Non-invaziv tanı yöntemleri

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Fibrozis ve nekroinflamasyon belirlenmesi

İnvaziv yöntemler

- Karaciğer biyopsisi
  - METAVIR
  - Ishak
- Fibrozis
  - Stage (F)
- Nekroinflamasyon
  - Grade (HAİ)

Non-İnvaziv yöntemler

- Serum biyokimyasal testleri
  - Fibrotest
  - Actitest
  - AST-Platelet Ratio Index (APRI)
  - Forns Index
  - FibroMeter
  - Hepascore
  - S index
  - FIB-4 index
- Görüntüleme yöntemleri
  - USG, MR/CT
  - Fibroscan

Fibrozis ve nekroinflamasyon belirlenmesi

Non-İnvaziv yöntemler

Serum biyokimyasal testleri

- Fibrotest
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- AST-Platelet Ratio Index (APRI)
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Görüntüleme yöntemleri

- USG,
- MR/CT
- Fibroscan

Serum biyokimyasal testleri

Test	Parametreler	Mevcut altyapı yeterli mi?	Türkiye açısından değerlendirme
Fibrotest	gGT, bilirubin, haptoglobin, apolipoprotein A1, a2 macroglobulin, cinsiyet, yaş	Maliyetli ve Ticari	
APRI	AST, Platelet	Kolay hesaplanabilir	TÜRKİYE ŞARTLARINA UYGUN Nonsirotiklerde ve düşük PLT düzeyinde gücü zayıf. Erken evrede tek başına gücü zayıf.
Fibrometer	Alfa 2 Makroglobulin, ALT, AST, GGT, Trombosit, Üre, Protrombin zamanı	Ticari	
Forns Index	platelet sayısı ,GGT , yaş, total kolesterol	Zor Gereklilik arzetmiyor	
FIB-4	Yaş, AST, ALT,Platelet sayısı	Kolay	TÜRKİYE ŞARTLARINA UYGUN
Hepascore	bilirubin, γ glutamyl transferase, hyaluranik asit, α2 makroglobulin ,yaş ve cinsiyet	Zor Gereklilik arzetmiyor	

APRI + FIB4
birlikte
değerlendirildiğinde
%86-%90 güce ulaşıyor.

Fibrozis (var/yok)
analizinde anlamlı.

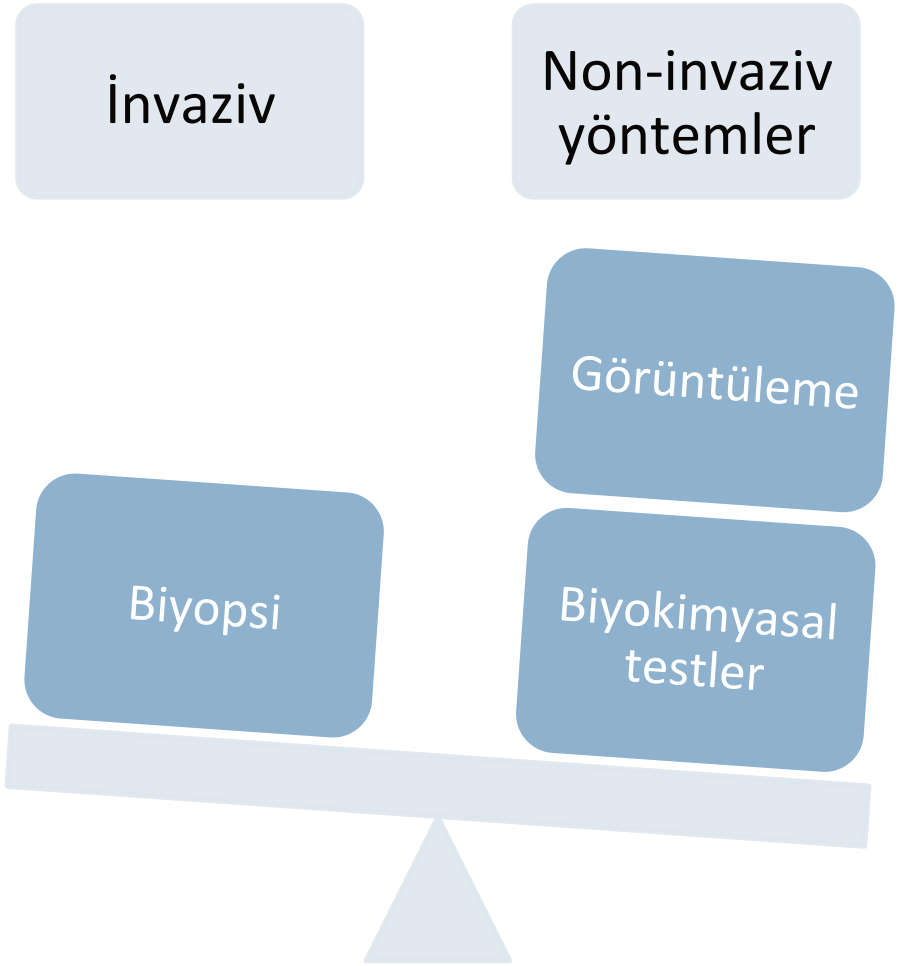
Fibroscan + Fib4
Veya
Fibroscan + APRI
Veya
Fibroscn + Forns Index

yeterli olabilir

Görüntüleme yöntemleri

Yöntem	HCV hastasında hangi amaçla kullanılır	Biyopsiye alternatif olabilir mi?	Fibrozis değerlendirme gücü
Elastografi	Fibrozis değerlendirmesi	Evet (fizik muayene ve diğer bulguları ile birlikte değerlendirerek)	Uygulayıcıya bağımlıdır. (False pozitif sonuç verebilir) Deneyim: 100 hasta min. Prognostik amaçlı da kullanılabilir. Ek olarak uygulanan diğer biyokimyasal testler ile (Fibrometer gibi) gücü artırılabilir
USG	Rutin inceleme	Tüm hepatobiliyer hastalıklarda. Biyopsi öncesi mutlaka bakılır.	Elastografi özelliği olan USG cihazları Fibrozis düzeyi verebilir ancak veriler sınırlı. Yorum önem kazanır.
MRI	Siroz açısından çok güvenilir sonuç vermeyebilir. KC patolojileri hakkında genel fikir verebilir.	Hayır	
CT			

Türkiye’de fibrozis ölçüm metodları



Tedavi Kılavuzlarının Önerileri
Türkiye Kronik Viral Hepatit Tanı ve Tedavi Rehberi 2015

- Biyopsi: Fibrozisin evresi tedavi zamanlaması ve tedavi sonrası prognozu belirlemede önemli olduğu için tedaviye başlamadan önce karaciğer hastalığının şiddetinin belirlenmesi tavsiye edilmektedir (III) .
- Ancak histopatolojik bozukluk tedavi verilmesi ve tedavinin şeklinin belirlenmesi için yol gösterici olmadığı sürece tedavi öncesinde biyopsi yapıması gereksizdir. ISHAK veya METAVIR skorlaması kullanılmalıdır.
- Non-invaziv testler: Fibroscan(elastografi) , biyomarkırlar (Fibrotest, APRI ve benzeri)
- Karaciğer biyopsisinin yapılamadığı durumlarda (koagülasyon bozuklukları , karaciğer biyopsisinin komplikasyonlarından kaçınmak, hasta isteksizliği, vb) karaciğer fibrozisini değerlendirmede elstografi kullanılabilir. Ancak obezite bu yöntemin performansını düşürür. Kan testleri ile birlikte değerlendirme yapıldığında biyopsiye olan ihtiyaç azalır.
- Hem elastografi hem de biyomarkırlar sirozu ve fibrozisin olmadığını göstermede başarılıdırlar. Ancak orta dereceli fibrozisi tanımlamada güvenilirlikleri düşüktür.

Tedavi Kılavuzları

EASL:

- Tedavi öncesi karaciğer hastalığının şiddeti değerlendirilmelidir. Sirozu olan hastaların tanımlanması özellikle önemlidir çünkü prognoz etkilenebileceğinden tedavi rejimleri adapte edilebilir (A1)
- Fibrozis düzeyi ilk olarak non-invazif yöntemlerle değerlendirilebilir, kesin sonuç alınamayn/ belirsizlik durumunda veya potansiyel ek etiyoloji varlığında biyopsi yapılabilir. (A1)
- Tedavi almamış kronik hepatit C hastaları ile önceki tedavileri başarısız olmuş hastalar düzenli takip edilmelidir. (A1)
- Non-invazif fibrozis belirleme yöntemleri için en iyi kullanım alanı düzenli takip değerlendirmeleridir. (A1)

AASLD:

- HCV ile enfekte tüm hastalar için uygun tedavi stratejisi belirlemede ve gerekli ek tarama ihtiyacını belirlemede (ör; HSK taraması) görüntüleme, biyopsi veya non-invazif yöntemlerin kullanılarak ileri evre fibrozisin değerlendirilmesi önerilmektedir. Sınıf I, Düzey B
- Hepatik fibrozis düzeyini belirlemede non-invazif testler veya biyopsi önerilmektedir. Sınıf I, Düzey A

tween them on how and when to perform liver biopsy in CHC patients[106].

Cost is a major issue for implementation of liver biopsy in clinical practice, especially in light of the recent broader screening strategies for hepatitis C. In the United States the cost is currently $1032 and can increase up to $2745 if complications occur during and after the procedure[107]. In Canada, the mean cost of a complicated liver biopsy requiring hospitalization is $4579[108].

Liver biopsy and non-invasive tools for assessment of liver fibrosis across guidelines

Given the drawbacks of liver biopsy, non-invasive tools for assessment of liver fibrosis have attracted the attention of hepatologists. Table 3 compares guidelines in terms of recommendations for liver biopsy and/or non-invasive tools for the staging of liver fibrosis in HCV-infected patients. Overall, in spite of a previous consensus that a stage of liver fibrosis of at least F2 represents a de-

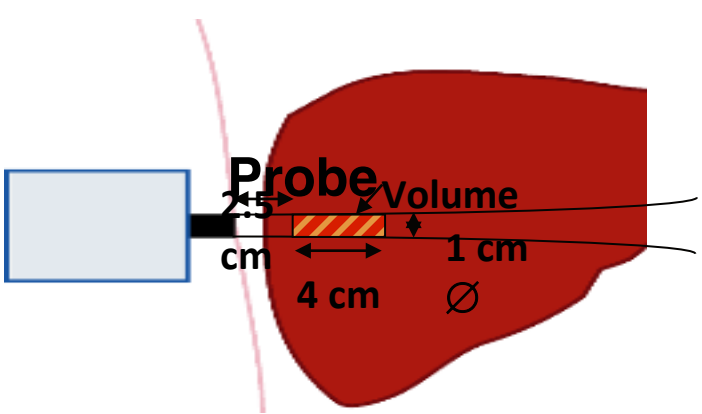
mends treatment for patients with a histolo
of F1 or above[109]. HCV patients with viral
1-3 can be treated regardless of the stage of
It is not compulsory for patients infected
genotypes 2 or 3 to have a liver biopsy in or
therapy. However, obtaining a liver biopsy bef
therapy could offer prognostic information. A
the APASL guidelines were issued, non-invasiv
were not recommended.

AASLD guidelines state that in CHC, li
should be considered if the patient and the
provider wish to know the fibrosis stage to en
formed decision on treatment options and/or
possible outcomes. A liver biopsy may be u
in persons infected with HCV genotypes 2 a
more than 80% of them achieve a sustained
response (SVR). There is, nevertheless, an o
gument on whether CHC patients with HCV
1 warrant a biopsy because of their lower

Sebastiani G, Gkouvatsos K, Pantopoulos K. Chronic hepati- tis C and liver fibrosis. *World J Gastroenterol* 2014; 20(32)

Liver stiffness measurement/ Transient Elastografi (Fibroscan)

KC elastisitesinin değerlendirilmesinde hızlı noninvaziv ve tekrarlanabilir bir yöntem



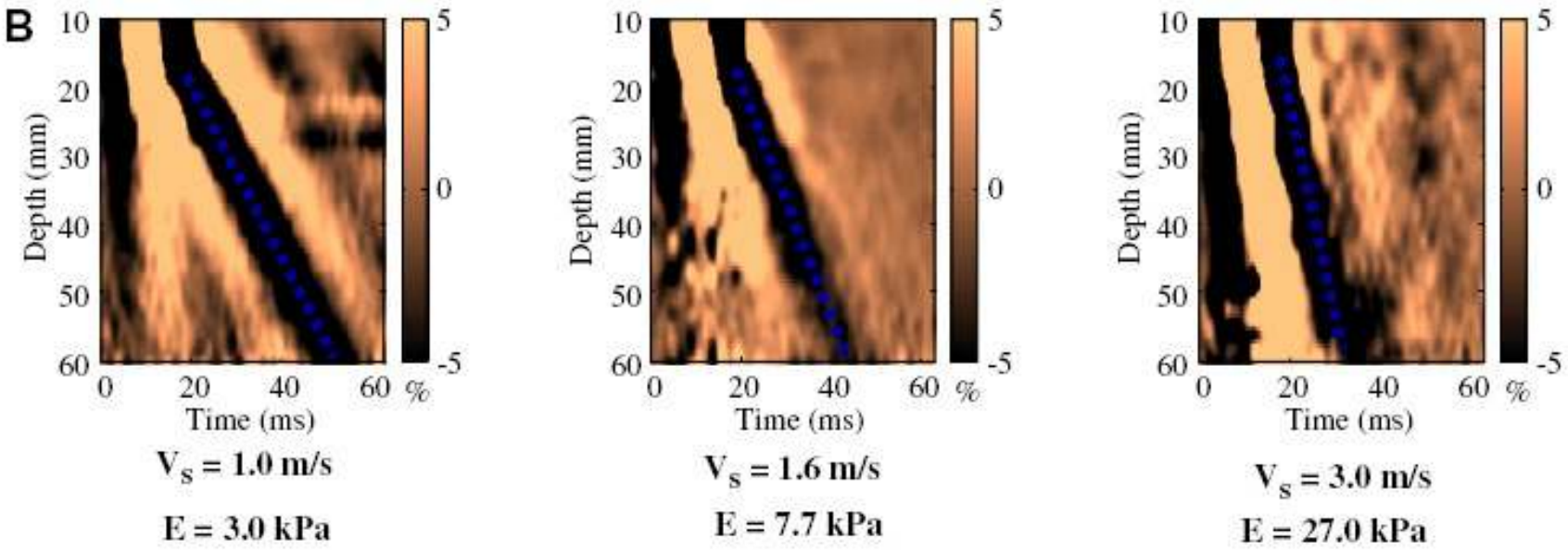
Sandrin et al. Ultrasound Med Biol 2003;29:1-8

Fibroscan (Elastografi)

- Ultrasonik prob ile düşük frekans ve amplitüdlü titreşimler gönderir
- Oluşan elastik dalgalar dokuda yayılır
- Dalganın iletim hızı dokunun sertliği ile ilişkilidir
- Esneklik (elastisite) ve sertlik (stiffness) saptanır
- Kilopascal (kPa) cinsinden sonuç verir
- Ölçülen karaciğer hacmi; 3 cm^3

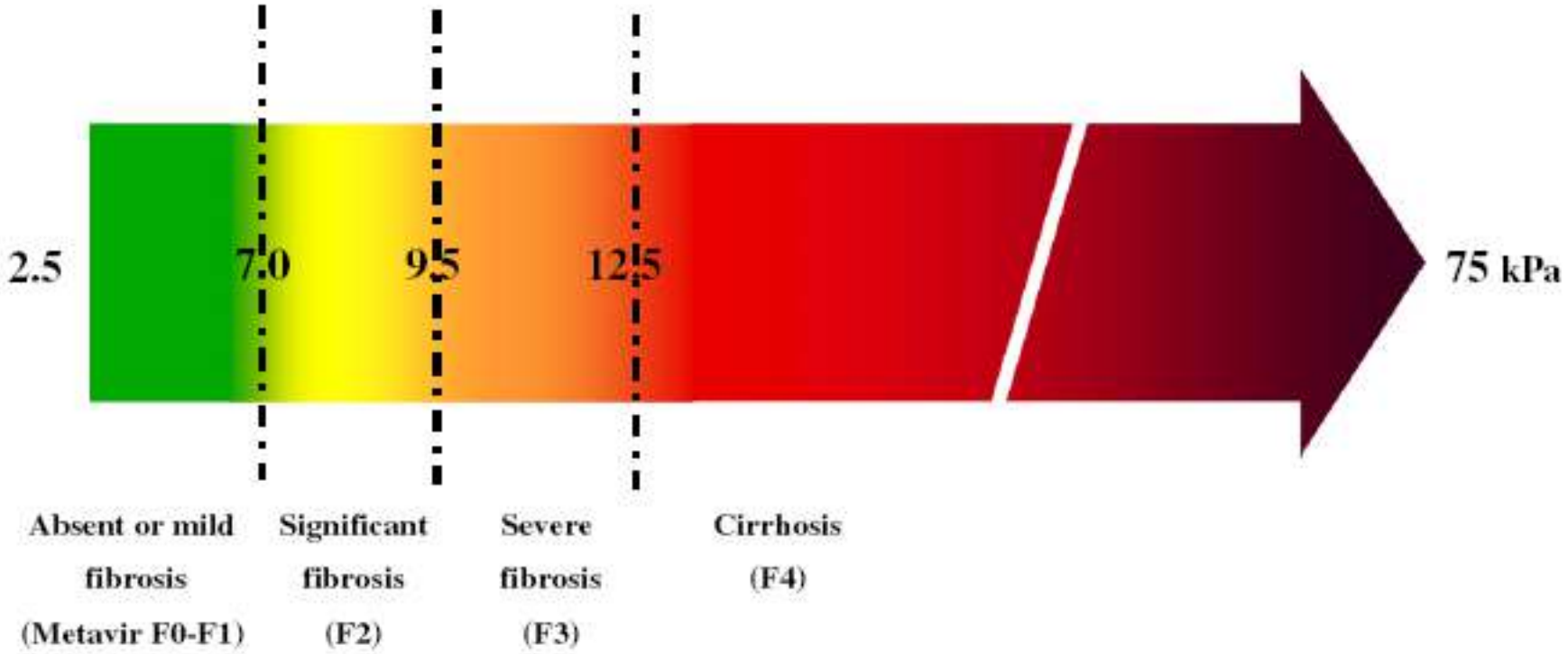
FibroScan

$E = 3 \rho v^2$



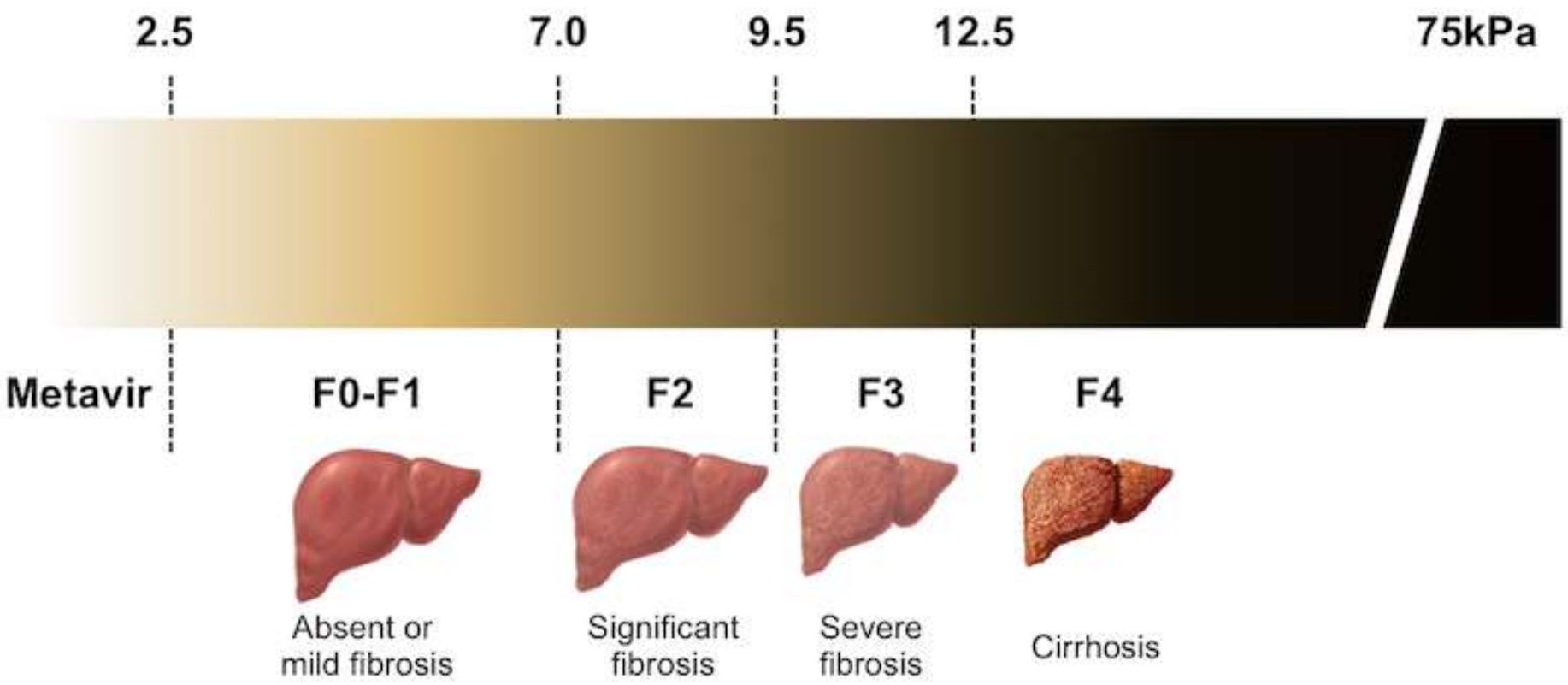
Journal of Hepatology 48 (2008) 835–847

FibroScan



Journal of Hepatology 48 (2008) 835–847

Castera Transient Elastography Breakpoints



require more operator training and expertise than FibroScan.

Castera: Determination of Liver Stiffness Cutoff Values with Transient Elastography

METAVIR Score	Optimal Cutoff*	Sensitivity	Specificity	PPV	NPV
F ≥ 2 (F0-1 vs. F2-3-4)	**7.1 kPa**	0.67	0.89	0.95	0.48
F ≥ 3 (F0-1-2 vs. F3-4)	**9.5 kPa**	0.73	0.91	0.87	0.81
F ≥ 4 (F0-1-2-3 vs. F4)	**12.5 kPa**	0.87	0.91	0.77	0.95

*Optimal Cutoff = value that provided higher total sensitivity and specificity
PPV = Positive Predictive Value
NPV = Negative Predictive Value

Hepatik Elastografinin Avantaj ve Dezavantajları

- Kolay
- İnceleme süresi < 5dk
- 10 ölçümün ortalaması alınıyor
- Transplant sonrası hastalığın rekürensini öngörme
- Özofagus varisleri, HVPG (hepatic venous pressure gradient) korelasyon
- MELD ve Childs-Pugh skorları ile artış
- Potensiyel eksiklikler: viseral yağ dokusu, steatoz, kolestaz

Elastografi ve Serum bazlı testlerin prediktif değeri

ROC eğirisi altında kalan alan (Area Under the ROC Curve) (Duyarlılık vs 1 – Özgüllük) Fibrosis belirleme metodlarına göre Metavir F0-1 vs F2-4[1]		
Yöntem	**AUROC**	**95% CI**
APRI	0.78	0.70-0.85
Elastografi	0.83	0.76-0.88
FibroTest	0.85	0.78-0.90
FibroTest + Elastografi	0.88	0.82-0.92

Geniş, çok merkezli çalışma verileri hepatik elastografinin anlamlı fibrozisi belirlemede efektif olmadığını ancak sirozu dışlamada efektif olduğunu göstermektedir.[2]

1. Castera L, et al. Gastroenterology. 2005;128:343-350.
2. Degos F, et al. EASL 2009. Abstract 96.

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	FIB-4 = age (yr) x AST [U/L]/(platelets [10^9/L] x (ALT [U/L])$^{1/2}$
	SHASTA index = -3.84 + 1.70 (1 if HA 41-85 ng/ml, 0 otherwise) + 3.28 (1 if HA >85 ng/ml, 0 otherwise) + 1.58 (albumin <3.5 g/dl 0 otherwise) + 1.78 (1 if AST >60 IU/L, 0 otherwise)
NAFLD	
	NAFLD Fibrosis Score (NFS) = (-1.675 + 0.037 x age (yr) + 0.094 x BMI (kg/m^2) + 1.13 x IFG/diabetes (yes = 1, no = 0) + 0.99 x ALT ratio - 0.013 x platelet count (x10^9/L) - 0.66 x albumin [g/dl])
	BARD score (BMI ≥28 = 1; AST/ALT ratio ≥0.8 = 2; diabetes = 1; score ≥2, odds ratio for advanced fibrosis = 17)

*Graded as 0–2.

summarized in Table 2. The FibroTest® (proprietary formula; Biopredictive, Paris, France, licensed under the name of Fibrosure® in the USA (LabCorp, Burlington, NC, USA)) was the first algorithm combining several parameters [21]. Several other scores or algorithms have been proposed in hepatitis C virus (HCV) [22–35], as well as in hepatitis B virus (HBV) [36,37], human immunodeficiency virus (HIV)-HCV coinfection [38,39], and NAFLD [40,41]. Four are protected by patents and commercially available: the FibroMeter® (Echosens, Paris, France), the FibroSpectII® (Prometheus Laboratory Inc. San Diego, CA, USA), the ELF® (Enhanced Liver Fibrosis Test, Siemens Healthcare, Erlangen, Germany) and the HepaScore® (PathWest, University of Western Australia, Australia). Non-patented methods use published models, based on routinely available laboratory values.

The practical advantages of analyzing serum biomarkers to measure fibrosis include their high applicability (>95%) [42], their good inter-laboratory reproducibility [43,44], and their potential widespread availability (non-patented) (Table 3). However, none are liver specific and their results may be influenced by changes in clearance and excretion of each individual parameters. For instance, increased levels of hyaluronate occur in the po dial state [45] or in aged patients with chronic inflamma cesses such as rheumatoid arthritis [46]. Also, the reproc of measurement of some parameters included in "indirec markers, such as aspartate aminotransferase (AST) level telet count, is questionable [47]. In addition, the interp of each test requires a critical analysis in order to avoid fa tive or false negative results. For instance, when using Fib the existence of hemolysis or Gilbert syndrome that ca false positive results (by a decrease haptoglobin or an in bilirubin, respectively) should be taken into accou Similarly, acute hepatitis can produce false positive r the aspartate-to-platelet ratio index (APRI), Forns ind or FibroMeter® tests, since all include serum levels o transferases in their formulas.

Liver stiffness measurement

Transient elastography

Liver fibrosis can be staged using 1-dimensional ultras (FibroScan(R), Echosens, Paris, France) [49], which meas

velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver. This velocity is directly related to tissue stiffness, called the elastic modulus (expressed as $E = 3 \rho v^2$, where v is the shear velocity and ρ is the density of tissue, assumed to be constant). The stiffer the tissue, the faster the shear wave propagates.

TE is performed on a patient lying supine, with the right arm elevated to facilitate access to the right liver lobe. The tip of the probe is contacted to the intercostal skin with coupling gel in the 9th to 11th intercostal space at the level where a liver biopsy would be performed. The operator, assisted by a time-motion image, locates a liver portion at least 6 cm deep and free of large vascular structures. The operator then presses the probe button to start the measurements (''shots''). TE measures LS in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 mm and 65 mm below the skin surface. The software determines whether each measurement is successful or not. When a shot is unsuccessful, the machine does not return a value. The entire procedure is considered to have failed when no value is obtained after ten shots. The final result of a TE session can be regarded as valid if the following criteria are fulfilled: 1) a number of valid shots of at least 10; 2) a success rate (the ratio of valid shots to the total number of shots) above 60%; and 3) an interquartile range (IQR, reflecting the variability of measurements) less than 30% of the median LS measurem (M) value (IQR/M ⩽0.30%) [50].

The results are expressed in kilopascals (kPa), and range f 1.5 to 75 kPa with normal values around 5 kPa, higher in men in patients with low or high body mass index (BMI) (U-sha distribution) [51–54].

Advantages of TE include a short procedure time (<5 n immediate results, and the ability to perform the test at the l side or in an outpatient clinic (Table 3). Finally, it is not a diffi procedure to learn which can be performed by a nurse or a t nician after minimal training (about 100 examinations) [Nevertheless, the clinical interpretation of TE results sh always be in the hands of an expert clinician and should be m with full knowledge of patient demographics, disease etio and essential laboratory parameters.

Although TE analysis has excellent inter- and intra-obse agreement [56,57] (with an intra-class correlation coeffic (ICC) of 0.98), its applicability is not as good as that of serum markers. In the largest TE series reported to date (n = 13, examinations), failure to obtain any measurement has b reported in 3.1% of cases and unreliable results (not mee manufacturer's recommendations) in 15.8% [58], mostly du patient obesity or limited operator experience. Similar res have been reported in a large series of Asian patients (n = 3

for the diagnosis of significant fibrosis [108–110]. As for patented tests, such as FibroTest®, FibroMeter®, and HepaScore®, they outperform the non-patented tests in HIV-HCV coinfection, particularly for significant fibrosis [111,112]. Importantly, one should be aware of false positive results with APRI and FIB-4 (related to HIV-induced thrombocytopenia) as well as with FibroTest® and HepaScore® (related to hyperbilirubinemia induced by the use of antiretroviral treatment such as atanazavir) or FibroTest® and Forns Index (related to increase in γ-glutamyl transferase induced by nevirapine) [111].

In patients with NAFLD, the NAFLD fibrosis score [40] is currently the most studied [85,113–118] and validated biomarker [119]. The NAFLD fibrosis score seems to perform better in Caucasians than Asians, probably related to the ethical difference in fat distribution and its influence on the BMI [102].

treatment-induced hyperbilirubinemia or increase
serum γ-glutamyl transferase levels (**A2**)

- FibroTest®, APRI and NAFLD fibrosis score are
most widely used and validated patented and no
patented tests (**A2**)

*Comparative performance of patented and non-pater
biomarkers for staging liver fibrosis*

When compared and validated externally in patients
atitis C [120–125], the different patented tests had sir
of performance in diagnosis of significant fibrosis. In
independent study (1370 patients with viral hepatitis

may be useful as an unrelated method.

The advantage of combining two unrelated methods, such as TE and serum biomarkers, over the combination of two serum biomarkers is that TE provides more direct measurement of the liver structure than biomarkers, and that there is no relationship between the applicability of TE (success rate and interquartile range) and that of a biomarker [204,211]. Also, the combination of TE and serum biomarkers might be more effective than the combination of two serum biomarkers for detecting significant fibrosis (significantly greater number of saved liver biopsies) [200,212]. However, this strategy has only been validated in studies of patients with hepatitis C, is more costly, and could be hampered by the lower applicability of TE, compared with biomarkers. Most importantly, in case of unexplained discordance of non-invasive tests, a liver biopsy should still be performed.

Fig. 2. Proposed algorithm for the use of transient elastography in treatment-naive patients with Hepatitis B.

once by non-invasive tests. Once a diagnosis of cirrhosis has been established, both AASLD and EASL guidelines recommend that those patients should be screened for PH and HCC [213,214]. Therefore all HCV patients need to be staged as part of routine HCV care to exclude cirrhosis. The diagnostic accuracy of TE for cirrhosis has been confirmed by multiple studies and meta-analyzes and has proven superior to that reported by serum biomarkers.

Recommendations

- All HCV patients should be screened to exclude cirrhosis by TE if available. Serum biomarkers can be used in the absence of TE (**A1**)
- HCV patients who were diagnosed with cirrhosis based on non-invasive diagnosis should undergo screening for HCC and PH and do not need confirmatory liver biopsy (**A1**)

HBV

In chronic hepatitis B, TE generally has a higher AUROC as compared to serum biomarkers for advanced liver fibrosis [198,202]. Among inactive carriers with normal transamir TE also has less fluctuation over time as compare FibroTest® or APRI score [155]. LS of <5–6 kPa often indi absent or minimal liver fibrosis [132,153]. On the other LS of >12–14 kPa often indicates liver cirrhosis (Tabl Among patients with intermediate LS measurements, accuracy of staging is lower. In doubtful cases, liver biop recommended (Fig. 2). Among chronic hepatitis B patients have elevated ALT levels or ALT flares, interpretation of LS surement should be taken with caution. LS can be mislead high among patients who have severe acute exacerbatic chronic hepatitis B, even 3–6 months after ALT has been no ized [215].

For HBeAg-positive patients, particularly among those are older than 35 years of age with high normal ALT l non-invasive assessment of liver fibrosis is useful to differer whether patients are in immune tolerance phase or already significant liver fibrosis secondary to immune clearance [21

In HBeAg-negative patients, the low replicative phase is cated by normal ALT level and low HBV DNA (<2000 IU/ml the other hand, the reactivation phase is characterized by vated HBV DNA levels with intermittent elevation of ALT l Patients who have repeated and prolonged reactivation higher risks of developing liver cirrhosis [217]. Non-inv assessment of liver fibrosis is preferred over liver biopsy a HBeAg-negative patients with low (<2000 IU/ml) or borde (>2000 to 20,000 IU/ml) HBV DNA and normal ALT levels, a

$$\textbf{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

$$\textbf{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

FibroIndex =

$$1.738 - 0.064 \times \text{platelet count } (10^4/\text{mm}^3) + 0.005 \times \text{AST (IU/L)} + 0.463 \times \text{gamma globulin (g/dL)}$$

Forns Index =

$$7.811 - 3.131 \times \ln(\text{platelet count } [10^9/\text{L}]) + 0.781 \times \ln(\text{GGT } [\text{IU/L}]) + 3.467 \times \ln(\text{age}) - 0.014 \times \text{cholesterol } [\text{mg/dL}]$$

ln = natural logarithm
GGT = gamma glutamyl transpeptidase

$$\textbf{HepaScore} = \frac{y}{y + 1}$$

$$y = \exp[-4.185818 - (0.0249 \times \text{age}) + (0.7464 \times \text{sex}) + (1.0039 \times \alpha2\text{-macroglobulin}) + (0.0302 \times \text{hyaluronic acid}) + 0.0691 \times \text{bilirubin}) - (0.012 \times \text{GGT})]$$

Units

age = years

sex (male = 1 and female = 0)

α2-macroglobulin (g/L)

hyaluronic acid (µg/L)

bilirubin (µmol/L)

GGT = gamma glutamyl transpeptidase (U/L)