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Editorial

# Chasing after novel non-invasive markers to identify advanced fibrosis in NAFLD

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See Article on Page 258

Non-alcoholic fatty liver disease (NAFLD) is an increasingly recognized cause of liver disease worldwide. It is estimated that approximately 20-30% of the population are affected by NAFLD in the world, including Korea.[1,2] The NAFLD spectrum ranges from relatively benign simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to liver cirrhosis and its complications such as liver failure and hepatocellular carcinoma.[1]

Patients with NASH-associated liver cirrhosis are considered to have a poor prognosis.[3] Therefore, it is important to screen subjects with advanced fibrosis. Currently, liver biopsy remains the gold standard for identifying the presence of steatohepatitis and liver fibrosis in patients with NAFLD. However, it is generally acknowledged that liver biopsy is limited by its invasiveness, cost, and potential procedure-related complications. Accordingly, there has been significant clinical interest in developing non-invasive tools for the detection of advanced fibrosis among patients with NAFLD.

Recently, transient elastography, which measures liver stiffness non-invasively, has been proposed for identifying advanced fibrosis in NAFLD.[4] Along with the assessment of the degree of liver fibrosis, a novel technology based on the properties of ultrasonic signals of transient elastography, referred to as the controlled attenuation parameter (CAP), has been proposed for the measurement of hepatic fat content.[5] Although the recent studies support the use of CAP as a non-invasive method for assessing the degree of hepatic steatosis, its use for identifying advanced fibrosis in NAFLD remains to be explored.[5,6]

Several clinical scoring systems have been developed for distinguishing advanced fibrosis in patients with NAFLD. Some of these scoring systems include the NAFLD fibrosis score, the BARD score, and the FIB-4 score.[7] The major advantage of using these scoring systems is that they are readily available from clinical and laboratory indices. Several biomarkers also have been investigated for the diagnosis of advanced fibrosis in NAFLD. Since the constituents of extracellular matrix (ECM) are expected to be released into circulation in advanced liver fibrosis, the ECM components have been studied for their association with liver fibrosis. These biomarkers include serum hyaluronic acid, type IV collagen 7S domain, tissue inhibitor of metalloproteinase 1 (TIMP1), and procollagen III (PIIINP).[8] However, studies on these scoring systems and biomarkers showed conflicting results and thus further validation is required prior to their widespread use.

The red blood cell distribution width (RDW), an automated

**Abbreviations:**

AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; ECM, extracellular matrix; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RDW, red cell distribution width

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measure of the variation of red blood cell sizes (i.e. anisocytosis), is routinely performed as part of a standard complete blood count. The RDW is utilized in the differential diagnosis of anemia, but otherwise has received little attention. Interestingly, several studies have recently reported that RDW was associated with adverse prognosis in patients with various conditions, including established cardiovascular diseases, cancer, and chronic lower respiratory diseases.[9,10]

In the current issue of Clinical and Molecular Hepatology, Kim et al have attempted to present the association of RDW with the degree of fibrosis in NAFLD.[11] In their retrospective cross-sectional analysis, study subjects with NAFLD were selected based on abdominal ultrasonography and history of alcohol intake from a large cohort of individuals who presented for a routine health check-up. The degree of fibrosis was determined according to the non-invasive fibrosis scoring systems including the BARD score and the FIB-4 score, and the relationship between the RDW and the degree of fibrosis was determined. Their results revealed a stepwise-increase in the RDW with increasing level of liver fibrosis. They concluded that higher RDW was associated with advanced fibrosis in NAFLD patients.

Although the concept per se is plausible for yielding novel insights on studying anisocytosis as an independent predictor of advanced fibrosis in NAFLD patients, there are several important issues that need attention.

First, although liver biopsy is currently considered as an imperfect gold standard due to interpretational variability and sampling errors, the diagnostic performance of a given non-invasive method still needs to be compared with liver biopsy to prevent further bias in this sort of cross-sectional study.[12] Although it seems inevitable to use other well-known non-invasive markers such as BARD score and FIB-4 score in this study instead of liver biopsy as a reference in the clinical setting of health check-up,[7] future studies would require validation of the significance of RDW for the prediction of advanced fibrosis in NAFLD using liver biopsy specimens.

Second, Kim et al[11] have excluded patients with liver cirrhosis in their study presumably because it was not easy to determine whether the patients had NASH-associated liver cirrhosis and also for the reason that the diagnostic performance of RDW in diagnosing liver cirrhosis was suboptimal. However, exclusion of subjects with liver cirrhosis when analysing the association between RDW and degree of fibrosis may result in spectrum bias, since advanced fibrosis and cirrhosis are not separate disease entity but belong to a continuous spectrum of liver fibrosis. Therefore, data from patients with liver cirrhosis should be considered for an accurate and complete validation of the utility of RDW in assessment of the degree of fibrosis in NAFLD in the future studies.

Finally, Kim et al[11] have assessed the association of RDW with the degree of fibrosis in NAFLD through cross-sectional analysis, as what most of other studies on non-invasive methods for evaluating liver fibrosis have employed. However, since liver biopsy –which is widely used as a gold standard for assessing liver fibrosis– is regarded as an 'imperfect' gold standard, the assessment of non-invasive methods for liver fibrosis through cross-sectional studies is limited.[13] In other words, it is futile to compare the performance of a non-invasive method using the area under the receiver operating characteristic curve in a cross-sectional study based on liver biopsy result as a reference. Therefore, it would be necessary to validate the diagnostic performance of non-invasive methods, such as RDW, in long-term follow-up longitudinal studies.

To summarize, despite the aforementioned issues, Kim et al[11] have conducted a meaningful pilot study for proposing the simple, readily-available RDW as a potential non-invasive prediction marker for assessment of advanced fibrosis in NAFLD patients in Korea. Future studies should be aimed at validating the diagnostic performance of RDW by comparing with other non-invasive methods in large-scale, biopsy-based longitudinal studies. Furthermore, once the diagnostic value of RDW has been validated, many questions will follow to be answered – what are the factors that affect the diagnostic accuracy of RDW; is the diagnostic performance of RDW affected by other etiologies of liver fibrosis; and so on. The widespread application of RDW in predicting advanced fibrosis in clinical practice will remain quiescent until the unanswered questions are fulfilled.

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## Conflicts of Interest

The authors have no conflicts to disclose.


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