Research Article

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# Histological subclassification of cirrhosis using the Laennec fibrosis scoring system correlates with clinical stage and grade of portal hypertension

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**Background & Aims**: Further histological subclassification of cirrhosis may be useful because of heterogeneity of severity within cirrhosis. We aimed to determine the relationship between histological subclassification and clinical stage of cirrhosis as well as grade of portal hypertension.

**Methods**: One hundred-twenty-three biopsy-proven cirrhosis patients, whose clinical stage of cirrhosis and hepatic venous pressure gradient (HVPG) could be estimated, were included in this prospective study. Histology of cirrhosis was blindly subclassified using the Laennec fibrosis scoring system semi-quantitatively without knowledge of the clinical stage or the HVPG results. The Laennec system subclassifies cirrhosis as mild – thin septa, moderate – at least two broad septa, and severe – at least one very broad septum or many minute nodules. Clinical stages were determined by the presence or absence of varices, ascites, and variceal hemorrhage. Biological and laboratory data were also collected.

**Results**: Alcohol intake was the most common cause of cirrhosis in this cohort (87, 70.7%). Histology of cirrhosis subclassified using the Laennec scoring system significantly correlated with both the clinical stage of cirrhosis ($p$ <0.001) and HVPG (mild: 8.1 ± 2.6 mm Hg, moderate: 12.4 ± 3.3 mm Hg, severe: 16.3 ± 4.0 mm Hg, $p$ <0.001). With higher grades of histological subclassification of cirrhosis, increased frequency in both severe portal hypertension (HVPG ⩾12 mm Hg) and episodes of variceal hemorrhage were observed ($p$ <0.001).

**Conclusions**: Histological subclassification of cirrhosis by the Laennec fibrosis scoring system is tightly correlated with both the clinical stage of cirrhosis and grade of portal hypertension. This suggests that cirrhosis should be subclassified into different stages according to its histological severity.



Keywords: Cirrhosis; Portal hypertension; Laennec fibrosis scoring system; Classification system; Severity.

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*Abbreviations:* HVPG, hepatic venous pressure gradient; MELD, model for end stage liver disease; H&E, hematoxylin and eosin; MTC, Masson-trichrome.

## Introduction

Cirrhosis is defined as regenerative nodules surrounded by extensive fibrosis. The distortion of architecture leads to an increase in intrahepatic vascular resistance and results in portal hypertension [1–3]. Therefore, with the progression to cirrhosis, portal pressure increases and severe complications, such as varices and ascites, can occur [4]. Hence, cirrhosis has different clinical stages in terms of severity. According to the presence or absence of varices, ascites, and bleeding, the clinical stage of cirrhosis can be classified as compensated or decompensated [4,5]. Thus, there exists an obvious histological variability of severity within cirrhosis; however, it is not widely used. Since various clinical stages do exist, further subclassification of histology of cirrhosis seems necessary. Furthermore, nowadays antiviral therapy for hepatitis B and C virus can lead to regression of fibrosis in patients with cirrhosis [6–10]. Thus, more detailed classification of cirrhosis needs to be made in order to properly evaluate the response to antifibrotic treatment. For semi-quantitative estimation of fibrosis, the Laennec system that is based on histological parameters of fibrous septa according to their width and number has been proposed. The Laennec system subdivides the highest fibrosis stage of 4(F4) as 4A, 4B, and 4C in order to recognize the variability of severity of cirrhosis [11–13].

The aim of the present study was to determine the correlation between the Laennec system and the clinical stage of cirrhosis as well as the grade of portal hypertension in patients with biopsy-proven cirrhosis.

## Patients and methods

### *Patient population*

Subjects were drawn from 215 patients who had been subjected to liver biopsy and were admitted to Wonju College of Medicine University Hospital between March 2007 and November 2009 to evaluate or manage cirrhosis. The patients were prospectively evaluated as part of the Korea-21 Cirrhosis Project. Those who did not provide informed consent were excluded from the study. In addition, patients with hepatocellular carcinoma (HCC), severe liver failure (serum bilirubin level >85 μmol/L or hepatic encephalopathy), spontaneous bacterial peritonitis, hepatorenal syndrome, acute renal impairment, underlying severe cardiac illness, noncirrhotic portal hypertension, or receiving nonselective ß-blockers, nitrates, or any other pharmacotherapy for prevention of variceal bleeding were excluded. Of 215 patients, 92 patients were excluded from the study. Reasons for the exclusion were: no informed consent given (21 patients), presence of HCC (5 patients), administration of nonselective ß-blockers (16 patients), or other pharmacological therapies such as carvedilol (7 patients). In addition, patients whose liver biopsies did not show cirrhosis (20 patients) or patients with fragmented and nodular shaped biopsy specimens (<2 mm length, more than 3 pieces, 12 patients) or specimens which were too small to interpret histological grade (<10 mm total length of specimen, 11 patients) were also excluded. Therefore, a total of 123 patients (104 men and 19 women; mean ages of 51.8 ± 8.8 years) were included in the study.

Esophagogastroduodenoscopy for the presence of varices, radiological imaging studies including ultrasonography, and computer tomography scan, hepatic venous pressure gradient (HVPG) measurement, and laboratory studies were conducted on each patient to determine the clinical stage of cirrhosis, Child-Pugh score, and model for end stage liver disease (MELD) score. The ethics committee of the hospital approved the protocol and the patients provided written informed consent for their participation. The general characteristics of the patients are shown in Table 1.

### *Liver biopsy and histomorphological analysis*

Ultrasound-assisted liver biopsy was performed using a needle biopsy gun (Acecut, TSK Laboratory, Japan) with a 16 gauge × 11.5 cm needle and a 15 mm biopsy specimen notch. Five micrometer sections were prepared and were stained with hematoxylin and eosin (H&E) and Masson-trichrome (MTC). A liver biopsy, size of at least 10 mm length and width of ⩾1.2 mm, was required for inclusion in the study. In fragmented biopsies, the total length was estimated by adding maximum dimensions of each individual fragment. The biopsies evaluated prospectively the degree of fibrosis and cirrhotic change according to the Laennec system. In using the Laennec system, the thickness of the predominant type of septa in each specimen was chosen and the smallest nodule was selected for scoring. Fibrosis was simultaneously evaluated prospectively by two liver pathologists (C.M.Y., E.M.S.) who were blinded to the clinical data. To estimate the chance adjusted agreement, the kappa value was calculated for inter-observer agreement equaling the value of 0.83. When the two pathologists disagreed, they discussed and reached a consensus on the fibrosis score.

### *HVPG examination*

The HVPG of each patient was estimated from three repeated measurements, and the mean value was calculated. An examiner (Y.J.K.) with 11 years of experience in HVPG measurement performed all HVPG procedures. The coefficient of variation of HVPG measurement at our institution is 7%. The right hepatic vein was catheterized percutaneously through the femoral vein, and the pressure in both the wedged position and the free position was recorded with a 7-F balloon-tipped catheter (Arrow Deutschland, Postfach Erding, Germany). The HVPG was determined by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure [14–17].

### *Definitions*

Histological subclassification of cirrhosis (F4 in METAVIR system) was determined using the Laennec fibrosis scoring system. For the Laennec system, a modification of the METAVIR system, fibrosis is scored in 7 grades, with 0 indicating no definite fibrosis; 1, minimal fibrosis (no septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis); 2, mild fibrosis (occasional thin septa); 3, moderate fibrosis (moderate thin septa; up to incomplete cirrhosis); 4A, mild cirrhosis, definite or probable; 4B, moderate cirrhosis (at least 2 broad septa); 4C, severe cirrhosis (at least one very broad septum or many minute nodules) (Table 2) (Fig. 1) [11–13]. The terms 'broad septum' and 'very broad septum' were defined according to the relative comparison between the thickness of

**Table 1. General characteristics ($n$ = 123).**

| General characteristics | |
|---|---|
| Age | 51.8 ± 8.8 (29-82) |
| Sex (M:F) | 104 (84.6%):19 (15.4%) |
| Etiology | |
| Alcohol | 87 (70.7%) |
| B-viral | 17 (13.8%) |
| C-viral | 13 (10.6%) |
| Cryptogenic | 6 (4.9%) |
| Albumin (g/dl) | 3.5 ± 0.5 (2.5-5.1) |
| AST (U/L) | 47.5 ± 12.6 (24-81) |
| ALT (U/L) | 46.7 ± 11.5 (12-83) |
| rGT (U/L) | 47.3 ± 15.7 (38-94) |
| Total bilirubin (mg/dl) | 1.9 ± 2.0 (0.4-5.3) |
| Prothrombin time (INR) | 1.2 ± 0.2 (0.9-1.9) |
| Platelet count (x10$^3$/L) | 136.7 ± 83.3 (35-510) |
| Child-Pugh's score | 6.4 ± 1.6 (5-13) |
| Child-Pugh's grade | |
| A | 72 (58.5%) |
| B | 38 (30.9%) |
| C | 13 (10.6%) |
| MELD score | 9.9 ± 3.4 (6-21) |
| Esophageal varices | |
| F0 | 45 (36.6%) |
| F1 | 29 (23.6%) |
| F2 | 38 (30.9%) |
| F3 | 11 (8.9%) |
| Ascites | |
| None | 78 (63.4%) |
| Mild | 30 (24.4%) |
| Severe | 15 (12.2%) |
| Clinical stage of cirrhosis | |
| Stage 1 | 29 (23.6%) |
| Stage 2 | 27 (21.9%) |
| Stage 3 | 29 (23.6%) |
| Stage 4 | 38 (30.9%) |
| Laennec fibrosis stage | |
| F4A (n) | 24 (19.5%) |
| F4B (n) | 59 (48.0%) |
| F4C (n) | 40 (32.5%) |
| HVPG (mmHg) | 13.0 ± 4.4 (5-24) |
| HVPG ≥10 mmHg (n, (%)) | 48 (39.0%) |
| HVPG ≥12 mmHg (n, (%)) | 28 (22.8%) |
| History of esophageal variceal hemorrhage* | 38/123 (30.9%) |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; rGT, gamma glutamyl transferase; HVPG, hepatic venous pressure gradient.
*Within 1 year before and after liver biopsy.