AST-to-Platelet Ratio Index (APRI) as Marker in Liver Disease

14

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Contents

Abstract

Liver fibrosis observed in various chronic disorders is a risk factor of unfavorable prognosis and usually leads to cirrhosis. To date, liver biopsy is the gold standard for assessment of fibrosis. Its invasiveness and risk of hemorrhage incline to looking for noninvasive markers of liver fibrosis. The APRI index includes two simple and cheap laboratory tests performed routinely in clinical practice. Usefulness of this marker seems to depend on the etiology of liver damage. The predictive accuracy of APRI for significant fibrosis and cirrhosis was tested by the areas under the receiver operating characteristic curves (AUROC). The APRI

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score correlates significantly to fibrosis stage in patients with chronic hepatitis C. The APRI in patients with autoimmune hepatitis, chronic hepatitis B, and alcoholic liver disease is controversial and does not seem to have a diagnostic value in significant fibrosis. It showed promising results for predicting the presence of fibrosis in pediatric patients with NAFLD. Transient elastography, a noninvasive and objective but expensive method, showed higher performance in diagnosing significant fibrosis than APRI.

Keywords

APRI • Liver fibrosis • Cirrhosis • Viral hepatitis • Liver biopsy

List of Abbreviations

AIH	Autoimmune hepatitis
ALD	Alcoholic liver disease
ALT	Alanine aminotransferase
APRI	Aspartate aminotransferase-to-platelet ratio index
AST	Aspartate aminotransferase
ATD	α-1-antitrypsin deficiency
AUROC	Area under the receiver operating characteristic curve
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
HAART	Highly active antiretroviral therapy
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
INR	International normalized ratio
NAFLD	Nonalcoholic fatty liver disease
NPV	Negative predictive value
OV	Esophageal varices
PBC	Primary biliary cirrhosis
PPV	Positive predictive value
UDCA	Ursodeoxycholic acid

Key Facts

1. Fibrosis is observed in various chronic disorders of the liver.
2. Liver biopsy is regarded as the best method in the diagnostics of liver fibrosis.
3. Liver biopsy is an invasive procedure with a risk of hemorrhage, but the management and prognosis often depend on its result.
4. A noninvasive, painless and cheap test for assessing liver fibrosis is needed.
5. APRI index as a combination of serum parameters, AST and platelet count, is an easily available marker.
6. Its usefulness in diagnosing liver fibrosis of various origin was described.

Definitions of Words and Terms

APRI	The aspartate aminotransferase-to-platelet ratio index is inexpensive, simple marker with value in predicting liver fibrosis of various origin.
Ishak score	The system assessing the histopathological degree of liver fibrosis from 0 to 6 in patients with chronic liver infection.
Liver cirrhosis	A final stage of fibrosis with severe scarring of the liver and poor liver function tests. It is usually caused by alcohol, viruses, autoimmune liver diseases, and toxic metals.
Liver fibrosis	Histological change caused by chronic liver inflammation with increased synthesis of extracellular matrix but without lobular regeneration of the liver.
METAVIR score	A system assessing the degree of inflammation and fibrosis from 0 to 4 in liver biopsy specimen
Transient elastography	Fibroscan is a new noninvasive, painless method that quantifies liver fibrosis. It measures liver elasticity using both ultrasound and low-frequency elastic waves.

Introduction

Liver fibrosis is a result of chronic damage caused by various factors. The major etiologies in adults are chronic infections with hepatitis B (HBV), C (HCV), autoimmune hepatitis, nonalcoholic and alcoholic fatty liver disease, and alpha-1-antitrypsin deficiency. The other metabolic causes such us Wilson disease (WD) or cholesterol ester storage disease (CESD) are uncommon. As many as 25–45% of 400 million patients with chronic HBV infection die of cirrhosis and its complications (Sorrell et al. 2009), while 40% of patients with cirrhosis remain asymptomatic (Fattovich et al. 1997). To date, liver biopsy has been regarded as the gold standard for assessment of fibrosis. It allows to assess staging of liver fibrosis, grade of inflammation, steatosis, iron overload, and copper overload and to obtain information on comorbidities, e.g., autoimmune hepatitis. The treatment decisions in chronic viral hepatitis are usually guided by the results of liver biopsy. However, there are some limitations of this procedure. The percutaneous biopsy is a highly invasive, expensive procedure, prone to sampling errors and underestimation of cirrhosis. Significant hemorrhage after percutaneous liver biopsy may lead to death in exceptional cases. The result of percutaneous biopsy depends on the size of liver biopsy, number of biopsies, and pathomorphologist's experience. It inclines to looking for noninvasive markers identifying patients with liver fibrosis and suitable for serial

assessment during therapy. The aspartate aminotransferase-to-platelet ratio index (APRI) was first reported in 2003 by Wai et al. in a group of patients with liver fibrosis due to chronic hepatitis C (Wai et al. 2003). The APRI as a combination of serum parameters is a cheap, simple, and easily available marker. Both laboratory parameters are performed regularly in clinical practice. AST level usually rises with the progression of liver fibrosis and hepatocytes damage and reduced clearance. The changes of portal blood flow, splenomegaly, and altered production of thrombopoietin lead to a decrease in platelet counts. That is why APRI should correlate with progression of liver disease. There are some limitations of this parameter. The AST level rises late in disease progression. Similarly, platelet counts fall relatively late. On the other hand, AST levels are usually normal in compensated cirrhosis. The limitations of AST depend on the laboratory method of AST assessment (Tables 1, 2, 3, 4, 5, 6, 7, and 8).

Usefulness of this marker seems to be dependent on the etiology of liver damage. The idea that APRI could obviate liver biopsy was analyzed by numerous researchers in many studies concerning various liver disorders, but the results were conflicting. Most authors suggest that the sensitivity of APRI depends on the etiology of liver injury. The predictive accuracy of APRI in significant fibrosis and cirrhosis was tested by the areas under the receiver operating characteristic curves (AUROC).

Diagnostic ability of APRI for prediction of liver fibrosis was assessed in patients with various liver disorders. In chronic hepatitis C (CHC), the sensitivity of APRI for significant fibrosis ranges between 41% and 91% and for cirrhosis between 38.4% and 65.8%. The specificity for fibrosis ranges between 47% and 95% and for cirrhosis between 86.7% and 93%. The accuracy of APRI to detect significant fibrosis and cirrhosis in patients with chronic hepatitis C was assessed as 60–82% and 60–88.4% compared to 76.1% and 79.2% in chronic hepatitis B, respectively.

Table 1 Discriminant ability of APRI in patients with HCV infection

Author	Compared groups		AUROC
Chun-Tao Wai et al.	Non significant fibrosis	Significant fibrosis	0.8
	No cirrhosis	Cirrhosis	0.89
Snyder et al.	Nonsignificant fibrosis	Significant fibrosis	0.889
Loaeza-del-Castillo et al.	Fibrosis stages 0–1	Fibrosis stages 2–4	0.776
	Fibrosis stages 0–2	Fibrosis stages 3–4	0.803
	No cirrhosis	Cirrhosis	0.83
Shaheen and Myers et al.	Non significant fibrosis	Significant fibrosis	0.76
	No cirrhosis	Cirrhosis	0.82
Ngo et al.	Survival without HCV complication	Survival with HCV complication	0.87
	Survival without HCV death	Survival with HCV death	0.73
Yu et al.	No HCC	HCC	0.715–0.87
	Overall survival		0.53–0.87

Table 2 Discriminant ability of APRI in patients with HCV/HIV coinfection

Author	Compared groups		AUROC
Macias et al.	Non significant fibrosis	Significant fibrosis	0.73–0.8
	No cirrhosis	Cirrhosis	0.77–0.8

Table 3 Discriminant ability of APRI in patients with alcoholic liver disease

Author	Compared groups		AUROC
Lieber et al.	No cirrhosis	Cirrhosis	0.79
	Fibrosis stages 0–1	Fibrosis stages 2–4	0.7
Naveau et al.	No cirrhosis	Cirrhosis	0.67
	Fibrosis stages 0–1	Fibrosis stages 2–4	0.59
Nguyen-Khac et al.	Fibrosis stages 0–2	Fibrosis stages 3–4	0.43
	Fibrosis stages 0–1	Fibrosis stages 2–4	0.54
	No fibrosis	Any fibrosis	0.76

Table 4 Discriminant ability of APRI in patients with nonalcoholic fatty liver disease

Author	Compared groups		AUROC
Loaeza-del-Castillo et al.	Fibrosis stages 0–1	Fibrosis stages 2–4	0.564
	Fibrosis stages 0–2	Fibrosis stages 3–4	0.568
	No cirrhosis	Cirrhosis	0.599
Kim et al.	No fibrosis	Fibrosis	0.875

Table 5 Discriminant ability of APRI in patients with autoimmune hepatitis

Author	Compared groups		AUROC
Loaeza-del-Castillo et al.	Fibrosis stages 0–1	Fibrosis stages 2–4	0.602
	Fibrosis stages 0–2	Fibrosis stages 3–4	0.532
	No cirrhosis	Cirrhosis	0.599

Table 6 Discriminant ability of APRI in patients with α-1-antitrypsin deficiency

Author	Compared groups		AUROC
Bakula et al.	Fibrosis stages 0–1	Fibrosis stages 2–4	0.74
	No cirrhosis	Cirrhosis	0.51

Table 7 Discriminant ability of APRI in patients with biliary atresia

Author	Compared groups		AUROC
Yang et al.	Fibrosis stages 0–1	Fibrosis stages 2–4	0.75
	No cirrhosis	Cirrhosis	0.81
	No postoperative jaundice	Postoperative jaundice	0.67

Table 8 Discriminant ability of APRI in patients with HBV infection

Author	Compared groups		AUROC
Jin W et al.	Non significant fibrosis	Significant fibrosis	0.79
	No cirrhosis	Cirrhosis	0.75
Lebensztejn et al.	Fibrosis stages 0–2	Fibrosis stages 3–4	0.748
Celikbilek et al.	Nonsignificant fibrosis	Significant fibrosis	0.62
	No cirrhosis	Cirrhosis	0.67

Potential Applications to Prognosis, Other Diseases, or Conditions

Chronic Hepatitis C

It is estimated that approximately 3% of the world population is infected with HCV. In the United States, it is a leading cause of liver transplantation and liver-related mortality. Most patients are at risk of significant liver fibrosis and cirrhosis.

Wai et al., found that APRI >1.5 predicted significant fibrosis (Ishak score ≥3) and cirrhosis (Ishak score ≥5) with a high degree of accuracy: AUROC of 0.8–0.88 and 0.89–0.94, respectively (Wai et al. 2003). In a cohort study of adult, treatment-naïve patients with CHC, APRI predicted accurately fibrosis and cirrhosis in 51% and 81%, respectively.

Since that report, an increasing number of analyses have assessed usefulness of APRI in the diagnosis of liver fibrosis in HCV-infected patients. Other studies found lower accuracy of APRI.

In a systematic review of 22 studies ($n = 4{,}266$) in 2007, the summary AUCs of APRI for significant fibrosis were 0.76 and for cirrhosis were 0.82 (Shaheen and Myers 2007). An APRI cutoff value of 0.5 had acceptable accuracy to exclude significant fibrosis (81% sensitivity, 50% specificity) and allowed to avoid at least 30% of biopsies. For cirrhosis, the cutoff value of 1.0 had sensitivity of 76% and specificity of 71%. The accuracy of APRI to detect cirrhosis was greater in younger patients, in studies with higher proportion of males and in patients coinfected with HIV/HCV. As a predictor of fibrosis in HCV patients, APRI seemed to have moderate utility but may have played a role in exclusion of significant fibrosis in at least one-third and cirrhosis in three quarters of patients.

In another meta-analysis published by Lin et al in 2011, which evaluated 40 studies ($n = 8{,}739$) comparing APRI with liver biopsy, the summary AUROC of APRI for diagnosis of significant fibrosis and cirrhosis was 0.77 and 0.83, respectively (Lin et al. 2011). The accuracy was less than that described by Wai et al. An APRI threshold of 0.7 for significant fibrosis had sensitivity of 77% and specificity of 72%, and for cirrhosis, the threshold of 1.0 had sensitivity of 76% and specificity of 72%, respectively. A cutoff of 2.0 had better specificity (92%) but was less sensitive (46%). The accuracy of APRI to identify fibrosis compared to liver biopsy in HCV-infected patients was assessed in that meta-analysis as moderate. In contrast

to the previous analysis, APRI was found to be less accurate in HIV/HCV coinfection than in HCV monoinfection.

The usefulness of APRI to predict the risk of hepatocellular carcinoma (HCC) and mortality in HCV-infected patients after interferon-based therapy was also explored. The APRI and other simple noninvasive parameters like platelet count, AST, and alpha-fetoprotein were evaluated 6 months after the end of treatment in the group of 776 chronic hepatitis C patients treated with interferon and at baseline in 562 untreated patients, during follow-up at 4.75 (1.0–12.2) and 5.15 (1.0–16) years, respectively. The APRI was significantly higher in all patients after interferon treatment who developed HCC and in those who died. Based on the ROC analysis, AUC of APRI to predict the long-term outcome was 0.649–0.909. The APRI of >0.75 was correlated with the incidence of posttreatment risk of HCC and mortality for all patients treated with interferon. In the subgroup of patients who did not respond to the therapy, the cumulative incidence of HCC and mortality was significantly higher for APRI >1.5, among those who responded to interferon- for APRI >0.5, and in the subgroup without cirrhosis- for APRI >0.6. To conclude, APRI can predict long-term follow-up results with a high degree of accuracy in patients treated with interferon. In the subgroup of patients with preexisting cirrhosis, the power of APRI for predicting HCC and mortality was not strong enough. The limitation of the study was the change in hepatic fibrosis and APRI after antiviral treatment in the long-term follow-up.

APRI levels are important to reduce the number of liver biopsies as, according to the Mata-Marin results, patients with APRI of less than 0.4 very rarely have significant liver fibrosis (Mata-Marin et al. 2009).

HCV-infected patients were also examined with paired liver biopsies to find out if longitudinal changes in APRI may correlate with an increase in the stage of fibrosis. The APRI was examined together with another noninvasive marker of liver fibrosis, FIB-4. Both parameters predicted two-stage progression of liver fibrosis in the second biopsy. The ΔAPRI of 0.18 may suggest progression in fibrosis of at least one stage with positive predictive value (PPV) of 80% and negative predictive value (NPV) of 67%. The ΔAPRI and ΔFIB-4 could be useful for clinicians to reconsider the decision on antiviral therapy. However, a limitation of the study was a small number of patients and its retrospective nature. Interestingly, in the initial biopsy, APRI did not predict the progression of liver fibrosis.

The AUROC of APRI to detect significant fibrosis and cirrhosis in HCV-infected patients is worse than a fibroscan (transient elastography) (Mummadi et al. 2010). According to a meta-analysis by Shaheen et al., AUROC was 0.83 and 0.95, respectively (Shaheen et al. 2007). But still, fibroscan being expensive had a limited availability, especially in regions with high prevalence of HCV infection.

Patients with liver cirrhosis due to HCV infection are the main group of liver recipients in Western countries. As the infection usually recurs in the grafts, a noninvasive test for liver fibrosis is needed. In the literature, the usefulness of APRI in liver-transplanted patients with hepatitis C virus was evaluated and compared to other noninvasive tests: age-platelet index, aspartate aminotransferase to alanine aminotransferase ratio, Forns' fibrosis index, and Bonacini's discriminant

score. With AUROC of 0.81, APRI was the best test for discriminating patients with significant fibrosis (>2) in liver biopsy as compared to noninvasive methods mentioned above. The accuracy of APRI was higher in female recipients, with sensitivity of 91% and specificity of 75%, compared to 60% and 77% in men, respectively (Toniutto et al. 2007).

HIV-HCV Coinfection

HCV infection is a leading cause of morbidity in HIV-positive individuals, especially with the use of HAART and improvement of survival of HIV-infected patients (Singal et al. 2011). HIV-HCV coinfection is common in drug users as a result of shared routes of transmission.

The use of APRI in HIV-HCV coinfected patients was studied in fewer studies. Additionally, their limitations were small sample size and well-controlled HIV in the participants. The APRI performed better for biopsy size of ≥15 mm than ≥10 mm (AUROC for significant fibrosis 0.8 vs. 0.73, for cirrhosis 0.79 vs. 0.77, respectively) (Macias et al. 2006). According to Kelleher et al., AUROC was 0.71 in HIV/HCV coinfected patients, and the authors confirmed the need for liver biopsy size larger than 10 mm. The APRI predicted significant fibrosis with 91% certainty. Nine percent of patients were misclassified with high APRI (1.5) and F0 to F1 stage of liver fibrosis on the biopsy. A total of 27–34% of the patients could be potentially excluded from liver biopsy and treated for HCV. To sum up, the diagnostic accuracy of APRI was lower in coinfection HIV/HCV than in HCV monoinfection, which is in line with a previous meta-analysis (Mata-Marin et al. 2009).

The APRI of >1.5 was validated in adults with HIV-HCV coinfection as evidence of significant fibrosis, with high specificity but low sensitivity (Al-Mohri et al. 2005; Nunes et al. 2005; Kelleher et al. 2005). However, the best cutoff of APRI in pediatric population has not been established.

In a group of 1,012 perinatally HIV-infected Latin American children, the median of APRI was 0.29 (range, 0.05–29.67) and was elevated to >1.5 in 3.2% of patients (95% CI: 2.2–4.4%). There were factors associated with APRI >1.5: younger age, HBV coinfection, higher activity of alanine aminotransferase, lower concentration of total cholesterol, higher $\log_{10}$ current viral load, lower current CD4 count, lower nadir CD4 count, and the use of hepatotoxic non-antiretroviral medications. HCV infection did not increase the risk of APRI elevation.

Children with APRI of ≤1.5 had a better controlled HIV infection than patients with elevated APRI. Effective HIV treatment with HAART appeared to be beneficial for the liver, with a reduction in APRI, but long-term use of toxic non-antiretroviral drugs and comorbidities could have had an influence on liver outcome. A higher proportion of children with APRI of ≤1.5 experienced prior non-antiretroviral medications use compared to children with elevated APRI (85.3% vs. 65.6%; $p = 0.0053$) (Siberry et al. 2014). The prevalence of APRI >1.5 in a cohort of 451 perinatally HIV-infected children in the United States was 0.8% and was lower than in the previously mentioned cohort of children in Latin America. It could be due

to lower rates of other factors that contribute to liver damage, like other viral hepatitis or alcohol use. In both pediatric studies, longer antiretroviral treatment decreased the risk of APRI elevation.

Chronic Hepatitis B

The usefulness of noninvasive markers for significant liver fibrosis in patients with chronic hepatitis B (CHB) is not well established. Some authors found APRI as an accurate marker of fibrosis, but a few studies suggest that APRI may be of lower accuracy in liver fibrosis due to hepatitis B. It may be explained by wider regenerative nodules in CHB, more severe and less localized piecemeal necrosis, and fluctuating course with acute attacks of hepatitis B. Significant fibrosis was defined as stage ≥ 2 in liver biopsy according to the METAVIR system. In CHC, progression of fibrosis is more latent and piecemeal necrosis less localized. The AUROC of APRI in CHB patients in predicting fibrosis ranges from only 0.63 (Wai et al. 2006) and 0.708 (Seto et al. 2011) to 0.86 (Shin et al. 2008). A diagnostic tool is considered as good if AUROC is greater than 0.8. In the study of 89 HBV-infected patients, the APRI score was significantly higher in cirrhotic patients than in non-cirrhotic patients and was higher in significant fibrosis, but not statistically significant. The accuracy of the APRI score to determine cirrhosis was 72%, and the optimum APRI score cutoff point to identify such patients was 1.01 (Celikbilek et al. 2013). In another study, the value of APRI in identifying significant fibrosis and cirrhosis in HBV-infected patients was also limited, with AUROC of 0.62 and 0.67 for fibrosis and cirrhosis, respectively (Jin et al. 2012). In a recent meta-analysis, by Jin et al., AUROC of 0.79 and 0.75 was found. Some authors emphasize that APRI may be useful in the prediction of the absence of both cirrhosis and significant fibrosis, with a negative predictive value of over 90% in this group of patients.

To conclude, the APRI score did not seem to be as effective in determining fibrosis and cirrhosis as in CHC patients.

In children, such data are even more limited. Chronic HCV and HBV infections remain a rare problem in pediatric population, especially due to HBV vaccinations. But the pediatric population still needs a noninvasive marker of fibrosis to control treatment efficacy without liver biopsy, even more than adult population. Children usually require general anesthesia for liver biopsy and prolonged hospital stay to assess potential complications. McGoogan et al. evaluated APRI in predicting fibrosis and cirrhosis of the liver in 36 children with HCV or HBV infection compared to liver biopsy. The median APRI was 0.44 (0.24–0.97) in the group with HBV infection and 0.33 (0.20–0.44) among patients with hepatitis C. The area under the receiver operator characteristic curves was 0.71 for fibrosis and 0.52 for cirrhosis on liver biopsy. The authors concluded that APRI was moderately useful in predicting fibrosis in that group of children and could be a substitute for liver biopsy with AUC of 0.71 (McGoogan et al. 2010). Lebensztejn et al., in a group of 63 children with chronic hepatitis B virus, found an AUC of 0.74 and the highest

sensitivity and specificity of APRI for a cutoff of 0.59 (76.5% and 70%, respectively) (Lebensztejn et al. 2005).

Alcoholic Liver Disease (ALD)

The risk of end-stage liver disease in ALD increases with cumulative alcohol intake, but only minority of heavy drinkers suffer from advanced disease of the liver. The relationship between alcohol consumption and progression of liver injury in patients with and without HCV infection using APRI was evaluated in 1,308 patients. The sensitivity and specificity of APRI for significant fibrosis in HCV-positive patients (10.2%) were low: 35.6% and 29.7%, respectively. In HCV-negative patients ($N = 507$), the sensitivity of APRI for significant fibrosis was 13.2% and the specificity was 77.6%. In those groups of patients, APRI had a limited value in the diagnosis of fibrosis (Lieber et al. 2006). Heavy alcohol intake affects both AST and platelet count independently to the development of liver fibrosis. The role of alcohol in liver disease progression among HIV-infected patients was not clear. Hazardous drinking was found to be associated with increased APRI in a group of 1,358 HIV-infected patients, and 11.6% of them had APRI of >1.5. Viral hepatitis, male gender, and injection drug use as an HIV transmission route were other factors that predisposed to increased APRI. But among coinfected patients, increased APRI was found in 18.3%, and association with hazardous drinking was not confirmed. The authors defined minimal liver disease as APRI <0.4, significant liver disease as APRI >1.5, and 40 U/L as the upper limit of normal for AST (Chaudhry et al. 2009).

Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD seems to be the growing problem in industrialized countries. Liver fibrosis is one of the symptoms of nonalcoholic fatty liver disease. The wide spectrum of NAFLD symptoms ranges from simple steatosis, steatohepatitis, to liver cirrhosis. In adult patients with NAFLD, APRI had lower sensitivity than other noninvasive parameters: BARD, FIB-4 (age $\times$ AST level/platelet count $\times$ $\sqrt{}$ALT), NAFLD-fibrosis score and FibroMeter scores for advanced fibrosis (70% vs. 70.0%, 73.3%, 70.0%, 66.7%, and 66.7%, respectively), and higher specificity (74.5% vs. 66.4, 71.8%, 71.8%, and 74.5%, respectively). But no significant differences in sensitivity, specificity, or AUROCs were evident for those five scores in the diagnosis of advanced fibrosis (Subasi et al. 2015). Other studies demonstrated that such simple baseline noninvasive scores as APRI, NAFLD-fibrosis score, FIB-4 score, and BARD score can identify patients with an increased risk of liver-related complications and death. Among them, the NAFLD-fibrosis score was the most accurate, based on the area under the ROC curve and the analysis separating patient risk for a long-term outcome (Angulo et al. 2013).

Pediatric NAFLD is a different entity than NAFLD in adults. In children, histopathologic findings revealed portal inflammation and fibrosis rather than lobular

inflammation, ballooning, Mallory's hyaline, or perisinusoidal fibrosis. Among the hepatic fibrosis scores showing promising results in adult patients, only APRI and FIB4 revealed statistically significant differences between patients with mild and significant fibrosis. These two indexes might be regarded as useful methods to evaluate liver fibrosis in pediatric patients with NAFLD, while no single clinical or laboratory parameter can reflect the presence or severity of fibrosis in these patients (Yang et al. 2012). A recent study proved that FIB-4 index was a poor predictor of fibrosis and only APRI showed promising results for predicting the presence of any fibrosis with AUROC of 0.8 (Mansoor et al. 2015).

Retrospective studies assessed diagnostic ability of APRI for prediction of liver fibrosis compared to liver biopsy graded using the METAVIR scale (Beddosa and Poynard 1996) in viral chronic hepatitis or the Kleiner system for nonalcoholic fatty liver disease (Kleiner et al. 2005). Yilmaz et al. showed in 2011 that APRI was significantly associated with fibrosis scores in patients with NAFLD and chronic hepatitis C, but not in patients with chronic hepatitis B. In patients with CHC, APRI showed a higher sensitivity (72.7% vs. 60%) and lower specificity (62.4% vs. 73.3%), compared to NAFLD, respectively. The accuracy of APRI for the assessment of fibrosis score of 1–4 in patients with chronic hepatitis B was not acceptable with sensitivity of 55% and specificity of 75.4% (Yilmaz et al. 2011). According to the authors, the sensitivity of APRI depends on the etiology of liver injury. In case of NAFLD, APRI very rare reach value of more than 1. In such a condition, patients usually present mild to moderate increases in aminotransferases activity, and that is why APRI is elevated only in advanced stages of fibrosis as a result of gradual increases of AST in the presence of normal platelet counts. Besides, one should remember that alcohol consumption might have confounded association between APRI and stage of fibrosis, and it can depend on established maximal cutoff value of alcohol consumption (50 g/day for men and 30 g/day for women vs. 30 g/day for men and 20 g/day for women) to have a diagnose of nonalcoholic fatty liver disease (Loaeza-del-Castillo et al. 2008).

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune slowly progressing cholestatic disease, in which outcome is largely dictated by development of cirrhosis. Up to one-third of patients treated with ursodeoxycholic acid (UDCA) do not show biochemical response. Patients not responding to UDCA treatment had a poorer outcome. APRI was related to histological progression in liver biopsy samples, and APRI of >0.54 at diagnosis may predict progression to liver failure. Elevated APRI is also associated with a risk of adverse events independently of treatment. However, compared with transient elastography (TE), APRI showed a low performance in diagnosing significant fibrosis. According to some authors, APRI at baseline and after 1 year following therapy may be an additive tool in identifying patients at risk of adverse outcome (Trivedi et al. 2014; Joshita et al. 2014).

Autoimmune Hepatitis

There were no correlations between the APRI score and stages of liver fibrosis in patients with autoimmune hepatitis (AIH). For the diagnosis of significant fibrosis (METAVIR $\geq$2) and cirrhosis (METAVIR 4), APRI values delimited an AUC of 0.602 and 0.599. In AIH, the portal, periportal, and lobular inflammation are observed in all stages of fibrosis. High AST levels are due to recurrent exacerbations and the impact of immunosuppressive treatments, irrespective of fibrosis stage. Both factors affect the value of APRI (Loaeza-del-Castillo et al. 2008).

Alpha-1-Antitrypsin Deficiency

Liver fibrosis is often seen in patients with α-1-antitrypsin deficiency (ATD), and in the literature, it was found to be an indicator of bad outcome in this group of patients. As the groups of patients with ATD are small, there are data from one study concerning APRI effectiveness in liver fibrosis due to alpha-1-antitripsin deficiency. In the group of 21 Polish children with ATD, APRI was 0.22 (0.12–0.39), median (Q1-Q3). For advanced fibrosis, the optimal cutoff value for APRI was 0.26 while for cirrhosis – 0.33. The sensitivity was low, i.e., 0.60 (95%CI 0.41–0.77) and 0.83 (0.36–0.99), and the specificity was 0.87 (95%CI 0.60–0.98) and 0.31 (0.17–0.48), respectively, for advanced fibrosis and cirrhosis. The usefulness of APRI in detection of liver cirrhosis (AUROC 0.51) in alpha-1-AT deficiency in children was assessed as doubtful (Bakula et al. 2012).

Biliary Atresia

APRI was also investigated in infants with biliary atresia. It was found to be effective in diagnosing significant liver fibrosis, especially cirrhosis at presentation with the area under the receiver operator characteristic curve of 0.75 and 0.81, respectively. APRI of >0.60 before the Kasai procedure could predict jaundice persistence but neither occurrence of cholangitis after surgery nor development of esophageal varices. In cases with highly suspected biliary atresia, APRI may decrease the need for liver biopsy (Yang et al. 2015). APRI was correlated with age, size of spleen, and bilirubin concentration. Survival with a native liver was better for patients with the lowest APRI (Grieve et al. 2013).

APRI was proposed as the first-line test in the diagnostic approach named SAFE (sequential algorithm for fibrosis evaluation) biopsy algorithm in patients with chronic hepatitis B and C (Sebastiani et al. 2007). The aim of the algorithm was to reduce the number of liver biopsies. According to this algorithm, the biopsy was used as the third-line test in cases of no enough accuracy of APRI and Fibrotest. Fibrotest combines total bilirubin, GGTP, haptoglobin, alpha-2-macroglobulin, apolipoprotein A1, age, and gender. To date, it is validated in viral hepatitis B and C coinfection, HIV/HCV, ALD, and NAFLD. In the SAFE biopsy algorithm in

significant fibrosis (METAVIR≥F2), APRI of ≤0,5 had a low NPV, and such patients could not avoid liver biopsy. There was no need of biopsy when APRI was higher than 1.5. In the range between 0.5 and 1.5, further decision was dependent on Fibrotest: >0.49 confirmed the presence of significant fibrosis without the need of liver biopsy. The 1 cutoff of APRI excluded cirrhosis, while 2 cutoff together with fibrotest ≥0.75 confirmed cirrhosis. Combination of algorithms could help in monitoring of both, disease progression and antiviral therapies. APRI was also modified as Lok index with improvement of the diagnostic accuracy: alanine aminotransferase (ALT) and international normalized ratio (INR) were added (Lok et al. 2005).

APRI and Lok index were investigated with other noninvasive parameters of liver fibrosis in predicting the presence of esophageal varices (OV) in cirrhotic patients. But neither these simple tests nor fibroscan could predict the presence of OV and replace endoscopy with screening of esophageal varices (Sebastiani et al. 2010).

Summary Points

1. The diagnostic usefulness of the APRI score depends on the etiology of chronic liver injury.
2. The APRI score correlates significantly with fibrosis stage in patients with chronic hepatitis C.
3. It does not seem to have a diagnostic value in patients with autoimmune hepatitis, chronic hepatitis B, or alcoholic liver disease.
4. APRI showed promising results for predicting the presence of any fibrosis in pediatric patients with NAFLD.
5. Compared with transient elastography, which is a new, noninvasive, painless, and objective method, APRI showed low performance in diagnosing significant fibrosis.
6. Neither APRI nor fibroscan could predict the presence of OV and replace endoscopy with screening of OV.

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