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Editorial

# Three-Step Algorithm for Screening High-Risk Group of Metabolic Dysfunction-Associated Steatotic Liver Disease in General Population

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**See "Proposal of a Novel Serological Algorithm Combining FIB-4 and Serum M2BPGi for Advanced Fibrosis in Nonalcoholic Fatty Liver Disease" by Sang Yi Moon, et al. on page 283, Vol. 18, No. 2, 2024**

Recently, there has been a shift in the nomenclature of fatty liver disease from nonalcoholic fatty liver disease, which previously excluded other conditions, to steatotic liver disease. This new terminology serves as an umbrella term that acknowledges the coexistence of various diseases. Specifically, the updated term is metabolic dysfunction-associated steatotic liver disease (MASLD). It is reported that the prevalence of MASLD is approximately 30%.[1] The unmet need in MASLD disease is to establish an effective linkage-to-care pathway that identifies high-risk groups requiring treatment among MASLD patients and efficiently refers them to specialists.[2] Currently, most treatment guidelines recommend a two-step algorithm based on fibrosis index based on four factors (FIB-4), but there are several unresolved issues with this approach.[3] First, the FIB-4-based screening test for identifying high-risk groups requires further data into real practice in the general population, particularly in settings with a low prevalence of fibrosis. Recent studies have indicated that the accuracy of the FIB-4-based two-step algorithm conducted in primary care clinics with a low prevalence of advanced hepatic fibrosis was unsatisfactory.[4] In the case of FIB-4, while the negative predictive value is relatively high, the sensitivity is somewhat low, leading to a risk of missing a significant number of patients with advanced hepatic fibrosis. When applying FIB-4 to the general population with a low prevalence of advanced hepatic fibrosis, high sensitivity becomes more crucial than a high negative predictive value. To address this, it may be beneficial to consider lowering the cutoff of FIB-4 or integrating additional non-invasive tests (NITs) in the screening process for linkage to care in the general population. Secondly, in FIB-4-based screening, it is recommended that the intermediate to high-risk group be referred to tertiary centers. However, a study conducted based on a health check-up cohort found that the proportion of the intermediate to high-risk group is approximately 30% to 35%.[5] Considering that MASLD accounts for approximately 30% of the total population, the estimated number of referred subjects to tertiary centers would be around 9% of the total population. Given the constraints of the national healthcare system, this could lead to an excessive burden on referral centers. Additionally, considering that the positive predictive value in referred patients is less than 7%, there is a need to explore more effective strategies for identifying high-risk groups among MASLD patients in the general population.[6]

Recently, Moon *et al.*[7] reported in a study that advanced hepatic fibrosis can be predicted more effectively when Mac2 binding protein glycosylation isomer (M2BPGi) is used in conjunction with the FIB-4 test. When considering the high-risk group screening for MASLD algorithm, two key factors must be kept in mind. Firstly, over 80% of MASLD cases are managed in primary care settings. Secondly, to reduce the social burden, it's imperative to not only ensure linkage to care but also minimize unnecessary referral rates. NITs that predict intrahepatic

fibrosis using serological biomarkers like M2BPGi and Enhanced Liver Fibrosis score are pivotal for the current FIB-4 and imaging-based three-step algorithm system for several reasons. Firstly, in groups with a low prevalence of advanced hepatic fibrosis, such as the general population, the sensitivity and positive predictive value of FIB-4 are notably low. Therefore, sequential or combined testing of NITs becomes necessary to compensate for this limitation in FIB-4 performance.[8] There is currently no data indicating whether the proposed FIB-4 can be directly applied in the general population, where the prevalence of advanced hepatic fibrosis is estimated to be less than 5%. Many previous studies suggest that applying the current FIB-4 cutoff in the general population may be challenging, thus indicating the need for additional NIT tests that can complement it with a lower cutoff. Currently, there are NIT tests based on blood tests and NIT tests based on imaging. In settings requiring mass screening, such as primary care or health check-ups, serological NITs are considered more feasible than image-based testing. Secondly, given that vibration-controlled transient elastography or magnetic resonance elastography is not accessible to most primary care clinics or primary physicians responsible for managing the majority of MASLD patients, the incorporation of additional serological NITs into a 'three-step screening algorithm' is anticipated to mitigate the social burden by reducing unnecessary vibration-controlled transient elastography or magnetic resonance elastography tests and referrals. Moreover, when periodically monitoring the intermediate FIB-4 group in the primary care setting (typically every 1 to 2 years), it is believed that this approach can facilitate timely referrals when warranted.

In conclusion, additional serologic NIT tests such as Enhanced Liver Fibrosis, including M2BPGi, are anticipated to play a crucial role in identifying high-risk patients in the primary care setting, where MASLD patients are primarily managed and treated. Furthermore, the current two-step screening algorithm, primarily based on tertiary centers with a high prevalence of advanced hepatic fibrosis, needs to be customized to regions with a low prevalence of advanced hepatic fibrosis and limited access to medical resources.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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