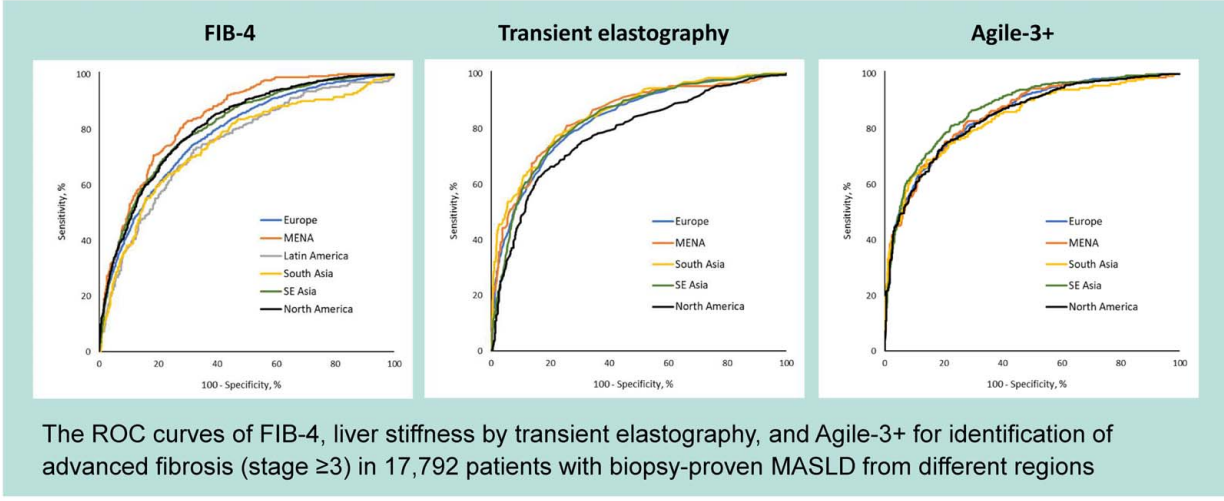
Global performance of non-invasive tests in MASLD: Insights from the G-MASLD study

VISUAL ABSTRACT

Global Performance of Non-invasive Tests in MASLD:
Insights from the G-MASLD Study



The ROC curves of FIB-4, liver stiffness by transient elastography, and Agile-3+ for identification of advanced fibrosis (stage ≥3) in 17,792 patients with biopsy-proven MASLD from different regions

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ORIGINAL ARTICLE

Global performance of non-invasive tests in MASLD: Insights from the G-MASLD study

Zobair M. Younossi[1,2] | Leyla de Avila[1,2] | Salvatore Petta[1,3] | Hannes Hagström[1,4] | Seung Up Kim[1,5] | Atsushi Nakajima[1,6] | Javier Crespo[1,7] | Laurent Castera[1,8] | Naim Alkhouri[1,9] | Ming-Hua Zheng[1,10] | Sombat Treeprasertsuk[1,11] | Prooksa Ananchuensook[1,11] | Shalimar[1,12] | Emmanuel Tsochatzis[1,13] | Shenoy Kotacherry Trivikrama[1,14] | Leena Kondarappassery Balakumaran[1,15] | Jian-Gao Fan[1,16] | Stuart K. Roberts[1,17] | Khalid Alswat[1,18] | Vincent Wai-Sun Wong[1,19] | Yusuf Yilmaz[1,20] | Winston Dunn[21] | Sven Francque[1,22] | Ahmed Cordie[1,23] | Ming-Lung Yu[1,24] | Mattias Ekstedt[25] | George Boon-Bee Goh[1,26] | Claudia P. Oliveira[1,27] | Mario Guimaraes Pessoa[1,28] | Wah Kheong Chan[1,29] | Marlen Ivon Castellanos Fernandez[1,30] | Ajay Duseja[1,31] | Juan Pablo Arab[1,32] | George Papatheodoridis[1,33] | Giada Sebastiani[1,34] | Cristiane Villela-Nogueira[1,35] | Roberta D'Ambrosio[36] | Pietro Lampertico[1,36] | Khalid Alnaamani[1,37] | A.G. Holleboom[1,38] | Arun Valsan[1,39] | Arathi Venu[39] | Mohamed El-Kassas[1,40] | Grazia Pennisi[3] | Ying Shang[41] | Wen-Yue Liu[42] | Hye Won Lee[5] | Takashi Kobayashi[6] | Satoru Kakizaki[1,43] | Cyrielle Caussy[1,44] | Brian Pearlman[1,45] | Paula Iruzubieta[7] | Rida Nadeem[46] | Felice Cinque[34] | Antonia Neonaki[33] | Mirko Zoncapé[47] | Rui-Xu Yang[16] | Sherlot Juan Song[19] | Nicholas Dunn[21] | Zouhir Gadi[22] | Ming-Lun Yeh[48] | Kevin Kim-Jun[26] | Sanjiv Mahadeva[29] | Licet Gonzalez Fabian[49] | Ahmed Almohsen[50] | Nathalie Leite[35] | Nicola Pugliese[1,51] | Johan Vessby[52] | Chencheng Xie[53] | Narendra Singh Choudhary[54] | Ethan Friend[55] | Maria Poca[56] | Takumi Kawaguchi[1,57] | Francesco Paolo Russo[58] | Adrian Gadano[1,59] | Luis Antonio Diaz[1,60] | Ashwani K. Singal[1,61] | Berenice Segrestin[1,44] | Nadege Gunn[1,55] | Didac Mauricio[1,62] | Marco Arrese[1,63] | Anna Fracanzani[64] | Rosa Lombardi[64] | Brian Lam[1,2] | Andrei Racila[1,2] | Saleh A. Alqahtani[1,65] | Maria Stepanova[1,2,66]on behalf of the Global NASH/MASH Council (GNC)

[1]The Global NASH/MASH Council (GNC), Washington, District of Columbia, USA

[2]Beatty Liver and Obesity Research Program, Inova Health System, Falls Church, Virginia, USA

[3]Section of Gastroenterology, PROMISE Department, University of Palermo, Palermo, Italy

[4]Division of Hepatology, Department of Upper GI Diseases, Karolinska University Hospital, Stockholm, Sweden

[5]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea,

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[6]Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

[7]Gastroenterology and Hepatology Department, Clinical and Translational Research in Digestive Diseases, Valdecilla Research Institute (IDIVAL), Marques de Valdecilla University Hospital, Santander, Spain

[8]Department of Hepatology, Hospital Beaujon, Assistance Publique-Hôpitaux de Paris, Université Paris-Cité, Paris, France

[9]Summit Clinical Research, San Antonio, Texas, USA

[10]MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

[11]Division of Gastroenterology, Department of Internal Medicine, Chulalongkorn University, Bangkok, Thailand

[12]Department of Gastroenterology and Human Nutrition Unit, All India Institute of Medical Sciences, New Delhi, India

[13]University College London Institute for Liver and Digestive Health, Royal Free Hospital, London, UK

[14]Department of Gastroenterology, Sree Gokulam Medical College and Research Foundation, Trivandrum, Kerala, India

[15]Population Health and Research Institute, Medical College PO, Trivandrum, Kerala, India

[16]Department of Gastroenterology, Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

[17]Alfred Hospital Gastroenterology Department, Monash University, Melbourne, Australia

[18]Liver Disease Research Center, Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia

[19]Medical Data Analytics Center, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China

[20]Department of Gastroenterology, School of Medicine, Recep Tayyip Erdogan University, Rize, Türkiye

[21]Internal Medicine, Kansas University Medical Center, Kansas City, Kansas, USA

[22]Department of Gastroenterology and Hepatology, Antwerp University Hospital, Edegem, Belgium

[23]Cairo University Hospitals HIV Clinic, Endemic Medicine Department, Cairo University Hospitals, Cairo, Egypt

[24]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[25]Department of Gastroenterology and Hepatology, Department of Health, Medicine, and Caring Sciences, Linköping University, Linköping, Sweden

[26]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore, Singapore

[27]Department of Gastroenterology, Faculdade Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil

[28]Department of Gastroenterology, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - HCFMUSP, São Paulo, Brazil

[29]Gastroenterology and Hepatology Unit, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[30]Department of Research and Teaching, Institute of Gastroenterology, University of Medical Sciences of Havana, Havana, Cuba

[31]Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[32]Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA

[33]First Academic Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens “Laiko”, Athens, Greece

[34]Division of Gastroenterology and Hepatology, Department of Medicine, McGill University Health Centre, Montreal, Canada

[35]School of Medicine, Internal Medicine Department and Hepatology Division, Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

[36]Division of Gastroenterology and Hepatology, Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy

[37]Division of Gastroenterology and Hepatology, Department of Medicine, The Medical City for Military and Security Services, Muscat, Oman

[38]Department of Vascular Medicine, Amsterdam University Medical Center, Amsterdam, The Netherlands

[39]Centre for Metabolic Liver Disease and Integrated Liver Care Unit, Amrita Institute of Medical Sciences, Kochi, Kerala, India

[40]Endemic Medicine Department, Faculty of Medicine, Helwan University, Cairo, Egypt

[41]Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden

[42]Department of Endocrinology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

[43]Department of Clinical Research, NHO Takasaki General Medical Center, Takasaki, Japan

[44]Département Endocrinologie, Diabète et Nutrition, Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, Lyon, France

[45]Department of Graduate Medical Education, Hamilton Medical Center, Medical College of Georgia, Dalton, United States

[46]Arizona Liver Health, Chandler, Arizona, United States

[47]Liver Unit, Department of Internal Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

[48]Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung, Taiwan

[49]Department of Pathological Anatomy, Institute of Gastroenterology, University of Medical Sciences of Havana, Havana, Cuba

[50]Department of Medicine, Schulich School of Medicine, Western University & London Health Sciences Centre, London, Ontario, Canada

[51]Division of Internal Medicine and Hepatology, Department of Gastroenterology, IRCCS Humanitas Research Hospital, Rozzano, Italy

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[52]Department of Medical Sciences, Gastroenterology Research Group, Uppsala University, Uppsala, Sweden

[53]Division of Hepatology, Avera McKennan Hospital & University Health Center, Sioux Falls, United States

[54]Hepatology, and Institute of Liver Transplantation and Regenerative Medicine, Medanta The Medicity, Gurugram, Haryana, India

[55]Velocity Clinical Research, Waco, Texas, United States

[56]Department of Gastroenterology, CIBEREHD, IR Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[57]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan

[58]Department of Surgery, Oncology and Gastroenterology, University of Padova Gastroenterology Unit, Azienda Ospedaliera - Universita Padova, Padova, Italy

[59]Liver Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[60]MASLD Research Center, Division of Gastroenterology and Hepatology, University of California San Diego, San Diego, California, United States

[61]Department of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, University of Louisville, Louisville, Kentucky, United States

[62]Department of Endocrinology & Nutrition, CIBERDEM, IR Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[63]Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

[64]Unit of Metabolic Disease, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[65]Liver, Digestive, and Lifestyle Health Research Section, and Organ Transplant Center of Excellence, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

[66]Center for Outcomes Research in Liver Disease, Washington, District of Columbia, United States

Correspondence
Zobair M. Younossi, Center for Outcomes Research in Liver Diseases, 2411 I Street, Washington, DC 20037, USA.
Email: Zobair.Younossi@cldq.org

Abstract

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is highly prevalent worldwide. Performance of non-invasive tests (NITs) in patients with MASLD recruited from different regions of the world was evaluated.

Methods: MASLD patients with liver biopsies and NIT data [fibrosis-4 index (FIB-4), enhanced liver fibrosis (ELF), and liver stiffness measurement (LSM)] were enrolled through the Global NASH Council collaboration (G-MASLD). FibroScan-AST (FAST) and Agile-3+/Agile-4 were calculated. NITs' performance for predicting $\geq$F2 (significant fibrosis), $\geq$F3 (advanced fibrosis), or cirrhosis (F4) was determined in patients from different regions.

Results: A total of 17,792 MASLD patients from 41 countries were included: 14% had F0, 32% F1, 18% F2, 22% F3, 13% F4 (cirrhosis); 48% NAS $\geq$5. Advanced fibrosis prediction by NITs was variable across regions for FIB-4 [pooled AUC (95% CI) = 0.80 (0.79–0.81)], the lowest in Latin America [0.75 (0.71–0.79)], the highest in MENA [0.84 (0.82–0.87)], and ELF [pooled AUC = 0.77 (0.76–0.79)], the lowest in Europe [0.72 (0.69–0.76)], the highest in North America [0.80 (0.78–0.82)]. Prediction of advanced fibrosis by LSM [pooled AUC = 0.84 (0.83–0.85)] was similar across regions except North America [0.78 (0.76–0.81)]. In addition, FAST [AUC = 0.75 (0.74–0.76)] and Agile-3+ [AUC = 0.87 (0.86–0.88)] performed similarly across regions. Similar trends were observed for the NITs predicting significant fibrosis. Finally, the accuracy of Agile-4 for predicting cirrhosis [AUC = 0.90 (0.89–0.91)] was

Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; FAST, FibroScan-AST; FIB-4, fibrosis-4 index; GNC, Global NASH/MASH Council; LSM, liver stiffness measurement; MAS, MASLD Activity Score; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MENA, Middle East and North Africa; NAS, NAFLD Activity Score; NITs, non-invasive tests; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.

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the lowest in North America [0.85 (0.83–0.87)], the highest in MENA [0.96 (0.94–0.98)].

Conclusions: The diagnostic performance of common NITs for fibrosis in MASLD varies across the world. In the large multinational G-MASLD sample, the most accurate NITs were Agile-3+ and Agile-4 composite scores.

Keywords: biomarkers, chronic liver disease, diagnostic thresholds, metabolic syndrome, non-communicable diseases, outcomes, steatohepatitis, steatotic liver disease

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is a spectrum that includes metabolic dysfunction–associated steatohepatitis (MASH), previously known as nonalcoholic steatohepatitis (NASH).[1,2] The global prevalence of MASLD is estimated at 38% while that of MASH could be as high as 5%–6%.[3] Driven by the dual epidemic of obesity and type 2 diabetes (T2D), the global burden of MASH is on the rise, making it the second most common indication for liver transplantation in the United States and Europe.[4,5]

Most natural history studies have suggested that more advanced histologic stages of liver disease can predict adverse outcomes in MASH.[6–8] Since liver biopsy to establish histologic stages in all MASH patients is not feasible or desirable, a number of noninvasive tests (NITs) for fibrosis have been developed.[9] Some of these NITs rely on relatively simple formulas [eg, fibrosis-4 index (FIB-4)] while others are based on imaging (eg, transient elastography) or serum biomarkers of fibrogenesis and fibrolysis (eg, enhanced liver fibrosis or ELF).[9] Recent data suggest that these NITs are able to predict adverse outcomes in patients with MASLD with accuracy comparable to that of histologic fibrosis stage.[10–13]

Despite recent advances, it has been unclear if the diagnostic performance of NITs and/or risk factors for adverse outcomes in MASLD are similar across different regions of the world. To cover this gap in knowledge, we evaluated the performance of common NITs using histologic and clinical data obtained from a multinational collaboration, Global MASLD (G-MASLD).

METHODS

Study sample

The G-MASLD project was established by the Global NASH/MASH Council (GNC) in 2023 as a joint effort among researchers from over 40 countries. Investigators who participated in the study obtained approval from their local Institutional Review Board or equivalent supervisory body to share retrospectively collected clinical and liver biopsy data from patients previously evaluated at their site. After deidentification of the data and signing the data use agreement, the data were shared with the GNC to be centrally stored in a secure electronic database and analyzed in aggregate.

According to the study protocol, eligible subjects were patients with a confirmed diagnosis of MASLD or MASH who had liver biopsy data available. Patients younger than 18 years at the time of biopsy, pregnant women, patients without basic demographic information (age, sex, country of enrollment) or without data from at least 1 liver biopsy, as well as patients without hepatic steatosis (NAS steatosis score = 0 and CAP < 238 dB/m) and those not meeting the criteria for MASLD (defined as having hepatic steatosis with at least 1 cardiometabolic risk factor in the absence of excessive alcohol use)[14] were excluded from the analysis.

All research was conducted in accordance to Declaration of Helsinki and Istanbul. The study was considered Exempt by Institutional Review Board of Inova Health System Institutional Review Board.

Data collection and definitions

The data collection form for this study included patients' demographic characteristics (age, sex, country), anthropometric measurements (height, weight, BMI, waist circumference), elements of medical history (T2D, hypertension, hyperlipidemia, cardiovascular disease), together with liver histology details [fibrosis stage F0–F4 according to the Kleiner system and MASLD Activity Score (MAS)]. Collected NITs included liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) by vibration-controlled transient elastography (VCTE), and laboratory parameters, which were subsequently used to calculate biomarker-based NIT scores; all NIT-related parameters were required to

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TABLE 1 Demographic and clinical parameters of included patients with MASLD by histologic fibrosis stage

	F0	F1	F2	F3	F4		All
N	**2579**	**5770**	**3169**	**3905**	**2369**	***p***	**17,792**
Region of enrollment							
Europe	883 (34.2%)	1452 (25.2%)	1023 (32.3%)	1141 (29.2%)	684 (28.9%)	< 0.0001	5183 (29.1%)
MENA	167 (6.5%)	590 (10.2%)	239 (7.5%)	209 (5.4%)	71 (3.0%)	< 0.0001	1276 (7.2%)
Latin America	195 (7.6%)	272 (4.7%)	166 (5.2%)	179 (4.6%)	74 (3.1%)	< 0.0001	886 (5.0%)
South Asia	284 (11.0%)	500 (8.7%)	139 (4.4%)	124 (3.2%)	95 (4.0%)	< 0.0001	1142 (6.4%)
Southeast Asia	808 (31.3%)	1523 (26.4%)	606 (19.1%)	770 (19.7%)	343 (14.5%)	< 0.0001	4050 (22.8%)
USA/Canada	243 (9.4%)	1433 (24.8%)	996 (31.4%)	1482 (38.0%)	1102 (46.5%)	< 0.0001	5256 (29.5%)
Age, y	45.5 ± 13.1	46.5 ± 13.1	50.3 ± 13.1	55.7 ± 11.4	58.1 ± 9.4	< 0.0001	50.6 ± 13.2
Male sex	1398 (54.2%)	2790 (48.4%)	1611 (50.8%)	1771 (45.4%)	935 (39.5%)	< 0.0001	8505 (47.8%)
College degree	215 (40.6%)	347 (30.6%)	175 (34.7%)	99 (29.0%)	51 (29.0%)	0.0003	887 (33.0%)
Alcohol use (any)	229 (13.9%)	536 (14.9%)	306 (18.1%)	220 (14.5%)	109 (14.3%)	0.0054	1400 (15.2%)
BMI, kg/m^2	33.1 ± 9.6	34.1 ± 9.4	33.8 ± 8.3	33.0 ± 6.7	33.3 ± 6.8	< 0.0001	33.5 ± 8.4
Lean[a]	282 (11.2%)	408 (7.2%)	167 (5.5%)	211 (5.5%)	134 (5.8%)	< 0.0001	1202 (6.9%)
Obese[a]	1579 (62.8%)	3973 (70.1%)	2183 (71.2%)	2769 (72.7%)	1654 (71.7%)	< 0.0001	12,158 (70.0%)
Type 2 diabetes	712 (27.8%)	1975 (35.1%)	1436 (46.2%)	2368 (62.0%)	1645 (70.0%)	< 0.0001	8136 (46.6%)
Hypertension	1020 (41.1%)	2494 (45.2%)	1591 (52.6%)	2231 (63.3%)	1386 (66.6%)	< 0.0001	8722 (52.5%)
Hyperlipidemia	1163 (49.2%)	2652 (49.4%)	1581 (53.4%)	2058 (59.3%)	1078 (52.8%)	< 0.0001	8532 (52.7%)
Cardiovascular disease	72 (4.7%)	154 (4.6%)	92 (6.6%)	92 (7.9%)	59 (10.1%)	< 0.0001	469 (5.8%)
NAS score	2.80 ± 1.59	3.92 ± 1.57	4.63 ± 1.58	5.05 ± 1.42	4.65 ± 1.47	< 0.0001	4.27 ± 1.68
NAS ≥ 5	306 (16.2%)	1763 (37.0%)	1474 (55.0%)	2299 (66.3%)	1223 (59.6%)	< 0.0001	7065 (47.6%)

[a]Lean is defined as BMI < 25 or < 23 in patients of East Asian origin; obese is defined as BMI > 30 or > 25, respectively.

Abbreviations: BMI, body mass index; MASLD, metabolic dysfunction–associated steatotic liver disease; MENA, Middle East and North Africa; NAS, NAFLD Activity Score.

TABLE 2 Non-invasive test (NIT) scores of MASLD patients by fibrosis stage

NIT score	F0	F1	F2	F3	F4	*p*	All
FIB-4	1.01 ± 0.76	1.07 ± 0.83	1.41 ± 1.23	1.93 ± 1.48	3.01 ± 2.27	< 0.0001	1.57 ± 1.48
ELF	9.08 ± 1.04	9.06 ± 0.99	9.41 ± 0.94	10.0 ± 1.0	10.7 ± 1.0	< 0.0001	9.92 ± 1.15
CAP, dB/m	307.7 ± 50.1	314.0 ± 47.7	319.0 ± 49.6	319.9 ± 50.6	315.2 ± 53.1	< 0.0001	315.6 ± 50.0
LSM, kPa	7.52 ± 4.88	8.55 ± 5.15	10.4 ± 6.8	14.1 ± 8.4	23.6 ± 14.3	< 0.0001	12.3 ± 9.8
FAST	0.311 ± 0.214	0.416 ± 0.224	0.505 ± 0.225	0.596 ± 0.220	0.685 ± 0.207	< 0.0001	0.498 ± 0.250
Agile-3+	0.337 ± 0.259	0.415 ± 0.274	0.544 ± 0.284	0.748 ± 0.235	0.911 ± 0.142	< 0.0001	0.580 ± 0.319
Agile-4	0.046 ± 0.091	0.061 ± 0.110	0.103 ± 0.151	0.233 ± 0.230	0.525 ± 0.288	< 0.0001	0.178 ± 0.247
ELF < 9.2	78 (58.6%)	404 (54.5%)	266 (41.7%)	339 (19.3%)	87 (7.1%)	< 0.0001	1174 (26.1%)
ELF ≥ 10.4	16 (12.0%)	63 (8.5%)	100 (15.7%)	583 (33.2%)	731 (59.3%)	< 0.0001	1493 (33.2%)
ELF ≥ 11.3	4 (3.0%)	11 (1.5%)	21 (3.3%)	174 (9.9%)	329 (26.7%)	< 0.0001	539 (12.0%)
FIB-4 < 1.30	1913 (78.7%)	4140 (75.7%)	1747 (58.4%)	1248 (33.4%)	299 (13.3%)	< 0.0001	9347 (55.4%)
FIB-4 ≥ 2.67	79 (3.3%)	211 (3.9%)	228 (7.6%)	698 (18.7%)	991 (44.1%)	< 0.0001	2207 (13.1%)
FIB-4 ≥ 3.25	50 (2.1%)	113 (2.1%)	129 (4.3%)	418 (11.2%)	724 (32.2%)	< 0.0001	1434 (8.5%)
LSM < 10 kPa	1255 (84.1%)	2447 (75.8%)	1150 (59.7%)	776 (31.7%)	153 (9.1%)	< 0.0001	5781 (53.7%)
LSM ≥ 15 kPa	75 (5.0%)	183 (5.7%)	214 (11.1%)	771 (31.5%)	1159 (69.2%)	< 0.0001	2402 (22.3%)
LSM ≥ 20 kPa	37 (2.5%)	88 (2.7%)	97 (5.0%)	376 (15.4%)	847 (50.6%)	< 0.0001	1445 (13.4%)
FAST ≥ 0.35	429 (36.3%)	1564 (58.2%)	1162 (74.2%)	1653 (84.1%)	1144 (91.2%)	< 0.0001	5952 (68.8%)
FAST ≥ 0.67	88 (7.4%)	412 (15.3%)	415 (26.5%)	862 (43.9%)	763 (60.8%)	< 0.0001	2540 (29.3%)
Agile-3+ ≥ 0.451	428 (30.4%)	1289 (42.0%)	1089 (60.1%)	2004 (86.5%)	1554 (97.4%)	< 0.0001	6364 (62.4%)
Agile-3+ ≥ 0.678	202 (14.3%)	665 (21.7%)	703 (38.8%)	1619 (69.9%)	1482 (92.9%)	< 0.0001	4671 (45.8%)
Agile-4 ≥ 0.251	48 (3.4%)	168 (5.5%)	211 (11.7%)	811 (35.0%)	1238 (77.6%)	< 0.0001	2476 (24.3%)
Agile-4 ≥ 0.842	0 (0.0%)	8 (0.3%)	9 (0.5%)	53 (2.3%)	283 (17.7%)	< 0.0001	353 (3.5%)

Abbreviations: CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; FAST, FibroScan-AST; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease.

have been collected within 1 year of the biopsy. Hepatic enzyme levels and platelet count were used to calculate FIB-4 scores; ELF scores were collected if available. In addition, the NITs combining blood variables and LSM (FAST, Agile-3+, Agile-4) were calculated using published formulas.[15–17]

Statistical analysis

All collected demographic and clinical parameters, as well as NIT scores, were summarized as n (%) or mean ± SD. In case of missing data, only observed data was used for any analysis.

Comparisons between groups were conducted using the Wilcoxon rank-sum test for continuous variables and the Pearson chi-square test for categorical variables. Performance of NITs to predict significant fibrosis (F2–F4), advanced fibrosis (F3–F4), or cirrhosis (F4) was determined by assessing the respective area under the ROC curve (AUC) values in the entire sample and in regional subgroups. In addition, commonly used cutoff values collected from the literature were applied, and cutoff values that would return pre-determined accuracy were calculated.

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TABLE 3 Area under the receiver operating characteristic curve (AUC) for predicting advanced fibrosis (F3–F4) by NITs in different regions

NIT score	Region	n/N (%) with advanced fibrosis	AUC (95% CI)
FIB-4	Europe	1762/5005 (35.2%)	0.783 (0.770–0.796)
	MENA	280/1268 (22.1%)	**0.843 (0.819–0.866)**
	Latin America	246/833 (29.5%)	0.750 (0.713–0.787)
	South Asia	209/1118 (18.7%)	0.749 (0.710–0.788)
	Southeast Asia	1006/3751 (26.8%)	0.811 (0.796–0.826)
	USA/Canada	2475/4892 (50.6%)	0.814 (0.803–0.826)
	All	5978/16,867 (35.4%)	0.797 (0.790–0.804)
ELF	Europe	600/952 (63.0%)	0.724 (0.691–0.757)
	Southeast Asia	366/591 (61.9%)	0.766 (0.727–0.805)
	USA/Canada	1908/2815 (67.8%)	0.800 (0.782–0.817)
	All	2987/4499 (66.4%)	0.774 (0.760–0.789)
LSM	Europe	1253/3131 (40.0%)	0.836 (0.821–0.850)
	MENA	223/865 (25.8%)	0.846 (0.815–0.877)
	South Asia	195/995 (19.6%)	0.855 (0.825–0.885)
	Southeast Asia	826/2782 (29.7%)	0.836 (0.820–0.852)
	USA/Canada	1228/1757 (69.9%)	0.783 (0.761–0.806)
	All	3832/9825 (39.0%)	0.841 (0.833–0.849)
FAST	Europe	994/2391 (41.6%)	0.759 (0.740–0.778)
	MENA	212/817 (25.9%)	0.757 (0.719–0.795)
	South Asia	184/931 (19.8%)	0.770 (0.729–0.810)
	Southeast Asia	669/2341 (28.6%)	0.740 (0.718–0.762)
	USA/Canada	914/1364 (67.0%)	0.705 (0.676–0.734)
	All	3025/7997 (37.8%)	0.753 (0.743–0.764)
Agile-3+	Europe	1219/3039 (40.1%)	0.853 (0.840–0.867)
	MENA	222/856 (25.9%)	0.853 (0.823–0.882)
	South Asia	189/984 (19.2%)	0.840 (0.806–0.874)
	Southeast Asia	707/2437 (29.0%)	0.872 (0.857–0.888)
	USA/Canada	1196/1697 (70.5%)	0.845 (0.826–0.865)
	All	3640/9306 (39.1%)	0.868 (0.860–0.875)
Agile-4	Europe	1219/3039 (40.1%)	0.844 (0.830–0.858)
	MENA	222/856 (25.9%)	0.854 (0.824–0.884)
	South Asia	189/984 (19.2%)	0.822 (0.785–0.859)
	Southeast Asia	707/2437 (29.0%)	0.856 (0.840–0.873)
	USA/Canada	1196/1697 (70.5%)	0.850 (0.831–0.869)
	All	3640/9306 (39.1%)	0.856 (0.848–0.864)

Note: Similarly assessed AUCs for predicting significant fibrosis (F2–F4) and cirrhosis (F4) are shown in Supplemental Table S3, http://links.lww.com/HEP/K291.
Abbreviations: ELF, enhanced liver fibrosis; FAST, FibroScan-AST; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; NITs, non-invasive tests.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

The study received approval from the INOVA Health Systems Instititonal Review Board (INOVA-2024-21) and from the respective Institutional Review Boards or equivalent supervisory institutions at each participating site. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul, and all subjects provided informed consent before enrollment in the research study at their respective sites.

RESULTS

There were 20,159 patients with MASLD records who were included in the G-MASLD project. After inclusion and exclusion criteria were applied (Supplemental Figure S1, http://links.lww.com/HEP/K291), 17,792 eligible MASLD patients with liver biopsy data were included in the analysis (Table 1). The patients were from 41 countries: 30% from the USA/Canada, 29% Europe, 23% Southeast Asia, 7% Middle East and North Africa (MENA) region, 6% South Asia, and 5% Latin America (Table 1). The mean (SD) age was 51 ± 13 years, BMI

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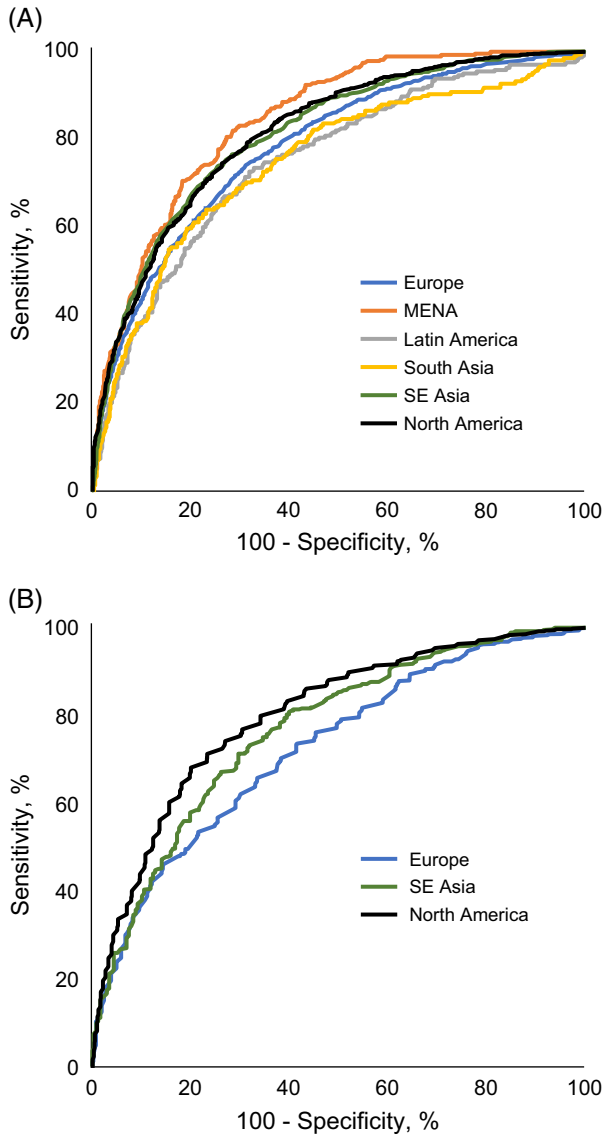


FIGURE 1 Receiver operating characteristic curves of (A) FIB-4 and (B) ELF for predicting advanced fibrosis in different regions. Abbreviations: ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; MENA, Middle East and North Africa; SE Asia, Southeast Asia.

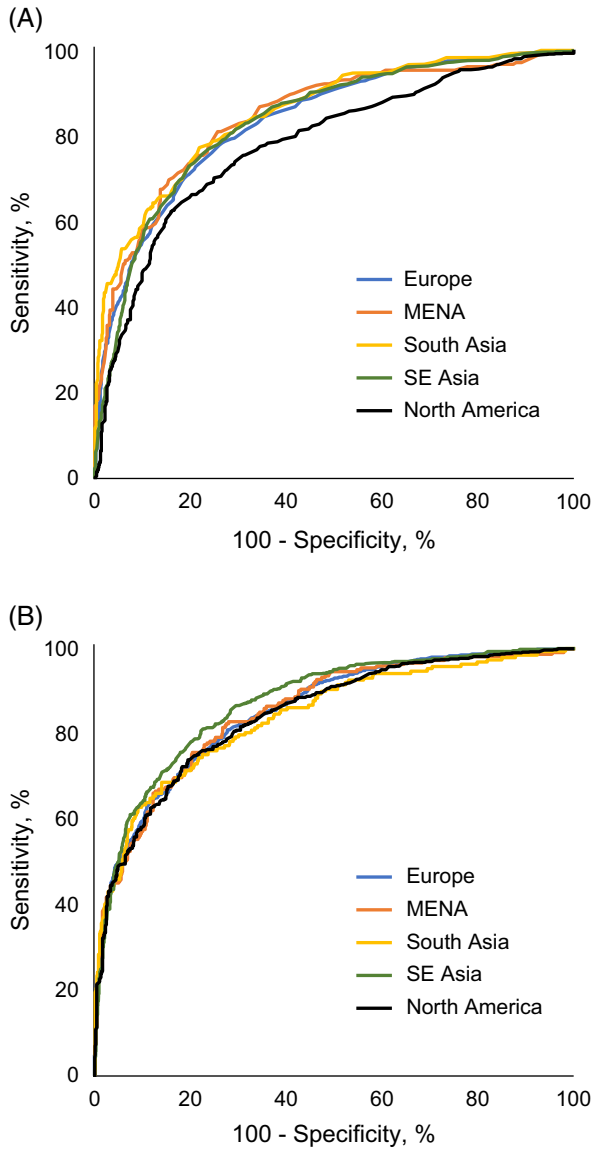


FIGURE 2 Receiver operating characteristic curves of (A) liver stiffness measurement and (B) Agile-3+ for predicting advanced fibrosis in different regions. Abbreviations: MENA, Middle East and North Africa; SE Asia, Southeast Asia.

33 ± 8 kg/m^2, 48% were male, 15% reported current alcohol use ($<60/50$ g/day for male/female), 70% obese, and 47% had T2D (Table 1). Based on the liver biopsies of the included patients with MASLD, 14% had fibrosis stage F0, 32% F1, 18% F2, 22% F3, and 13% F4 (cirrhosis), while 48% had NAS ≥ 5 (Table 1 and Supplemental Table S1, http://links.lww.com/HEP/K291). Patients with higher fibrosis stages were older, more commonly female, and had more components of metabolic syndrome ($p < 0.01$) (Table 1).

Across regions, significant fibrosis (F2–F4), advanced fibrosis (F3–F4), and cirrhosis (F4) were the most prevalent in USA/Canada (68%, 49%, and 21%, respectively) while the lowest prevalence was seen in South Asia (31%, 19%, and 8%, respectively) (all $p < 0.01$).

Fibrosis and NITs

All studied NITs were strongly correlated with histologic fibrosis stages F0–F4, as continuous variables and with commonly used cutoff values applied (Table 2 and Supplemental Table S2, http://links.lww.com/HEP/K291). Quantified via area under the receiver operating characteristic curve (AUC) metric (with 95% CI), the performance of the studied NITs for predicting advanced fibrosis in the study population was as follows: FIB-4 0.80 (0.79–0.81), ELF 0.77 (0.76–0.79), LSM 0.84 (0.83–0.85), FAST 0.75 (0.74–0.76), Agile-3+ 0.87 (0.86–0.88), and Agile-4 0.86 (0.85–0.86) (Table 3). The AUC values of Agile-3+ and Agile-4

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TABLE 4 Cutoffs for predicting advanced fibrosis (F3–F4) by NITs in different regions

Region/criterion	Sensitivity 95%	Sensitivity 90%	Sensitivity 80%	Specificity 85%	Specificity 90%	Specificity 95%	Specificity 98%
FIB-4 score							
Europe	≥ 0.74	≥ 0.92	≥ 1.16	≥ 1.74	≥ 2.00	≥ 2.45	≥ 3.10
MENA	≥ 0.73	≥ 0.83	≥ 1.07	≥ 1.38	≥ 1.61	≥ 1.94	≥ 2.43
Latin America	≥ 0.69	≥ 0.82	≥ 1.01	≥ 1.63	≥ 1.90	≥ 2.35	≥ 3.35
South Asia	≥ 0.52	≥ 0.78	≥ 1.13	≥ 2.27	≥ 2.85	≥ 3.72	≥ 6.21
Southeast Asia	≥ 0.68	≥ 0.87	≥ 1.15	≥ 1.81	≥ 2.20	≥ 2.86	≥ 3.86
North America	≥ 0.71	≥ 0.90	≥ 1.17	≥ 1.66	≥ 1.97	≥ 2.40	≥ 3.18
ELF score							
Europe	≥ 8.7	≥ 9.0	≥ 9.4	≥ 10.4	≥ 10.6	≥ 10.9	≥ 11.3
Southeast Asia	≥ 8.9	≥ 9.2	≥ 9.7	≥ 10.6	≥ 10.8	≥ 11.3	≥ 11.6
North America	≥ 8.6	≥ 8.9	≥ 9.4	≥ 10.0	≥ 10.3	≥ 10.7	≥ 11.2
LSM, kPa							
Europe	≥ 6.9	≥ 8.0	≥ 9.7	≥ 12.0	≥ 13.3	≥ 16.4	≥ 21.3
MENA	≥ 6.8	≥ 8.0	≥ 9.3	≥ 10.9	≥ 12.1	≥ 14.3	≥ 17.6
South Asia	≥ 6.2	≥ 7.0	≥ 8.3	≥ 9.9	≥ 11.1	≥ 12.7	≥ 16.7
Southeast Asia	≥ 6.7	≥ 7.9	≥ 9.7	≥ 11.9	≥ 13.2	≥ 16.8	≥ 21.3
North America	≥ 7.3	≥ 8.4	≥ 10.3	≥ 13.9	≥ 16.4	≥ 21.4	≥ 30.9

Abbreviations: ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MENA, Middle East and North Africa; NITs, non-invasive tests.

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were significantly higher in comparison to those returned by FIB-4, ELF, and LSM (all $p < 0.01$).

The NIT performance showed variability across regions (Figures 1, 2). Accuracy of FIB-4 for predicting advanced fibrosis was the lowest in Latin America [AUC = 0.75 (0.71–0.79)], the highest in MENA [0.84 (0.82–0.87)] ($p < 0.01$) (Table 3). Accuracy of ELF was the lowest in Europe [0.72 (0.69–0.76)], the highest in the USA/Canada [0.80 (0.78–0.82)] ($p < 0.01$) (Table 3). In contrast, the accuracy of LSM was similar across regions (all AUC > 0.83) except USA/Canada, where it was 0.78 ($p < 0.01$) (Table 3). The AUC of FAST was again similar in all regions except USA/Canada [0.70 (0.67–0.73)] ($p = 0.01$) (Table 3). Finally, the accuracy of Agile-3+ for advanced fibrosis was similar (≥ 0.84) in all regions ($p > 0.05$) (Table 3).

The AUCs of the studied NITs for predicting significant fibrosis in the pooled sample were as follows: FIB-4 0.76 (0.76–0.77), ELF 0.77 (0.75–0.78), LSM 0.80 (0.79–0.81), FAST 0.74 (0.73–0.75), Agile-3+ 0.82 (0.81–0.83), with additional regional variability (Supplemental Table S3, http://links.lww.com/HEP/K291). The AUC of Agile-4 for predicting cirrhosis was 0.90 (0.89–0.91), the lowest in the USA/Canada [0.85 (0.83–0.87)], the highest in MENA [0.96 (0.94–0.98)], $p < 0.001$ (Supplemental Table S3, http://links.lww.com/HEP/K291).

Since patient subgroups from different regions were not balanced across several clinically relevant parameters (Supplemental Table S4, http://links.lww.com/HEP/K291), we sought to explore whether these imbalances could be linked to the observed differences in NIT performance. In this context, the AUC of FIB-4 was the highest in patients from MENA, the lowest in patients from Latin America and South Asia (Table 3). This pattern was not correlated with the differences in mean age (46 y in MENA vs. 54 y in Latin America and 42 y in South Asia), the prevalence of obesity (69% vs. 64% and 23%, respectively), the proportion of BMI > 35 (37% vs. 27% and 5%, respectively) or T2D (39% vs. 49% and 32%, respectively) (Supplemental Table S4, http://links.lww.com/HEP/K291). Similarly, the lowest accuracy of ELF in Europe versus the highest in the USA/Canada was not correlated with the differences in age (similar between the 2 regions), the rates of obesity or T2D (higher in patients from the USA/Canada region) (Supplemental Table S4, http://links.lww.com/HEP/K291).

In contrast, the accuracy of LSM (the lowest in USA/Canada in comparison to all other regions), could potentially be related to the substantially higher rate of obesity and, especially, morbid obesity (BMI > 35) in patients enrolled from the USA/Canada region (57% vs. 5-37%) (Supplemental Table S4, http://links.lww.com/HEP/K291). To examine this, we recalculated the AUC for LSM in the USA/Canada subgroup after excluding patients with BMI > 35. The resulting AUC increased from 0.78 to 0.80 ($p = 0.36$) but remained significantly lower than the pooled AUC of 0.84 across all other regions ($p = 0.01$).

Cutoff values for the identification of advanced fibrosis with NITs

In addition to variability in AUCs, there was also regional variability in the accuracy of predicting advanced fibrosis when commonly used NIT cutoffs were applied as follows: < 1.30, ≥ 2.67, and ≥ 3.25 for FIB-4; < 9.2, ≥ 10.4, and ≥ 11.3 for ELF; < 10 kPa, ≥ 15 kPa, and ≥ 20 kPa for LSM (Supplemental Table S5, http://links.lww.com/HEP/K291). The 2.67 cutoff for FIB-4 returned 95% specificity, which was similar across all regions except South Asia (88%); however, the cutoff of 1.30 for FIB-4 returned a pooled sensitivity of 74% which varied between 67% (Latin America) and 76% (Southeast Asia) (Supplemental Table S5, http://links.lww.com/HEP/K291).

The variability in ELF performance for predicting advanced fibrosis with the cutoff of 10.4 was more pronounced: pooled specificity 88%, varied from 82% (Southeast Asia) to 90% (USA/Canada) (Supplemental Table S5, http://links.lww.com/HEP/K291).

The cutoff of 15 kPa for LSM returned a specificity of 94% which was similar in all regions except USA/Canada (88%), while the cutoff of 10 kPa had a pooled sensitivity of 79% which was as low as 66% in South Asia and 71% in Latin America (Supplemental Table S5, http://links.lww.com/HEP/K291).

The cutoff values needed to achieve predefined accuracy also varied among regions, particularly those needed to achieve high specificity (ie, rule-in or diagnostic cutoffs) (Table 4). In fact, while an 80% sensitivity of FIB-4 for predicting advanced fibrosis could be achieved by applying cutoff values between 1.01 and 1.17 for all regions, the cutoff for specificity of 95% needs to be as low as 1.94 in MENA and as high as 3.72 in South Asia (Table 4). For ELF, regional variability was less pronounced and returned cutoff values between 9.4 and 9.7 for a sensitivity of 80%, between 10.7 and 11.3 for a specificity of 95% (Table 4). In contrast, regional variability in LSM was substantial and included cutoffs between 8.3 kPa (South Asia) and 10.3 kPa (USA/Canada) to predict advanced fibrosis with 80% sensitivity, between 12.7 kPa (South Asia) and 21.4 kPa (USA/Canada) to achieve 95% specificity (Table 4). The associated positive predictive values (PPVs) and negative predictive values (NPVs) for the calculated NIT cutoffs by region are shown in Supplemental Table S6, http://links.lww.com/HEP/K291.

In addition to prespecified sensitivity and specificity, we aimed to find combinations of commonly used NITs (FIB-4 followed by either LSM or ELF) that would return

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superior PPV or NPV (95% or the highest possible) for identifying advanced fibrosis in our sample. The dynamic cutoff search in the entire sample yielded a PPV of 95% for a combination of FIB-4 $\geq$1.36 and LSM $\geq$22.4 kPa (sensitivity 20%, specificity 99.3%, NPV 65%), with some regional variability (Supplemental Table S7, http://links.lww.com/HEP/K291). In contrast, the NPV of >90% was returned by the cutoffs of 0.70 and 7.0 kPa for FIB-4 and LSM, respectively, similar across the regions (Supplemental Table S7, http://links.lww.com/HEP/K291). Similarly, the identified combination of FIB-4 and ELF in the pooled sample was as follows: FIB-4 $\geq$2.82 and ELF $\geq$10.1 for a PPV of 95% (Supplemental Table S7, http://links.lww.com/HEP/K291). The highest possible NPV for this combination was 79%, and region-specific cutoff search was not available due to limited sample size.

DISCUSSION

In this large, multinational study of nearly 18,000 biopsy-confirmed patients with MASLD from 41 countries, we identified significant geographic variability in histologic fibrosis severity and NIT performance. Our results confirm that the prevalence of advanced fibrosis and cirrhosis in MASLD may vary across regions of the world, with the highest rates in our sample observed in patients from the USA/Canada and the lowest in South Asia.

We demonstrated that all evaluated NITs, including FIB-4, ELF, LSM, FAST, Agile-3+, and Agile-4, were significantly associated with histologic severity of fibrosis. However, performance metrics moderately varied by region, suggesting the potential influence of population characteristics and environmental factors on NIT accuracy. Importantly, Agile-3+ and Agile-4 outperformed other NITs in predicting advanced fibrosis and cirrhosis, with high AUC values and minimal regional variability, suggesting their robustness across diverse settings. On the other hand, the lowest performance of the FAST score might be explained by the fact that this score was originally developed to identify patients with active steatohepatitis and not specifically to stage fibrosis or diagnose cirrhosis. Other commonly used tools, like FIB-4, showed modest-to-moderate regional differences in AUCs, sensitivity, and specificity, which were not directly attributable to the observed regional differences in patients' demographic and basic clinical parameters. These differences highlight the need for region-specific thresholds to optimize diagnostic accuracy and support the continual development and/or validation of geographically tailored NIT algorithms.[18–24]

Therefore, we aimed to identify combinations of cutoff values that would provide improved predictive value for advanced fibrosis. A high PPV ($\geq$95% in this sample) was achievable using combinations such as FIB-4 $\geq$1.36 with LSM $\geq$22.4 kPa, with some regional variability consistent with that seen for sensitivity/specificity. It is important to note that the prevalence of advanced fibrosis in our sample (35%) was likely higher than that expected in general or primary care populations, affecting observed PPV rates. However, this rate is similar to those reported in patients with T2D[8,25] and potentially other groups who are targets for risk stratification according to guidelines.[22–27] It is important to note that achieving similarly high NPV in this group of patients, with more than one-third having advanced fibrosis, was not feasible. Despite this, the findings seem to support the clinical strategy of using sequential NITs to refine fibrosis risk stratification in MASLD and minimize the need for liver biopsy in many patients.

In addition to diagnostic accuracy, the practical aspects of cost and accessibility are highly relevant for the implementation of NITs in real-world practice. Importantly, FIB-4 relies solely on age and routinely available laboratory tests, making it easily applicable in most clinical settings. By contrast, algorithms such as FAST, Agile-3+, and Agile-4 incorporate LSM, which requires access to transient elastography. While LSM has become a standard of care in many hepatology centers in the United States, it is not universally available, particularly in low-income or underserved regions of the world. The requirement for specialized equipment, trained operators, and higher costs may limit the scalability of these more advanced tools. Given that, although Agile-3+ demonstrated superior diagnostic performance, FIB-4 also showed acceptable accuracy and, thus, may remain a pragmatic first-line test with broad feasibility, especially where resources are constrained.

While this study represents one of the largest international analyses of biopsy-confirmed MASLD, several limitations should be considered. First, the observational nature of the study may introduce selection bias, particularly in centers where liver biopsy is reserved for more severe or atypical cases. Second, although we included diverse regions, some countries were underrepresented, limiting region-specific analyses; furthermore, select NITs such as ELF were only available from a limited number of participating sites. Another key limitation was the restricted range of available clinical parameters, which constrained our ability to explore and test potentially relevant hypotheses. In addition, the study did not include centrally controlled measurement of laboratory parameters or central reading of included biopsies so data consistency may be affected by differences in preanalytical handling, assay platforms, reagent lots, or calibration procedures for the blood/serum samples; operator expertise, probe selection (XL vs. M probe), or reliability criteria for VCTE; or interobserver variability for the biopsy readings.

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In conclusion, this study highlights the global heterogeneity in MASLD as well as validates the utility of NITs in diverse populations. However, the diagnostic performance of NITs varies regionally, emphasizing the potential need for population-specific cutoff values. Overall, our data support the use of NITs instead of liver biopsy in clinical practice and clinical trials of MASLD/MASH. Nevertheless, future efforts should focus on refining non-invasive diagnostic pathways tailored to regional demographics to enhance early detection and management of advanced MASLD.

DATA AVAILABILITY STATEMENT

Deidentified data used in this study may be available upon written request to the corresponding author.

AUTHOR CONTRIBUTIONS

Zobair M. Younossi was responsible for study design, study oversight, data interpretation, manuscript writing, and critical review of the final manuscript. Maria Stepanova was responsible for data analysis, data interpretation, manuscript writing, and critical review of the final manuscript. Andrei Racila and Leyla de Avila were responsible for data management, manuscript writing, and critical review of the final manuscript. All other authors were responsible for their own sites' data collection, data management as well as data interpretation, manuscript writing, and critical review of the final manuscript. All authors had access to their own data and to the analysis.

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CONFLICTS OF INTEREST

Zobair M. Younossi consults for or received grants from Intercept, Cymabay, Boehringer Ingelheim, Ipsen, Gilead, Inventiva, BMS, GSK, Novo Nordisk, Siemens Healthineers, Madrigal, Merck, Akero, and Abbott. Laurent Castera consults for and received grants from Echosens, Gilead, Madrigal, and Novo Nordisk. He consults for Boehringer Ingelheim, Boston Pharmaceutical, GSK, MSD, Pfizer, Sagimet, and Siemens Healthineers. He is on the speakers' bureau for AstraZeneca and Inventiva. Naim Alkhouri consults for, is on the speakers' bureau for, and received grants from Echosens, Gilead, Ipsen, Madrigal, Novo Nordisk, and Pfizer. He consults for and is on the speakers' bureau for Fibronostics. He consults for and received grants from 89bio, Akero, Boehringer Ingelheim, Intercept Pharmaceuticals, and Perspectum. He is on the speakers' bureau and received grants from AstraZeneca. He consults for Regeneron and Sonic Incytes. He is on the speakers' bureau for AbbVie and Mirum. He received grants from Akero Therapeutics, Arbutus Biopharma, BioAge, BMS, Corcept Therapeutics, Galectin Therapeutics, Genentech, Healio, Hepagene Therapeutics, Inventiva, Ionis Pharmaceuticals, Lilly, Merck, NGM Biopharmaceuticals, Noom, NorthSea Therapeutics, PharmaIN, Viking Therapeutics, and Zydus Pharmaceuticals. Emmanuel Tsochatzis consults for and is on the speakers' bureau for Novo Nordisk and Boehringer Ingelheim. He consults for Madrigal, Siemens Healthineers, and MSD. He is on the speakers' bureau for Echosens, AbbVie, and AstraZeneca. Stuart K. Roberts advises Novo Nordisk. Vincent Wai-Sun Wong advises, consults for, is on the speakers' bureau, and has received grants from Gilead. He advises, consults for, and is on the speakers' bureau for Echosens and AbbVie. He advises and consults for AstraZeneca, Boehringer Ingelheim, Lilly, Merck, Novo Nordisk, Pfizer, and TARGET PharmaSolutions. He is on the speakers' bureau for Abbott. He owns stock in Illuminatio Medical Technology. Yusuf Yilmaz advises Novo Nordisk. He consults for Zydus. Ming-Lung Yu consults for, is on the speakers' bureau for, and has received grants from AbbVie, BMS, Gilead, and Roche. He consults for and received grants from Abbott and Novo Nordisk. He is on the speakers' bureau for Eisai. He received grants from Merck. Mattias Ekstedt advises AMRA Medical AB and Decisive Consulting. He is on the speakers' bureau for Novo Nordisk, Echosens, and All About Meetings. He received grants from Takeda and AstraZeneca. Claudia P. Oliveira consults for, is on the speakers' bureau for, and received grants from Novo Nordisk and Boehringer Ingelheim. She received grants from Merz. Mario Guimaraes Pessoa consults for and is on the speakers' bureau for Novo Nordisk. He consults for and received grants from Boehringer Ingelheim and GSK. He is on the speakers' bureau for Leo Pharma. He received grants from Takeda and Intercept. Wah Kheong Chan advises and is on the speakers' bureau for and received grants from Abbott and Roche. He advises and consults for Boehringer Ingelheim. He advises AbbVie, Ipsen, and Zuellig. He is on the speakers' bureau for Echosens, Hisky Medical, and Viatris. George Papatheodoridis advises and is on the speakers' bureau for, and received grants from AbbVie and Roche. He advises and is on the speakers' bureau for AstraZeneca, Gilead, Ipsen, and Novo Nordisk. He advises GSK. Giada Sebastiani consults for and is on the speakers' bureau for Novo Nordisk, Gilead, and Lilly. She is on the speakers' bureau for AbbVie and Merck. Cristiane Villela-Nogueira consults for and is on the speakers' bureau for Novo Nordisk and Boehringer Ingelheim. Roberta D'Ambrosio advises, consults for, is on the speakers' bureau for, and has received grants from AbbVie. She advises, consults for, and is on the speakers' bureau for Gilead. Pietro Lampertico advises and is on the speakers' bureau for

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AbbVie, Altona, Aligos, Antios, Eiger, Gilead, GSK, Grifols, Janssen, MYR, Roboscreen, Roche, and Vir. Cyrielle Caussy consults for and received grants from Novo Nordisk. She consults for Boehringer Ingelheim and MSD. She received grants from Lilly, AstraZeneca, Echosens, Gilead, Madrigal, and E-scopics. Brian Pearlman is on the speakers' bureau for AbbVie. Rida Nadeem advises Boehringer Ingelheim. She is employed by Arizona Liver Health. Johan Vessby advises Novo Nordisk and Janssen. Takumi Kawaguchi is on the speakers' bureau for ASKA, Taisho, Kowa, AbbVie, Eisai, EA Pharma, Boehringer Ingelheim, Sumitomo Pharma, Novo Nordisk, Otsuka Pharma, and Janssen. Francesco Paolo Russo is on the speakers' bureau and has received grants from Gilead and Biotest. He advises GSK. He is on the speakers' bureau for AbbVie. Berenice Segrestin consults for and received grants from Lilly and RHYTHM. She received grants from Novo Nordisk. Nadege Gunn is on the speakers' bureau for Madrigal, Gilead, Ipsen, Novo Nordisk, and Boehringer Ingelheim. Didac Mauricio advises and is on the speakers' bureau for Novo Nordisk, Sanofi, and Abbott. He advises Amrana Therapeutics, Daiichi Sankyo, AB Biotics, and Lilly. He is on the speakers' bureau for Menarini and Medtronic. Marco Arrese advises AstraZeneca. He consults for Inventiva. He is on the speakers' bureau for Siemens Healthineers and Novo Nordisk. Brian Lam advises and is on the speakers' bureau for Madrigal. He advises 89bio. The remaining authors have no conflicts to report.

GUARANTOR

Zobair M. Younossi is the guarantor of this work and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of the manuscript.

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