Spleen and Liver Volumetrics as Surrogate Markers of Hepatic Venous Pressure Gradient in Patients With Noncirrhotic Portal Hypertension

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Noncirrhotic portal hypertension (NCPH) is a rare disease that may lead to serious clinical consequences. Currently, noninvasive tools for the assessment of NCPH are absent. We investigated the utility of spleen and liver volumetrics as a marker of the presence and severity of portal hypertension in this population. A cohort of NCPH patients evaluated between 2003 and 2015 was retrospectively studied. The association of spleen and liver volumes with the hepatic venous pressure gradient (HVPG) level was evaluated using locally weighted scatterplot smoothing curves. A cohort of patients with viral hepatitis-related liver disease was used as controls. Of the 86 patients with NCPH evaluated during the study period, 75 (mean age, 35 ± 17; 73% males) were included in the final analysis. Patients with portal hypertension had significantly higher spleen and liver to body mass index (BMI) ratios compared to patients with HVPG <5 mm Hg (39.5 ± 27.9 versus 22.8 ± 10.6 cm³/kg/m², P = 0.003; 91.1 ± 40.1 versus 71.4 ± 16.7 cm³/kg/m², P = 0.014, for spleen/BMI and liver/BMI, respectively). In contrast to the patients with viral hepatitis, a positive linear correlation was observed in the NCPH cohort between spleen/BMI and liver/BMI (above a cutoff of 25 and 80 cm³/kg/m², respectively) and HVPG level. Additionally, only in the NCPH cohort was an increase in spleen/BMI range quartile predictive of a higher prevalence of portal hypertension and clinically significant portal hypertension (trend, P = 0.014 and 0.031, respectively).

Conclusion: Spleen and liver volumetrics may have utility in the assessment of NCPH as a noninvasive biomarker that can be performed using routine radiologic examinations. Further studies are needed to validate these findings. (Hepatology Communications 2018;2:923-932)

Portal hypertension (PH) is a clinical syndrome with hallmarks that entail the development of portosystemic collaterals, splenomegaly, ascites, and encephalopathy. PH occurs most often in the context of cirrhosis; however, in approximately 10% of cases, PH can develop in the absence of liver architectural changes associated with advanced fibrosis or cirrhosis. This entity, referred to as noncirrhotic PH (NCPH), comprises a diverse group of disorders in which PH results from increased resistance to portal blood flow at the prehepatic, intrahepatic, or posthepatic vascular compartments. Contrary to early...
suggestions that NCPH is a relatively benign clinical entity, there is increasing evidence that NCPH may be associated with increased morbidity and mortality. These observations now underscore the importance of early detection and appropriate management of this condition. (3–6)

One of the major challenges in NCPH is the lack of reliable noninvasive markers for the diagnosis and monitoring of disease progression. Unlike cirrhosis-related liver diseases, liver enzymes are unreliable markers of disease activity, and hepatic synthetic function markers are generally preserved even in advanced stages of NCPH. (7) Thus, given these difficulties, patients with NCPH are often undiagnosed until they develop overt clinical signs, such as gastrointestinal bleeding or ascites.

Over the past few decades, measurement of the hepatic venous pressure gradient (HVPG) has been established as a gold standard for diagnosis and staging of PH. (8–13) However, the use of HVPG measurement in routine clinical practice is limited by the invasiveness of the procedure and the technical expertise required for its performance. Consequently, different biomarkers and imaging modalities have undergone exploration for their ability to serve as noninvasive surrogate markers of PH. (14–19)

Splenomegaly is one of the clinical manifestations of PH and a prominent clinical sign in many conditions associated with NCPH. (2,20,21) Previous studies have shown that spleen and liver volumes are capable of predicting liver fibrosis severity across the spectrum of disease stages as well as the severity of PH in patients with cirrhosis. (22–24), however, the usefulness of these measures as markers for the presence and severity of PH in patients with NCPH have not been explored. Given the lack of useful noninvasive biomarkers in the assessment of NCPH, we assessed the utility of liver and spleen volumetrics as markers of PH in a large and diverse group of patients with NCPH.

Materials and Methods

PATIENTS

From January 2003 to December 2015, patients with various systemic diseases known to be associated with NCPH were evaluated at the National Institutes of Health Clinical Center as part of a natural history protocol (NCT00001971). Patients were evaluated clinically and underwent routine laboratory and radiographic workup for liver disease assessment. Evaluation for NCPH was performed when the following criteria were met:

1. Patients presented with a primary systemic disease known or suspected to be associated with NCPH (such as a primary immunodeficiency that has been associated with the development of NCPH).
2. No known history of cirrhosis or the presence of a chronic liver disease known to cause cirrhosis.

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3. Presence of abnormal liver tests and/or unexplained cytopenias with or without hepatic or splenic enlargement.

Subjects meeting these criteria were evaluated with cross-sectional imaging studies (computed tomography or magnetic resonance imaging) and with transjugular liver biopsies (TJLBs), with HVPG measurements performed when clinically indicated.

Changes in spleen and liver volumes have been shown to be associated with the severity of PH in patients with liver fibrosis or cirrhosis.\(^{(22-24)}\) Subjects with suspected NCPH were therefore compared with a cohort of patients with chronic viral hepatitis (hepatitis B, C, or B/D) with mostly advanced fibrosis or cirrhosis who underwent a TJLB with HVPG measurements as a part of clinical disease staging during the same time period.

**CLINICAL DATA**

Clinical, anthropometric, and laboratory data were retrospectively collected from patients’ electronic medical charts. Baseline laboratory workup for patients with suspected NCPH included complete blood count (hemoglobin, hematocrit, and white blood cells and platelet counts), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin, albumin, lactate dehydrogenase, prothrombin time (PT), internationalized normalized ratio, and alpha-fetoprotein levels. Patients were also tested for anti-HCV antibody and hepatitis B surface antigen levels to exclude chronic viral hepatitis. Aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4), two validated noninvasive markers of liver fibrosis, were calculated according to published formulas.\(^{(25,26)}\) All laboratory workup except for serologic tests for hepatitis B and C were performed within 3 months of a TJLB with portal hemodynamic measurements.

**HISTOPATHOLOGIC ASSESSMENT**

Formalin-fixed paraffin-embedded liver biopsy sections were stained with hematoxylin and eosin, Masson’s trichrome, and for reticulin and were interpreted by a single hepatopathologist (D.E.K.). For patients with NCPH, location and descriptive staging related to the presence or absence of fibrosis was extracted from the clinical histologic report. In biopsy sections of patients with viral hepatitis, scoring of fibrosis was done using the Ishak scoring system.\(^{(27)}\)

**RADIOLOGIC STUDIES**

Computed tomography or magnetic resonance imaging studies were reviewed with particular attention to liver and spleen size. All measurements were performed using Picture Archiving Communication System (PACS) software (General Electric, Milwaukee, WI). First, mapping of liver and spleen images in the transverse plane was performed. Second, the cross-sectional area of liver and spleen on each image was measured by manual tracing of the organ outline, using the PACS region of interest free-hand tool. For liver images, organ tracing excluded large vessels and the gallbladder. Third, volumes of liver and spleen were calculated as the total sum of the organs’ cross-sectional area in each image multiplied by the slice width (10 mm). Finally, liver and spleen volumes were standardized to height and body mass index (BMI) to account for age- and anthropometric-dependent effects.

**HEMODYNAMIC MEASUREMENTS**

HVPG measurements were determined using standard venous catheterization techniques.\(^{(10)}\) Access to the hepatic veins was obtained through the transjugular approach in all cases. When technically feasible, measurements were obtained from more than one hepatic vein and the mean value of HVPG measurements was presented in addition to the highest HVPG level recorded.

**STATISTICAL ANALYSIS**

Summary statistics for continuous variables were presented as means ± SDs and medians with interquartile ranges (IQRs). Patient characteristics were compared using chi-square or Fisher’s exact tests for categorical variables and analysis of variance test for continuous variables. Non-normally distributed variables were presented as medians with IQR and compared with the Kruskal-Wallis test. Spearman’s rho was used for correlation analysis.

Associations between liver and spleen volumes standardized by BMI and HVPG were assessed by fitting locally weighted scatterplot smoothing (LOESS) curves. Based on the visual assessment of LOESS, standardized spleen volume was further stratified into four groups: <20, 20-40, 41-60, >60 cm\(^3\)/kg/m\(^2\). Multivariate analysis was performed to evaluate the association between grouped spleen volume standardized by BMI and max HVPG above 5 mm Hg by
forward stepwise logistic regression model (stay criteria, $P < 0.15$). Variables were introduced to the model based on clinical and statistical significance ($P < 0.1$ in univariate analysis). A final parsimonious model included the following variables: grouped standardized spleen volume, sex, and hemoglobin levels. C-statistics was used to evaluate model discriminatory ability. $P < 0.05$ was considered statistically significant. Data were analyzed using IBM SPSS version 20 software (SPSS Inc., Chicago, IL).

We defined two prespecified thresholds for the HVPG based on the clinical significance found in patients with cirrhosis: PH was considered to be present when HVPG $>5$ mm Hg and values $\geq 10$ mm Hg defined a clinically significant PH (CSPH).\(^{8,9,11-13}\)

**Results**

**PATIENT DEMOGRAPHICS**

During the study period, 86 patients with clinically suspected NCPH were evaluated with laboratory assessments, cross-sectional imaging, and TJLB with HVPG measurements. Eleven patients were excluded: 4 due to serologic evidence of chronic viral hepatitis in addition to histopathologic diagnosis consistent with NCPH, 2 with poor quality cross-sectional imaging studies that did not allow for accurate volumetric measurements, and 5 with histologic evidence of advanced fibrosis or cirrhosis (Ishak fibrosis range 3-6). Seventy-five patients were included in the final analysis (Fig. 1). Of those, technical failure of HVPG measurement occurred in 1 patient and failure to obtain liver tissue in another 3. Spleen volumes were not measured in 7 patients: 4 who had undergone splenectomy (3 with common variable immunodeficiency and 1 with nuclear factor kappa B essential modulator deficiency syndrome) and 3 who developed splenic involution (2 with common variable immunodeficiency and 1 unknown primary immunodeficiency).

Demographic clinical characteristic data of patients in the two cohorts are described in Table 1. Patients with NCPH were younger, more often Caucasian, and had lower mean weight and BMI values compared to patients in the viral hepatitis group. The most common disease categories associated with NCPH in this cohort were primary immunodeficiencies (56%) followed by hematologic disorders (21%) and genetic diseases (15%) (Supporting Table S1). Laboratory indices were generally comparable between the two groups except for alkaline phosphatase levels, which were significantly higher in the NCPH cohort ($203 \pm 182$ versus $109 \pm 41$ U/L, $P = 0.02$) and hemoglobin and PT values that were significantly higher in patients with viral hepatitis ($13.3 \pm 1.9$ versus $11.6 \pm 2.4$ g/dL, $P = 0.003$; $16.4 \pm 6.4$ versus $14.4 \pm 2.0$ seconds, $P = 0.02$, respectively). Of the different radiologic measurements performed, only mean liver volume to BMI ratio had higher values in the NCPH versus viral hepatitis groups ($82.6 \pm 33.9$ versus $66.3 \pm 24.8$ cm$^3$/kg/m$^2$, $P = 0.04$). Comparison of hemodynamic measurements between the two cohorts showed that both peak and mean HVPG values tended to be lower in the NCPH compared to viral hepatitis cohorts, although the difference between groups only trended toward statistical significance ($8.1 \pm 6.2$ versus $11.0 \pm 5.9$ mm Hg, $P = 0.06$ for peak HVPG; $7.2 \pm 5.8$ versus $10.1 \pm 6.0$ mm Hg, $P = 0.05$ for mean HVPG, respectively). Furthermore, while the proportion of patients with PH was comparable between the two cohorts, significantly more patients in the viral hepatitis group had CSPH (43 versus 13%, $P = 0.008$, respectively).

**HISTOPATHOLOGIC FINDINGS**

Of the 72 patients evaluated for NCPH in whom liver tissue was obtained, histopathologic features accounting for NCPH\(^{28}\) were diagnosed in 58 (81%). The most common diagnosis observed was nodular regenerative hyperplasia or regenerative changes (32%) followed by perisinusoidal/perivenular fibrosis (19%) and diffuse granulomatous changes (11%). In 10 (14%) patients, more than one histologic feature accounting for NCPH was detected. Eight biopsies demonstrated pathologic changes consistent with either graft versus host disease (4 [6%] patients) or isolated chronic cholestatic changes (4 [5%] patients). Six

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**FIG. 1.** Study flow chart.
(8%) additional biopsies displayed either nonspecific inflammatory changes or normal findings (Supporting Table S1).

Of the 20 biopsies obtained in patients with viral hepatitis, 15 (75%) showed evidence of incomplete cirrhosis or cirrhosis (Ishak 5-6), another 3 (15%) demonstrated either early or advanced bridging fibrosis (Ishak 3-4), and 2 had evidence of fibrous expansion of most portal areas with or without short fibrous septa (Ishak 2).

### DIFFERENCES IN HVPG DISTRIBUTION IN THE NCPH AND VIRAL HEPATITIS COHORTS

Cumulative distribution of maximal HVPG values in the 74 patients in whom measurements were successfully obtained are shown in Fig. 2A. In 30 patients (41%), values measured were within the normal range (2-5 mm Hg). PH was diagnosed in 44 (59%). Of those, 28 (39%) displayed mild increase in pressure (6-10 mm Hg), while 16 (22%) showed evidence of CSPH (>10 mm Hg). Distribution of HVPG values among the 21 patients with viral hepatitis was significantly different compared to the NCPH population, with over 50% of patients showing evidence of CSPH (Table 1; Fig. 2B).

### CLINICAL, BIOCHEMICAL, AND VOLUMETRIC COMPARISONS IN NCPH PATIENTS STRATIFIED BY HVPG LEVEL

In patients with NCPH, we evaluated for clinical, biochemical, and radiologic differences in those with...
and without classically defined PH (HVPG ≤5 and >5 mm Hg) (Supporting Table S2). Of the 74 hemodynamic measurements obtained, 44 (59.4%) were consistent with the presence of PH (HVPG >5 mm Hg). There were no differences in mean age, sex distribution, or mean BMI levels in patients with or without PH. However, compared to patients with an HVPG ≤5 mm Hg, patients with PH had significantly lower mean hemoglobin and albumin levels (10.8 ± 2.0 versus 12.5 ± 2.4 g/dL, P = 0.002; 3.1 ± 0.8 versus 3.5 ± 0.8 g/dL, P = 0.02, respectively). Interestingly, although the individual components of the FIB-4 biomarker were not significant between groups, the FIB-4 demonstrated significantly higher median values in patients with PH compared to those without PH (2.0 [IQR, 1.0-4.8] versus 1.0 [0.8-3.0], P = 0.03, respectively). The APRI displayed a similar trend, although not reaching statistical significance.

In the evaluation of spleen and liver volumetrics, HVPG levels were again stratified by the presence or absence of PH. In patients with NCPH and PH, mean spleen volumes were significantly higher compared to those without PH (894.0 ± 649.0 versus 532.2 ± 251.9 cm³, P = 0.006, respectively). When spleen volume was standardized to height and BMI, this difference remained significant (527.2 ± 360.4 versus 323.7 ± 140.7 cm³/m², P = 0.005; 39.5 ± 27.9 versus 22.8 ± 10.6 cm³/kg/m², P = 0.003, for spleen/height and spleen/BMI ratios, respectively). Differences in liver volumetric measurements between NCPH patients with and without PH were less pronounced, with only the mean liver/BMI ratio demonstrating significantly higher values in patients with PH (91.1 ± 40.1 versus 71.4 ± 16.7 cm³/kg/m², P = 0.014, respectively) (Table 2).

**EXPLORATION OF THE RELATIONSHIP BETWEEN SPLEEN AND LIVER VOLUMETRICS WITH SEVERITY OF PH IN PATIENTS WITH NCPH AND VIRAL HEPATITIS**

Given the significant volumetric findings during the binary analysis of HVPG in subjects with NCPH (above), we sought to further explore the relationship between spleen and liver volumes with the severity of PH. The relationship between the spleen volume adjusted to BMI ratio and HVPG in subjects with NCPH is illustrated in Fig. 3A. At a lower range of spleen volume/BMI (10-25 cm³/kg/m²), no correlation was demonstrated between spleen volume and HVPG levels (reflected by the plateau region of the LOESS curve). However, when spleen volume/BMI exceeded 25 cm³/kg/m², a positive linear correlation was observed.

Similarly, a LOESS regression curve was applied to study the correlation between liver volume/BMI and HVPG level (Fig. 3B). This analysis demonstrated a
positive linear correlation between the liver volume and HVPG above a liver volume/BMI cutoff of 80 cm$^3$/kg/m$^2$.

In comparison to the findings demonstrated in NPCH patients, a similar analysis was conducted in the viral hepatitis cohort. Unlike that of NCPH patients, the LOESS regression curve did not identify a consistent pattern of correlation between spleen or liver volumes to BMI ratios and HVPG levels (Fig. 3C,D).

**TABLE 2. LIVER AND SPLEEN VOLUMETRICS IN THE NCPH PATIENT COHORT STRATIFIED BY MAXIMAL HVPG LEVELS (≤5 AND >5 MM HG)**

|                      | Max Hepatic Vein Pressure Gradient ≤5 mm Hg | Max Hepatic Vein Pressure Gradient >5 mm Hg | P Value |
|----------------------|---------------------------------------------|---------------------------------------------|---------|
| Spleen volume, cm$^3$| 532.2 ± 251.9 | 894.0 ± 649.0 | 0.006 |
| Spleen volume/height, cm$^3$/m | 323.7 ± 140.7 | 527.2 ± 360.4 | 0.005 |
| Spleen volume/BMI, cm$^3$/kg/m$^2$ | 22.8 ± 10.6 | 39.5 ± 27.9 | 0.003 |
| Liver volume, cm$^3$ | 1,703.4 ± 587.1 | 2,023.1 ± 838.4 | 0.08 |
| Liver volume/height, cm$^3$/m | 1,038.9 ± 326.0 | 1,213.7 ± 475.8 | 0.09 |
| Liver volume/BMI, cm$^3$/kg/m$^2$ | 71.4 ± 16.7 | 91.1 ± 40.1 | 0.014 |
| Spleen to liver volume ratio (median and IQR) | 0.33 (0.20-0.42) | 0.50 (0.25-0.50) | 0.05 |

**FIG. 3.** LOESS for spleen and liver volumes adjusted to BMI ratio and HVPG in the two cohorts. (A) Spleen/BMI versus HVPG and (B) liver/BMI versus HVPG in the NCPH cohort; (C) spleen/BMI versus HVPG and (D) liver/BMI versus HVPG in the viral hepatitis cohort.
EVALUATION OF SPLEEN VOLUMETRICS WITH THE PRESENCE OF CSPH

Given the demonstrated clinical importance of CSPH, the relationship between spleen volumetrics and the presence of CSPH was evaluated. In both NCPH and viral hepatitis cohorts, subjects were grouped into 4 quartiles of spleen volume/BMI values (<20, 21-40, 41-60, and >60 cm$^3$/kg/m$^2$) and compared by the presence of PH (>5 mm Hg) and CSPH (>10 mm Hg) (Fig. 4). In NCPH patients, stepwise increments in spleen/BMI quartile range (from <20 and up to >60 cm$^3$/kg/m$^2$) were associated with increasing prevalence of both PH and CSPH (trend, $P = 0.014$ and 0.031, respectively) (Fig. 4A). In the viral hepatitis cohort on the other hand, a similar association was observed for PH but not for CSPH (Fig. 4B) (trend, $P = 0.045$ and 0.17 for HVPG >5 and >10 mm Hg, respectively).

MODEL FOR PREDICTION OF PH IN PATIENTS WITH NCPH

Finally, a multivariate linear regression model generated on the basis of significant parameters identified in univariate analysis (Supporting Tables S2 and S3) was used to predict the presence of PH in patients with NCPH. Multivariate analysis demonstrated that hemoglobin level and spleen volume to BMI per group increase were the only independent variables predictive of PH in this population (Table 3).

Discussion

In this retrospective study evaluating the utility of liver and spleen volumetrics in subjects with cirrhosis-related PH and NCPH, we demonstrate that spleen and liver volumes are intimately related to invasive measurements of PH in subjects with NCPH. Additionally, in subjects with NCPH, we demonstrate that

| TABLE 3. MODEL FOR PREDICTION OF MAXIMUM HVPG >5 MM HG |
|----------------------------------------------------------|
|                          | Odds Ratio | 95% Confidence Interval | $P$ Value |
|----------------------------|------------|-------------------------|-----------|
| Spleen volume to BMI per group increase* | 2.3        | 1.2 - 4.4               | 0.01      |
| Hemoglobin, per g/dL     | 0.7        | 0.5 - 0.9               | 0.01      |
| Female sex               | 3.1        | 0.8 - 12.0              | 0.11      |

*Divided into <20, 20-40, 41-60, >60. C-statistics for the model 0.81 (95% confidence interval, 0.71-0.92). Forward (conditional) stepwise model with stay criteria of 0.15. The following variables were included: sex, hemoglobin, albumin, FIB-4, spleen to BMI ratio (grouped*).
once spleen and liver volumes (corrected for BMI) exceed a certain level, a positive linear relationship exists between volumetrics and severity of HVPG, which differs from cirrhosis-related PH (Fig. 3). Finally, we identified that together with declining hemoglobin levels, transition from lower to higher range spleen volume/BMI quartiles is predictive of a higher prevalence of PH and CSPH. To the best of our knowledge, this study is the first to demonstrate that the presence and severity of PH in patients with NCPH can be predicted using a readily available non-invasive marker.

Splenomegaly has long been considered a marker of cirrhotic- and noncirrhotic-related liver disease. Indeed, Gunay-Aygun et al. (29) reported on an inverse correlation between spleen volume and platelet counts in patients with congenital hepatic fibrosis (a rare presinusoidal form of NCPH). The current study goes further to establish a relationship between spleen and liver volumes and PH in patients with NCPH by demonstrating a positive correlation between organ volumetric indices and HVPG level, the gold standard for assessment of PH severity. Additionally, findings from the current study may be more generalizable to the NCPH population at large as our cohort included patients with diverse causes of NCPH.

Our comparator cohorts demonstrated several noticeable differences. First, patients with NCPH were younger and had lower weight and BMI. This difference is not surprising given that NCPH has been associated with primary immunodeficiencies that are often diagnosed during childhood and that these individuals are often underweight as a result of chronic or recurrent infections. Conversely, advanced fibrosis or cirrhosis as a result of viral hepatitis often develops at an older age following several decades of infection, and weight loss does not typically occur until late stages of the disease. Second, the NCPH cohort demonstrated lower albumin levels compared to the chronic viral hepatitis cohort. In the NCPH cohort, hypoalbuminemia is likely a reflection of a chronic catabolic state rather than of decreased hepatic synthetic function. Finally, the NCPH cohort demonstrated significantly lower hemoglobin levels compared to the viral hepatitis cohort. Although anemia can occur in late-stage cirrhosis, our viral hepatitis cohort had compensated disease, which may account for the normal or slightly decreased mean hemoglobin levels in this group. With regards to the NCPH cohort, the low hemoglobin level may be a result of a chronic inflammatory state contributing to poor utilization of iron with resultant anemia. (30) Additionally, high occurrence of cytopenias in patients with NCPH has been described that often attributes the clinical feature to hypersplenism (20,21). Our results support this conclusion as low hemoglobin levels in the NCPH cohort were shown to be independently associated with the presence of PH, a major mechanism contributing to the development of hypersplenism.

Spleen and liver volumetrics have been shown to be useful tools for assessing disease severity in patients with cirrhosis, both independently and in conjunction with other disease severity markers. (22-24) Interestingly, a much weaker association between these variables and HVPG levels was found in patients with viral hepatitis in our study. The relatively small size of the viral hepatitis cohort may partially account for this observation. Alternatively, in our cohort, liver and spleen volumes were standardized to BMI compared to other studies that have used body surface area for normalization. More importantly, the discrepancy between previous reports and our study may be explained by differences in underlying patient characteristics. While previous studies have included patients across the spectrum of liver fibrosis, patients in the viral hepatitis cohort in the current study mostly had cirrhosis, with a majority of them having HVPG values in the clinically significant range (Fig. 2A). It is possible that dynamic changes in spleen size in association with portal pressure elevation are more pronounced during the transition from advanced stages of fibrosis to cirrhosis rather than when cirrhosis with CSPH has already been established.

This study has several limitations. First, its findings need to be seen within the limitations of retrospective reports. Second, its cross-sectional design does not allow assessment of the association between changes in organ volumetrics and portal hemodynamics over time. Third, the viral hepatitis comparator group was relatively small, a factor that may have influenced the differences found between the two populations. Finally, while findings from this study show promise for using spleen and liver volumetrics for assessment of disease severity in NCPH, these need to be confirmed in an independent validation cohort.

In conclusion, NCPH is an infrequent and often under-recognized cause of PH that can lead to significant morbidity and mortality. (3-6) Unfortunately, optimal management of this condition is often compromised by the lack of noninvasive tests for assessing disease severity and monitoring its progression. We demonstrate that spleen and liver volumetrics may have utility in the assessment of NCPH as a
noninvasive biomarker that can be performed using routine radiologic examinations. While future studies are needed to validate these findings, we provide the beginnings of a possible metric to evaluate this rare disease with potentially devastating consequences.

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