

## Histological-hemodynamic correlation in cirrhosis—a histological classification of the severity of cirrhosis

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**Background/Aims:** While the definitive diagnosis of cirrhosis is histological, it is the degree of portal hypertension, as determined by the hepatic venous pressure gradient (HVPG), that is an important determinant of the severity of cirrhosis. An HVPG  $\geq 10$  mmHg (termed clinically significant portal hypertension or CSPH) is predictive of the development of complications of cirrhosis, including death. This study aimed to determine the relationship between specific histological parameters and HVPG in cirrhosis.

**Methods:** Forty-three patients with biopsy-proven cirrhosis and HVPG measurements within 6 months of the biopsy were included in the study. The following parameters were scored semiquantitatively and without knowledge of HVPG results: sinusoidal fibrosis, septal thickness, loss of portal tracts and central veins, nodule size, inflammation, steatosis, and iron.

**Results:** Septal thickness ( $p=0.03$ ), small nodularity ( $p=0.003$ ), loss of portal tracts ( $p=0.01$ ), inflammation ( $p=0.04$ ) and alcoholic etiology ( $p=0.01$ ) correlated with the presence of CSPH. However, small nodularity and septal thickness were the only parameters independently predictive of CSPH ( $r=0.658$ ,  $p<0.05$ ).

**Conclusions:** We describe a subclassification of histological cirrhosis based on the severity of portal hypertension that consists of a combination of nodule size and septal thickness, with small nodularity and thick septa being independent predictors of the presence of CSPH.

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**Keywords:** Hepatic venous pressure gradient; Cirrhosis; Liver biopsy; Portal hypertension

### 1. Introduction

Cirrhosis is the end result of chronic liver disease and is defined histologically by the presence of regenerative nodules surrounded by fibrous tissue. This architectural distortion leads to increased intrahepatic resistance that in turn leads to portal hypertension. Complications of

cirrhosis, including esophageal varices and ascites, develop once portal pressure reaches a threshold level of 10–12 mmHg, as assessed by the hepatic venous pressure gradient (HVPG) [1–3]. This threshold level has been found to be of great prognostic value and has been termed ‘clinically significant portal hypertension’ (CSPH) [4,5].

The extent of fibrosis on liver biopsy is used to evaluate the stage or severity of chronic liver disease, with the most severe stage being the cirrhotic stage. However, the sole histological diagnosis of cirrhosis does not denote the clinical severity of cirrhosis. Determining a relationship between specific histologic parameters on liver biopsies from cirrhotic patients and portal pressure would be valuable in determining whether certain histologic parameters can be used to sub-classify cirrhosis by its

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‘severity’. This relationship would be of prognostic value, not only regarding the development of clinical complications, but also regarding the potential for reversibility.

Additionally, this correlation would provide further insight into the pathophysiology of portal hypertension and the relationship that various histologic parameters, such as steatosis and inflammatory activity, have on portal pressure.

Therefore, the aim of this study is to determine the relationship between portal pressure, as determined by the HVPG, and specific histologic parameters on liver biopsies diagnosed as having cirrhosis, and to determine whether any of these parameters correlate with the presence of CSPH and can, therefore, identify different severities of histologic cirrhosis.

## 2. Methods

### 2.1. Patients

Patients who had a liver biopsy specimen (obtained via a transjugular or percutaneous approach) and hepatic venous pressure measurements (HVPG) performed within six months of each other were included in the study. At our institution, HVPG measurements are performed routinely at the time of transjugular liver biopsy.

### 2.2. Histological assessment

In our institution, all liver biopsies performed for medical disorders are fixed in formalin and routinely stained with the hematoxylin-eosin (H&E), reticulin, Masson trichrome, DPAS (PAS stain with diastase digestion) and iron stain. Slides of each biopsy were prospectively and simultaneously reviewed by two observers (DJ and SN) blinded to the results of HVPG measurements and who, after discussion, concurred on the grading of each histological parameter (see below). A liver biopsy size of at least 10 mm was required for inclusion in the study. In fragmented biopsies, the total length was estimated by adding maximum dimensions of each individual fragment. Liver fibrosis was staged according to the Batts and Ludwig classification [6] (a modification of the Scheuer classification) in which

stage 0 corresponds to no fibrosis, stage 1 is portal fibrosis, stage 2 is periportal fibrosis, stage 3 is bridging fibrosis and stage 4 is cirrhosis. Only biopsies categorized as being stage 4 (cirrhotic stage) were included in the study.

The biopsies were evaluated on the following parameters: sinusoidal fibrosis, septal thickness (width of the connective scar tissue separating cirrhotic nodules), loss of portal tracts and central veins, nodule size, inflammation, steatosis and iron. Each parameter was scored (Table 1) on a prospectively designed scale that was standardized and validated on a separate set of liver biopsies prior to initiation of the study. In case of heterogeneous pattern of sinusoidal fibrosis, the worst pattern was scored. For septal thickness, the thickness of the predominant type of septae in each specimen was scored. Regarding nodule size, the presence of even one small nodule would lead to a ‘mixed’ classification. Regarding the loss of portal tracts and portal veins, we anticipated 4–6 portal tracts and central veins per centimeter of core needle biopsy, therefore, the absence of identifiable portal tracts in the liver biopsy was scored as “4” (maximal abnormality), while their presence as expected for a normal biopsy (at least 4 portal tracts/cm) was scored as “0”. Similarly, a central vein is expected for each lobule in a normal biopsy and by comparison in each nodule of a cirrhotic liver. The loss of central veins was also subjectively scored on a 0–4 scale. Absence of identifiable central veins in all cirrhotic nodules was scored as “4”, while their presence in each cirrhotic nodule was scored as “0”. Representative micrographs of nodule size and septal thickness are shown in Figs. 1 and 2.

### 2.3. Hepatic venous pressure gradient measurements

Hepatic venous pressures were measured by either the Hepatic Hemodynamic Laboratory at the VA CT Healthcare System or by Interventional Radiology at Yale-New Haven Hospital. As previously described [7], the right hepatic vein was catheterized via a transjugular or femoral approach. Pressures were recorded in the wedged (occluded) and free position using a balloon catheter and a strain gauge transducer. The HVPG was calculated by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure. Clinically significant portal hypertension (CSPH) was defined as an HVPG  $\geq 10$  mmHg.

### 2.4. Statistical analysis

Analysis was performed on a database in which the results of the histological evaluation were entered prior to entering the HVPG data. Using non-parametric statistics, HVPG and the presence (or absence) of CSPH were correlated to each histologic parameter as well as to gender, sex and etiology of cirrhosis with the Kruskal–Wallis and Fisher’s exact tests. Multivariable linear regression and logistic regression models were

**Table 1**  
Histological parameters and grading scale

Histological parameter	Range	Scale
Fibrosis		
Sinusoidal	0–3	0, 1 (mild), 2 (moderate), 3 (severe)
Septal Thickness <sup>a</sup>	0–3	0, 1 (thin), 2 (medium), 3 (thick)
Nodularity		
Small nodules		Nodule size is comparable to width of needle biopsy specimen
Mixed nodules		Presence of both small and large nodules <sup>b</sup>
Large nodules		Nodule size larger than biopsy width
Portal tracts lost	0–4	0, 1 (1–25%), 2 (26–50%), 3 (51–75%), 4 (76–100%)
Central veins lost	0–4	0, 1 (1–25%), 2 (26–50%), 3 (51–75%), 4 (76–100%)
Inflammation		
Lobular	0–3	0, 1 (mild), 2 (moderate), 3 (severe)
Interface	0–3	0, 1 (mild), 2 (moderate), 3 (severe)
Steatosis	0–4	0, 1 (1–25%), 2 (26–50%), 3 (51–75%), 4 (76–100%)
Iron	0–4	0, 1 (visible at 250 $\times$ magnification), 2 (100 $\times$ ), 3 (25 $\times$ ), 4 (10 $\times$ )

<sup>a</sup> Thickness of the predominant type of septae in each specimen.

<sup>b</sup> The presence of even one small nodule would lead to a ‘mixed’ classification.

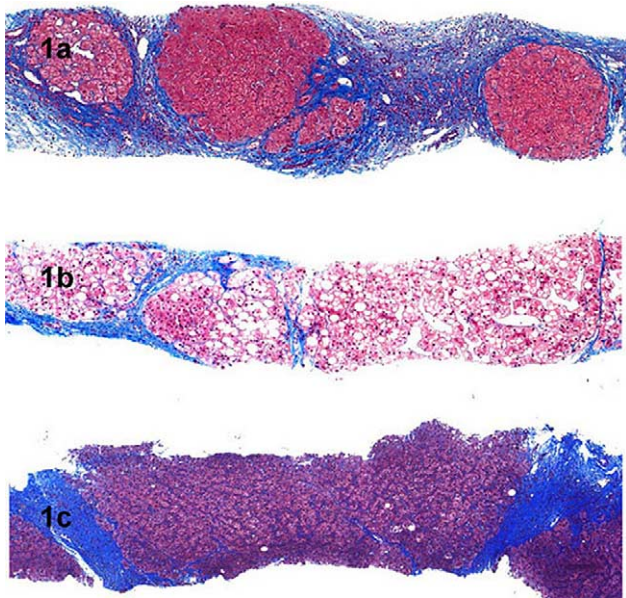


Fig. 1. Representative slides (trichrome stain, 40 $\times$ ) demonstrating different nodule size: small (a), mixed (b), and large (c).

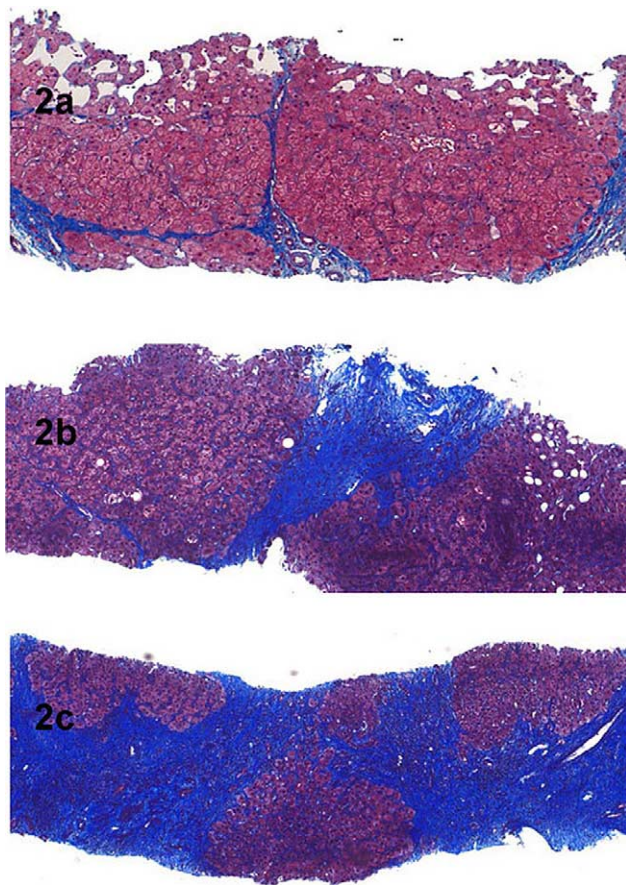


Fig. 2. Representative slides (trichrome stain, 40 $\times$ ) demonstrating different septal thicknesses: thin (a), intermediate (b), and thick (c).

generated to identify the histologic factors correlated with HVPg or the presence of CSPH, respectively. Statistical analysis was performed with the SPSS statistical package.

### 3. Results

In the period between 1994 and 2002, 88 patients had a liver biopsy performed within 6 months of HVPg measurements. Nineteen patients were excluded due to (i) fragmented, small specimens ( $n=2$ ), or (ii) a histological diagnosis unrelated to chronic liver diseases (passive congestion ( $n=4$ ); graft vs. host disease ( $n=8$ ), chronic rejection ( $n=2$ ), sarcoidosis ( $n=1$ ), drug reaction ( $n=2$ )). Of the 69 remaining patients, 19 patients had earlier stages of chronic liver disease (stages 1–3), and seven patients had no fibrosis (stage 0). Histological cirrhosis (stage 4) was present in the liver biopsies of 43 patients who constitute the basis of the present study.

As shown in Table 2, the median age of patients included was 47 years and 74% were male. Hepatitis C was the most common etiologic factor and was present in 23 cases (55%). Alcohol abuse was the etiology of cirrhosis in 11 patients (26%). The median HVPg was 11.5 mmHg with a range of 5–28 mmHg; 25 patients (58%) had CSPH.

#### 3.1. Correlation between HVPg and histological parameters

As shown in Table 3, HVPg was statistically different among the subcategories of etiology ( $p=0.014$ ), septal thickness ( $p=0.007$ ), and nodule size ( $p=0.034$ ). These factors were entered into a stepwise multivariable linear regression model, which revealed small nodule size and septal thickness as the only two independent predictive factors for HVPg ( $r=0.646$ ,  $p<0.001$ ). The independent effects of nodule size and septal thickness on HVPg in cirrhotic patients are illustrated in Fig. 3. When

Table 2  
Clinical characteristics of study population

Patient characteristics	
Total number of patients	$n=43$
Percutaneous biopsies	$n=9$
Transjugular biopsies	$n=34$
Male gender	32 (74%)
Age (median, range)	47 years (23–79)
Etiology of Liver Disease	
Hepatitis C	$n=21$
Alcohol	$n=9$
Hepatitis C + alcohol	$n=2$
Autoimmune hepatitis	$n=5$
Hepatitis B	$n=1$
Idiopathic	$n=5$
HVPg (median, range)	11.5 (5–28)
HVPg $\geq 10$ mmHg (CSPH <sup>a</sup> )	25 (58%)

<sup>a</sup> CSPH, clinically significant portal hypertension.



**Table 3**  
Median HVPG for each histological parameter

Histological parameter	n	Median HVPG (range) (mmHg)	P
<i>Sinusoidal fibrosis</i>			NS
None	6	11.25 (6–17)	
Mild	22	9.5 (5–20)	
Moderate	13	15 (5–28)	
Severe	2	17.5 (12–23)	
<i>Septal thickness</i>			0.007 <sup>a</sup>
Thin	7	8 (6–12)	
Medium	14	10 (5–17)	
Thick	22	14.75 (6–28)	
<i>Nodule size</i>			0.034 <sup>b</sup>
Small	13	14 (7–28)	
Mixed	27	9 (5–21)	
Large	3	8.5 (6–17)	
<i>Portal tracts lost</i>			NS
0–25%	0	n/a	
26–50%	2	6.75 (5–9)	
51–75%	5	6.75 (6–15)	
76–100%	36	12 (5–28)	
<i>Central veins lost</i>			NS
0–25%	0	n/a	
26–50%	4	7.75 (6–17)	
51–75%	4	13.25 (6–20)	
76–100%	35	11.5 (5–28)	
<i>Lobular inflammation</i>			NS
None	6	11.75 (8–17)	
Mild	37	11.3 (5–28)	
Moderate	0	n/a	
Severe	0	n/a	
<i>Interface inflammation</i>			NS
None	5	12 (11–17)	
Mild	35	11.3 (5–28)	
Moderate	3	8 (5–12)	
Severe	0	n/a	
<i>Steatosis</i>			NS
0–25%	13	12 (5–21)	
26–50%	24	10.4 (6–28)	
51–75%	4	12.25 (7–15)	
76–100%	2	11.5 (11–12)	
<i>Iron</i>			NS
Grade 1	22	10.25 (5–23)	
Grade 2	12	10.25 (5–28)	
Grade 3	7	14 (6–21)	
Grade 4	2	15.5 (10–21)	
<i>Etiology of cirrhosis</i>			0.014
Non alcoholic	32	9.25 (5–28)	
Alcoholic	11	14 (7–23)	

*p* values reflect the comparison among HVPG values of each subcategory (Kruskal–Wallis test). NS, not statistically significant.

<sup>a</sup> Thin vs. medium NS; thin vs. thick *p*=0.01; medium vs. thick *p*=0.015.

<sup>b</sup> Small vs. mixed *p*=0.012, small vs. large NS, mixed vs. large NS.

comparing histological parameters between patients with alcoholic and a non-alcoholic etiology (Table 4), it is clear that small nodularity was significantly more frequent in alcoholic cirrhosis and this close correlation led to the elimination of etiology on multivariable analysis.

### 3.2. Correlation between clinically significant portal hypertension (CSPH) and histological parameters

Patients with and without CSPH were compared in terms of each histological parameter, gender, and etiology for each group (Table 5). On univariate analysis, septal thickness, presence of small nodules, percentage of portal tracts lost, interface inflammation, hepatic iron and alcoholic etiology were found to be significantly different between patients with and without CSPH. These factors were entered into a forward logistic regression model, and the presence of small nodules and septal thickness were once more found to be the only significant histological factors predictive of the presence of CSPH ( $r=0.658$ ,  $p<0.05$ ).

Table 6 illustrates the proportion of patients with clinically significant portal hypertension grouped by the two significant predictors: nodule size and septal thickness. Every patient with thick fibrous septa and small nodule size had CSPH. Additionally, a greater proportion of patients have CSPH with increasing septal thickness and with decreasing nodule size.

## 4. Discussion

Liver biopsy remains the gold standard for staging diffuse liver disease. Staging is based on the extent of fibrosis and architectural distortion, and in all classification systems, the most advanced stage is the cirrhotic stage. Although it has been suggested that histological cirrhosis can be further subclassified into different severities [8], this assessment has been based solely on the characteristics of fibrous septae.

Since most complications of cirrhosis are secondary to portal hypertension, it is logical that measurements of portal pressure, determined by the hepatic venous pressure gradient (HVPG), have been found to be of major prognostic significance. Importantly, a threshold level of 10 mmHg has been identified as a predictor of the development of complications of cirrhosis (varices, variceal hemorrhage and ascites) and death [5]. Patients with an HVPG  $\geq 10$  mmHg are denominated as having clinically significant portal hypertension (CSPH) [4]. The objectives of our study were to correlate specific histological parameters on liver biopsies of cirrhotic patients to the HVPG and to identify parameters predictive of the presence of CSPH. We found that septal thickness and nodule size were the only two independent predictors of the presence of CSPH, thereby providing evidence that histological cirrhosis can in fact be sub-classified in to at least two different severities.

Establishing the concept of ‘severity of cirrhosis’ has significant clinical implications. Upon diagnosis of cirrhosis, specific histological findings on biopsy could predict the likelihood of developing ascites or esophageal varices. With this correlation between histology and HVPG, additional

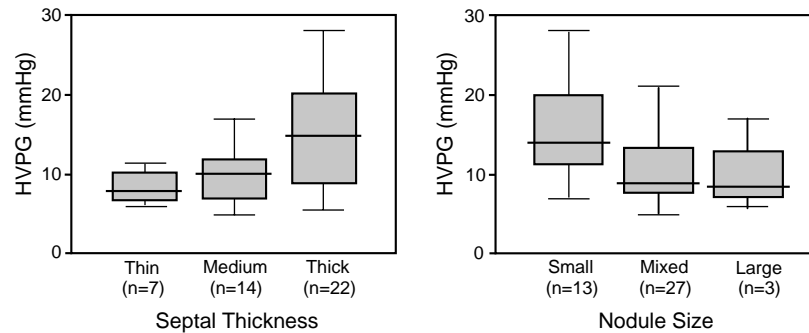


Fig. 3. Boxplots of HVPG vs. septal thickness and nodule size showing median HVPG, 25–75th percentile box, and complete range of measurements.

support is added to the large body of research examining HVPG and prognosis in cirrhotic patients. Identifying patients with mild and severe cirrhosis may potentially be helpful in evaluating the response to current antiviral or antifibrotic therapies.

Our findings are not unexpected and are consistent with the pathophysiology of portal hypertension in cirrhosis, where an increased intrahepatic resistance plays a major role [9]. The thicker the septae, the greater the passive obstruction to portal flow and the greater the HVPG. Small nodule size is also indicative of greater damage and greater architectural distortion and will further increase intrahepatic resistance. Although other factors, such as active constriction of intrahepatic vessels [9] and an increase in portal venous inflow secondary to splanchnic vasodilatation [10] play an important role in the pathogenesis of portal hypertension, our findings support the role of intrahepatic structural abnormalities in the pathophysiology of portal hypertension.

Interestingly, alcoholic cirrhosis was associated with a significantly higher HVPG than non-alcoholic cirrhosis (14.0 vs. 9.2 mmHg). Alcoholic cirrhosis, described classically by Laennec as a micronodular process, was significantly correlated with small nodule size ( $p < 0.01$ ). However, only half of the patients with small nodule size on biopsy had alcohol-related cirrhosis, and nearly all patients

with small nodule size had CSPH. Consequently, the multivariable analysis found small nodule size to be more predictive of HVPG than alcohol-induced cirrhosis. Furthermore, the transition from micro to macronodular cirrhosis has been described in alcoholic cirrhosis [11].

The issue of reversibility or regression of cirrhosis is an evolving and controversial concept [12], which has become

Table 5

Mean scores of each of the histological parameters grouped by the presence or absence of CSPH

Histological parameter	No CSPH (n = 18)	CSPH (n = 25)	p
Fibrosis			
Sinusoidal	1.06	1.40	NS
Septal	2.06	2.56	0.03*
Nodularity			
Small	n = 1	n = 12	0.003*
Mixed	n = 15	n = 12	NS
Large	n = 2	n = 1	NS
Portal tracts lost	3.56	3.96	0.001
Central veins lost	3.61	3.80	NS
Inflammation			
Interface	1.11	0.84	0.04
Lobular	0.94	0.80	NS
Steatosis	0.78	0.96	NS
Iron	0.44	0.96	0.065
Alcohol etiology	n = 1	n = 10	0.01
Male gender	n = 14	n = 18	NS

p values obtained by Fisher's exact test. NS, not statistically significant.

Table 4

Mean scores of histological parameters in relation to etiology of cirrhosis

	Alcoholic etiology	Non-alcoholic etiology	p
N	11	32	
Sinusoidal fibrosis	1.64 (0–3)	1.13 (0–2)	0.71
Septal thickness	2.36 (1–3)	2.34 (1–3)	0.08
Nodule Size			0.017
Small nodules	7 (64%)	6 (21%)	
Mixed nodules	3 (27%)	2 (6%)	
Large nodules	1 (9%)	24 (75%)	
Lost portal tracts	4 (4)	3.72 (2–4)	0.09
Lost central veins	3.55 (2–4)	3.78 (2–4)	0.35
Lobular inflammation	0.73 (0–1)	0.91 (0–1)	0.04
Interface inflammation	0.73 (0–1)	1.03 (0–2)	0.14
Steatosis	0.82 (0–3)	0.91 (0–3)	0.47
Iron	0.91 (0–3)	0.69 (0–3)	0.72

Table 6

Proportion of patients with CSPH according to septal thickness and nodule size

		Septal thickness		
		Thin	Medium	Thick
Nodule size	Large	0	0/2 (0%) (7 mmHg)	1/1 (100%) (17 mmHg)
	Mixed	0/4 (7 mmHg)	5/10 (50%) (10 mmHg)	7/13 (54%) (13 mmHg)
	Small	2/3 (66%) (11 mmHg)	2/2 (100%) (13 mmHg)	8/8 (100%) (20 mmHg)

Median HVPG for each category (mm Hg) is shown in parenthesis.

more prominent with the development of new treatments for chronic liver disease and even antifibrotic therapy. It will be of great interest to identify histological patterns in cirrhosis that are more likely to reverse and to evaluate whether clinical and/or hemodynamic improvements in cirrhotic patients correlate with changes from a more severe to a less severe histological pattern.

Several, mostly pathophysiological, studies have correlated histopathologic features on liver biopsy with the degree of portal hypertension in patients with liver disease. In patients with alcoholic liver disease, a positive correlation has been identified between intrahepatic pressure and both hepatocyte size and collagen in the space of Disse [13], parameters that are not routinely assessed. Other studies have shown progressive increases in HVPG with increasing severity of liver disease (normal, chronic hepatitis, pre-cirrhosis and cirrhosis) both in alcoholic [14] and in non-alcoholic liver disease [15] that in turn is associated with greater periportal and lobular abnormalities [16]. Only two studies have correlated histopathologic features with the degree of portal hypertension in cirrhotic patients. In a study that included only alcoholic cirrhotics, no relevant correlation was found between HVPG and any histological parameter, although HVPG was higher in those with alcoholic hepatitis [17]. Of note, three of our patients with an alcoholic etiology had features of steatohepatitis on biopsy and HVPG did not appear to differ from those without steatohepatitis. In another study examining histomorphometry using an image analyzer, the only significant (negative) correlation identified was between HVPG and the number of residual portal spaces, i.e. portal spaces not involved in the process of bridging fibrosis [18]. Our findings may be reflective of this process and are of greater practical relevance given that the assessment of residual portal tracts in cirrhotic and/or fragmented specimens is almost impossible.

The majority of our patients had a transjugular liver biopsy (TJLB) and this may introduce a selection bias toward patients with severe chronic liver disease. TJLB is readily available and very successful at our institution and thus, patients and physicians may often prefer this procedure. This is supported by the fact that many of the specimens were excluded because of earlier histological stages. There is also a perceived notion that transjugular liver biopsies are smaller than those obtained percutaneously. At our center, specimens obtained through the transjugular route are comparable to percutaneously-obtained specimens regarding adequacy for analysis. Although it has been mentioned that a length of at least 25 mm is necessary to evaluate fibrosis accurately using semi-quantitative scores [19], our study demonstrates that with cirrhotic livers, a smaller specimen size is sufficient to assess the severity of cirrhosis, given the significant and consistent correlation that we found between histological features and HVPG.

Follow-up studies need to be undertaken in a larger population to validate the proposed sub-classification of cirrhosis. If validated, a modification of the staging system of biopsies with chronic liver disease could be proposed in which stage 4 (cirrhotic stage) would be subclassified into stages 4a, 4b and even 4c. A prospective analysis examining serial biopsies and HVPG measurements in patients with cirrhosis would provide significant insight into the histological progression (or regression) of cirrhosis and its association with portal pressure. It will be interesting to compare a quantitative determination of fibrosis (e.g. by computerized image analysis) to our semi-quantitative assessment of septal thickness and nodule size. While this assessment was performed on a subjective basis, we can make rough objective estimates based on some of the representative cases, whereby thin septae are  $<0.2$  mm, thick septae are  $>0.4$  mm, small nodules are  $<1.0$  mm and large nodules are  $>2$  mm.

In conclusion, we describe a sub-classification of histological cirrhosis based on the severity of portal hypertension that consists of a combination of nodule size and septal thickness. Our study identifies small nodularity and thick septa as independent predictors of the presence of CSPH, and are, therefore, predictive of the clinical severity of cirrhosis.

## References

- [1] Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* 1985;5:419–424.
- [2] Morali GA, Sniderman KW, Deitel KM, Tobe S, Witt-Sullivan H, Simon M, et al. Is sinusoidal portal hypertension a necessary factor for the development of hepatic ascites? *J Hepatol* 1992;16: 249–250.
- [3] Casado M, Bosch J, Garcia-Pagan JC, Bru C, Banares R, Bandi JC, et al. Clinical events after transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings. *Gastroenterology* 1998;114:1296–1303.
- [4] D'Amico G, Garcia-Tsao G, Cales P, Escorsell A, Nevens F, Cestari R, et al. Diagnosis of portal hypertension: how and when. In: De Franchis R (Ed.). *Portal Hypertension III. Proceedings of the III Baveno International Consensus Workshop on Definition, Methodology and Therapeutic Strategies*. Blackwell Science. 2001 p. 36–64.
- [5] Groszmann RJ, Garcia-Tsao G, Makuch RW, Bosch J, Escorsell A, Garcia-Pagan JC, et al. Multicenter randomized placebo-controlled trial of non-selective beta-blockers in the prevention of the complications of portal hypertension: final results and identification of a predictive factors. *Hepatology* 2003;38(Suppl. 1):206A [abstract].
- [6] Batts KP, Ludwig J. Chronic hepatitis. an update on terminology and reporting. *Am J Surg Pathol* 1995;19:1409–1417.
- [7] Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. *Hepatology* 2004;39:280–283.
- [8] Kutami R, Girgrah N, Wanless IR, Sniderman K, Wong FS, Sherman M, et al. The Laennec grading system for assessment of hepatic fibrosis: validation by correlation with wedged hepatic vein pressure and clinical features. *Hepatology* 2000;32:407A [abstract].

- [9] Bhathal PS, Grossman HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. *J Hepatol* 1985;1:325–337.
- [10] Vorobioff J, Bredfeldt JE, Groszmann RJ. Increased blood flow through the portal system in cirrhotic rats. *Gastroenterology* 1984;87: 1120–1126.
- [11] Fauerholdt L, Schlichting P, Christensen E, Poulsen H, Tygstrup N, Juhl E. Conversion of micronodular cirrhosis into macronodular cirrhosis. *Hepatology* 1983;3:928–931.
- [12] Desmet VJ, Roskams T. Cirrhosis reversal: a duel between dogma and myth. *J Hepatol* 2004;40:860–867.
- [13] Orrego H, Blendis LM, Crossley IR, Medline A, Macdonald A, Ritchie S, et al. Correlation of intrahepatic pressure with collagen in the Disse space and hepatomegaly in humans and in the rat. *Gastroenterology* 1981;80:546–556.
- [14] Krogsgaard K, Gluud C, Henriksen JH, Christoffersen P. Correlation between liver morphology and portal pressure in alcoholic liver disease. *Hepatology* 1984;4:699–703.
- [15] Van Leeuwen DJ, Sherlock S, Scheuer PJ, Dick R. Wedged hepatic venous pressure recording and venography for the assessment of pre-cirrhotic and cirrhotic liver disease. *Scand J Gastroenterol* 1989;24: 65–73.
- [16] Van Leeuwen DJ, Howe SC, Scheuer PJ, Sherlock S. Portal hypertension in chronic hepatitis: relationship to morphological changes. *Gut* 1990;31:339–343.
- [17] Poynard T, Degott C, Munoz C, Lebrec D. Relationship between degree of portal hypertension and liver histologic lesions in patients with alcoholic cirrhosis. Effect of acute alcoholic hepatitis on portal hypertension. *Dig Dis Sci* 1987;32:337–343.
- [18] Picchiotti R, Mingazzini PL, Scucchi L, Bressan M, Di Stefano D, Donnetti M, et al. Correlations between sinusoidal pressure and liver morphology in cirrhosis. *J Hepatol* 1994;20: 364–369.
- [19] Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003;38:1449–1457.