REVIEW ARTICLE

Noninvasive assessment of liver fibrosis: key messages for clinicians

Gian P. Caviglia[1], Giovanni A. Touscoz[2], Antonina Smedile[1], Rinaldo Pellicano[2]

1 Department of Medical Sciences, University of Turin, Turin, Italy
2 Department of Gastroenterology, Azienda Ospedaliera Città della Scienza e della Salute, Turin, Italy

KEY WORDS

chronic liver disease, liver biopsy, liver fibrosis, noninvasive fibrosis assessment

ABSTRACT

The management of patients with chronic liver disease (CLD) requires an accurate definition of the staging and grading, as the latter is related to the progression of liver fibrosis. Albeit liver biopsy (LB) is an invasive procedure with possible complications, it is currently the "gold standard" for the assessment of hepatic fibrosis. Over the past decade, several noninvasive approaches have been proposed as surrogates in the evaluation of liver fibrosis. These include serum direct and indirect markers of fibrosis linked, respectively, to fibrogenesis and hepatic function, and instrumental techniques, which measure liver stiffness, a parameter directly correlated with liver fibrosis. Although accuracy of noninvasive methods was initially investigated in chronic hepatitis C, there are now increasing data referred to their application in other CLDs. While in specific settings, there is still need for LB, noninvasive methods have an increasing and crucial role in clinical practice to monitor fibrosis progression in patients with CLD. The aim of this review is to present the current status of knowledge in this new exciting field and to highlight the key messages useful for clinicians.

Correspondence to:
Dr. Rinaldo Pellicano, Department of Gastroenterology, Azienda Ospedaliera Città della Scienza e della Salute, San Giovanni Antica Sede, Via Cavour 31, 10100, Turin, Italy, phone: +39-011-6333913, fax: +39-011--6333976, e-mail: rinaldo_pellican@hotmail.com
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Introduction Chronic liver diseases (CLDs), particularly those related to hepatitis C and B viruses and to alcoholic and nonalcoholic fatty liver (nonalcoholic fatty liver disease – NAFLD; nonalcoholic steatohepatitis – NASH), are diffuse worldwide.[1,2] The natural history of CLD in the long term varies widely in relation to host and causal factors. Since prognosis and management of CLD are strongly influenced by the degree of liver fibrosis, the precise definition of fibrosis stage is crucial to assess the risk of disease progression toward cirrhosis and its complications, and to prompt immediate treatment.[3,4]

The different causes of CLD have a common histopathological pathway, the formation and accumulation of fibrosis that leads to the distortion of the hepatic architecture and the subsequent evolution to cirrhosis. The development of liver fibrosis starts from the minimal degree limited to the portal tracts followed by more extensive fibrosis with septa forming bridges between two portal tracts or portal tracts and central veins. With time, this process progresses to widespread fibrosis and nodule formation.[5]

Liver biopsy (LB) is the gold standard for the evaluation of hepatic fibrosis. However, the recent introduction of new imaging techniques, improvement in statistical tests capable of diagnosing CLD noninvasively, and a reconsideration of its potential complications have contributed to an audit of the evolving role of the bioptic approach. At present, there is an increasing interest for noninvasive methods to evaluate the stage of liver fibrosis in the clinical workup of patients with CLD.[6]

The aim of this review was to present the current status of knowledge in this new exciting field.

Liver biopsy LB enables not only the evaluation of hepatic fibrosis but also provides useful information on numerous processes such as inflammation, necrosis, or steatosis. It also enables to identify and quantify iron and copper within the liver parenchyma, allowing to identify suspected or unexpected cofactors and comorbidities.[7] To investigate the activity grade of inflammation and to stage the amount and type of liver fibrosis, many scoring systems have been proposed. Among those specifically designed for chronic

hepatitis, there are the histological activity index proposed by Knodell et al.,[8] Ishak's score, and the METAVIR scoring system.[8-10]

The Knodell index (Histology Activity Index or HAI) evaluates 4 parameters, namely, periportal necrosis, parenchymal damage, portal inflammation, and fibrosis.[8] The main limitation of the HAI is the lack of distinction between necroinflammation score (grading) and fibrosis score (staging). The Ishak's system is a modified version of the HAI, which describes grading and staging separately. It is more sensitive and accurate in assessing fibrosis, which is observed in absent, mild, moderate, and severe/cirrhosis.[9] The METAVIR scoring system distinguishes 5 degrees of liver fibrosis: F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (portal fibrosis with few septa), F3 (septal fibrosis without cirrhosis), and F4 (cirrhosis).[10]

LB has some limitations and risks that make it unsuitable for tight monitoring of the patients: it is an invasive procedure and can lead to complications such as bleeding, pain at a biopsy site, infection, and accidental injury to nearby organs.[11] A study, including 835 subjects admitted to a third-level day-hospital of gastro-hepatology for LB, reported 22% of unwanted effects and 3.8% of hospitalizations.[12] Moreover, the accuracy of LB in assessing hepatic fibrosis may be reduced because of sampling error.[13] In fact, histological distribution of fibrosis within liver parenchyma is heterogeneous, and usually, the diagnosis of cirrhosis is based on a biopsy specimen that represents only 1/50,000 of the total liver mass. It has been estimated that a biopsy specimen of 25 mm gives an error rate of 25%, rising to 35% if the LB length is less than 15 mm.[14] Colloredo et al.[15] analyzed the importance of the sample size for correct staging of liver fibrosis in CLD and concluded that an adequate LB sample should be at least 20 mm in length with at least 11 complete portal tracts.[15] In addition, the accuracy of LB in assessing fibrosis varies depending on intra- and interobserver variability, resulting in up to 30% of false negative results.[16] Hence, there is need for accurate noninvasive methods for measuring the degree of liver fibrosis.

Noninvasive fibrosis biomarkers Liver fibrogenesis derives from the balance between deposition and removal of the extracellular matrix. The hepatic stellate cells are the major source of the extracellular matrix. During liver injury, activation of quiescent hepatic stellate cells to a proliferative, fibrogenic, and contractile type of myofibroblasts is the main event that leads to fibrogenesis. This activation is supported by several cytokines such as transforming growth factor β (TGF-β), tumor necrosis factor α (TNF-α), and platelet-derived growth factor (PDGF), secreted in response to liver injury. At the same time, other signals such as interleukin 10 (IL-10) promote degradation of hepatic stellate cells.[17]

Two different types of noninvasive markers of liver fibrogenesis activity and fibrosis stage have been identified: direct markers of fibrogenesis, such as expression of either deposition or removal of extracellular matrix in the liver, or indirect markers of fibrosis, which reflect liver changes induced by fibrosis without a direct link to fibrogenetic mechanisms.[18] The former evaluates the turnover or metabolism of the extracellular matrix in the peripheral blood, hence, dynamic processes such as fibrogenesis or fibrolysis rather than existent fibrosis. Direct markers include several glycoproteins such as hyaluronic acid and laminin, the collagen family such as type IV collagen, type III collagen N-terminal peptide, matrix metalloproteinases, and cytokines such as TNF-α and TGF-β.[19] However, fibrosis in not a liver-specific process and these markers can be affected by changes in their clearance and excretion.[20] The second approach consists in the employment of single or combined hematological or biochemical tests that reflect alteration of hepatic function. Frequently, the included markers are platelet count, the ratio of aspartate to alanine transaminases (AST/ALT ratio), and the ratio of AST to platelets (APRI).[21,22] Until now, the accuracy of these indirect markers has been extremely variable, which makes it difficult to evaluate the degree of liver fibrosis.

More sophisticated and expensive methods are those that can be compiled into either biochemical scores or biomarker panels generated by various statistical methods, such as Fibrotest (Biopredictive, Paris, France), Forns' index, Hepascore (PathWest, University of Western Australia, Perth, Australia) and Enhanced Liver Fibrosis (ELF) Test (**TABLE**).[7,20,23-28] The most known is Fibrotest that combines, into an equation, the values of haptoglobin, α_2-macroglobulin, apolipoprotein A1, γ-glutamyl transpepdtidase, and bilirubin with the patient's age and sex to generate a measure of fibrosis stage. Although these panels are able to reliably exclude or detect significant fibrosis, the major trouble is their lack of ability to reflect small changes in the early stages of fibrosis.[20]

Imaging techniques Imaging methods have been usually reserved for the evaluation of the presence of portal hypertension or hepatocellular carcinoma in patients with cirrhosis. In recent years, several imaging methods have been proposed for noninvasive assessment of liver fibrosis. These procedures include ultrasound-based elastography, computed tomography-based texture analysis, and magnetic resonance imaging--based techniques.[29]

Ultrasound elastography There are different types of ultrasound elastography, including acoustic radiation force impulse (ARFI) imaging and real time-tissue elastography (RTE), but the most widely used type in clinical practice is transient elastography (TE).

TE (FibroScan; Echosens, Paris, France) is a rapid and noninvasive technique proposed in

TABLE Performance of the main serological tests for noninvasive diagnosis of significant fibrosis (F0/1 vs. F2/3/4) and cirrhosis (F0/1/2/3 vs. F4)

Test	Parameters	F0/1 vs. F2/3/4 (AUC)	F0/1/2/3 vs. F4 (AUC)
APRI	AST, platelets	0.69–0.88	0.61–0.94
FibroTest	age, sex, α_2-macroglobulin, γ-GT, apolipoprotein A1, haptoglobin, bilirubin	0.74–0.89	0.82–0.92
Forns' index	age, platelets, γ-GT, cholesterol	0.75–0.91	0.87
Hepascore	age, sex, bilirubin, γ-GT, hyaluronic acid, α_2-macroglobulin	0.76–0.81	0.88–0.90
ELF score	age, hyaluronic acid, N-terminal peptide of collagen III, TIMP-1	0.78–0.88	0.70–0.89
Fibrometer	age, AST, α_2-macroglobulin, urea, hyaluronic acid, platelets, prothrombin index	0.78–0.89	0.88–0.94
Lok Index	INR, AST, ALT, platelets	0.62–0.70	0.73–0.87
GlycoFibrotest	N-glycans profile	0.78	–
GlycoCirrhotest	N-glycans profile	–	0.87
FibroIndex	γ-globulin, AST, platelets	0.72–0.86	0.81

Abbreviations: ALT – alanine aminotransferase, APRI – ratio of aspartate transaminase to platelets, AST – aspartate transaminase, AUC – area under the curve, ELF – enhanced liver fibrosis, INR – international normalized ratio, TIMP-1 – tissue inhibitor of metal protease-1, γ-GT – γ-glutamyl transpeptidase

2003 for the indirect detection of liver fibrosis by providing a quantitative measurement of liver stiffness. The FibroScan system is equipped with a probe including an ultrasonic transducer mounted on the axis of a vibrator. A vibration of mild amplitude and low frequency (50 Hz) is transmitted from the vibrator towards the tissue by the transducer itself. This vibration induces an elastic shear wave that propagates through the tissue. In the meantime, pulse-echo ultrasound acquisitions are performed to follow the propagation of the shear wave and measure its velocity, which is directly related to tissue stiffness. The harder the tissue, the faster the shear wave propagates.[30] Liver stiffness measurement is expressed in KiloPascals (kPa), with ranges between 2.5 to 75 kPa, and related to the METAVIR score.

Several authors have shown that TE is more accurate in identifying severe fibrosis and cirrhosis than initial stages of CLD. A study on 1257 patients with CLD suggested that a cut-off value of 14.6 kPa is the threshold with optimal accuracy of FibroScan, and it is better for the exclusion than for prediction of cirrhosis.[31] A prospective study including 711 patients with CLD, showed that TE is an accurate method to diagnose liver fibrosis, with a significant correlation with fibrosis stage (r = 0.73; P <0.0001). Using a cut-off value of 17.6 kPa, patients with cirrhosis were shown to have a positive and negative predictive value of 90%.[32] Similar results were obtained in 327 patients with chronic hepatitis C (CHC).[33]

However, for patients with low or mild fibrosis, the accuracy of TE is lower and more variable when compared with the results for detecting cirrhosis.[34] Furthermore, a recent prospective study of 219 consecutive patients with CLD (35%, chronic hepatitis C; 32%, chronic hepatitis B; and 33%, NAFLD) pointed out a less strong correlation of liver stiffness measurement with fibrosis stage in chronic hepatitis B (CHB) and NAFLD than in CHC.[35] This study suggested that TE can be considered a valid support to detect fibrosis in CLD related to HCV, but it should be interpreted with caution in liver diseases of other etiologies where host or disease-related factors may modify its accuracy.

Two recent studies involving CHB patients pointed out a significant decrease in TE values during and after antiviral therapy.[36,37] Moreover, the decrease in TE values correlated significantly with an increase in albumin, decrease in bilirubin, as well as decrease in ALT and AST levels. However, among a subgroup of patients with available paired LB, a decrease in TE values was significantly correlated with improved necroinflammatory scores, but not with fibrosis regression. Indeed, the effect of ALT reduction caused by antiviral therapy led to a decline in TE values without a significant histological change in liver fibrosis.

TE diagnostic accuracy is not only limited by the extent of necroinflammatory activity but extrahepatic cholestasis and congestive heart failure may also contribute to the overestimation of TE.[38] Moreover, the performance of TE may be limited in patients with a high body mass index, narrow intercostal space, or ascites.[38]

ARFI is an ultrasound-based method that allows to evaluate the elastic properties of a region of the liver by inducing short duration acoustic pulses that generate shear waves causing tissue displacement. The stiffness is measured quantitatively with the shear wave velocity by repeating push pulses and detection pulses across the region of interest.[39]

The major advantage of ARFI over TE is that it can be easily integrated into a standard ultrasound examination, allowing the visualization of the area of interest. However, a recent meta-analysis showed that diagnostic accuracy of TE was slightly higher than that of ARFI for the diagnosis of significant fibrosis and cirrhosis.[40] Moreover, another study on 223 subjects reported a strong linear correlation (r = 0.870; P <0.0001) between TE and fibrosis and a weaker

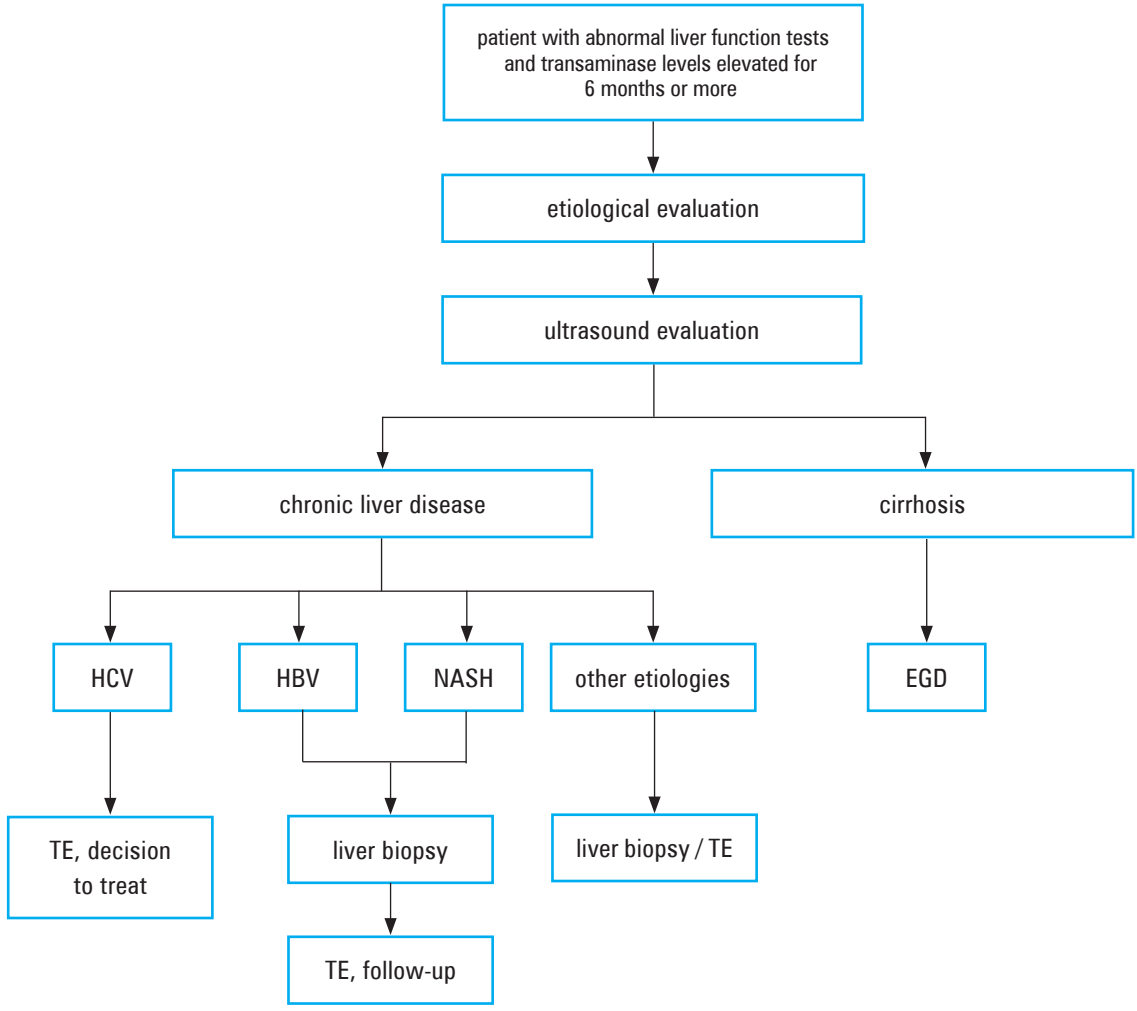

FIGURE Proposed algorithm for the evaluation of liver fibrosis in patients with chronic liver disease
Abbreviations: EGD – esophagogastroduodenoscopy, HBV – hepatitis B virus, HCV – hepatitis C virus, NASH – nonalcoholic steatohepatitis, TE – transient elastography

correlation between ARFI and fibrosis (r = 0.646; P <0.0001). The diagnostic accuracy values for predicting significant fibrosis (F ≥2) were 0.953 for TE and 0.890 for ARFI, and for predicting cirrhosis (F = 4) they were 0.985 for TE and 0.931 for ARFI.[41]

RTE is another technique that can be used during conventional abdominal ultrasound examination to evaluate liver stiffness. In this case, tissue stiffness is expressed according to a color scale with soft areas represented in green/red and hard areas in blue.[42] In a head-to-head comparison of TE, RTE, and ARFI in the diagnosis of liver fibrosis, all 3 methods presented fair (area under the curve [AUC] >0.7) to good (AUC >0.8) diagnostic accuracy in diagnosing fibrosis (F ≥1) and significant fibrosis (F ≥2). However, TE showed the best performance for the diagnosis of fibrosis and significant fibrosis (AUC = 0.878 and AUC = 0.897, respectively).[43]

Computed tomography Traditionally, computed tomography (CT) scan has been used to explore the liver parenchyma providing information on significant fibrosis, cirrhosis and its complication including hepatocellular carcinoma and portal hypertension. Only limited evaluation of this methods has been made in patients with less advanced stages of fibrosis. A recent study has assessed, prospectively, the utility of perfusion CT for differentiating minimal from intermediate fibrosis in treatment-naive patients with CHC. The authors reported that the method allowed to discriminate between minimal and intermediate fibrosis with a sensitivity of 71% and a specificity of 65%.[44] In another study, optical analysis of CT images of the liver has been evaluated to assess fibrosis in patients with CHC. The reported diagnostic accuracies were 0.83 and 0.86 for the diagnosis of significant fibrosis (≥F2) and advanced fibrosis (≥F3), respectively.[45] However, CT is much more expensive than other noninvasive methods currently in use. Furthermore, it exposes patients to radiation and contrast media.

Magnetic resonance imaging Conventional magnetic resonance imaging (MRI) techniques are highly specific for liver morphological alterations in severe liver disease but have low sensitivity for earlier stages of CLD.[29] However, liver fibrosis may be visible with advanced MRI techniques such as magnetic resonance elastography (MRE). This technique allows to noninvasively quantify liver fibrosis providing quantitative maps of tissue stiffness over large regions of the liver, instead of localized spot measurements at limited depth provided by TE.[46] MRE uses a vibration device to induce a shear wave that propagates in

the liver. The waves are detected by a modified phase-contrast pulse sequence and then analyzed by specialized computer-based algorithms to generate elastograms that depict tissue stiffness.[47]

Several studies evaluated the diagnostic accuracy of MRE in detecting hepatic fibrosis. In a study involving 50 patients with CLD and 35 healthy controls, a sensitivity of 98% and a specificity of 99% for differentiating any stage of liver fibrosis from normal liver tissue has been reported. Moreover, MRE showed a sensitivity of 86% and a specificity of 85% for identifying patients with moderate/severe fibrosis from those with mild fibrosis (F2/3/4 vs. F0/1).[48] Another prospective study compared the diagnostic accuracy of MRE, TE, and APRI measurements for the noninvasive staging of fibrosis in 141 patients with CLD. The authors reported that MRE had a higher technical success rate than TE and a better diagnostic accuracy than TE and APRI, and the combination of TE and APRI.[49]

MRE offers several advantages: it can be performed in obese patients; an acoustic window is not required; and a conventional MR can be obtained at the same time of MRE.[50] However, it cannot be performed in patients with moderate--to-severe hepatic iron overload owing to the interferences on wave visualization.[50] Nevertheless, cost may limit the use of MRE.

Conclusions The following key messages may be highlighted for clinicians. Noninvasive tests for the assessment of liver fibrosis show several advantages that may reduce the need for LB. Serum biomarkers and imaging techniques, in particular TE, have been mainly investigated in patients with CHC and can lend valid support to detect fibrosis. In CLD from other causes such as CHB, alcoholic liver disease or NAFLD/NASH, different specific cut-off values have been proposed but inflammation and steatosis can limit the accuracy of liver stiffness measurement. Therefore, the algorithm we propose (**FIGURE**) illustrates a possible integrated approach of needle biopsy and TE for the evaluation and management of fibrosis evaluation in patients with CLD according to different etiologies.

At the moment, LB is still necessary to assess the presence of comorbidities and metabolic disorders but noninvasive methods may be relevant at least for monitoring the progression of CLD.

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ARTYKUŁ POGLĄDOWY

Nieinwazyjna ocena włóknienia wątroby – najważniejsze informacje dla lekarzy praktyków

Gian P. Caviglia[1], Giovanni A. Touscoz[2], Antonina Smedile[1], Rinaldo Pellicano[2]

1 Department of Medical Sciences, University of Turin, Turyn, Włochy
2 Department of Gastroenterology, Azienda Ospedaliera Città della Scienza e della Salute, Turyn, Włochy

SŁOWA KLUCZOWE

biopsja wątroby, nieinwazyjna ocena włóknienia, przewlekła choroba wątroby, włóknienie wątroby

STRESZCZENIE

Leczenie chorych na przewlekłe choroby wątroby (*chronic liver disease* – CLD) wymaga dokładnego określenia zaawansowania (*staging*) i aktywności (*grading*) choroby; ta ostatnia wiąże się z postępem włóknienia wątroby. Biopsja wątroby (*liver biopsy* – LB), choć jest procedurą inwazyjną obarczoną ryzykiem powikłań, stanowi obecnie złoty standard w ocenie włóknienia wątroby. W ostatnich latach zaproponowano kilka nieinwazyjnych metod mających zastąpić biopsję w ocenie włóknienia. Zalicza się tu oznaczanie w surowicy bezpośrednich i pośrednich markerów włóknienia, odzwierciedlających odpowiednio fibrogenezę i czynność wątroby, a także techniki instrumentalne pozwalające mierzyć sztywność wątroby, która bezpośrednio koreluje z włóknieniem. Pierwotnie dokładność metod nieinwazyjnych badano u chorych na przewlekłe wirusowe zapalenie wątroby typu C, ale jest coraz więcej danych o ich stosowaniu w innych CLD. W niektórych sytuacjach LB jest wciąż niezbędna, ale metody nieinwazyjne odgrywają coraz większą i już niezastąpioną rolę w praktyce klinicznej, pozwalając monitorować postęp włóknienia u pacjentów z CLD. Celem niniejszego przeglądu jest przedstawienie obecnego stanu wiedzy w tej nowej, ekscytującej dziedzinie i wskazanie kluczowych informacji przydatnych dla lekarzy praktyków.

Adres do korespondencji:
Dr. Rinaldo Pellicano, Department of Gastroenterology, Azienda Ospedaliera Città della Scienza e della Salute, San Giovanni Antica Sede, Via Cavour 31, 10100, Turyn, Włochy, tel.: +39-011-633-39-13, fax: +39-011-633-39-76, e-mail: rinaldo_pellican@hotmail.com
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