New blood test multi-targeted for liver fibrosis outperforms elastometry for most outcomes

Paul Calès, Jérôme Boursier, Frédéric Oberti, Valérie Moal, Isabelle Fouchard Hubert, Sandrine Bertrais, Gilles Hunault, Marie Christine Rousselet and multicentric groups (SNIFF, ANRS HC 23)
University Hospital, Angers, France

Background & aim

Most blood tests for liver fibrosis are targeted, by construction, for a single diagnostic target, usually significant fibrosis.
However, in clinical practice, another important diagnostic target is cirrhosis for which the non-invasive diagnostic reference is elastography.
The only blood test targeted for cirrhosis (CirrhoMeter: CM) by construction had a better accuracy for cirrhosis than the test using the same biomarkers targeted for significant fibrosis (FibroMeter: FM).
However, it was difficult to use simultaneously both tests in the same patient.
Therefore, we have recently developed a new statistical method to dispose a unique blood test having multiple diagnostic targets, called multi-targeted FibroMeter (MFM).
Our **aim** was to compare the accuracy of MFM and liver vibration controlled transient elastography (VCTE) by Fibroscan.

Methods

1746 patients with chronic liver disease of various etiologies were included.
Reference was Metavir fibrosis (F) staging by liver biopsy.
Liver automated morphometry was available in a subgroup of 484 patients.
The 4 judgement criteria included:

- AUROC for significant fibrosis (≥F2) or cirrhosis,
- Obuchowski index evaluating AUROC for all F stages,
- The rate (%) of correctly classified patients by non-invasive classifications (including 6 fibrosis classes from F0/1 to F4).

Objective: these criteria had to be significantly increased for MFM compared to VCTE, except equivalence required for cirrhosis AUROC.
MFM included hyaluronate (MFM^{V2G}) or not (MFM^{V3G}).

Results

MFMs and FMs were derived in another population of 1012 patients with chronic hepatitis C; thus, there was no optimism bias in the comparisons.
The 4 judgement criteria were reached with MFM^{V2G} (tables 1 & 2, figures 1 & 2).
When comparing a blood test and VCTE, MFM^{V2G} provided a statistical advantage over FM^{V2G} in 3 out of the 4 judgement criteria (table 2).
The Spearman correlation coefficient between non-invasive tests and pathological characteristics are described in the following table:

	FM^{V2G}	MFM^{V2G}	VCTE
Metavir F	0.619	0.635	0.600
Area of porto-septal fibrosis	0.534	0.543	0.550

Table 1. Diagnostic performance of FibroMeter family and VCTE in 1746 patients.

	AUROC for				Obuchowski index		Classification	
	F≥1	F≥2	F≥3	F=4	Value	Rank	Rate (%)	Rank
FibroMeter^{V2G}	**0.783**	**0.819**	0.811	0.857	0.776	2	79.1	4
Multi-FibroMeter^{V2G}	0.765	0.817*	**0.825**	0.885*	**0.777***	1	**83.0***	1
FibroMeter^{V3G}	0.760	0.806	0.797	0.832	0.758	4	75.7	5
Multi-FibroMeter^{V3G}	0.745	0.804	0.804	0.860	0.759	3	82.7*	2
VCTE	0.708	0.786	0.844	**0.898**	0.755	5	80.0	3

The best result per diagnostic target is indicated in bold. * depicts a reached objective criterion. Color codes: AUROC and classification: <0.7, 0.7-0.8, 0.8-0.9, >0.9; Obuchowski index: <0.6, 0.6-0.7, 0.7-0.8, 0.8-0.9.

Table 2. Comparison of Multi-FibroMeters and FibroMeters with VCTE in the classification metric in 1746 patients.

	Correctly classified patients	
	Rate (%)	*p vs VCTE[a]*
FibroMeter^{V2G}	79.1	*0.446*
Multi-FibroMeter^{V2G}	83.0*	***0.004***
VCTE	80.0	-
FibroMeter^{V3G}	75.7	***<0.001***
Multi-FibroMeter^{V3G}	82.7*	***0.013***
Tests^{V2G} VCTE comparison (p [b])	***<0.001***	-
Tests^{V3G} VCTE comparison (p [c])	***<0.001***	-
Test^{V2G} vs Test^{V3G} (p [d]):		
FibroMeters	***<0.001***	-
Multi-FibroMeters	*0.545*	-

Significant differences (p) are shown in bold. * depicts a reached objective criterion. Red characters indicate a significant gain of Multi-FibroMeters vs corresponding FibroMeter in the comparison with VCTE. Color codes: 0.7-0.8, 0.8-0.9, >0.9.
[a] Comparison of Multi-FibroMeter or FibroMeter with VCTE by paired McNemar test.
[b] Comparison of FibroMeter^{V2G}, Multi-FibroMeter^{V2G} and VCTE by paired Cochran test.
[c] Comparison of FibroMeter^{V3G}, Multi-FibroMeter^{V3G} and VCTE by paired Cochran test.
[d] Comparison of FibroMeter^{V2G} vs FibroMeter^{V3G} or Multi-FibroMeter^{V2G} vs Multi-FibroMeter^{V3G} by paired McNemar test.

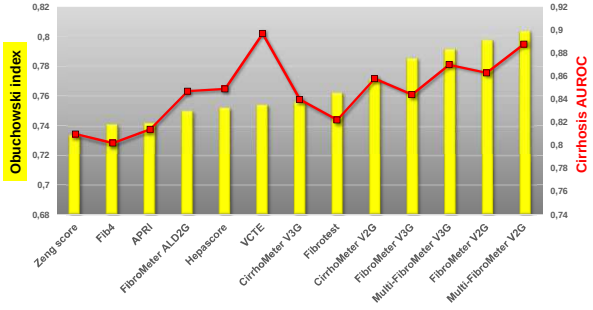

Figure 1. Comparison of AUROCs for cirrhosis and Obuchowski indices between 13 tests in a group of 641 patients. Tests are ranked according to increasing Obuchowski index. This graph shows that AUROCs for cirrhosis and Obuchowski indices are globally proportional with one noteworthy exception: VCTE (Fibroscan).

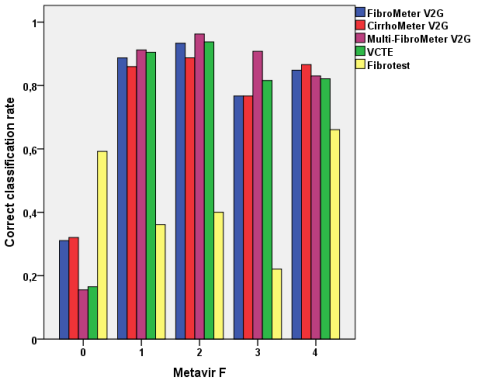

Figure 2. Correct classification rate of 5 tests, with available classification metrics, as a function of Metavir F stages in a group of 1017 patients.

Conclusion

Multi-targeting biomarkers very significantly improves the fibrosis staging accuracy of classical single-targeted blood tests in comparison with VCTE.
This allows a blood test to outperform VCTE for overall fibrosis staging and even matching VCTE for cirrhosis diagnosis.

Conflicts of interest: Paul Calès, Jérôme Boursier: Echosens consultancy