Research Article

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Accurate computed tomography-based portal pressure assessment in patients with hepatocellular carcinoma

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Background & Aims: Liver resection is generally restricted to patients without clinically significant portal hypertension (Hepatic Venous Pressure Gradient – HVPG – ⩽10 mmHg) and several teams perform transjugular HVPG measurements as part of the pre-operative work-up. The present study investigates whether a non-invasive Computed Tomography (CT)-based assessment could be as accurate as the invasive transjugular measurement.

Methods: A cohort of patients with hepatocellular carcinoma (HCC) treated by resection (n = 36) or transplantation (n = 39) was selected (mean age: 61 ± 9.2 years, male/female ratio: 4/1). Pre-operative CTs were read by two independent investigators, and potential CT-based HVPG predictors were compared to the transjugular HVPG measurements. A validation was conducted on another cohort of 70 non-surgical patients.

Results: The invasive HVPG values were significantly correlated to liver/spleen volume ratio, spleen volume, platelet count, and peri-hepatic ascites (p <0.001), which all showed high inter-observer agreements (intra-class correlation coefficients ⩾0.927, Kappa ⩾0.945). The presence of a HVPG >10 mmHg was best predicted by the liver/spleen volume ratio (AUC: 0.883 [0.805–0.960]) and the peri-hepatic ascites (p <0.001). These two variables were combined into an accurate model for predicting HVPG >10 mmHg (AUC: 0.911 [0.847–0.975]), with sensitivity, specificity, and positive and negative predictive values of 92%, 79%, 91%, and 81%. The model was also accurate in the validation cohort with an AUC of 0.820 [0.719–0.921]. The computed formula was:

$$\text{HVPG score} = 17.37 - 4.91 * \ln(\text{Liver/Spleen volume ratio}) + 3.8\ [\text{if presence of peri-hepatic ascites}]$$

Conclusions: The proposed CT-based model showed a high accuracy in the prediction of HVPG and, if further confirmed by prospective validation, could replace the invasive transjugular assessment in patients not requiring a biopsy of the non-tumoral liver.

Keywords: Hepatic venous pressure gradient; Portal hypertension; Liver transplantation; Liver resection; Hepatocellular carcinoma; Computed tomography.

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Abbreviations: HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; CT, computed tomography; ROI, region of interest; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; ICC, intra-class correlation coefficient; ROC, receiver operator characteristic; AUC, area under the curve; HCV, hepatitis C virus; PPV, positive predictive value; NPV, negative predictive value.

Introduction

Liver resection and transplantation are effective treatments for selected patients with hepatocellular carcinoma (HCC) [1–4]. The choice between the two options is based on cancer stage (size, number and alpha-fetoprotein level), hepatocellular function and the presence of portal hypertension [3,5–8].

Among other available markers, the hepatic venous pressure gradient (HVPG >10 mmHg) accurately predicts the risk of peri-operative morbidity and death and many Western centers perform transjugular pressure measurements as part of their standard pre-surgical work-up [3,9,10]. However, the transjugular exploration is invasive and not available at all institutions. In addition, a biopsy of the non-tumoral liver (which can be performed during the transjugular assessment) is not always necessary. As a result, a number of less invasive portal pressure assessment techniques have been tested over the recent years [11,12]. They were based on ultrasonography with the exploration of splanchnic vessels size [13], blood velocity [14–16] or blood-flow resistance [17] and on the assessment of the liver stiffness [18]. Overall, none of these techniques gained clinical acceptance, because of the small sample size, the lack of external validation and/or simply because of their low accuracy in the

prediction of HVPG. The present study is exploring whether a simple, non-invasive Computed Tomography (CT)-based assessment could be as accurate as the invasive transjugular HVPG measurement. We hypothesized that a combination of CT-based parameters could allow an accurate quantitative HVPG estimation.

Materials and methods

Study design

The present study was based on retrospective chart and CT analyses of patients with HCC, treated by liver resection or transplantation from September 2003 to December 2012. It included all consecutive patients who had a transjugular HVPG measurement, contrast-enhanced abdominal CT and platelet count performed as part of their pre-surgical work-up. A validation of the developed HVPG predictive model included non-surgical patients with both transjugular HVPG measurement and contrast-enhanced abdominal CT (June 2011–May 2013). Patients with portal vein thrombosis were excluded.

CT assessments

All patients underwent contrast-enhanced multi-detector computed tomography of the abdomen on 16-row or 64-row scanners with intravenous administration of iohexol 350 mgI/ml (Accupaque, GE, Opfikon, Switzerland). The following parameters were used: tube voltage, 120 kVp; tube current, automatic dose modulation; pitch, 1.5:1; slice thickness, 1 mm; slice interval, 0.75 mm; contrast volume, 2 ml/kg of body weight; injection rate, 3–4 ml/s.

CT images were analyzed independently and blindly by a surgery resident (PI) and a medical student (OV) on the portal phase (60 s after the start of the contrast material injection) of CT acquisition, using the widely-available Osirix open-source software (The Osirix Foundation, Geneva, Switzerland). An expert radiologist (ST) trained both readers by performing 20 consecutive cases with them and supervising their measurements.

The assessed variables included liver and spleen volumes, the presence or absence of ascites in the peri-hepatic (including the pouch of Morisson), peri-splenic, medio-abdominal (between the bowel loops and/or within the paracolic gutters) and pelvic (around the rectum and/or over the bladder, including the pouch of Douglas) compartments, the presence or absence of gastro-esophageal, peri-splenic, retroperitoneal (along the aorta and/or inferior vena cava), peri-umbilical and rectal venous collaterals, as well as the presence or absence of a patent umbilical vein in the round ligament. The volumes of the liver and the spleen were individually obtained after manual selection of the appropriate regions of interest (ROI), respecting organ contours with the exclusion of large vessels and large fissures. The cranio-caudal diameter of the spleen was measured on coronal reformatted images. The spleen/liver volume ratio was computed. The presence of ascites was defined as a minimal layer (at least 3 mm) of fluid (density between 0 and 30 Hounsfield units) in the peritoneal spaces. The presence of ascites was assessed separately for the various studied peritoneal compartments.

Transjugular hepatic venous pressure gradient measurements

The HVPG measurements were performed using transjugular access. All patients were placed in supine position and received a light sedation with 1 to 2 mg of IV midazolam associated to 25 μg of IV fentanyl. After local anesthesia, the right jugular vein was cannulated using a 9F introducer (Maxxim Medical Europe, Hertogenbosch, The Netherlands). Then, an 8F curved catheter (Cordis Europa, Amsterdam, The Netherlands) was placed under fluoroscopic control into the right hepatic vein. Once in the proper position, the catheter was advanced until the tip of the catheter was wedged in a small hepatic vein. Contrast medium was injected to ensure that the catheter was in a proper wedge position. The external zero reference was set at mid-chest. The wedged hepatic venous pressure (WHVP) was measured when the catheter was wedged in the right hepatic vein and only when a stable pressure tracing (>45 s) with fine venous fluctuations was obtained. The free hepatic venous pressure (FHVP) was measured while the catheter was floating at the ostium of the right hepatic vein close to the inferior vena cava. The difference between WHVP and FHVP yielded the HVPG. Instant pressure tracings were recorded on the monitor and printed. At least three measurements were performed in each patient, and the mean value was kept for analysis. HVPG and CT assessments were performed 33 ± 91 days apart. All patients had a complete blood count performed within 24 h before the transjugular HVPG assessment.

Inter-observer assessment

The inter-observer agreement of continuous variables was assessed by scatterplots and by calculating the intra-class correlation coefficients (ICC), while inter-observer agreement of categorical variables was assessed by kappa values. Only variables with high inter-observer agreements were considered for building a model predicting HVPG.

Assessment of predictors of HVPG, and design and validation of a model

Normality was assessed with histograms, and variables were used with or without logarithm transformation in order to be the closest to normality. In a first set of analyses, HVPG was used as a continuous parameter and correlation between continuous variables and transjugular HVPG was assessed with Pearson and Spearman's correlation coefficients. The association between categorical variables and transjugular HVPG was assessed with a Wilcoxon-Mann-Whitney test. The performances of continuous variables in predicting an HVPG >10 mmHg were assessed using Receiver Operator Characteristic (ROC) curves and calculating the Area Under the Curve (AUC), while the capacity of categorical variables in predicting an HVPG >10 mmHg was assessed with Fisher's exact test. Parameters with the highest correlations/performances with the HVPG were entered into a multivariate linear regression model to construct a more valuable score to predict an HVPG >10 mmHg. The proposed HVPG predictive models were subsequently tested on the validation cohort, which included 70 patients with various levels of cirrhosis (none of them underwent surgery or transplantation). In all analyses, p values <0.05 were considered statistically significant.

Results

Demographics

Seventy-five patients with HCC were included, 39 underwent transplantation and 36 resection (including 11 control patients without cirrhosis). The male:female ratio was 4:1 in both groups, with a mean age of 61 ± 9.2 years (Table 1). The main causes of liver disease were alcohol and hepatitis C virus (HCV). Overall, the mean HVPG was 11 ± 6 mmHg, with expected higher values in the transplant group (15 ± 4 *vs.* 6 ± 3 mmHg). The spleen volume and the spleen cranio-caudal length were also higher in the transplant group (Table 2).

Inter-observer agreement

The inter-observer agreements were high for the assessments of spleen volume, liver/spleen volume ratio and spleen cranio-caudal length with ICC >0.9, and peri-hepatic, peri-splenic, and medio-abdominal ascites with kappa scores >0.9 (Fig. 1 and Table 3). The other assessments demonstrated low inter-observer agreements and were not further considered for the analysis.

Predictors of HVPG

Univariate analysis of the continuous variables showed that spleen volume, liver/spleen volume ratios and platelet count were all significantly correlated to the invasive HVPG levels. Conversely, liver volume did not correlate with the HVPG (Table 4). Among categorical variables, the presence of peri-hepatic (yes: 16.6 ± 3.6 mmHg *vs.* no: 9.7 ± 5.3 mmHg, p <0.001), peri-splenic (yes: 16.5 ± 3.9 mmHg *vs.* no: 10.0 ± 5.4 mmHg, p <0.001) and medio-abdominal (yes: 16.2 ± 4.0 mmHg *vs.* no: 10.4 ± 5.6 mmHg, p = 0.007) ascites showed a statistically significant association with the HVPG levels. A gastroscopy was available in 46 patients, and the presence of esophageal varices also showed an association with the HVPG levels (yes: 15.2 ± 4.4 mmHg *vs.* no: 9.2 ± 5.7 mmHg, p <0.001).