Comprehensive Predictors of Portal Pressure from Functional Liver Reserve in Patients Who Underwent Hepatectomy

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Abstract Portal hypertension is a major risk factor for hepatic failure or intestinal bleeding in patients with liver disease but cannot be measured indirectly. We attempted to comprehensively evaluate preoperative parameters of functional liver reserve that correlated with portal pressure (PP) in patients with various liver diseases. We examined 93 patients in whom portal pressure was directly measured during preoperative portal vein embolization (PVE) or operation. Background liver included chronic viral liver disease in 43 patients, obstructive jaundice in 29 patients, and normal liver in 21. Multivariate logistic analysis and linear regression analysis were applied to create a predictive formula for PP. Mean PP was 13.4 ± 4.9 cm H₂O, and PP was significantly associated with severity of liver injury, hepatic fibrosis, intraoperative blood loss, and post-hepatectomy morbidity ($p < 0.05$ each). Mean PP after PVE (22.5 ± 7.8 cm H₂O) was significantly increased compared to that before embolization (13.1 ± 4.7 cm H₂O; $p < 0.01$). Univariate analysis identified seven significant parameters of preoperative liver function associated with PP: indocyanine green (ICG) test result, liver uptake and clearance index (HH15) on ^{99m}Tc-galactosyl serum albumin liver scintigraphy, total bilirubin level, prothrombin

activity, and hyaluronate level. Using multiple linear regression analysis, the predictive formula using ICG and HH15 was as follows: Y (estimated PP) = $0.273 + 0.086 \times \text{ICGR15} + 0.193 \times \text{HH15}$. The calculated PP (11.5 ± 4.6 cm H₂O (-1.9 cm H₂O)) was lower than true PP, which was significantly associated with post-hepatectomy morbidity ($p < 0.05$). The correlation between true and calculated PP was weak, and prediction using the conventional liver functional parameters was limited at present and, however, estimating PP appears to be useful in evaluating portal hypertension and post-hepatectomy morbidity.

Keywords Hepatectomy · Liver functional reserve · Portal pressure · ^{99m}Tc-GSA liver scintigraphy · Portal vein embolization

Introduction

Operative morbidity and mortality rates in patients with liver disease who undergo hepatic resection have decreased markedly in recent years, thanks to improvements in preoperative evaluation of liver functional reserve and perioperative management [1]. Portal hypertension remains to be a lethal operative risk in patients with liver dysfunction such as cirrhosis and should be carefully evaluated on imaging analysis [2]. However, portal pressure (PP) can be measured directly by insertion of a catheter via a trans-hepatic or trans-intestinal venous approach [3]. This approach is an invasive and complicated measure, requiring either puncture of the liver or laparotomy. Measurement of PP cannot currently be achieved using indirect tests. Gradient flow velocity or volume of the cardiac tricuspid valve on ultrasonography can be applied to predict pulmonary arterial pressure [4]. The gradient of hepatic portal venous pressure can be evaluated by various means [5–7]. However, indirectly evaluating PP itself

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remains to be difficult. Some investigators have attempted to identify factors associated with portal hypertension [8, 9], but clear predictors of PP have yet to be clarified. In the recent report of Hidaka [10], the intraoperative measurement of PP was important to clarify not only operative risks but also patient outcomes. Attempt of pre- or intraoperative evaluation of portal hypertension with the noninvasive test should be clinically necessary. To the best of our knowledge, no useful predictive formula for PP has yet been reported. Analysis of PP using a predictive formula would be useful to evaluate operative risk and reduce portal hypertension-related hepatic complications in patients with liver disease undergoing hepatectomy. We therefore attempted to examine parameters of liver functional reserve correlated with PP in patients for whom PP could be measured directly either during preoperative portal vein embolization or intraoperatively.

The present study examined relationships between reliable parameters of functional liver reserve such as conventional liver function tests, the indocyanine green (ICG) clearance test [11], serum hyaluronic acid (HA) level [12], and ^{99m}Tc -galactosyl human serum albumin liver scintigraphy (^{99m}Tc -GSA scintigraphy) [13] in 93 patients with various liver diseases in whom PP was directly measured. Furthermore, we attempted to derive a comprehensive analytical formula by multivariate analysis to predict PP and then compared predictive PP and true PP.

Methods

Patients

Subjects comprised 93 patients (67 men and 26 women) with or without liver injury who underwent hepatectomy in the Division of Surgical Oncology or Department of Surgery at Nagasaki University Graduate School of Biomedical Sciences between 1997 and 2012. Mean ($\pm$ standard deviation (SD)) age was 65 ± 10 years (range, 39–84 years). Liver diseases warranting hepatic resection included hepatocellular carcinoma in 41 patients, metastatic liver carcinoma in 14, intrahepatic cholangiocarcinoma in 10, gallbladder carcinoma in 11, bile duct carcinoma in 15, and other liver diseases in 2. The background liver condition was chronic viral liver disease in 43 patients, cirrhosis in 16, obstructive jaundice in 21, and normal liver in 29.

The volume of the liver to be resected is estimated before surgery based on the results of the ICG retention rate at 15 min (ICGR15) [14]. Liver volume, excluding the tumor, is measured by computed tomography (CT) volumetry [15]. Since 2004, we have applied ^{99m}Tc -GSA scintigraphy and the associated functional hepatic volumetry, serum HA level, and prothrombin activity based on ICGR15 testing to decide the extent of hepatectomy [16]. In this cohort, we performed

limited resection in seven patients, segmentectomy in 17, lobectomy in 32, and extended lobectomy in 19. Hepatectomy was not performed in 18 patients due to advanced tumor stage or liver function that was considered too poor for the estimated hepatectomy. Preoperative portal vein embolization was performed in 27 patients, and PP was measured by the catheter in the major portal trunk before embolization [17]. PP after portal vein embolization was measured intraoperatively at 3–4 weeks after portal vein embolization. Intraoperatively, a 5-French venous catheter was inserted via the iliac vein using the cutdown method. The tip of catheter was placed at the major portal trunk, and PP was measured using blood pressure monitors.

The study design was approved by the ethics review board at our university hospital, and informed consent for data collection was obtained from each patient prior to participation.

Evaluated Parameters

Clinical data, results of conventional liver function tests, and surgical data were analyzed. ICG 15-min retention rate was measured using a photopiece applied to the fingertip (RK-1000; Sumitomo Electric, Tokyo, Japan) without blood sampling [16, 17].

Patients received 3 mg (185 MBq) of ^{99m}Tc -GSA (Nihon Medi-Physics, Nishinomiya, Japan) as a bolus dose into the antecubital vein. The clearance index of ^{99m}Tc -GSA (HH15) and the hepatic uptake ratio of ^{99m}Tc -GSA (LHL15; count ratio in the liver compared to the sum of count ratios for the heart and liver at 15 min after injection of ^{99m}Tc -GSA) were calculated after injection of ^{99m}Tc -GSA [17]. We calculated the ratio of LHL15 and HH15 (LHL/HH15) in the present study. Peripheral blood samples for serum HA level were collected from every patient, and HA was assayed using the sandwich-binding protein assay (SRL, Tokyo, Japan). The normal value of serum HA is ≤ 50 ng/ml [12, 16, 17]. We performed histological staging using Knodell's score [18].

Statistical Analysis

Continuous data are expressed as mean $\pm$ SD. Data from different groups were compared using one-way analysis of variance and examined by Mann-Whitney's *U* test. Comparison of continuous data between groups was examined using Dunnett's multicomparison analysis. Correlation between continuous data was evaluated using Pearson's correlation analysis, and the correlation coefficient (*r*) was calculated. Potentially predictive variables were identified using a significance level of $p < 0.05$ by univariate analysis, and the identified factors were then entered into logistic regression multivariate analysis with a method of decreasing the variables. A two-tailed *p* value < 0.05 was considered significant. Statistical

Package for the Social Science (SPSS) version 18.0 software (SPSS, Chicago, IL) was used for all statistical analyses.

Results

Relationship with Clinicopathological Parameters and Portal Pressure

Mean PP in the 93 patients was 13.4 ± 4.9 cm H₂O. Table 1 shows PP for each background liver condition. PP in patients with cirrhosis and obstructive jaundice was significantly increased compared with that for normal liver ($p < 0.05$). PP after portal vein embolization (22.5 ± 7.8 cm H₂O) was significantly increased compared with that before embolization (13.1 ± 4.7 cm H₂O; $p < 0.001$). PP was significantly higher in patients with Child-Pugh B (17.9 ± 5.2 cm H₂O, $n = 5$) than in patients with Child-Pugh A (13.1 ± 4.8 cm H₂O, $n = 88$; $p = 0.036$). PP tended to be associated with post-operative complications such as hepatic failure ($n = 10$; 12.7 ± 4.8 and 14.3 ± 3.1 cm H₂O, $p = 0.088$) and uncontrolled ascites ($n = 29$; 11.6 ± 4.5 and 14.9 ± 4.2 cm H₂O, $p = 0.002$).

Table 2 shows correlations between PP and other comparable parameters. Correlation analysis identified 10 variables as significantly correlated with PP: ICGR15, ICGK value, LHL15, HH15, LHL15/HH15, total bilirubin level, prothrombin activity, serum HA level, and histological staging of fibrosis ($p < 0.05$). PP was significantly correlated with intraoperative blood loss ($r = 0.309$, $p = 0.007$). Given the need for parameters to predict PP before hepatectomy, histological staging of fibrosis and intraoperative blood loss were excluded from the next step of analysis.

Making Predictive Formula of Portal Pressure

The eight selected preoperative parameters were examined for correlations with PP using multiple linear regression analysis with the stepwise method (Table 3). After seven steps, two parameters of ICGR15 and HH15 were still significant (see models 6 and 7 in Table 3). Based on this result, the regression equation was established as

$$Y(\text{estimated PP}) = 0.273 + 0.086 \times \text{ICGR15} + 0.193 \times \text{HH15}$$

Correlation between PP after portal vein embolization in 27 patients and other comparable parameters was examined, and 10 variables significantly correlated with PP after portal vein embolization, including ICGR15, ICGK value, LHL15, total bilirubin level, prothrombin activity, platelet count, and serum HA level ($p < 0.05$). The seven preoperative parameters selected were examined for correlation with PP after embolization using multiple linear regression analysis in the model 1 with

Table 1 Portal pressures with each background liver disease

	Portal pressure (mmHg)
Normal ($n = 29$)	11.1 ± 5.6
Chronic hepatitis ($n = 27$)	13.3 ± 4.8
Cirrhosis ($n = 16$)	$15.6 \pm 4.3^*$
Obstructive jaundice ($n = 21$)	$15.0 \pm 3.5^*$

* $p < 0.05$ vs. normal liver

the stepwise method (Table 4). After eight steps, no parameters showed correlations with PP after embolization (see model 8 in Table 4).

Correlation Between Predictive Portal Pressure and True Portal Pressure

Mean estimated PP using the predictive formula was 11.5 ± 4.6 cm H₂O, lower than true PP (13.4 ± 4.9 cm H₂O; $p = 0.027$). The correlation between true PP and estimated PP was significant (correlation coefficient, 0.302; $p = 0.034$). Mean difference between true PP and calculated PP was 1.92 ± 1.64 cm H₂O. Calculated PP in patients with uncontrolled ascites and hepatic failure (13.7 ± 3.6 and 14.4 ± 2.9 cm H₂O) was significantly higher than that in those without (11.0 ± 3.9 and 11.7 ± 4.0 cm H₂O; $p = 0.001$ and $p = 0.042$, respectively). The weak correlation between blood loss and calculated PP was observed (correlation coefficient, 0.174; $p = 0.125$).

Table 2 Correlations between portal pressure and pathological or liver functional parameter or surgical result

	Correlation (r value)	p
ICGR15 (%)	0.335	0.001
ICGK value	-0.330	0.003
LHL15	-0.301	0.005
HH15	0.525	<0.001
LHL15/HH15	-0.523	<0.001
Total bilirubin (mg/dl)	0.223	0.032
AST (IU/l)	0.214	0.051
ALT (IU/l)	0.146	0.163
Total cholesterol (mg/dl)	-0.172	0.102
Platelet count (/mm ³)	0.017	0.871
Prothrombin activity (%)	-0.368	<0.001
Hyaluronic acid (ng/ml)	0.228	0.036
Staging (degree of fibrosis)	0.346	0.005
Grading (necroinflammatory response)	-0.073	0.570
Knodell's histological score	0.167	0.233

Data are presented by the correlation coefficient (r value)

ICG indocyanine green, LHL15 liver uptake ratio at 15 min, HH15 heart clearance at 15 min, AST aspartate aminotransferase, ALT alanine aminotransferase

Table 3 Multiple linear regression stepwise method output using data from 93 patients for correlations with portal pressure

Model		Unstandardized coefficients		Standardized coefficient	<i>t</i> value	<i>p</i> value	95 % confidence interval	
		β	Standard error	β			Lower limit	Upper limit
1	(Constant)	−22.996	29.388		−.783	0.437	−81.639	35.646
	ICGR15	0.171	0.080	0.422	2.133	0.037	0.011	0.331
	HH15	0.216	0.245	0.462	0.883	0.381	−0.272	0.704
	Total bilirubin	−0.218	0.426	−0.063	−0.512	0.611	−1.067	0.632
	ICGK value	5.290	16.247	0.048	0.326	0.746	−27.131	37.712
	Prothrombin	−0.038	0.046	−0.098	−0.823	0.413	−0.129	0.054
	Hyaluronate	−0.004	0.005	−0.104	−0.779	0.439	−0.014	0.006
	LHL15	0.296	0.185	0.318	1.602	0.114	−0.073	0.666
	LHL15/HH15	−1.896	8.042	−0.131	−0.236	0.814	−17.943	14.151
6	(Constant)	−21.501	17.806		−1.207	0.231	−56.989	13.988
	ICGR15	0.115	0.051	0.284	2.242	0.028	0.013	0.217
	HH15	0.250	0.070	0.536	3.562	0.001	0.110	0.391
	LHL15	0.195	0.157	0.209	1.239	0.219	−0.118	0.508
7	(Constant)	0.273	2.902		0.094	0.925	−5.510	6.056
	ICGR15	0.086	0.046	0.213	1.878	0.064	−0.005	0.177
	HH15	0.193	0.053	0.412	3.644	0.000	0.087	0.298

Dependent variable is portal pressure (cm H₂O) (dependent variable: step 7 total). Models between steps 2 and 5 were not indicated. The standardized β coefficient provides a measure of the contribution of each variable to the model. The *t* and *p* values provide an indication of the impact of each predictor variable. Abbreviations were as in Table 2

Discussion

Portal hypertension is the most important consequence of cirrhosis, and its presence represents a hard end point for

clinical outcomes such as varices, ascites, hepatorenal syndrome, and encephalopathy [19]. The current standard for measuring portal hypertension and severity is usually measurement of the hepatic venous pressure gradient.

Table 4 Multiple linear regression stepwise method output using data from 27 patients who underwent portal vein embolization for correlations with portal pressure after embolization

Model		Unstandardized coefficients		Standardized coefficient	<i>t</i> value	<i>p</i> value	95 % confidence interval	
		β	Standard error	β			Lower limit	Upper limit
1	(Constant)	35.914	44.164		0.813	0.426	−56.522	128.350
	ICGR15	0.107	0.177	0.143	0.607	0.551	−0.263	0.478
	LHL15	−0.243	0.487	−0.120	−0.499	0.624	−1.263	0.777
	Total bilirubin	−1.114	1.600	−0.165	−0.696	0.495	−4.462	2.235
	ICGK value	0.031	0.040	0.197	0.771	0.450	−0.053	0.115
	Platelet	0.218	0.136	0.374	1.605	0.125	−0.066	0.502
	Prothrombin	−0.044	0.107	−0.093	−0.413	0.684	−0.268	0.179
	Hyaluronate	0.022	0.012	0.428	1.841	0.081	−0.003	0.047
6	(Constant)	12.501	4.033		3.100	0.005	4.177	20.825
	Platelet	0.187	0.120	0.320	1.551	0.134	−0.062	0.435
	Hyaluronate	0.024	0.011	0.466	2.260	0.033	0.002	0.046
7	(Constant)	18.070	1.885		9.584	0.000	14.187	21.954
	Hyaluronate	0.016	0.010	0.322	1.702	0.101	−0.003	0.036
8	(Constant)	20.526	1.257		16.329	0.000	17.942	23.110

Dependent variable is portal pressure (cm H₂O) Models between steps 2 and 5 were not indicated (dependent variable: step 8 total). Explanation and abbreviations were as in Tables 2 and 3

Measurement of this gradient is safe and relatively simple to perform but is invasive and costly [5, 6]. Clinical features associated with the presence of portal hypertension include ascites, splenomegaly, and venous dilatation as caput medusa [20]. Thrombocytopenia is an important predictor of significant portal hypertension and the presence of esophageal-gastric varices [21]. The ratio of platelet count to spleen size is thought to offer a surrogate marker [22]. Hepatic fibrosis or liver stiffness also correlates with portal hypertension [23]. Some serum parameters have been proposed to correlate with portal hypertension, such as insulin-like growth factor [24, 25]. Zhang et al. and Wiechowska-Kozłowska et al. recently reported the usefulness of measuring Doppler flow to evaluate portal hypertension [26, 27]. However, distinct markers representing PP have yet to be clarified. Hidaka et al. recently reported that the intraoperatively direct measurement of PP was important to clarify not only operative risks but also patient outcomes [10]. However, the direct measurement of PP is invasive and possible to injure portal trunk, leading to portal thrombosis or stenosis. Therefore, noninvasive prediction by the predictive formula like our present study is clinically necessary as the previous report [28]. Until a very reliable marker for PP is identified, definition of a predictive formula using conventional correlates may prove useful.

The present study applied the reliable liver function markers from ^{99m}Tc -GSA liver scintigraphy, ICGR15, and serum HA level, along with conventional parameters [12, 13, 16, 17]. These noninvasive tests can be routinely performed before hepatectomy. HH15 and LHL15 from ^{99m}Tc -GSA liver scintigraphy have been applied recently to evaluate indications for surgical resection as a reliable marker [13, 16, 17, 29]. Our report showed a close correlation between functional volumetry by ^{99m}Tc -GSA scintigraphy and PP [29], suggesting HH15 and LHL15 as reliable predictors of PP. To evaluate both parameters, the ratio of LHL15 and HH15 was examined as a new value in the present study. Serum HA is a marker of hepatic fibrosis and deserialization of endothelial cell function in the liver [12], which offers a good reflection of post-hepatectomy complications such as uncontrolled ascites or hepatic failure [12, 30]. These complications must be caused by portal hypertension. The present study revealed that PP was significantly increased according to the degree of liver injury, supporting previous findings that PP reflects the severity of liver damage [31]. According to the present results, the histological degree of fibrosis and Knodell's histological score [18] are also closely correlated with increased PP.

We identified 10 parameters closely correlated with PP. Among these parameters, PP correlated with increased blood loss during operation, possibly due to histological fibrosis or increased venous pressure within the hepatic parenchyma. The ability to estimate PP is thus clinically important for predicting operative risks, as reported previously [2, 32]. By

selecting seven parameters that could be evaluated preoperatively, the present study attempted to create a comprehensively predictive formula. To the best of our knowledge, an attempt to make such a formula has not previously been reported. However, PP after portal vein embolization could not be predicted based on functional parameters. PP might increase due to a decrease in the vascular bed after embolization, but this increase might not reflect clinical outcomes in our series. As post-embolization PP did not correlate with any markers of liver function after embolization, this increase appears to be clinically ignorable. With respect to PP without embolization, a formula applying the two parameters of ICGR15 and HH15 was achieved. Both parameters were very reliable functional tests to define post-hepatectomy risk of morbidity [13, 16, 17, 29]. The formula using these reliable hepatic functional parameters were noninvasive and clinically useful. As such tests can be routinely examined in our situation under the usual national health insurance, the calculating predictive PP using the present formula is not expensive. The present subject in the study included various background liver diseases and heterogenous, and therefore, the operative indication was supposed to be different. However, as our previous report, we have aimed to establish the ideal indication for hepatectomy in various liver diseases using ICGR15, GSA liver scintigraphy, and so on [33]. Then, we examined the present study in heterogenous subject.

By comparing the calculated PP with the true PP, close correlations could be clarified even though the estimated PP value was 2 cm H₂O lower than the true PP. Estimated PP can be used to predict real PP. To evaluate portal hypertension, the cutoff value should be established. As the definition of portal hypertension was reported as PP > 15 cm H₂O, an estimated PP > 11.5 cm H₂O was thought to indicate a true PP > 15 cm H₂O. True PP > 15 cm H₂O was seen in 38 patients (41 %), whereas calculated PP > 15 cm H₂O was seen in 16 patients. As the mean difference between true and calculated PP was 1.9, the number of patients with calculated PP > 13 cm H₂O was 37 patients, basically equivalent to the number with true PP. We consider that calculated PP might be about 2 cm H₂O lower than true PP according to the present results. When the relationship between clinical outcomes and calculated PP was considered in light of the present results, a calculated PP > 13 cm H₂O must be carefully treated to predict severe post-hepatectomy morbidity, as portal hypertension is an important factor for clinical manifestations in liver disease [31, 32]. Although true PP correlated with intraoperative blood loss, the correlation with calculated PP was not significant. The correlation between true and calculated PP was weak according to the present results, so prediction using the present factors clearly has limitations. As described above, Doppler ultrasonography shows portal flow. Use of variables from this modality may yield more reliable data and better predictive formula in the future prospective analyses [26, 27].

Conclusion

Among patients who underwent measurement of PP before or during hepatic resection, certain markers of liver function determined before treatment correlated with PP, including histological fibrotic grade or intraoperative blood loss. A comprehensive predictive formula for PP was determined, and the calculated values showed mild correlations with true PP and associations with post-operative morbidity. Predictors using Doppler ultrasonography are necessary in the next step. Application of the current predictive formula is noninvasive and may allow adequate comprehensive assessment of functional liver reserve, thus providing useful information in patients with portal hypertension and liver injury.

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Conflict of Interest None to declare.

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