

Liver biopsy or transient elastography? First, do not harm!

To the Editor,

We read with interest the editorial by Sporea [1] and we would like to comment on the present and future role of transient elastography (TE) for staging liver fibrosis in patients with chronic hepatitis C (CHC). Sporea [1] raised two questions and partially offered the answers. Concerning the first question - should we, at this moment, still regard liver biopsy (LB) as the “gold standard” for staging liver fibrosis? – the answer is, obviously, “no” and this has been extensively underlined by recent literature, which shows that LB is an “imperfect” standard. The LB limitations and its invasive nature have instigated great interest in the development of non-invasive methods for assessing liver fibrosis. Among these, TE (FibroScan, Echosens Paris) is probably the most widely used in routine clinical care of CHC patients in many countries, including Romania. The diagnostic accuracy of TE is at least “good” for significant fibrosis (METAVIR, $F \geq 2$ or Ishak, ≥ 3) (AUROC 0.80-0.85) and “excellent” for cirrhosis (AUROC 90-95) [2]. Despite its accuracy, TE is not accepted by some expert hepatologists and professional associations (i.e., AASLD) as a valid alternative to LB for evaluating fibrosis in CHC [3]. The main argument is the apparent failure of non-invasive methods to make an accurate distinction between the different stages of intermediate fibrosis (F1 vs F2), F2 being considered the threshold for initiating antiviral therapy. Consequently, LB has been performed for many years in nearly all patients with CHC on the basis that it was the only reliable method to discriminate between F1 and F2. Poynard et al [4] have recently shown that LB has a low diagnostic performance for F1-F2 stages, and suggested that recommendations for a biopsy instead of a validated non-invasive method such as the FibroTest, is misleading. The same recommendation is most probably misleading when it comes to TE and other non-invasive methods. Their performance was evaluated

using LB as a reference standard. Considering that LB is an “imperfect” standard, TE might be as inaccurate as LB in discriminating between different stages of intermediate fibrosis. With protease inhibitors-based triple therapy and high rates of sustained virological response, the need to accurately stage liver fibrosis is decreasing in treatment decision and, in the most recent European guidelines [5, 6], TE or other validated non-invasive methods can be used instead of LB in CHC before deciding on antiviral therapy. It is hard to understand that some expert hepatologists and the latest AASLD guidelines [3] still favor LB before treatment initiation.

As to the second question, namely if elastographic methods are ready for clinical use, we agree with Sporea [1] that the answer is “yes” for some of the elastographic methods. It is obvious that, from all elastographic methods excellently reviewed in the editorial, the only one ready for clinical use at present and in the near future is TE. In addition to its diagnostic performance for staging fibrosis, TE has several other advantages over LB: results are immediately available and highly reproducible, it is inexpensive and easy to be performed in outpatients, it can be repeated over time for disease monitoring and used as a screening tool for the detection of fibrosis/cirrhosis [2]. But the most important advantage is that TE is risk-free for the patient.

We believe that the time has come to change what has long stood as dogma, and to move from LB to TE (or other validated non-invasive methods) in assessing fibrosis in patients with CHC. First, do not harm!

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“Quo vadis” liver biopsy? A multi-centre Romanian study regarding the number of liver biopsies performed for chronic viral hepatitis

To the Editor,

Evaluation of liver morphopathology in patients with chronic liver disease was considered mandatory for prognosis assessment and treatment decisions. Very recently, Schiano and Fiel [1] wrote an interesting editorial in *Clinical Gastroenterology and Hepatology* concerning the liver biopsy (LB) in autoimmune hepatitis, with a very provocative title: “To B(iopsy) or Not to B(iopsy)...”.

In Romania, a new administrative regulation (Order No. 461/477, 18.05.2010 of the National Health Insurance Company) regarding therapeutic protocols in chronic hepatitis was introduced in 2010, allowing the noninvasive assessment of liver fibrosis for patients with chronic B or C hepatitis. We invited several centers in Romania to respond to a questionnaire regarding the number of LBs performed during two periods, before and after the Order was issued: 01.01.2010-30.06.2010 and 01.07.2010-31.12.2010, respectively, in order to determine the impact of the new legislation on clinical practice.

Eleven university centers (most experienced in performing LB) responded to our invitation. In the two study periods, a total of 1391 LBs were performed, 1003 (72.1%) for HCV, 338 (24.3%) for HBV chronic hepatitis and 50 (3.6%) for other etiologies. In the second period the number of LBs sharply decreased, by approximately 60%, from 985 to 406 LB. The decrease was more consistent in HCV (by 66%) vs. HBV chronic infection (with only 34% decrease). This can be explained by the fact that in HBV chronic hepatitis the LB is still mandatory in some situations.

“Quo vadis” liver biopsy for chronic hepatitis? Probably towards a dramatic decrease in number, especially in HCV infection. Since powerful drugs will soon be available, all HCV chronic infected subjects will be treated, without considering the severity of fibrosis. Maybe in HBV chronic infections, because the patient can be in different stages of the disease (immunotolerant), LB still has a place, at least for a period of time.

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Is the role of liver biopsy changing in hemochromatosis? A non invasive approach is ready

To the Editor,

The role of liver biopsy in hemochromatosis is changing [1]. MRI for liver iron concentration determination (LIC) is becoming the gold standard for the diagnosis of iron overload in hemochromatosis patients [2, 3]. Each machine must be calibrated so that the results can be reproducible between different MR centers. Alustiza et al [4] designed a phantom that correctly calibrated 40 MRI centres in Spain [4].

There is a wide variation in measures of LIC by liver biopsy, especially in cirrhotic patients [5]. If iron-free foci are biopsied, LIC will never be raised, and different values will be determined in different places of the liver [6]. All of these problems do not occur with MRI.

Steatosis represents a problem for LIC determination [7]. All the iron quantification sequences must be performed as in-phase sequences to be sure that fat does not interfere in signal intensity measurements. Decreased signal intensity at in-phase imaging should be the reason to perform a rapid study of LIC. MRI may be useful for fibrosis prediction in hemochromatosis patients [8]. The product of age and LIC (fibrosis-index) obtained by liver biopsy or by MRI, with a 480,000 cut-off resulted in a 100% sensitivity and 86% specificity for the diagnosis of high-degree fibrosis.

Some authors continue to say that biopsy is particularly useful in non-*hfe* hemochromatosis, to confirm iron overload [1]. LIC determination by MRI is the first diagnostic tool to be used in these cases. Non-invasive approach is ready and preferable, and if mutation determination is made, MRI will establish the need for treatment.

Non-invasive fibrosis markers, as laboratory tests, are very useful in fibrosis prediction in these patients.

The role of liver biopsy in the study of hemochromatosis must be for the diagnosis of associated diseases, or in patients where discrepancies between radiologic and biochemical markers exist.

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Buried haemoclips: how long do they remain?

To the Editor,

Upper gastrointestinal (GI) bleeding caused by endoscopic treatment such as polypectomy or mucosal resection is becoming more frequent as the use of such treatments increases. Endoscopic clips (haemoclips) can be deployed to control bleeding by achieving immediate haemostasis, and are generally sloughed off 1–3 weeks after placement [1–3]. Here we present a case of haemoclip retention in the stomach, identified endoscopically as ‘buried haemoclip’, and its successful management.

A 22-year-old female patient with vomiting for two months underwent an upper GI examination in another hospital. A mucosal swelling, reported to be endocrine cell hyperplasia, was found on the greater curvature of the stomach, which bled after biopsy, and required two haemoclips for haemostasis. The patient was re-evaluated in our hospital 6 months after the index endoscopy, and upper GI endoscopy showed retention of the haemoclips (Fig. 1a), which were easily extracted using endoscopic biopsy forceps without any complications (Fig. 1b). Polypectomy of the remaining tissue was performed without complications.

Haemoclips are frequently used for nonvariceal upper

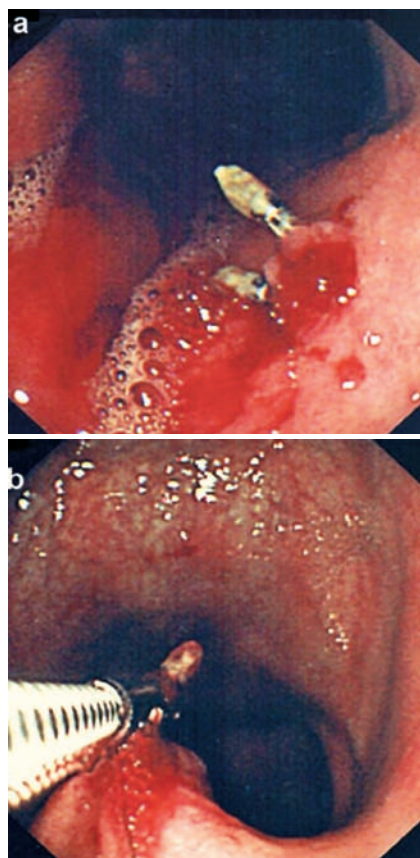


Fig 1. A: Two partially “buried” haemoclips were seen on the greater wall of the stomach; B) The haemoclips were grasped using biopsy forceps; the “tenting” of the mucosa indicated that the underlying tissue was not fibrotic or adherent to the gastric wall.

GI bleeding, perforations, anastomotic leaks, marking the site of GI tumours before treatment, and fixation of tubes and stents to the GI wall [3]. The ability of a haemoclip to remain attached for longer than expected could facilitate the outcome in the aforementioned situations. To date, no complications have been reported due to retention of haemoclips. However, given the physical properties of the material from which they are made, they could interfere with therapeutic and diagnostic interventions; for example, the electrical conductivity of a haemoclip may limit completion of the polypectomy or may not be compatible with MRI due to magnetic deflection [4].

Why did these haemoclips remain in this patient for so long? Possible explanations could be: the tissue of the polyp stalk is not as brittle as that of an ulcer, enabling the clips to hold the tissue with sufficient force to delay detachment. As seen in the figures, the clips were deployed perpendicularly to the mucosa, which may have bestowed more holding power. Lastly, the haemoclips were applied to the submucosa and regeneration of the surrounding tissue had buried the clips. It should be noted that different types of endoscopic clips grasp the mucosa with differing strength, which, in turn, affects the retention period [2]. In conclusion, if an intervention at the site of a clip retention is required and if, on using forceps, it is not fibrotic, removal is relatively easy.

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bloating caused by insufflation of air during colonoscopy leads to reduced tolerance of the subsequent OGD.

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Same day bidirectional endoscopy - does the procedural order matter?

To the Editor,

Oesophagoduodenoscopy (OGD) and colonoscopy are frequently performed in combination, so called bidirectional endoscopy to evaluate gastrointestinal symptoms [1-3]. Despite the frequency of same day bidirectional endoscopy, there is a paucity of data regarding procedural order and tolerability. Two recent Asian studies have suggested that OGD followed by colonoscopy should be the procedural order of choice. However, one of these studies is restricted to patients receiving propofol, a drug that is rarely used in the United Kingdom (UK) for endoscopy [4, 5].

From a single UK centre, we report our experience of procedural order with patients being randomised to either having an OGD first followed by a colonoscopy (Group A, n=35), or a colonoscopy first followed by an OGD (Group B, n=35), with discomfort measured using a validated 10-point numeric rating scale [6]. No significant difference was noted between the two groups with regards to age, BMI, anxiety state, depression or indications for undergoing bidirectional endoscopy with four Joint Advisory Group (JAG) accredited endoscopists undertaking the procedures. There was no statistically significant difference noted in the mean discomfort scores given for colonoscopy between the two groups (5.2 vs 5.4, $p=0.80$). However, there was a significant reduction in the discomfort scores given for OGD when this was performed first rather than the second (mean score 4.6 v 6.3; $p=0.02$).

Our work adds to the literature in being the first study to evaluate endoscopic procedural order for bidirectional endoscopy in a Western population and identifies that OGD followed by colonoscopy should be the preferential order of choice, supporting findings from the Asian studies. A plausible explanation for this could be that the abdominal

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Superficial venous thrombophlebitis associated with pegylated interferon alpha-2a treatment in a patient with chronic hepatitis B

To the Editor,

There are several case reports of thrombotic effects attributed to interferon- α (IFN α) in patients with multiple sclerosis, hematologic malignancies and hepatitis C [1, 2]. These effects include renal and cutaneous thrombotic microangiopathy, portal and mesenteric thrombosis, retinal vein occlusion and deep vein thrombosis [1, 2]. This is the first report of superficial venous thrombophlebitis (SVT) related to IFN α during treatment for chronic hepatitis B.

An otherwise healthy 39-year-old male presented to the outpatient clinic with abnormal liver function tests and positive HbsAg. HbeAg was negative and viral load was 84,700 IU/ml. The patient consented to be treated with PegIFN α -2a for 48 weeks. On week 26, he presented with pain, tenderness and erythema along the course of a non-varicose superficial vein of his right shin. Diagnosis of SVT was confirmed by color-coded ultrasound. Screening for cryoglobulinemia, disseminated intravascular coagulation, paroxysmal nocturnal hemoglobinuria, antiphospholipid antibodies, autoimmune disorders, protein C and S deficiency or factor Von Leiden was negative. PegIFN α was discontinued and Fondaparinux sodium was prescribed for 6 weeks. Complete resolution of the lesion was accomplished within 2 months.

The purpose of our communication is to describe SVT during treatment for hepatitis B. Hepatitis B virus has been associated with the presence of antiphospholipid antibodies (18-42%), but an association with thrombotic effects has not been reported [3] and they were ruled out in our patient. The pathogenetic mechanism related to IFN α -associated thrombotic lesions is unknown. IFN α enhances the production of anti-phospholipid [4] or other thrombogenic antibodies [5], as well as cryoglobulins (tested negative in our patient), induces leukocyte adherence to vessel walls [6] and favors apoptosis of endothelial cells [7], increasing the risk for thrombosis.

In conclusion, SVT should be considered as a potential adverse event of PegIFN α -2a treatment. Further research is needed to elucidate the underlying molecular mechanism.

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Post-polypectomy bleeding in a patient with undiagnosed Moschowitz syndrome

To the Editor,

A 67-year-old male with a recurrence of rectal bleeding episodes underwent colonoscopy, and a 3 cm large, sessile

polyp was removed in the sigmoid tract. An immediate bleeding was observed that was stopped by injecting epinephrine solution and positioning five endoclips. Three hours later, a massive bleeding preventing a new endoscopic haemostasis occurred, and the patient underwent an urgent surgical bowel resection. Twenty-four hours later, a severe thrombocytopenia (PLT: 15,000/mm³), a 12-fold increase of unconjugated bilirubin and 5-fold increase of lactate dehydrogenase were observed. Direct and indirect Coombs tests, anti-nuclear and antiphospholipid antibodies were negative, serum complement and cryoglobulin levels being normal. Coagulation tests showed a slightly elevated level of fibrinogen degradation products with normal clotting values. A bone marrow aspirate showed the presence of hyperplastic megakaryocytes. ADAMTS-13 activity was <10% in the absence of ADAMTS-13 inhibitors. Therefore, a Thrombotic Thrombocytopenic Purpura (TTP) was diagnosed. During the following 15 days, the patient received plasma and concentrated red cell transfusions, and oral steroid therapy. At discharge, the patient had mild anaemia, improved thrombocytopenia (PLT: 85,000/mm³) and ADAMTS-13 activity >90%, that normalized three months later.

Intestinal bleeding occurs in 0.1%-0.6% of colonoscopies, the risk being largely associated with a polypectomy [1]. Clotting impairment and recent anticoagulant therapy are risk factors, but they were absent in our case. Only when a post-surgical severe thrombocytopenia and haemolytic anaemia unexpectedly occurred, TTP diagnosis was achieved. This is a devastating haematological disorder, and ADAMTS-13 deficiency is the major cause of TTP-associated mortality [2, 3]. Thrombotic thrombocytopenic purpura occurs following several physiological and pathological states, and is induced by some drugs [2]. These conditions were absent in our patient. To our knowledge, this is the first case of post-polypectomy bleeding occurring in a patient with TTP. Of note, post-polypectomy bleeding was also the reason for which TTP was eventually diagnosed. Therefore, endoscopists should be suspicious of TTP when a severe post-polypectomy bleeding occurs, even if the pre-procedure haematological parameters are normal.

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