

Non-invasive alternative methods to hepatic venous pressure gradient measurement

To the Editor,

I read the review article by Procopet et al with interest [1]. They overviewed several alternative non-invasive methods for hepatic venous pressure gradient (HVPG) measurement, including ultrasound technique, serum (plasma) bio-markers and acoustic radiation force impulse imaging. I agree with their opinion that the alternative methods to HVPG measurement should be accepted with satisfactory validation data by using HVPG as the gold standard for the diagnosis of portal hypertension.

Besides the methods in the review, small intestinal mucosal findings have been selected as non-invasive methods for HVPG measurement. Ascites development in patients with cirrhosis can be explained by portal venous pressure, and Aoyama et al reported descriptive statistics showing that findings of small bowel abnormalities by using capsule endoscopy were associated with compensated liver cirrhosis [2]. By using the same method, Takahashi et al [3] in a preliminary study showed that small intestinal edema correlated significantly with hepatic venous pressure gradient. The number of samples was limited in these studies, and recommendation should be done to keep validity with enough number of samples and adequate adjustment in their study.

I have a query on the handling of receiver operating characteristics (ROC) curve analysis in the review article by Procopet et al. The ROC curve analysis is a univariate procedure, and related factors including confounders and mediators cannot be adjusted. I suppose that the variability of cut-off values would partly derive from a different test situation including different characteristics of patients. In addition, clinically significant portal hypertension is sometimes judged by different HVPG values, ranging from 5 to 10 mmHg. I recommend adopting multivariate analysis such as logistic model or regression procedure to conduct simultaneous assessment of independent variables to validate non-invasive methods for HVPG measurement.

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3. Takahashi Y, Fujimori S, Narahara Y, et al. Small intestinal edema had the strongest correlation with portal venous pressure amongst capsule endoscopy findings. *Digestion* 2012;86:48-54.

Reply,

We are thankful to Dr. Kawada for the interest in our review article and his comments.

Based on the two articles [1, 2], Kawada proposes capsule endoscopy as an alternative non-invasive method of HVPG measurement. If you look closer at the two articles there are some details that must be highlighted. In the study of Aoyama et al [1], the studied population included patients with liver cirrhosis and associated anemia and there was no HVPG measurement for the portal hypertension confirmation. Moreover, 60% of patients had hepatocellular carcinoma and 33% had ascites. Therefore, there are some doubts about the compensation status of this cohort.

The Takahashi et al study [2] included only 35 patients and the conclusion of the study was that HVPG values positively correlated with the risk of small intestinal edema, which is not surprising at all.

Based on these studies we cannot agree that capsule endoscopy may be a surrogate marker for HVPG measurement.

There is some evidence regarding the role of capsule endoscopy in esophageal varices screening, although unfortunately, as a screening test, it is still not favoured as being cost effective [3].

Regarding the query handling the receiver operating characteristics (ROC) curve analysis, in order to avoid confusion, some statistical details must be given. The ROC analysis is the graphical representation of sensibility and 1-specificity of a diagnostic test, and therefore it is related to the true positive and true negative results of a given test. Usually, these performances are established in comparison with a "gold standard" test. Therefore the ROC analysis is dedicated to assess the test performance. We agree that when a diagnostic method is proposed, a univariate and multivariate analysis must be performed and only the variables well correlated with a given condition must be considered as a potential diagnostic tool. ROC analysis and multivariate analysis are different statistical tools with different statistical outputs, test performance and correlations, respectively.

Finally, according to the existent evidence, clinically significant portal hypertension, which predisposes to decompensation, is considered when HVP > 10 mmHg whereas an HVP between 5 and 10 mmHg is considered to be portal hypertension without risk of decompensation [4].

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Porcelain gallbladder and cancer - an association to be revised

To the Editor,

Calcification of the gallbladder is an unusual form of vicarious soft tissue calcification. The marked intramural

calcification of a calcified gallbladder (CG) is much more frequent than a completely calcified gallbladder also known as a porcelain gallbladder (PG). The PG is described as a large, stony-hard, egg-shaped mass having a pale, avascular surface with a shaggy fibrinous serosa [1].

The pathogenesis of PG, still undemonstrated, is probably due to an irritation by gallstones, leading to a chronic inflammation, associated with calcium deposits.

At microscopy, thin calcification is described as a continuous band in the muscular layer, or multiple punctates in the glandular spaces of the mucosa [1]. The carcinogenesis in a CG probably follows the metaplasia-dysplasia-carcinoma sequence.

In a review of the literature [2], the incidence of carcinoma on a CG is quoted to be very high (12%-61%). Because of this PG was classically one of the few indications for surgery in asymptomatic gallbladder lithiasis [3]. However, there is a tendency to revise what has seemed to be almost an axiom. On 25,900 gallbladder specimens, Stephen et al found 150 patients with gallbladder cancer and 44 patients with calcified gallbladders. Gallbladders with selective mucosal calcification (n=27) had an incidence of cancer of 7% while complete intramural calcification or PG (n=17) had no association with cancer [2].

Kane et al [3] describes three patterns of the ultrasound appearance of CG. While a biconvex curvilinear echogenic structure with variable acoustic shadowing is associated with carcinoma (type II), hyperechoic semilunar structure (type I) and irregular clump of echoes, both with posterior acoustic shadowing (type III) are not.

Some authors describe PG as asymptomatic or, if symptoms are present, without any pathognomonic symptoms [4]. In our series (data not published), CG frequently had a long history of biliary disease. In 10,586 laparoscopic cholecystectomies performed between 2005 and 2011, micropoints of calcification were identified in 14 cases, none associated with cancer. Only 2 gallbladders presented complete calcification, without any malignancy.

At the beginning of the videolaparoscopy era, PG was considered a relative contraindication for laparoscopic cholecystectomy. The main problems were the retraction of the gallbladder and hemorrhage [5]. In suspect cases frozen sections and, in positive cases, subsequent subsegmentectomy were mandatory [6].

Considering the presented data, not only the causal relationship with cancer has still to be established, but also the postulated high risk of malignant transformation in CG and PG requires reassessment.

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Celiac disease in older adults

To the Editor,

Celiac disease (CD) was considered for a long time to affect only children; however, it is now realized that it affects people of any age [1, 2]. Recent literature suggests a trend towards increasing incidence of CD even in elderly people in western countries [2]. We retrospectively analyzed a cohort of patients followed

up in the "Celiac Disease Clinic" to find out the proportion of patients diagnosed at ≥ 50 years of age and whether their clinical, laboratory, serological and histological characteristics were different from those diagnosed before that age.

Of 353 patients with CD, 32 (9.1%) were diagnosed at age ≥ 50 years. The mean duration of symptoms at the time of presentation in those diagnosed at ≥ 50 years of age was significantly higher as compared to those diagnosed before that (9.7 ± 8.1 vs. 5.9 ± 6.2 years; $P = 0.006$).

The mode of presentation in those diagnosed at ≥ 50 years of age were chronic diarrhea in 23 (74.2%) and refractory anemia in 5 (16.1%) patients. One patient presented with chronic liver disease, dyspepsia and irritable bowel syndrome and one was detected with family screening. Notably, there were no major differences in the clinical or laboratory parameters except for a significantly higher number of patients diagnosed at ≥ 50 years of age having hypoalbuminemia than those diagnosed before that (40.9% vs 13.9%; $P < 0.001$) (Table I). The results of serology, histology and other associations have been summarized in Table I.

According to our data, 9.1% of patients were diagnosed at ≥ 50 years of age. This is in agreement with other studies reporting 4.4-12.4% of patients being diagnosed with CD at ≥ 60 years of age [3-5].

Table I. Comparison of clinical, laboratory, serological and histological characteristics of older (≥ 50 years) and younger (< 50 years) patients with celiac disease

Demographic details	≥ 50 years (n=32)	< 50 years (n=321)	p value
Age years (SD)	55.4 (± 5.2)	23.87 (± 9.89)	< 0.001
Gender			
Male	14 (43.7%)	152 (47.3%)	0.685
Female	18 (56.3%)	169 (52.7%)	
Duration of symptoms before diagnosis in years (SD)	9.7 (± 8.1)	5.9 (± 6.2)	0.006
Clinical symptoms - no (%)			
Chronic diarrhea	25 (78.1%)	204 (63.6%)	0.1
Fatigue	24 (75%)	216 (67.3%)	0.373
Loss of appetite	16 (50%)	138 (43%)	0.446
Oral ulcers	10 (31.3%)	110 (34.3%)	0.731
Abdominal distention	10 (31.3%)	119 (37.1%)	0.514
Abdominal pain	6 (18.8%)	104 (32.4%)	0.112
Constipation	2 (6.3%)	30 (9.3%)	0.561
Associated conditions - no (%)			
Autoimmune disorders (total)	8 (25%)	46 (14.3%)	0.110
Autoimmune thyroiditis	5 (15.6%)	27 (8.4%)	0.179
Type 1 Diabetes mellitus	0	8 (2.5%)	0.366
Laboratory parameters - no (%)			
Anemia	26/27 (96.3%)	256/300 (85.3%)	0.113
Hypoalbuminemia	9/22 (40.9%)	38/273 (13.9%)	< 0.001
Abnormal D-xylose test	15/23 (65.2%)	149/202 (73.8%)	0.382
Serology			
Mean anti-tTG ab fold rise (from the cut-off for a positive test)	8.4 \pm 5.5	8.6 \pm 7.6	0.907
Histological features - no (%)			
Marsh grade 3a	8 (25%)	59 (18.4%)	0.362
Marsh grade 3b	13 (40.6%)	72 (22.4%)	0.021
Marsh grade 3c	11 (34.4%)	190 (59.2%)	0.006

While some studies have reported that elderly patients with CD present with less prominent gastrointestinal manifestations such as bloating as opposed to classical features of malabsorption, others have not reported such differences [3-6]. We also did not find any difference in the clinical and laboratory features of the two groups except for hypoalbuminemia which was more often present in the old-aged group. The time lag from onset of the symptoms to diagnosis was significantly higher (10 years) in those diagnosed with CD at ≥ 50 years of age suggesting that the diagnosis of CD was not considered on their earlier visits to their physicians.

There is a belief that CD has emerged in many countries with the introduction of western kind of diets. Occurrence of CD in people ≥ 50 years of age suggests that even in these societies, CD existed and is now recognized because of an increase in awareness and availability of CD specific serological tests.

In conclusion, CD can occur in people older than 50 years and should be considered in appropriate clinical settings, irrespective of age.

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"Standard of care" treatment for chronic viral C hepatitis in 2013 in Romania

To the Editor,

Triple therapy (TT) has become available in the latter years (double therapy - DT plus a protease inhibitor), with markedly improved rates of sustained virologic response (SVR) [1, 2], so that the latest AASLD guidelines recommend TT as the

optimal one for genotype 1 HCV infection [3]. Adding a protease inhibitor to DT increases the costs: approximately 1,100 US dollars/week for Boceprevir and 4,100 US dollars/week for Telaprevir [4].

IL28B genotype is an essential predictive factor in the decision to treat patients with DT versus TT: in patients with CC genotype, the SVR is 70% with DT and 90% with TT (delta 20%), while in non-CC genotype patients the SVR is 30% with DT, vs. 70% with TT (delta 40%) [5-7].

The TT is the most cost-efficient strategy in naïve patients, non-responders or relapsers with severe fibrosis and cirrhosis (F3, F4), with costs of approximately 50,000 US dollars/quality-adjusted-life year (QALY) as compared to DT. In patients with mild fibrosis (<F2), IL28B genotyping can stratify the patients who will benefit the most from TT, since it is the most cost-efficient in patients with non-CC genotype (62,900 US dollars/QALY as compared with DT) [4].

Five therapeutic strategies for TT in naïve HCV genotype 1 patients have been analyzed [8]. Boceprevir response-guided therapy (BOC-RVR) and Telaprevir IL28B genotype-guided strategy (TVR-IL28B) were the most cost-efficient ones, with 4.04 and 4.42 life-years gained (LYG), respectively. The incremental cost-effectiveness ratio as compared to DT was 8,304 Euros/LYG for BOC-RVR and 11,455 Euros/LYG for TVR-IL28B [8].

Due to limited financial resources, similar strategies should be followed in Romania, where the standard of care for HCV chronic infection is still pegylated Interferon associated with Ribavirin (DT). For genotype 1 HCV patients with cirrhosis (F4), the best option would be TT (considering all the factors which could impair the patients' compliance or predict severe adverse events). For relapsers and non-responders, TT should also be recommended, considering the same caveats. For naïve HCV patients with moderate and severe fibrosis (F2-F3), IL28B genotyping should be performed. In those with CC genotype, DT should be administered, in the others, TT should be performed. Alternatively, we could use lead-in therapy for 4 weeks; if RVR occurs, DT; if no RVR, a „response guided” TT for 24, 36 or 48 weeks.

Finally, for naïve HCV patients with mild fibrosis (F1), either the same strategy or DT for all patients should be adopted. Postponing the treatment will be considered in these patients, because of the relatively close perspective of new, more potent treatments.

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Abdominal pain after minor trauma in a patient with Crohn's disease

To the Editor,

A 46-year old male patient, regularly followed in our unit for ileal Crohn's disease, presented with acute abdominal pain after a minor trauma while he was skiing two days before. He was struck in the abdomen by another skier. At the time, the impact was considered to be irrelevant. The next day, he started to feel progressively worsening abdominal pain, so he came for a consultation. The patient had no previous surgery and at the time of the trauma was on immunomodulant therapy (anti-TNF alpha). At ambulatory visit, he complained of diffuse severe abdominal pain, without fever or changes in bowel habits. On physical examination he showed abdominal pain and distension, with signs suggesting peritonitis. An abdominal and intestinal ultrasound was promptly performed in our Unit, revealing markedly thickened intestinal walls, peri-intestinal hypoechoic areas suggestive of enteric fistulae surrounded by severe and diffuse mesenteric hypertrophy, containing free gaseous artifacts. The patient was immediately sent to the Emergency Department. Blood tests indicated only highly raised inflammatory markers. Computed tomography (CT) scan showed thickened bowel loops and an ileo-sigmoid fistula,

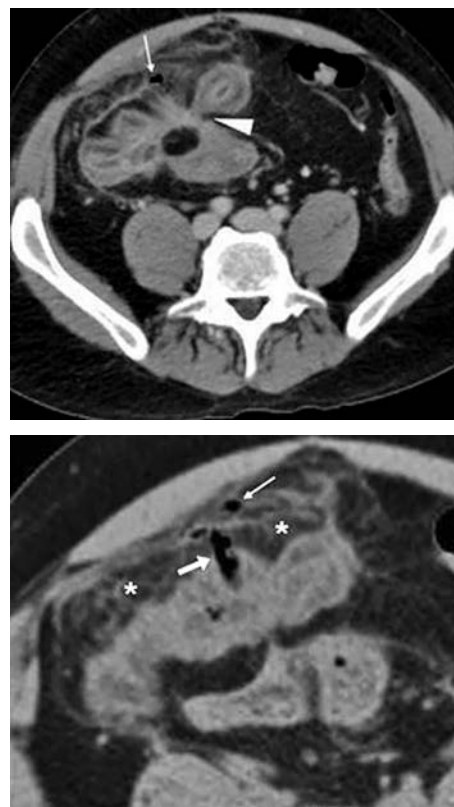


Fig. 1. Urgent unenhanced and contrast-enhanced multidetector CT, performed without any bowel preparation nor distension. Panoramic axial (upper panel) image shows thickened bowel loops in the right lower quadrant consistent with known Crohn's disease.

and revealed mesenteric hypertrophic hyperdensity with fascial fluid and small extraluminal gas bubbles (Fig. 1).

Diagnosis of free perforation of the ileum was made by ultrasonography and CT examination. The patient underwent an urgent laparotomy, which confirmed the Crohn's disease involvement of the distal ileum, the ileum-sigmoid fistula and the presence of the perforation of the distal ileum. There were no apparent strictures distally to the perforation that could have resulted in a distended area of the ruptured bowel. An ileo-cecal bowel resection and sigmoid resection were performed and an immediate recanalization was obtained by ileum-ascending manual T-T anastomosis and descending-rectal mechanical L-T anastomosis with circular end-to-end anastomosis at 31 mm. Morphological conditions of the intestinal tissue allowed the avoidance of a protective stoma. Histology confirmed macroscopic and microscopic features of Crohn's disease. There were no post-operative complications and two years after the operation, the patient is still in a good clinical condition.

Free perforation is a rare complication of Crohn's disease. About 1-3% of patients with Crohn's disease will present free perforation during their disease course. In the literature, only eight cases of free bowel perforation following a trauma in IBD have been reported [1, 2].

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Cardiac arrest after transjugular intrahepatic porto-systemic shunt creation in a 28 year-old patient with end stage liver disease secondary to cystic fibrosis

To the Editor,

Transjugular intrahepatic porto-systemic shunt (TIPS) creation for portal decompression in patients with cystic fibrosis (CF) has been reported in isolated case reports or case series of pediatric [1-4] and young adult patients [5]. This 28 year-old cystic fibrosis (CF) patient was referred with refractory ascites, poor nutritional status, and severe thrombocytopenia.

The TIPS creation was performed under general anesthesia. All monitored parameters remained within the normal range during all procedures. Hemodynamic measurement showed a porto-systemic gradient of 18 mmHg (right atrial pressure 14 mmHg, inferior vena cava pressure 14 mmHg, portal vein pressure 32 mmHg) and subsequently a 10 mm diameter e-PTFE covered stent (Viatorr®; W.L.GORE & Associates, Inc. Flagstaff, Arizona) was deployed. Hemodynamic measurement showed a porto-systemic gradient of 4 mmHg with a severe increase in the right atrial pressure (right atrial pressure 24 mmHg, inferior vena cava pressure 24 mmHg, portal vein pressure 28 mmHg).

A quick reduction in the end-tidal carbon dioxide concentration (from 40mmHg to 5mmHg) was observed for a few minutes following completion of the procedure. Although the fraction of inspired oxygen was increased to 100%, the oxygen saturation decreased progressively with severe bradycardia and cardiac arrest. Adrenaline intravenous infusion, cardiac massage and administration of 20ppm of inhaled nitric oxide (Opti Kinokx system, Air Liquide, Puteaux, France) were performed for around two minutes until spontaneous cardiac activity was restored. A pulmonary

pressure of 30mmHg was measured using a Swan-Ganz catheter placed through the jugular introducer. The patient was transferred to the intensive care unit where levels of inhaled nitric oxide were progressively reduced in the next 12 hours. The pulmonary pressure was reduced further to 20mmHg, and the patient was extubated 24 hours after the procedure and transferred from the intensive care unit to the hepatology department. Eight days following this post-procedural complication, the patient was discharged home. The patient no longer requires paracentesis for ascites given that it has resolved in 6 months of follow up.

Based on this single experience, we suggest the quick availability of a nitric oxide inhalation system in the interventional suite during the procedure. This gas, with its vasodilatory activity, immediately acts on the lungs' ventilated zones and enables pulmonary arterial hypertension to be effectively and quickly treated. The activity of nitric oxide administered by inhalation is moreover confined to the pulmonary circulation; therefore, therapy is not accompanied by decreases in systemic blood pressure. Based on this case, great attention should be given to potential cardio-respiratory complications in this specific cohort of patients, given the reduced compliance of the pulmonary circulation and the advanced pulmonary parenchymal disease.

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