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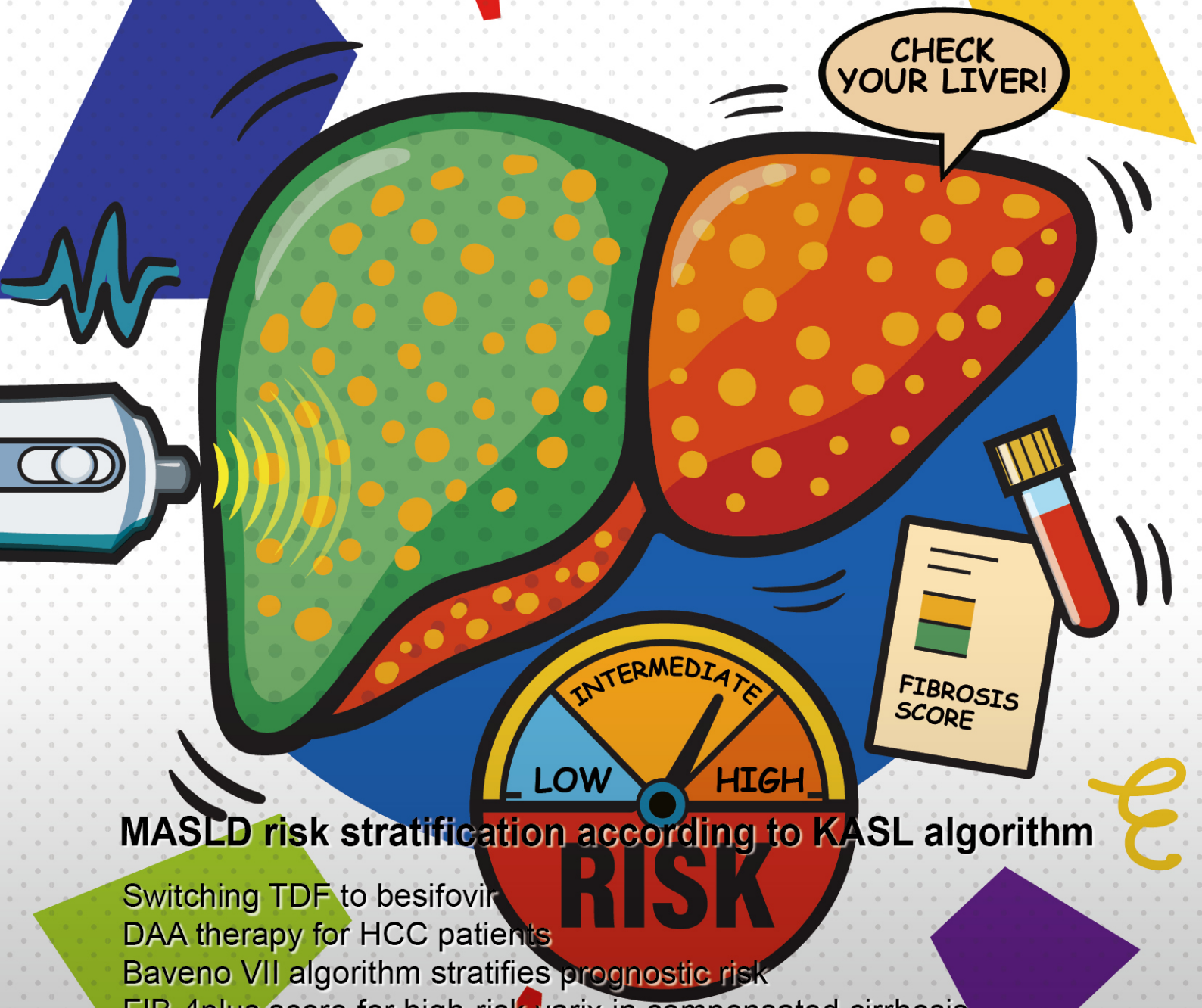

MASLD risk stratification according to KASL algorithm

Switching TDF to besifovir
DAA therapy for HCC patients
Baveno VII algorithm stratifies prognostic risk
FIB-4plus score for high-risk varix in compensated cirrhosis

KASL

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Original Article

Risk stratification by noninvasive tests in patients with metabolic dysfunction-associated steatotic liver disease

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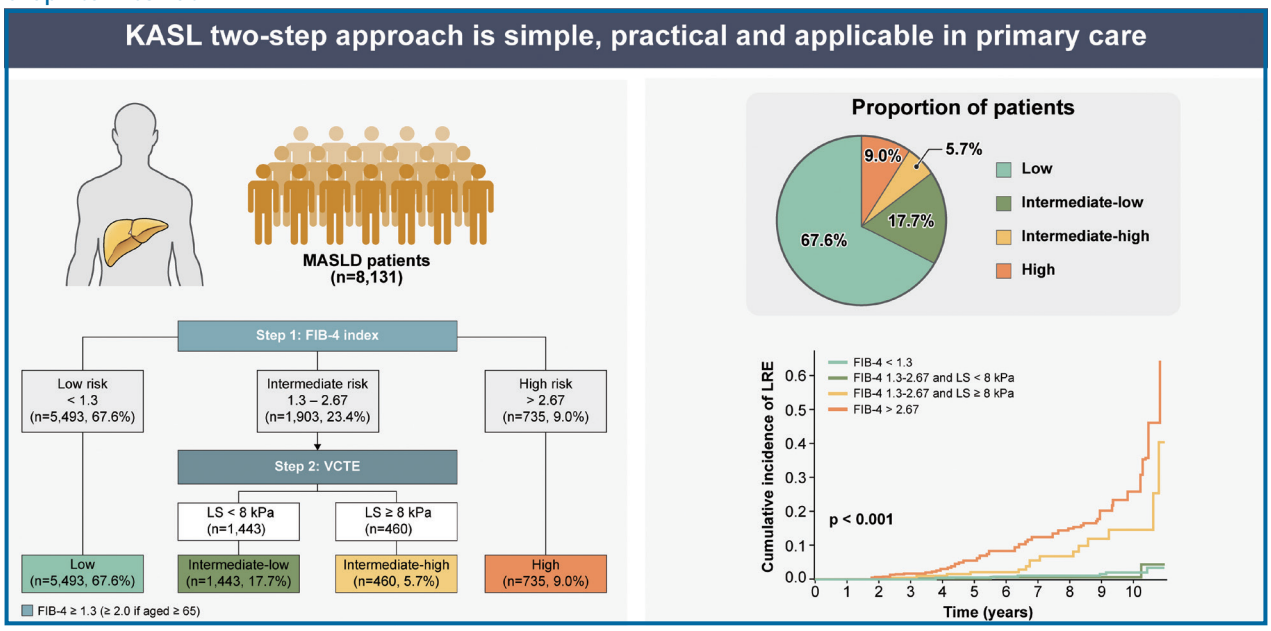
Graphical Abstract



Study Highlights

- This study validated the two-step risk stratification algorithm proposed by the Korean Association for the Study of the Liver (KASL) in a real-world MASLD cohort. The approach utilizes FIB-4 followed by transient elastography to identify patients at risk of liver-related events. The simplified three-risk group model preserved predictive accuracy while improving usability. These findings support the use of the KASL algorithm as a practical, noninvasive, and scalable tool in both primary and specialty care setting

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Background/Aims: Recently, the Korean Association for the Study of the Liver (KASL) introduced a noninvasive test-based approach that uses the fibrosis-4 (FIB-4) index followed by vibration-controlled transient elastography (VCTE) to identify high-risk patients with metabolic-associated steatotic liver disease (MASLD). In this study, the KASL two-step approach was validated by assessing the risk of liver-related event (LRE) development.

Methods: We retrospectively analyzed 8,131 patients with MASLD who underwent VCTE between 2012 and 2020. The index date was defined as the date of the VCTE measurement. Using the KASL two-step approach (FIB-4 index and subsequent VCTE), patients were stratified into four groups (low-, intermediate-low-, intermediate-high-, and high-risk groups). Outcomes, including LREs such as decompensation (DCC) or hepatocellular carcinoma (HCC) were evaluated.

Results: During the follow-up (median 46.6 months), 86 (1.1%) patients developed LREs (39 [0.5%] with DCC and 47 [0.6%] with HCC). The KASL two-step approach classified 67.6%, 17.7%, 5.7% and 9.0% of patients in the low-, intermediate-low-, intermediate-high-, and high-risk groups, respectively. The cumulative incidences of LREs increased proportionally according to risk stratification (0.07%, 0.10%, 0.29%, and 1.51% at 3 years and 0.35%, 0.26%, 1.94% and 5.46% at 5 years). The overall accuracy in predicting LREs ranged from 67.7–99.8%. The FIB-4 index and subsequent Agile3+, Agile 4, or FibroScan aspartate aminotransferase scores showed similar predictive abilities compared to the KASL approach.

Conclusions: The KASL two-step approach is an effective and practical method for risk stratification in patients with MASLD, optimizing patient care through early identification of high-risk individuals. **(Clin Mol Hepatol 2025;31:1018-1031)**

Keywords: Metabolic-associated steatotic liver disease; Noninvasive test; Transient elastography; Liver-related event

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a significant global health issue, paralleling the increased incidences of obesity, diabetes, and metabolic syndrome. Recent epidemiological studies suggest that MASLD affects approximately 30% of the global population, with different characteristics according to ethnicity and region.[1-3] The increasing burden of MASLD is a major concern due to its potential to progress to more severe liver diseases, including cirrhosis and hepatocellular carcinoma (HCC). Therefore, identifying high-risk patients within the MASLD population is critical for implementing early interventions and preventing disease progression.

In clinical practice, the identification of high-risk patients with MASLD is sometimes challenging. Although liver biopsy remains the gold standard of diagnosis, it is invasive, subject to inter-observer variability, and associated with potential complications.[4] Consequently, noninvasive tests (NITs) have gained attention as potential tools for assessing liver fibrosis and disease severity.[5,6] These tests range from simple biochemical markers and scoring systems such as the fibrosis-4 (FIB-4) index and non-alcoholic fatty liver disease fibrosis score to advanced imaging techniques such as vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE).[7] However, the clinical application of these tests is limited due to variations in their accuracy and the lack of consensus on their optimal use. Moreover, clinicians remain uncertain about which NITs are most appropriate for different clinical scenarios, leading to inconsistent patient management strategies.

To address these challenges, the Korean Association for

Abbreviations:

AGA, American Gastroenterological Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; DCC, decompensated cirrhosis; ELF, enhanced liver fibrosis; FAST, FibroScan AST; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; IQR, interquartile range; KASL, Korean Association for the Study of the Liver; LRE, liver-related event; LS, liver stiffness; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; NIT, noninvasive test; NPV, negative predictive value; VCTE, vibration-controlled transient elastography

the Study of the Liver (KASL) recently published a clinical practice guideline on the use of NITs in the assessment of MASLD.[8] This guideline aims to provide a standardized approach for clinicians, enhancing the accuracy of risk stratification and improving patient outcomes. The KASL guideline suggests evaluations using NITs, initially using the FIB-4, followed by the VCTE for those identified as at risk for advanced fibrosis. If the FIB-4 index is greater than 1.3, then VCTE can be performed. When the VCTE result is greater than 8 kPa, additional NITs, such as MRE, enhanced liver fibrosis (ELF), and the Agile score, should be considered. However, MRE and ELF are not easy to perform in clinical practice due to their high cost or issues with availability.

Therefore, we evaluated the performance of the KASL NIT-based two-step approach (FIB-4 index and subsequent VCTE) in identifying high-risk patients with MASLD and predicting liver-related events (LREs). In addition, the performance of the KASL two-step approach was compared with those of other algorithms.

MATERIALS AND METHODS

Study population

This study included patients with MASLD who underwent VCTE (FibroScan®; EchoSens, Paris, France) at least once from 2012 to 2020 (Fig. 1). This was a retrospective cohort study of patients with MASLD who had undergone VCTE examination at a single center (Severance Hospital, Seoul, Korea). The exclusion criteria were as follows: (1) younger than 19 years of age, (2) previous history of decompensated cirrhosis (DCC) or HCC, (3) previous liver resection or liver transplantation, or (4) unable to calculate the FIB-4 index

The study protocol was approved by the institutional review boards of the participating sites and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital (IRB number: 4-2023-0082). Informed consent was waived due to the retrospective nature of the study.

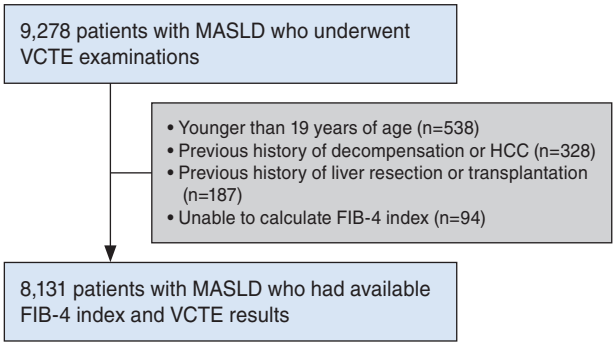

Figure 1. Flow chart of the study population. FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

Clinical assessment

MASLD was defined as the coexistence of steatotic liver disease diagnosed by histology, image tests, or VCTE (controlled attenuation parameter [CAP] values ≥248 dB/m)[9] and any of the cardiometabolic criteria, excluding other known causes of steatosis.[10] VCTE was performed on the right lobe of the liver through the intercostal space of patients lying in the dorsal decubitus position with the right arm in maximal abduction. VCTE was performed by experienced technicians blind to patients' clinical information (the technicians had previously performed more than 1,000 examinations). Only liver stiffness (LS) values with at least 10 successful measurements with a success rate of >60% were recorded. LS values with an interquartile range (IQR)-to-median ratio of >0.3 were excluded. The CAP value was previously described and was calculated only when the LS value was valid for the same signals. The FIB-4 index was calculated as (age [years]×aspartate aminotransferase [AST, U/L])/(platelets [10^9/L]×alanine aminotransferase [ALT, U/L])$^{1/2}$.[11] The patients were followed up every 6–12 months with laboratory tests and/or imaging studies. Cirrhosis is defined as a platelet count <150,000/μl and either ultrasonographic findings suggestive of cirrhosis (including a blunted, nodular liver surface accompanied by splenomegaly of >12 cm) or the presence of esophageal or gastric varices.[12] For patients with cirrhosis, follow-up examinations included imaging studies and tumor marker tests, such as alpha-fetoprotein.

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Two-step approaches

The KASL two-step approach involves performing FIB-4 index in patients with MASLD, followed by VCTE (Supplementary Fig. 1A). According to this two-step approach, the patients were classified into four groups of low-, intermediate-low-, intermediate-high-, and high-risk. Low-risk patients were defined as those with a FIB-4 index <1.3, with an age-specific cutoff of 1.3 for patients under 65 and 2.0 for those aged 65 and older, as recommended in the KASL guidelines.[8] The intermediate-low group was defined as those with FIB 1.3–2.67 and a subsequent LS value <8 kPa. The intermediate-high group was those with FIB 1.3–2.67 and an LS value ≥8 kPa. High-risk patients were defined as those with FIB-4>2.67.

The American Gastroenterological Association (AGA) guideline suggests the use of FIB-4 index followed by VCTE measurement with LS values categorized as ≤8.0, 8.1–12 kPa, and >12 kPa (Supplementary Fig. 1B). Other approaches have examined the use of the FIB-4 index in combination with the Agile 3+ score, Agile 4 score or FibroScan AST (FAST) score.[13,14]

Endpoints

The primary outcome was the development of LREs, which included DCC (uncontrolled ascites, variceal bleeding, hepatic encephalopathy or hepatorenal syndrome), or HCC. LREs were identified using medical records and ICD codes, and were observed up to the last follow-up. Uncontrolled ascites refers to ascites that is refractory to medical treatment, characterized by either the recurrence of ascites despite repeated paracentesis or the inability to manage ascites with optimal medical interventions, including diuretics.[15] The secondary outcomes were the individual development of DCC or HCC.

Statistical analysis

Variables were expressed using the means (standard deviation) or numbers (percentages) for continuous and categorical variables, respectively. Differences between variables were calculated using the paired *t*-test and McNemar's test for continuous and categorical variables, respectively. The index date was defined as the date of the first VCTE measurement. The cumulative incidence of LRE was analyzed by Kaplan–Meier curves, and statistical significance was determined using the log-rank test. To determine the predictive capacity for mortality of the KASL model in patients with MASLD, we focused on calculating the sensitivity, specificity, positive predictive value, and negative predictive value (NPV) at key time points, specifically at 3, 5 and 7 years. These values are detailed to provide a clear and comprehensive view of the model's prognostic performance at each interval, highlighting its accuracy in classifying patient outcomes. Time-dependent ROC curves were also generated and are provided in the Supplementary Figure to offer a visual representation of the model's performance trends across different time points. These curves serve as complementary data, enhancing the interpretability of the tabulated results.

Statistical analyses were performed using SPSS 25.0 for Windows (IBM Co., Armonk, NY, USA) and R (V.4.0.1, http://cran.r-project.org/). Two-tailed *P*-values of <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

After excluding 1,147 patients according to exclusion criteria, 8,131 patients with MASLD who had available FIB-4 and VCTE results were included in the analysis (Fig. 1). The baseline characteristics of the study population are summarized in Table 1. The mean age was 51.4 years with female accounting for 59.4% of the cohort. The median body mass index was 26.5 kg/m^2. The proportions of patients with diabetes and hypertension were 33.9% and 34.1%, respectively. The median AST, ALT, platelet count, and fasting glucose were 29.0 IU/L, 34.0 IU/L, 241×10^3/μl, and 104.1 mg/dL, respectively. The median FIB-4 score, LS by VCTE, Agile 3+, Agile 4, and FAST score were 1.10, 5.5 kPa, 0.15, 0.01, and 0.23, respectively. The median CAP value by VCTE was 300 dB/m.

Application of the KASL two-step approach

As described in Figure 2, 67.6% (n=5,493), 17.7% (n=1,443), 5.7% (n=460) and 9.0% (n=735) of patients were

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Table 1. Baseline characteristics of the study population (n=8,131)

Variable	Value
Demographic variables	
Age (yr)	51.4±14.0
Female sex	4,832 (59.4)
BMI (kg/m^2)	26.5 (24.3–29.1)
Diabetes	2,760 (33.9)
Hypertension	2,770 (34.1)
Number of metabolic risk factors	
1	1,088 (13.4)
2	1,848 (22.7)
3	2,237 (27.5)
4	2,442 (30.0)
5	516 (6.3)
Laboratory variables	
AST (IU/L)	29.0 (22.0–44.0)
ALT (IU/L)	34.0 (21.0–58.0)
Platelet count (10^3/μl)	241 (202–284)
Fasting glucose (mg/dL)	104.1 (95.1–122.2)
Noninvasive tests	
FIB-4 index	1.10 (0.74–1.65)
LS by VCTE (kPa)	5.5 (4.5–7.3)
CAP by VCTE (dB/m)	300 (274–329)
Agile 3+	0.15 (0.06–0.37)
Agile 4	0.01 (0.00–0.04)
FAST score	0.23 (0.10–0.45)

Values are expressed as mean±standard deviation, number (%), or median (interquartile range).
Metabolic risk factors: (1) BMI ≥23 kg/m^2, (2) diabetes, HbA1c ≥5.7, or fasting blood glucose ≥100, (3) blood pressure ≥130/85 or the use of antihypertensive medications (4) TG ≥150 or the use of lipid lowering medications, (5) HDL <40 mg/dL (male) or <50 mg/dL (female), or the use of lipid lowering medications.
ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuated parameter; FAST, FibroScan AST; FIB-4, fibrosis-4; HDL, high-density lipoprotein; LSM, liver stiffness measurement; TG, triglyceride; VCTE, vibration-controlled transient elastography.

classified as low-, intermediate-low-, intermediate-high-, and high-risk, respectively. Patients in the high-risk group tended to be older (mean 64.6 years vs. 47.7–58.1 years), female (57.7% vs. 37.6–49.6%), and had higher AST (median 56.0 IU/L vs. 26.0–50.0 IU/L) and fasting glucose (median 109.2 mg/dL vs. 102.2–111.2 mg/dL) compared with the other lower-risk groups (Table 2).

Fibrotic burden showed a progressive increase across the intermediate-high and high-risk groups when assessed using the FIB-4 index, Agile 3+, and Agile 4 scores, as well as LS values, with significant differences between the risk groups (P<0.001 for all). However, the low- and intermediate-low-risk groups had similar levels of fibrotic burden. Specifically, the FIB-4 index medians were 0.86, 1.67, 1.90, and 3.74; Agile 3+ scores were 0.09, 0.23, 0.67, and 0.77; and Agile 4 scores were 0.01, 0.02, 0.16, and 0.26 across the risk groups. For LS values, the medians were 5.3 kPa, 5.1 kPa, 10.8 kPa, and 9.1 kPa, respectively. The FAST score and CAP score also demonstrated significant differences between the risk groups, with FAST score medians of 0.18, 0.23, 0.62, and 0.58, and CAP scores of 303 dB/m, 289 dB/m, 314 dB/m, and 291 dB/m. However, no consistent or sequential increase was observed across all the risk groups.

Clinical outcomes

During the follow-up period (median 46.6 months [IQR 24.0–67.1]), 86 (1.1%) patients developed LREs, including 39 (0.5%) patients with hepatic decompensation and 47 (0.6%) with HCC. Patients who developed LREs (n=86) were older (60.8 years vs. 51.4 years) and had higher AST levels (39.5 IU/L vs. 29.0 IU/L), lower platelet counts (159x10^3/μ vs. 242x10^3/μl), higher FIB-4 indices (2.97 vs. 1.09), higher LS values (16.5 kPa vs. 5.5 kPa), lower CAP scores (285 dB/m vs. 300 dB/m), and higher Agile 3+ (0.91 vs. 0.15), Agile 4 (0.49 vs. 0.01), and FAST (0.64 vs. 0.23) scores compared with those without LREs (all P<0.05, Supplementary Table 1).

According to the KASL two-step approach, the 3-, 5- and 7-year cumulative incidences of LREs were 0.07% (95% confidence interval [CI] 0.02–0.20), 0.35% (95% CI 0.18–0.64), and 0.96% (95% CI 0.53–1.64) in the low-risk group, 0.10% (95% CI 0.01–0.57), 0.26% (95% CI 0.05–0.92), and 0.5% (95% CI 0.13–1.43) in the intermediate-low risk group, 0.28% (95% CI 0.03–1.48), 1.94% (95% CI 0.71–4.32), and 5.51% (95% CI 2.51–10.2) in the intermediate-high risk group, and 1.51% (95% CI 0.71–2.85), 5.46% (95% CI 3.43–8.15) and 12.40% (95% CI 8.38–17.3) in the high-risk group (Figs. 2, 3A).

The 3-, 5- and 7-year cumulative incidences of HCC were 0.03% (95% CI 0.00–0.15), 0.22% (95% CI 0.09–0.47) and 0.84% (95% CI 0.42–1.51) in the low-risk group, 0.00%,

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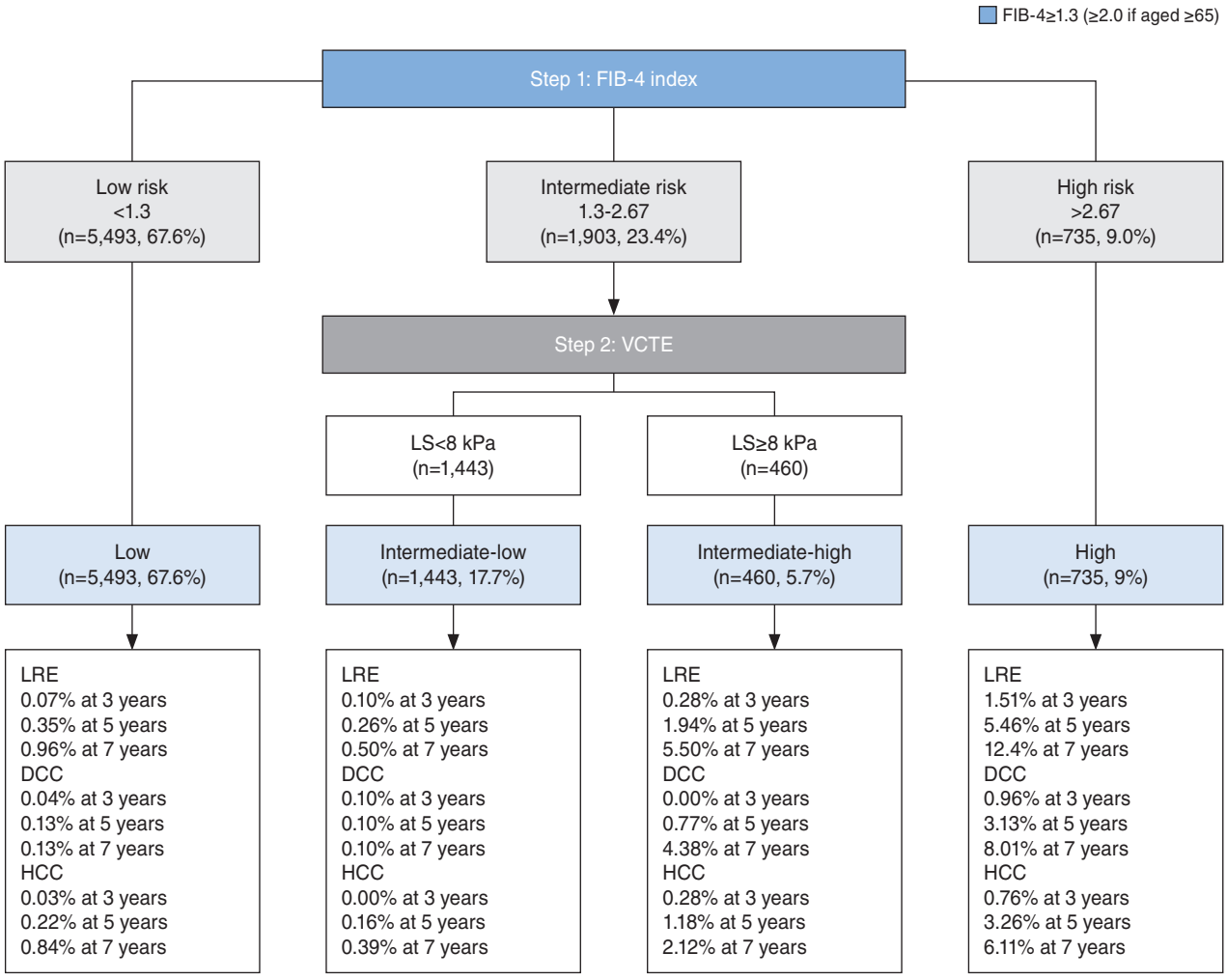

Figure 2. Application of the KASL two-step approach in our MASLD cohort. DCC, decompensated cirrhosis; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; KASL, Korean Association for the Study of the Liver; MASLD, metabolic dysfunction-associated steatotic liver disease; LRE, liver-related event; LS, liver stiffness; VCTE, vibration-controlled transient elastography.

0.16% (95% CI 0.02–0.86), and 0.39% (95% CI 0.08–1.36) in the intermediate-low risk group, 0.28% (95% CI 0.03–1.48), 1.18% (95% CI 0.31–3.32), and 2.12% (95% CI 0.61–5.46) in the intermediate-high risk group, and 0.76% (95% CI 0.26–1.85), 3.26% (95% CI 1.74–5.53) and 6.11% (95% CI 3.48–9.76) in the high-risk group, respectively (Figs. 2, 3B).

The 3-, 5- and 7-year cumulative incidences of DCC were 0.04% (95% CI 0.01–0.15), 0.13% (95% CI 0.04–0.34) and 0.13% (95% CI 0.04–0.34) in the low-risk group, 0.10% (95% CI 0.01–0.57), 0.10% (95% CI 0.01–0.57), and 0.10% (95% CI 0.01–0.57) in the intermediate-low risk group, 0.00%, 0.77% (95% CI 0.15–2.58), and 4.38% (95% CI 1.69–9.09) in the intermediate-high risk group, and 0.96% (95% CI 0.37–2.13), 3.13% (95% CI 1.67–5.32) and 8.01% (95% CI 4.75–12.30) in the high-risk group, respectively (Figs. 2, 3C).

Prognostic performance of KASL approach

At 3 years, the sensitivity and NPV of the low-risk group in identifying patients unlikely to develop LREs were 75.6% (95% CI 49.4–91.6) and 99.9% (95% CI 99.8–100), respectively (Table 3). The specificity of the high-risk group was 100%. The overall accuracy of the KASL two-step approach ranged from 67.7% (95% CI 66.6–68.7) to 99.8% (95% CI 99.7–99.9). Compared with other algorithms such as AGA, FIB-4 index–Agile 3+, FIB-4 index–Agile 4, or FIB-4 index–FAST, the KASL two-step approach was non-infe-

Table 2. Comparisons among different risk groups according to KASL algorithm

Variable	Low (n=5,493)	Intermediate-low (n=1,443)	Intermediate-high (n=460)	High (n=735)	*P*-value
Demographic variables					
Age (yr)	47.7±14.0	58.1±8.6	55.2±10.8	64.6±10.4	<0.001*
Female sex	2,068 (37.6)	579 (40.1)	228 (49.6)	424 (57.7)	<0.001†
BMI (kg/m^2)	26.7 (24.4–29.3)	25.7 (24.0–27.7)	27.8 (25.3–30.9)	26.1 (24.0–28.8)	<0.001*
Diabetes	1,731 (31.5)	509 (35.3)	231 (50.2)	289 (39.3)	<0.001†
Hypertension	1,665 (30.3)	532 (36.9)	228 (49.6)	345 (46.9)	<0.001†
Number of metabolic risk factors					<0.001†
1	835 (15.2)	158 (10.9)	28 (6.1)	67 (9.1)	
2	1,296 (23.6)	321 (22.2)	67 (14.6)	164 (22.3)	
3	1,513 (27.5)	406 (28.1)	118 (25.7)	200 (27.2)	
4	1,537 (28.0)	468 (32.4)	185 (40.2)	252 (34.3)	
5	312 (5.7)	90 (6.2)	62 (13.5)	52 (7.1)	
Laboratory variables					
AST (IU/L)	26.0 (20.0–36.0)	33.0 (24.0–48.0)	50.0 (35.0–72.0)	56.0 (38.0–86.0)	<0.001*
ALT (IU/L)	33.0 (22.0–58.0)	30.0 (19.0–52.0)	49.0 (29.0–84.5)	33.0 (19.0–56.0)	<0.001*
Platelet count (10^3/μl)	262 (229–300)	205 (180–233)	206 (178–243)	164 (129–203)	<0.001*
Fasting glucose (mg/dL)	102.2 (94.1–119.1)	105.0 (96.0–123.1)	111.2 (99.1–133.0)	109.2 (97.1–127.2)	<0.001*
Noninvasive tests					
FIB-4 index	0.86 (0.62–1.11)	1.67 (1.44–2.07)	1.90 (1.58–2.31)	3.74 (3.06–4.86)	<0.001*
LS by VCTE (kPa)	5.3 (4.4–6.6)	5.1 (4.3–6.2)	10.8 (8.9–14.1)	9.1 (6.3–14.8)	<0.001*
CAP by VCTE (dB/m)	303 (276–333)	289 (267–318)	314 (283–344)	291 (260–316)	<0.001*
Agile 3+	0.09 (0.04–0.20)	0.23 (0.13–0.40)	0.67 (0.46–0.83)	0.77 (0.52–0.93)	<0.001*
Agile 4	0.01 (0.00–0.04)	0.02 (0.01–0.04)	0.16 (0.08–0.32)	0.26 (0.10–0.59)	<0.001*
FAST score	0.18 (0.08–0.36)	0.23 (0.12–0.41)	0.62 (0.47–0.76)	0.58 (0.39–0.75)	<0.001*

Values are expressed as mean±standard deviation, number (%), or median (interquartile range).
ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuated parameter; FAST, FibroScan AST; FIB-4, fibrosis-4; KASL, Korean Association for the Study of the Liver; LSM, liver stiffness measurement; VCTE, vibration-controlled transient elastography.
*One-way ANOVA, †chi-square test.

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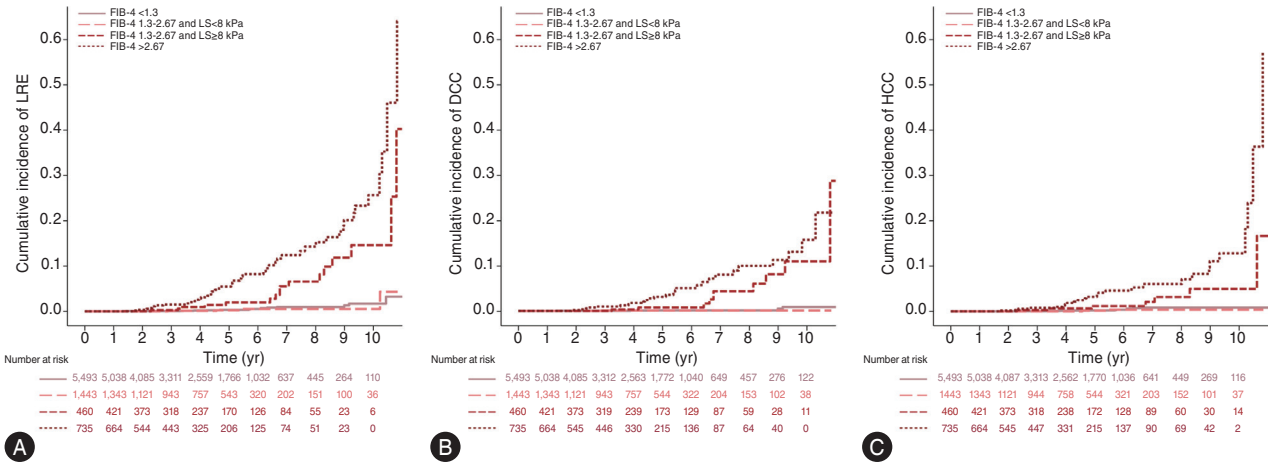

Figure 3. Cumulative incidences of (A) LREs, (B) DCC, and (C) HCC according to risk calculated using the KASL two-step approach. DCC, decompensated cirrhosis; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; KASL, Korean Association for the Study of the Liver; LRE, liver-related event.

rior to ruling out or predicting LRE development among patients with MASLD.

At 5 years, the sensitivity and NPV of the low-risk group in ruling out LREs were 70.2% (95% CI 54.3–82.3) and 99.8% (95% CI 99.7–99.9), respectively. The specificity of the high-risk group was 100%, and the overall accuracy of the high-risk group was 99.5% (95% CI 99.4–99.7). The robust prognostic performance of the KASL two-step approach was still sustained over a 5-year period.

At 7 years, the sensitivity and NPV of the low-risk group were 65.7% (95% CI 53.2–76.4) and 99.6% (95% CI 99.4–99.8), respectively. The specificity of the high-risk group was 68.3% (95% CI 67.3–69.3), and the overall accuracy remained consistent over the extended follow-up period.

Simplified KASL algorithm

Given the similarity in fibrotic and steatotic burdens between the low-and intermediate-low-risk groups, we reclassfied patients into three simplified risk categories: low- (n=5,493) and intermediate-low-risk (n=1,443) as the low-risk group (n=6,936), intermediate-high-risk as the intermediate-risk group (n=460), and high-risk as the high-risk group (n=735) (Supplementary Table 2). Patients in the high-risk group tended to be older (mean 64.6 years vs. 49.8–55.2 years) and female predominant (57.7% vs. 38.2-49.6%) and had lower BMIs (mean 26.1 kg/m^2 vs. 26.5-27.8 kg/m^2), higher AST levels (56.0 IU/L vs. 27.0-50.0 IU/L), lower platelet counts (164×10^3/μl vs. 206-249×10^3/μl), and higher FIB-4 indices (3.74 vs. 0.98-1.90), Agile 3+ scores (0.77 vs. 0.11-0.67), and Agile 4 scores (0.26 vs. 0.01-0.16) compared with the low- and intermediate-risk groups (all P<0.001). Although the distinction between referral and non-referral groups remains unchanged, the simplified classification system offers primary care physicians a more practical and efficient tool for risk stratification and patient management.

Regarding the simplified KASL two-step approach, the sensitivity and NPV for the low-risk group were 68.0% and 99.9% at 3 years and 66.4% and 99.8% at 5 years, respectively (Supplementary Table 3). The specificity of the high-risk group was 100%, and the overall predictive accuracies for the high-risk group were 99.8% at 3 years and 99.5% at 5 years.

According to the simplified KASL approach, the 3-, 5- and 7-year cumulative incidences of LRE were 0.08% (95% CI 0.03–0.19), 0.33% (95% CI 0.18–0.57), and 0.85% (95% CI 0.50–1.39) in the low-risk group, 0.28% (95% CI 0.03–1.48), 1.94% (95% CI 0.71–4.32), and 5.51% (95% CI 2.51–10.20) in the intermediate risk group, and 1.51% (95% CI 0.71–2.85), 5.45% (95% CI 3.43–8.14), and 12.4% (95% CI 8.37–17.3) in the high-risk group (Supplementary Fig. 2). The incidence rates of HCC were 0.02% (95% CI 0–0.12) at 3 years, 0.21% (95% CI 0.09–0.42) at 5 years, and 0.73% (95% CI 0.39–1.26) at 7 years. The incidence rates of DCC were 0.06% (95% CI 0.02–0.16) at 3 years, 0.12%

Table 3. Prognostic performance of the KASL and other algorithms in patients with MASLD

Method	Risk	Patients	LRE	Sensitivity	Specificity	PPV	NPV	Overall accuracy
3 years								
KASL	Low	3,314	3	75.6 (49.4–91.6)	67.7 (66.6–68.7)	3.8 (2.0–7.0)	99.9 (99.8–100)	67.7 (66.6–68.7)
	Intermediate-low	944	1	68.0 (41.2–86.5)	85.4 (84.6–86.2)	7.4 (4.0–14.0)	99.9 (99.8–100)	85.4 (84.6–86.1)
	Intermediate-high	319	1	62.3 (36.2–82.8)	91.1 (90.4–91.7)	11.1 (6.0–22.0)	99.9 (99.8–100)	91.0 (90.4–91.6)
	High	451	8	0 (0–22.8)	100 (100–100)	-	99.8 (99.7–99.9)	99.8 (99.7–99.9)
AGA	Low	4,258	4	68.0 (41.2–86.5)	85.4 (84.6–86.2)	7.4 (4.0–14.0)	99.9 (99.8–100)	85.4 (84.6–86.1)
	Intermediate	203	1	61.5 (35.5–82.3)	89.0 (88.3–89.6)	8.9 (4.0–17.0)	99.9 (99.8–100)	88.9 (88.2–89.6)
	High	567	8	0 (0–22.8)	100 (100–100)	-	99.8 (99.7–99.9)	99.8 (99.7–99.9)
FIB-4–Agile 3+	Low	4,125	5	59.8 (34.0–81.1)	83.3 (82.4–84.1)	5.7 (3.0–11.0)	99.9 (99.8–100)	83.2 (82.4–84.0)
	Intermediate	252	0	60.5 (34.7–81.6)	87.7 (86.9–88.3)	7.8 (4.0–15.0)	99.9 (99.8–100)	87.6 (86.9–88.3)
	High	651	8	0 (0–0.228)	100 (100–100)	-	99.8 (99.7–99.9)	99.8 (99.7–99.9)
FIB-4–Agile 4	Low	4,464	5	61.1 (35.2–82.0)	89.2 (88.5–89.8)	9.0 (5.0–18.0)	99.9 (99.8–100)	89.1 (88.4–89.8)
	Intermediate	80	0	62.0 (35.9–82.6)	90.5 (89.9–91.2)	10.4 (5.0–20.0)	99.9 (99.8–100)	90.5 (89.8–91.1)
	High	484	8	0 (0–22.8)	100 (100–100)	-	99.8 (99.7–99.9)	99.8 (99.7–99.9)
FIB-4–FAST	Low	4,041	4	70.3 (43.4–88.0)	80.5 (79.6–81.3)	5.7 (3.0–11.0)	99.9 (99.8–100)	80.5 (79.6–81.3)
	Intermediate	405	1	62.6 (36.4–83.0)	88.4 (87.6–89.0)	8.5 (4.0–17.0)	99.9 (99.8–100)	88.3 (87.6–89.0)
	High	582	8	0 (0–22.8)	100 (100–100)	-	99.8 (99.7–99.9)	99.8 (99.7–99.9)
5 years								
KASL	Low	1,776	10	70.2 (54.3–82.3)	67.9 (66.9–68.9)	1.02 (0.7–1.5)	99.8 (99.6–99.7)	67.9 (66.9–68.9)
	Intermediate-low	545	2	66.4 (50.5–79.3)	85.8 (85.0–86.5)	2.14 (1.5–3.1)	99.8 (99.7–99.9)	85.7 (84.9–86.4)
	Intermediate-high	175	5	55.4 (39.8–70.0)	91.4 (90.5–92.0)	2.93 (1.9–4.4)	99.8 (99.6–99.9)	91.2 (90.6–91.8)
	High	227	21	0 (0–0)	100 (100–100)	-	99.5 (99.4–99.7)	99.5 (99.4–99.7)
AGA	Low							
	Intermediate	111	12	66.5 (50.6–79.3)	85.8 (85.0–86.5)	2.15 (1.5–3.1)	99.8 (99.7–99.9)	85.7 (84.9–86.4)
	High	291	26	0 (0–9.2)	100 (100–100)	-	99.5 (99.4–99.7)	99.5 (99.4–99.7)
FIB-4–Agile 3+	Low	2,246	13	62.8 (46.9–76.3)	83.6 (82.8–84.4)	1.76 (1.2–2.6)	99.8 (99.7–99.9)	83.5 (82.7–84.3)
	Intermediate	143	1	62.5 (46.7–76.1)	88.0 (87.3–88.7)	2.39 (1.6–3.5)	99.8 (99.7–99.9)	87.9 (87.1–88.6)
	High	334	24	0 (0–0.092)	100 (100–100)	-	99.5 (99.4–99.7)	99.5 (99.4–99.7)
FIB-4–Agile 4	Low	2,437	14	63.4 (47.5–76.8)	89.5 (88.8–90.2)	2.76 (1.9–4.1)	99.8 (99.7–99.9)	89.4 (88.7–90.1)
	Intermediate	43	3	55.0 (39.5–69.6)	90.8 (90.2–91.4)	2.74 (1.8–4.2)	99.8 (99.6–99.9)	90.7 (90.0–91.3)
	High	243	21	0 (0–9.2)	100 (100–100)	-	99.5 (99.4–99.7)	99.5 (99.4–99.7)

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Table 3. Continued.

Method	Risk	Patients	LRE	Sensitivity	Specificity	PPV	NPV	Overall accuracy
FIB-4–FAST	Low	2,193	12	68.0 (52.1–80.6)	80.8 (79.9–81.7)	1.64 (1.1–2.4)	99.8 (99.7–99.9)	80.8 (79.9–81.6)
	Intermediate	232	5	56.3 (40.6–70.7)	88.6 (87.9–89.3)	2.27 (1.5–3.4)	99.8 (99.6–99.9)	88.5 (87.8–89.2)
	High	298	21	0 (0–9.2)	100 (100–100)	-	99.5 (99.4–99.7)	99.5 (99.4–99.7)
7 years								
KASL	Low	653	16	65.7 (53.2–76.4)	68.4 (67.3–69.4)	1.5 (1.1–2.1)	99.6 (99.4–99.8)	68.3 (67.3–69.3)
	Intermediate-low	205	3	59.5 (46.9–70.9)	86.4 (85.6–87.1)	3.2 (2.3–4.4)	99.6 (99.5–99.8)	86.2 (85.4–86.9)
	Intermediate-high	93	9	47.8 (35.8–60.1)	91.9 (91.3–92.5)	4.3 (3.0–6.1)	99.6 (99.4–99.7)	91.6 (90.9–92.1)
	High	107	33	0 (0–5.9)	100 (100–100)	-	99.2 (99.0–99.4)	99.2 (99.0–99.4)
AGA	Low	858	19	59.5 (46.9–70.9)	86.4 (85.6–87.1)	3.2 (2.3–4.4)	99.6 (99.5–99.8)	86.2 (85.4–86.9)
	Intermediate	56	3	55.3 (42.9–67.1)	89.9 (89.3–90.6)	4.0 (2.9–5.5)	99.6 (99.5–99.7)	89.7 (89.0–90.3)
	High	144	39	0 (0–5.9)	100 (100–100)	-	99.2 (99.0–99.4)	99.2 (99.0–99.4)
FIB-4–Agile 3+	Low	847	20	59.9 (47.4–71.3)	0.3 (0.2–0.4)	1.4 (1.0–1.9)	0.4 (0.3–0.7)	84.0 (83.2–84.8)
	Intermediate	49	2	56.5 (44.0–68.2)	0.3 (0.2–0.5)	5.0 (3.6–6.9)	0.4 (0.2–0.5)	88.4 (87.6–89.0)
	High	162	39	0 (0–5.9)	0.8 (0.6–1.0)	-	0.8 (0.6–1.0)	99.2 (99.0–99.4)
FIB-4–Agile 4	Low	921	22	57.4 (44.9–69.0)	90.2 (89.5–90.8)	4.2 (3.1–5.8)	99.6 (99.5–99.8)	89.9 (89.3–90.6)
	Intermediate	23	4	53.0 (40.7–65.0)	91.5 (90.8–92.1)	4.5 (3.2–6.3)	99.6 (99.4–99.7)	91.2 (90.5–91.8)
	High	114	35	0 (0–5.9)	100 (100.0–100.0)	-	99.2 (99.0–99.4)	99.2 (99.0–99.4)
FIB-4–FAST	Low	813	20	59.9 (47.4–71.3)	81.4 (80.5–82.2)	2.4 (1.7–3.3)	99.6 (99.5–99.7)	81.2 (80.3–82.0)
	Intermediate	100	7	50.8 (38.6–62.9)	89.2 (88.5–89.8)	3.4 (2.4–4.8)	99.6 (99.4–99.7)	88.9 (88.2–89.6)
	High	145	4	0 (0–5.9)	100 (100–100)	-	99.2 (99.0–99.4)	99.2 (99.0–99.4)

Values are expressed as number or percentage (95% confidence intervals).
AGA, American Gastroenterological Association; FAST, FibroScan AST; FIB-4, fibrosis-4; KASL, Korean Association for the Study of the Liver; LRE, liver-related event; MASLD, metabolic dysfunction-associated steatotic liver disease; NPV, negative predictive value; PPV, positive predictive value.

(95% CI 0.05–0.29) at 5 years, and 0.12% (95% CI 0.05–0.29) at 7 years (Supplementary Fig. 3).

Comparison of AUCs according to the different approaches

The KASL two-step approach showed an integrated time-dependent AUC of 0.801 (c-index 0.880) in predicting LREs (Supplementary Fig. 4A). The similar AGA approach using FIB-4 and an LS cut-off value of 10 kPa showed an integrated time-dependent AUC of 0.807 (c-index 0.920). Substituting the LS value with the Agile 3+ (AUC 0.815, c-index 0.901), Agile 4 (AUC 0.792, c-index 0.923), and FAST scores (AUC 0.776, c-index 0.885) as the second step showed good LRE prediction ability. Moreover, the simplified KASL approach (AUC 0.807) showed a similar AUC compared with different NIT approaches (AGA 0.807, FIB-4–Agile 3+ 0.815, FIB-4–Agile 4 0.792, FIB-4–FAST 0.776) (Supplementary Fig. 4B). The AUCs of FIB-4 alone and liver stiffness measurement alone are 0.796 and 0.835, respectively.

DISCUSSION

In this study, which was based on a large and diverse spectrum of patients with MASLD, we evaluated the effectiveness of the KASL two-step approach in assessing LREs in patients with MASLD. Our results demonstrated that the KASL two-step approach, consisting of the FIB-4 index and VCTE, effectively stratified patients into risk categories with significant differences in the cumulative incidence of LREs, including DCC and HCC. In our cohort, a significant proportion of patients were categorized as low-risk (67.6%) or intermediate-low-risk (17.7%), with very low cumulative incidences of LREs over the 3- to 7-year follow-up period. Conversely, high-risk patients, who accounted for 9.0% of the cohort, had a notably higher risk of developing LREs. These findings are consistent with previous reports showing that higher FIB-4 scores and LS values by VCTE are associated with a greater risk of fibrosis progression and liver-related mortality among patients with MASLD.

Our current study has several clinical implications. First, our study builds upon these findings by independently validating the recently published KASL NIT guidelines in a Korean cohort. Given the growing emphasis on non-invasive fibrosis assessment, real-world validation is essential. The simplicity of this two-step approach based on FIB-4 index and subsequent use of VCTE makes it particularly appealing for clinical application. In 2021, the AGA recommended a two-step clinical care pathway for the assessment of MASLD.[16] The AGA two-step method classified low-, indeterminate-, and high-risk groups according to their FIB-4 index and subsequent LS values. We initially classified patients with low-, intermediate-low-, intermediate-high- and high-risk groups according to the KASL recommendation. Our study highlights the effectiveness of the KASL two-step approach in predicting LREs, with high-risk patients showing a higher incidence of LREs. Early identification of these patients allows for proactive management strategies, potentially improving patient outcomes and reducing the burden of advanced liver disease.

Second, in contrast to our expectation, there were no significant differences between low- and intermediate-low-risk groups. To simplify the algorithm, we also validated the simplified KASL approach with low-, intermediate-, and high-risk groups. We can confirm that LREs increased based on risk stratification by FIB-4 and LS values. However, this approach did not reflect the changes in fibrotic burden over time. Not only baseline fibrosis but also changes in fibrotic burden are important for predicting LRE development in patients with MASLD. A retrospective study showed that longitudinal changes in the FIB-4 score were associated with disease progression in patients with MASLD. High FIB-4 scores at baseline and 3 years were associated with > 50-fold higher risk of HCC than persistently low FIB-4 values. To overcome the low sensitivity of the FIB-4, changes in the LS value can also be used to predict the prognosis of patients with MASLD. Changes in the LS value over 3 years also could predict clinical outcomes in patients with MASLD. LS value changes and the platelet count were independent factors in predicting the development of cirrhosis or HCC. However, the number of events was small (8.6%), and the 3-year follow-up was not sufficient to monitor disease progression in all MASLD fibrosis groups. In addition, the overall risk of LREs was low in our study, even among high-risk patients, when using non-invasive tests for hepatic steatosis. This contrasts with biopsy-based cohorts, which show a higher risk of LREs.

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However, VCTE-based cohorts better reflect routine clinical practice, capturing a broader patient population. Biopsy cohorts typically include patients with more advanced disease, leading to higher LRE risks. This underscores the value of non-invasive tests for managing MASLD in real-world settings.

Third, fibrotic burden, as assessed by LS value, FAST score, and steatotic burden, as evaluated by CAP score showed differences between groups, but did not show sequential increase across the groups. This discrepancy may be due to the multifactorial nature of MASLD, where fibrosis progression is influenced by various factors, including metabolic comorbidities and inflammation, which may not always correlate with steatosis or CAP score.[17,18] Additionally, the relationship between fibrosis and steatosis is complex, as some patients with advanced fibrosis may have mild steatosis and vice versa. The relatively small number of high-risk patients in our cohort might have limited the ability to detect gradual increases in these parameters. Furthermore, fibrosis and steatosis may not follow a linear progression, and the baseline measurements used may not fully capture their dynamic nature over time. Longitudinal monitoring could provide a clearer understanding of how these factors evolve and interact in MASLD. Finally, treatment interventions or lifestyle factors during follow-up could have influenced the observed fibrotic and steatotic burden.

Fourth, the combination of FIB-4 and Agile score could be applied to classify the risk of patients with MASLD. The Agile score has shown strong power for predicting the development of LREs. A recent study showed that single or serial Agile scores are highly accurate in predicting LREs among patients with MASLD.[9] In particular, Agile 3+ and Agile 4 scores classified fewer patients between the low and high cutoffs than most other fibrosis scores. Agile scores also showed the highest discriminatory power in predicting LREs. The incidences of LREs were 0.6 per 1,000 person-years in patients with persistently low Agile 3+ scores and 30.1 per 1000 person-years in patients with persistently high Agile 3+ scores. These data supported the importance of NIT assessment and serial monitoring using NITs. However, the complexity and intricate formula required for the calculation of the Agile score can pose challenges for everyday clinical use. Therefore, although the Agile score enhances risk stratification, its application might be limited due to these practical difficulties. Simplifying the formula or integrating it into user-friendly methods such as the KASL two-step method could improve its usability in routine practice.

Although complex algorithms like Agile and FAST were expected to offer more precise risk stratification than the FIB-4 and VCTE approach, our study found similar predictive performance between the two. For 7-year LRE prediction, the specificity of 68.4% indicated moderate success in avoiding unnecessary referrals, but 31.6% of low-risk patients were misclassified as high-risk. The sensitivity of 66% showed that while most LRE cases were identified, about one-third were missed. Our analysis of referral rates showed that the KASL approach led to a referral rate of 14.7%, which was comparable to FIB-4 Agile 3+ (12.5%) and FIB-4 Agile 4 (9.6%) but higher than FIB-4-FAST (3.1%). While lower referral rates may reduce the burden on healthcare systems, they must be interpreted alongside diagnostic accuracy to avoid missing at-risk individuals. The observed differences in referral rates highlight the need for further validation in diverse cohorts to determine the most clinically efficient strategy. Another important aspect of risk prediction models is the consideration of competing risks, particularly non-liver-related mortality. In our cohort, 14 patients (0.17%) died from non-liver-related causes during follow-up. Given that this represents a very small proportion of the study population, we did not perform a competing risk analysis, as its impact on our overall findings would likely be minimal. However, we acknowledge that competing risks may play a more significant role in longer-term follow-up studies or populations with higher comorbidity burdens.

Despite its clinical strengths, our study has several limitations. First, the observational nature of the study limits our ability to establish causality between the KASL two-step approach and the prevention of liver-related outcomes. While our results suggest that the approach is effective for risk stratification, prospective randomized controlled trials are needed to confirm its impact on patient outcomes. Second, this study was conducted at a single tertiary center, which may limit the external validity of our findings. Patients who underwent VCTE may represent a subset with greater access to specialized care, introducing potential selection bias. Additionally, factors such as obesity and concomitant liver diseases may influence the accuracy of

VCTE-based LSMs, which should be considered when interpreting the results. Third, the discordance between FIB-4 and LSM, as well as the interpretation of changes in these measurements over time, presents an additional limitation. This discordance may affect the accuracy of risk stratification and needs further exploration. Furthermore, the limited number of LREs and short follow-up duration in some groups poses another limitation. While the relatively small events and varying follow-up duration may limit the ability to detect significant differences in risk stratification, it also highlights the promising potential of our findings, suggesting that the KASL two-step approach can effectively stratify patients and identify risk groups with meaningful clinical implications. Importantly, this study not only validates previously reported pathways in Eastern and Western cohorts but also serves as the first validation of the recently published KASL NIT guidelines. Given the significance of validating these guidelines in a Korean cohort, our findings provide crucial insights. Additionally, patients with severe obesity may be underrepresented in our study, which could limit the generalizability of our findings to this group. Lastly, while we accounted for a broad range of confounding factors, residual confounding cannot be ruled out due to the observational design of the study. Despite the advantages of non-invasive tests, liver biopsy can still offer important insights into fibrotic changes and histological patterns such as MASH, which may further refine LRE risk stratification. This could be particularly useful in cases where non-invasive markers present conflicting or ambiguous results.

In conclusion, the KASL two-step approach provides an efficient and practical framework for risk stratification in patients with MASLD, facilitating the early detection of high-risk individuals and enabling timely interventions to optimize patient care.

Authors' contribution

Conceptualization: Seung Up Kim; Data collection: Hye Won Lee, Jae Seung Lee, Mi Na Kim, Beom Kyung Kim, Do Young Kim, Sang Hoon Ahn; Analysis: Hye Won Lee; Manuscript Writing: Hye Won Lee and Seung Up Kim. All authors have full access to all data used in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest

The authors have no conflicts to disclose.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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