)            | 141.7 (20.0)            | 0.507   |
| WBC, mean (SD), 10^9/L        | 5.3 (2.9)    | 5.0 (1.5)               | 5.8 (4.2)               | 0.269   |
| PLT, mean (SD), 10^9/L        | 150.0 (59.4) | 148.1 (54.8)            | 152.7 (66.9)            | 0.772   |
| PT, mean (SD), s              | 11.7 (0.8)   | 11.7 (0.7)              | 11.8 (1.0)              | 0.607   |
| INR, mean (SD)                | 1.01 (0.07)  | 1.01 (0.07)             | 1.02 (0.09)             | 0.612   |
| TB, median (IQR), µmol/L      | 13.3 (7.8)   | 12.6 (8.0)              | 15.0 (7.7)              | 0.597   |
| ALB, mean (SD), g/L           | 42.6 (4.4)   | 42.8 (4.0)              | 42.2 (5.0)              | 0.587   |
| ALT, median (IQR), U/L        | 29.5 (27.5)  | 31.0 (26.8)             | 28.0 (24.3)             | 0.483   |
| GGT, median (IQR), U/L        | 86.0 (104.8) | 86.0 (119.8)            | 85.5 (80.75)            | 0.751   |

Abbreviations: SD, standard deviation; IQR, interquartile range; PVPG, portal vein pressure gradient; ΔPVPG, post-hepatectomy PVPG – pre-hepatectomy PVPG; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; Hb, haemoglobin; WBC, white blood cell; PLT, platelet; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; PT, prothrombin time; INR, international normalized ratio; HA, hyaluronic acid; LN, laminin; P-NP, precollagen N-terminal peptide; -col, type I collagen; LS, liver stiffness; CSPH, clinically significant portal hypertension. * hepatic cyst (n = 2), HCC (n = 48), ICC (n = 4), and HCC-ICC (n = 6)
| Variable                                      | Total n = 60 | ΔPVPG < 1.5 mmHg n = 36 | ΔPVPG ≥ 1.5 mmHg n = 24 | P value |
|-----------------------------------------------|--------------|-------------------------|-------------------------|---------|
| HA, median (IQR), ng/mL                      | 111.8 (134.8)| 111.8 (100.6)           | 107.3 (122.6)           | 0.988   |
| PIIINP, median (IQR), ng/mL                  | 9.2 (3.1)    | 9.6 (3.0)               | 8.7 (3.1)               | 0.536   |
| LN, median (IQR), ng/mL                      | 63.9 (37.7)  | 61.9 (39.3)             | 68.2 (37.5)             | 0.701   |
| IVcol, median (IQR), ng/mL                   | 65.4 (46.6)  | 55.7 (45.5)             | 71.3 (40.3)             | 0.235   |
| LS, mean (SD), Kpa                           | 13.9 (4.9)   | 13.8 (4.2)              | 14.1 (5.9)              | 0.847   |
| CSPH, yes/no                                 | 15/45        | 8/28                    | 7/17                    | 0.543   |
| Pre-hepatectomy PVPG, mean (SD), mmHg        | 5.2 (4.8)    | 6.5 (4.7)               | 3.2 (4.2)               | 0.0008  |
| Resected liver segments, ≤/≥ 3               | 37/23        | 24/12                   | 13/11                   | 0.329   |
| Intraoperative bleeding, ≤/> 150 ml          | 32/28        | 22/14                   | 10/14                   | 0.139   |
| Intraoperative blood transfusion, yes/no     | 5/55         | 1/35                    | 4/20                    | 0.147   |
| Hilar occlusion, ≤/> 20 min                  | 42/18        | 27/9                    | 15/9                    | 0.301   |
| Tumor size, ≤/> 5 cm                         | 39/21        | 27/9                    | 12/12                   | 0.058   |
| Tumor number, ≤/> 2                         | 41/19        | 25/11                   | 16/8                    | 1.000   |
| Fibrosis stage, S0-S3/S4                     | 22/38        | 10/26                   | 12/12                   | 0.080   |

Abbreviations: SD, standard deviation; IQR, interquartile range; PVPG, portal vein pressure gradient; ΔPVPG, post-hepatectomy PVPG – pre-hepatectomy PVPG; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; Hb, haemoglobin; WBC, white blood cell; PLT, platelet; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; PT, prothrombin time; INR, international normalized ratio; HA, hyaluronic acid; LN, laminin; PⅢNP, precollagen III N-terminal peptide; IVcol, type IV collagen; LS, liver stiffness; CSPH, clinically significant portal hypertension. * hepatic cyst (n = 2), HCC (n = 48), ICC (n = 4), and HCC-ICC (n = 6)
Acute intraoperative changes of PVP and PVPG

PVP and PVPG before and after hepatectomy were observed (Fig. 2). PVPG increased from 5.17 ± 4.78 mmHg before hepatectomy to 6.37 ± 4.44 mmHg after hepatectomy. However, PVP showed no remarkable changes (Fig. 2A).

The median ΔPVP was 0 mmHg, ranging from −7 to 6 mmHg with a mean (SD) of -0.2 (3.1) mmHg. The median ΔPVPG was 1 mmHg, ranging from −7 to 11 mmHg with a mean (SD) of 1.2 (3.5) mmHg.

The classifications of PVP (≤/> 12 mmHg) before hepatectomy were set referring to Chen's work.[9] In the pre-hepatectomy PVP > 12 mmHg group, PVP decreased after hepatectomy while PVPG remained stable (Fig. 2B). While there were significant increments of PVPG in the patients with major resection or PHLF, no remarkable changes of PVP were seen (Fig. 2D, F).

PVPG increment cut-off before and post hepatectomy

The ROC curve shows that a ΔPVPG ≥ 1.5 mmHg is the optimal cut-off for the occurrence of PHLF, with a sensitivity of 65% and specificity of 70% (AUC = 0.67, p = 0.038) as shown in Fig. 1. Thus, we adopt a binary classification of “ΔPVPG ≥ 1.5 mmHg.”

Dynamic changes of liver function, PHLF and complications

Liver function was tested before and once every 2 days after the operation. Worse liver function was observed in patients in the “ΔPVPG ≥ 1.5 mmHg” group compared with the “ΔPVPG < 1.5 mmHg” group (Fig. 3).

Of the 60 patients, 13 (21.7%) developed one or more postoperative complications including subphrenic effusion in 2 patients (3.3%), pleural effusion in 2 patients (3.3%), ascites in 2 patients (3.3%), and wound infection in 1 patient (1.7%). Using the modified Clavien–Dindo classification, complications were categorized as grade I in 3 patients (5.0%), grade II in 6 patients (10.0%), grade IIIa in 4 patients (6.7%), and grade IV and grade V in 0 patients. Due to the low complication rate, grades 0-I and grades II-III were merged, respectively. The complication rate for the “ΔPVPG ≥ 1.5 mmHg” group was significantly higher than that of the “ΔPVPG < 1.5 mmHg” group (Table 2).
Table 2
Complications and PHLF after liver resection

| ΔPVPG,mmHg | < 1.5 (n = 36) | ≥ 1.5 (n = 24) | P value |
|------------|----------------|----------------|---------|
| Complications |                |                | 0.005** |
| Grade 0-I   | 34             | 16             |         |
| Grade II-III| 2              | 8              |         |
| PHLF        | 6              | 11             | 0.014*  |

** Fisher's exact test; * Student's t test

Of the 60 patients, 17 (28.3%) developed PHLF, with all of them defined as PHLF grade A according to ISGLS criteria. A PVPG increment ≥ 1.5 mmHg was associated with a greater risk of PHLF (p = 0.014) than a PVPG increase < 1.5 mmHg (Table 2). There was no mortality within 3 months after hepatectomy for any of the patients enrolled.

Univariate analysis showed that Haemoglobin (per 10 g/L), PT, type ≥ collagen > 95 ng/ml, major resection and ΔPVPG ≥ 1.5 mmHg were associated with incidence of PHLF. On the basis of multivariate analysis, PT, major resection, and ΔPVPG ≥ 1.5 mmHg were independently associated with PHLF defined by ISGLS criteria [21] (Table 3).
Table 3
Risk factors for PHLF

| variable          | No. | Uni |          |        | Multi |          |        |
|-------------------|-----|-----|----------|--------|-------|----------|--------|
|                   |     | OR  | 95% CI   | P      | OR    | 95% CI   | P      |
| Age, years        | 60  | 1.017| 0.957–1.018 | 0.583  | 0.907 | 0.577–1.425 | 0.672  |
| Gender, F/M       | 6/54| 0.475| 0.051–4.396 | 0.512  | 0.907 | 0.577–1.425 | 0.672  |
| Hb, per 10 g/L    | 60  | 0.664| 0.473–0.930 | 0.017  | 0.907 | 0.577–1.425 | 0.672  |
| WBC, ≤/> 3.5 × 10^9 /L | 13/37| 0.356| 0.099–1.285 | 0.115  |       |          |        |
| PLT, ≥/> 100 × 10^9 /L | 55/5 | 0.389| 0.101–1.507 | 0.172  |       |          |        |
| TB, ≤/> 20 µmol/ L| 55/5 | 0.609| 0.063–5.882 | 0.669  |       |          |        |
| ALB, ≥/> 35 g/L   | 55/5 | 0.563| 0.085–3.705 | 0.550  |       |          |        |
| ALT, ≤/> 50 U/L   | 49/11| 0.938| 0.217–4.055 | 0.931  |       |          |        |
| GGT, ≤/> 60 U/L   | 23/37| 1.728| 0.517–5.774 | 0.374  |       |          |        |
| PT, s             | 60  | 3.885| 1.582–9.541 | 0.003  | 5.571 | 1.526–20.338 | 0.009  |
| HA, ≤/> 120 ng/ mL| 34/26| 2.411| 0.766–7.590 | 0.133  |       |          |        |
| LN, ≤/> 130 ng/ mL| 55/5 | 4.393| 0.664–29.056 | 0.125  |       |          |        |

Abbreviations: ISGLS, International Study Group of Liver Surgery; PHLF, post-hepatectomy liver failure; PVP, portal vein pressure; PVPG, portal vein pressure gradient; OR, risk ratio; Hb, haemoglobin; WBC, white blood cell; PLT, platelet; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; PT, prothrombin time; INR, international normalized ratio; HA, hyaluronic acid; LN, laminin; P-NP, precollagen N-terminal peptide; -col, type I collagen; LS, liver stiffness; CSPH, clinically significant portal hypertension; ΔPVPG, post-hepatectomy PVPG – pre-hepatectomy PVPG
| variable                  | No.   | Uni | Multi |
|--------------------------|-------|-----|-------|
| | | OR | 95% CI | P | OR | 95% CI | P |
| PNP, ≤/> 15 ng/mL        | 56/4  | 9.000 | 0.865–93.675 | 0.066 | | |
| 0-coll, ≤/> 95 ng/mL     | 44/16 | 4.444 | 1.272–15.532 | 0.019 | 1.200 | 0.188–7.663 | 0.874 |
| HBsAg, +/-               | 50/10 | 1.714 | 0.325–9.046  | 0.525 | | |
| HBeAg, +/-               | 10/50 | 0.583 | 0.111–3.078  | 0.525 | | |
| LS, ≤/> 12 kPa           | 17/43 | 0.651 | 0.194–2.180  | 0.486 | | |
| CSPH, yes/no             | 15/45 | 3.062 | 0.892–10.520 | 0.075 | | |
| Fibrosis stage, S0-S3/S4 | 22/38 | 1.569 | 0.468–5.258  | 0.465 | | |
| Resected liver segments, ≤/> 3 | 37/23 | 3.297 | 1.029–10.566 | 0.045 | 6.613 | 1.106–39.545 | 0.038 |
| Intraoperative bleeding, ≤/> 150 ml | 32/28 | 1.984 | 0.634–6.205  | 0.239 | | |
| Blood transfusion, Yes/no | 5/55  | 4.393 | 0.664–29.056 | 0.125 | | |

Abbreviations: ISGLS, International Study Group of Liver Surgery; PHLF, post-hepatectomy liver failure; PVP, portal vein pressure; PVPG, portal vein pressure gradient; OR, risk ratio; Hb, haemoglobin; WBC, white blood cell; PLT, platelet; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; PT, prothrombin time; INR, international normalized ratio; HA, hyaluronic acid; LN, laminin; PNP, precollagen N-terminal peptide; 0-coll, type  collagen; LS, liver stiffness; CSPH, clinically significant portal hypertension; ΔPVPG, post-hepatectomy PVPG – pre-hepatectomy PVPG
| variable                                           | No.   | Uni | Multi |
|----------------------------------------------------|-------|-----|-------|
| Hepatic occlusion time, \( \leq / \geq \) 20 min   | 32/18 | 2.036 | 0.623–6.655 | 0.239 |
| Pre-hepatectomy PVP, \( \leq / \geq \) 12 mmHg     | 25/35 | 1.451 | 0.454–4.642 | 0.530 |
| \( \Delta \) PVPG, \( \leq / \geq \) 1.5 mmHg       | 24/36 | 4.231 | 1.289–13.889 | 0.017 |

Abbreviations: ISGLS, International Study Group of Liver Surgery; PHLF, post-hepatectomy liver failure; PVP, portal vein pressure; PVPG, portal vein pressure gradient; OR, risk ratio; Hb, haemoglobin; WBC, white blood cell; PLT, platelet; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; GGT, \( \gamma \)-glutamyl transpeptidase; PT, prothrombin time; INR, international normalized ratio; HA, hyaluronic acid; LN, laminin; \( \Delta \) NP, precollagen \( N \)-terminal peptide; \( \alpha \)-col, \( \beta \)-col, \( \gamma \)-collagen; LS, liver stiffness; CSPH, clinically significant portal hypertension; \( \Delta \) PVPG, post-hepatectomy PVPG – pre-hepatectomy PVPG

**Discussion**

The present study demonstrated that the acute increase of PVPG after hepatectomy (\( \Delta \)PVPG) could predict PHLF in patients with Child-Pugh A cirrhosis. To our knowledge, this is the first report to focus on acute changes of PVPG after hepatectomy and show a clear correlation between \( \Delta \)PVPG and PHLF after liver resection. More importantly, \( \Delta \)PVPG may be used as an indicator for potential portal pressure adjustment.

Although many techniques have been applied to evaluate liver function reserve or liver injury \([4, 9, 25]\), the results have not been satisfactory so far. In the present study, we focused on the acute change of PVPG after liver resection and its effect on PHLF. The results showed that major liver resection and \( \Delta \)PVPG \( \geq \) 1.5 mmHg were independent risk factors for PHLF, which supports the pathophysiological mechanism of PHLF \([3, 26]\). Major hepatectomy usually resulted in an acute increase of PVPG, which led to portal hyperfusion and compensatory decrease in hepatic arterial inflow (hepatic arterial buffer response), followed by sinusoidal endothelial cell injury, then activated sinusoidal endothelial cells generating increased reactive oxygen species and cytokines, causing the aetiology of PHLF. There is another mechanism involved in PHT-related liver dysfunction: acute PVPG increase could induce excessive regeneration factors, leading to hyperplasia of hepatocyte without the support of an organized sinusoidal network, ultimately leading to liver dysfunction \([27]\).
The present study suggested PVPG to be a better indicator of PHT than the pure PVP value. PHT is pathologic increase in the pressure gradient between the portal vein and the inferior vena cava [28]. Previous clinical studies have demonstrated that postoperative PHT is associated with liver dysfunction and poor outcome [8–11]. Chen et al. found that Child-Pugh A patients with postoperative PVP of 12 mmHg or above had a higher risk of PHLF compared with patients with PVP below 12 mmHg. [9] In patients without cirrhosis, Allard and his colleagues [8] reported that post-hepatectomy PVP of 22 mmHg was the best cut-off for predicting PHLF defined by ISGLS [21]. However, the evaluation of PHT severity could be misled by PVP. Experimental and clinical studies have shown that increases in CVP were transmitted to PVP [12–18]. When CVP was raised by 5 and 12 mmHg, 50% and 75% of the increased CVP was transferred to PVP, respectively [13]. Furthermore, experimental study showed portal pressure rose by 0.91 mmHg for every mmHg increase in caval pressure [14].

PVPG is the pressure gradient between the portal vein and central vein. An experimental study based on PHT canines model after haemorrhagic shock showed that, when compared with PVP, PVPG increased earlier and more significantly in the large volume infusion group [29]. In the present study, we noticed that PVP did not significantly increase in the “major hepatectomy group” and “PHLF + group” (Fig. 1D, F), in contradiction with previous findings [8, 9, 11]. In contrast, increased PVPG was observed in these two groups. Therefore, PVPG may be a more reliable indicator to evaluate portal pressure and predict PHLF.

In the study reported by Lan et al., PVP and CVP were measured every day for a week after hepatectomy through portal and central vein catheterization [30]. It was found that PVPG was affected by extent of resection only in patients with moderate and severe cirrhosis. However, the comparison between PVP and PVPG was not mentioned. Furthermore, Lan's study provided a unique opportunity to observe the dynamic changes of PVPG after hepatectomy. However, it is impossible to measure PVPG after closure of the abdomen in most cases; therefore, we believe monitoring the early response of PVPG is more practical, in addition to which it may provide the opportunity for early portal pressure modulation in order to prevent PHLF.

There were some limitations in the present study. Firstly, the number of patients involved in this study was small. Secondly, the incidence of PHLF is low and most of them were Grade A PHLF, which may be not clinically critical, because many HCC patients with more severe cirrhosis were treated by radiofrequency ablation or liver transplantation. Thirdly, the cut-off value for increase of PVPG is made based on the study cohort, external validation cohort is needed for further study.

Conclusions

In summary, the present study showed that acute increase of PVPG after hepatectomy can predict PHLF in patients with Child-Pugh A cirrhosis. A post-hepatectomy PVPG increment of 1.5 mmHg or greater was an immediate and independent predictor for PHLF. The advantage of this evaluation index is early prediction of PHLF during operation. Although these data require external validation, they further support
future trials to investigate the role of PVPG as a therapeutic target that might be modified by surgical or medical treatments to prevent PHLF.

**Abbreviations**

- **PHLF**: post-hepatectomy liver failure
- **PVPG**: portal venous pressure gradient
- **ROC**: receiver operating characteristic
- **PT**: prothrombin time
- **PHT**: portal hypertension
- **HCC**: hepatocellular carcinoma
- **PVP**: portal vein pressure
- **CVP**: central venous pressure
- **LS**: liver stiffness
- **ISGLS**: international study group of liver surgery
- **CSPH**: clinically significant portal hypertension
- **SD**: standard deviation
- **IQR**: interquartile range
- **ICC**: intrahepatic cholangiocarcinoma

**Declarations**

**Ethics approval and consent to participate**

Written consent was obtained from all patients. Ethics approval and consent to participate this prospective study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University. All methods were conducted in accordance with the approved guidelines.
Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no potential conflicts of interest.

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Authors’ contributions

N Xiao, X-L Li, and H-C Sun had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. N Xiao, X-L Li, and H-C Sun were responsible for the conception and design of the study, the acquisition, statistical analysis, and interpretation of the data, and the drafting of the manuscript. X-D Zhu, C Huang, Y-H Shen, J Zhou, and J Fan were responsible for the acquisition and interpretation of the data. All authors contributed to manuscript writing and final manuscript approval.

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Figure 1

ROC curve was used to define PVPG variation (AUC was 0.67, p=0.038) cut-off for the occurrence of PHLF defined by ISGLS.
Figure 2

Intraoperative changes of PVP and PVPG (A) Acute changes of PVP and PVPG among 60 enrolled patients. Intraoperative changes of PVP and PVPG are presented separately for (B, C) patients with pre-hepatectomy PVP > 12 mmHg (n=35) and patients with pre-hepatectomy PVP ≤ 12 mmHg (n=25); (D, E) patients underwent major hepatectomy (n=37) and patients underwent minor hepatectomy (n=23); (F, G) patients with PHLH (n=17) and patients without PHLF (n=43). Abbreviations: PHLF, post-hepatectomy liver failure; n.s., not significant.
Figure 3

Changes in liver function following liver resection (LR) (A, B, C) For TBL, ALT, and GGT, values and error bars represent median and interquartile range respectively. (D) For ALB, values and error bars represent mean and standard deviation respectively. *P < 0.05, Mann-Whitney U test, #P < 0.05, Student’s t test. Abbreviations: TBIL, serum total bilirubin; ALT, alanine aminotransferase; gamma-glutamyl transpeptidase; ALB, albumin; PROP, pre-operation; POD, post-operation day.