

# AGILE3+ DEVELOPMENT AND VALIDATION: NOVEL FIBROSCAN BASED SCORE TO DIAGNOSE ADVANCED FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE PATIENTS

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## INTRODUCTION

Although NAFLD is common<sup>1-3</sup>, only those with advanced fibrosis (F≥3) and cirrhosis are at significantly higher risk of liver related mortality<sup>4,5</sup>.

Available noninvasive tests, including FIB-4 and liver stiffness measurement (LSM) by Vibration Controlled Transient Elastography (VCTE) are highly effective in excluding advanced fibrosis yet their ability to rule it in is moderate<sup>6</sup>.

Agile 4 score combining LSM with simple clinical parameters was recently introduced to better rule-in cirrhosis<sup>7</sup>. Our objective was to develop and validate a new score (Agile 3+), combining LSM with routine clinical parameters to identify advanced fibrosis in NAFLD patients, with optimized positive predictive value (PPV) and reduced cases with indeterminate results.

## METHOD

### Sites and patient population

This multi-national, retrospective study included 7 cohorts of NAFLD adults with liver biopsy, LSM by VCTE, and blood sampling in routine clinical practice or during clinical trials screening.

The population was randomly divided into:

- A training set (TS; n=1434; F≥3 prevalence: 54%), on which the best fitting logistic regression model was built
- An internal validation set (VS; n=700; F≥3 prevalence: 54%), on which performance and goodness of fit of the model were assessed.

Agile 3+ was externally validated in :

- NASH CRN cohort (8 US centers, n=585; F≥3 prevalence: 37%)
- French NAFLD cohort (3 centers, n=1042; F≥3 prevalence: 38%).

### Statistical analysis

#### Score and cut-off development – Training set

14 variables were considered for combination with LSM. Multivariate logistic regression model. Rule-out (high sensitivity) and rule-in (high specificity) cut-off values chosen to:

- Decrease number of indeterminate cases
- Increase PPV in rule-in zone.

#### Validation

AUROC comparison using Delong test. Comparison with FIB-4 and LSM using cut-off from training set (avoid optimism bias).

F3/F4 prevalence higher in training and internal validation sets; reported predictive values adjusted to external validation sets prevalence.

## RESULTS

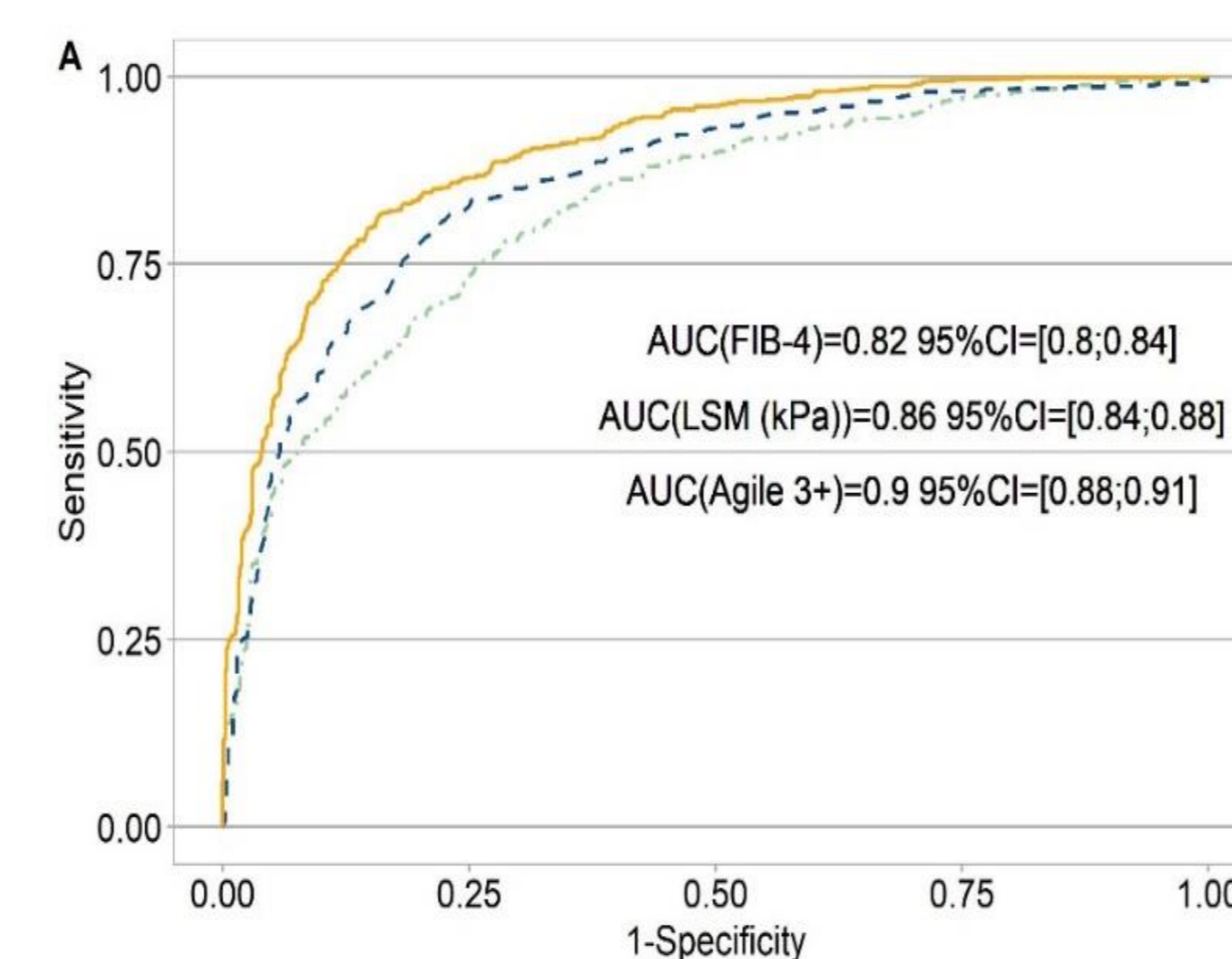
### Patient characteristics

	Training	Internal validation	NASH CRN external validation	French NAFLD external validation
N	1434	700	585	1042
Age (years)	55.0 (16.0)	55.5 (16.0)	54.0 (17.0)	58.0 (15.4)
Male sex	729 (50.8%)	359 (51.3%)	219 (37.4%)	622 (59.7%)
BMI (kg/m <sup>2</sup> )	31.7 (7.8)	31.6 (8.1)	34.6 (9.1)	31.2 (7.7)
Diabetes	723 (50.4%)	357 (51.0%)	268 (45.8%)	508 (48.8%)
AST (U/L)	39 (31)	38 (29)	37 (28)	40 (26)
ALT (U/L)	49 (47)	47 (45)	48 (42)	57 (45)
GGT (U/L)	58 (70)	61 (72)	43 (53)	78 (106)
Platelet count (G/L)	219 (94)	222 (95)	228 (92)	218 (85)
Fibrosis stage				
F0	202 (14.1%)	97 (13.9%)	121 (20.7%)	116 (11.1%)
F1	269 (18.8%)	130 (18.6%)	134 (22.9%)	240 (23.0%)
F2	191 (13.3%)	93 (13.3%)	116 (19.8%)	286 (27.5%)
F3	437 (30.5%)	215 (30.7%)	139 (23.8%)	267 (25.6%)
F4	335 (23.4%)	165 (23.6%)	75 (12.8%)	133 (12.8%)

Median [IQR] or N (%)

### Performance in training set

#### - ROC curve



ROC curves of FIB-4, LSM and Agile 3+ for the diagnosis of advanced fibrosis in the training set

### Performance in validation sets

#### - AUROCs

	Internal VS			NASH CRN cohort			French NAFLD cohort		
	FIB-4	LSM	Agile 3+	FIB-4	LSM	Agile 3+	FIB-4	LSM	Agile 3+
AUC [95% CI]	0.84 [0.81;0.86]	0.85 [0.82;0.88]	<b>0.90</b> [0.88;0.92]	0.78 [0.74;0.82]	0.83 [0.80;0.87]	<b>0.86</b> [0.84;0.89]	0.78 [0.76;0.81]	0.84 [0.81;0.86]	<b>0.87</b> [0.85;0.89]
Delong test p-value (vs Agile 3+)	< 0.0001	< 0.0001	NA	< 0.0001	0.0042	NA	< 0.0001	0.0011	NA

#### - Dual cut-off approach

	Internal VS			NASH CRN cohort			French NAFLD cohort		
	FIB-4	LSM	Agile 3+	FIB-4	LSM	Agile 3+	FIB-4	LSM	Agile 3+
Rule-out cut-off <sup>#</sup>	<1.12	<9.2 kPa	<0.451	<1.12	<9.2 kPa	<0.451	<1.12	<9.2 kPa	<0.451
% patients	36%	41%	42%	41%	55%	54%	35%	57%	53%
Se/Sp	0.84/0.61	0.83/0.69	<b>0.87/0.76</b>	0.86/0.56	0.76/0.73	<b>0.82/0.75</b>	0.88/0.49	0.75/0.77	<b>0.83/0.75</b>
NPV	0.87*	0.88*	0.91*	0.88	0.84	0.88	0.87	0.83	0.87
LR-	0.26	0.24	0.17	0.24	0.33	0.24	0.25	0.33	0.23
Indeterminate <sup>#</sup>	[1.12;1.81]	[9.2;13.6] kPa	[0.451; 0.679]	[1.12;1.81]	[9.2;13.6] kPa	[0.451; 0.679]	[1.12;1.81]	[9.2;13.6] kPa	[0.451; 0.679]
% patients	28%	24%	<b>17%</b>	31%	20%	<b>13%</b>	32%	20%	<b>18%</b>
Rule-in cut-off <sup>#</sup>	≥1.81	≥13.6 kPa	≥0.679	≥1.81	≥13.6 kPa	≥0.679	≥1.81	≥13.6 kPa	≥0.679
% patients	36%	36%	42%	28%	25%	30%	33%	23%	29%
Se/Sp	0.57/0.90	0.57/0.90	<b>0.69/0.91</b>	0.50/0.84	0.53/0.91	<b>0.61/0.87</b>	0.56/0.82	0.48/0.92	<b>0.61/0.90</b>
PPV	0.77*	0.77*	0.81*	0.64	0.78	0.73	0.65	0.79	0.79
LR+	5.56	5.71	7.33	3.11	6.12	4.70	3.04	5.86	6.20

<sup>#</sup> using 85% Se and 90% Sp cut-off values derived on the training set for FIB-4, LSM and Agile 3+; \*adjusted to a prevalence of 37% for F≥3;

### Agile 3+ score



## CONCLUSIONS

A novel noninvasive score including LSM by VCTE and routine clinical parameters significantly improve the diagnostic accuracy, improve the sensitivity to rule-in, reduce the percentage of cases with indeterminate results.

Moreover, external validation on primary and secondary care centers could assess its potential as a new tool to refer patients to liver specialists.



This new Agile 3+ score is public and available on myFibroScan app.

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