APPENDIX 1

LIST OF COINVESTIGATORS

*APHP: Hôpital Beaujon Professor P Bedossa, Dr F Degos, Professor P Marcellin, Professor M Vidaud; Hôpital Cochin-Necker: Professor S Pol, Professor Ph Sogni, Professor Salmon; Hôpital Jean Verdier: Dr A Mahmoudi; Hôpital Paul Brousse: Professor D Samuel, Dr B Roche; Hôpital Saint Antoine: Professor Poupon, Dr L Serfaty; Hôpital Pitié-Salpétrière: Professor Katlama, Dr Munteanu, Dr Lebray; CHU Amiens: Dr E Nguyen Khac; CHU Angers: Professor P Cales; CHU Besançon: Professor V Di Martino; CHU Bordeaux Pessac: Professor V de Ledinghen; CHU Brest: Professor JB Nousbaum; CHU Clermont Ferrand: Dr A Abergel; CHU Grenoble: Professor JP Zarski; CHU Lille: Professor Ph Mathurin; CHU Limoges: Dr D Loustau-Ratti; CHU Hôtel Dieu Lyon: Professor C Trépo; Hôpital Saint Joseph Marseille: Dr M Bourlière; CHU Montpellier: Professor D Larrey; CHU Nice: Professor A Tran; CHU Nancy: Professor JP Bronowicki; CHU Nantes: Dr J Gournay; Hôpital d'Orleans: Dr X Causse; CHU Rennes: Professor D Guyader; CHU Tours: Professor Y Bacq; CHU Strasbourg: Professor M Doffoel.

APPENDIX 2

TECHNIQUE RECOMMENDED FOR FIBROSCAN®

The right lobe of the liver is targeted through an intercostal space access while the patient is lying in the dorsal decubitus position with the right arm in maximal abduction. An area of the liver at least 6 cm thick and free of large vessels is identified for examination under FibroScan® guidance. The rate of successful measurements, i.e. the ratio of validated to total measurements, is calculated by the machine. Liver elasticity is expressed as the median value of all valid measurements in kiloPascals (kPa).

APPENDIX 3

DETAILS OF THE COMPONENTS OF LIVER FIBROSIS BIOMARKERS

Fibrometre® score includes platelet count, prothrombine time, urea, aspartate aminotransferase-AST, hyaluronic acid, alpha2-macroglobulin

Fibrotest® score includes alpha 2 macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, gamma-glutamyl transpeptidase-GGT and taking into account gender and age. At the request of the manufacturer, alanine aminotransferase (ALT) results of each patient were provided to Biopredictive for interpreting Fibrotest® scores.

APRI: ratio AST/platelet count

Hepascore includes alpha2-macroglobulin, hyaluronic acid, bilirubin, GGT

APPENDIX 4

REPRODUCIBILITY OF THE METAVIR FIBROSIS SCORE: INTER-OSERVER AGREEMENT OF METAVIR RESULTS BETWEEN CENTRAL LABORATORY AND ON SITE READINGS

METHODS

A sample of 400 liver biopsies > 20 mm was randomly selected for central assessment of the METAVIR score at Hôpital Beaujon.

Agreement between METAVIR scores, as measured by each center and by the central pathology laboratory, was assessed by estimating weighted (five-point METAVIR score) and crude (presence versus absence of significant fibrosis or cirrhosis) Kappas (Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley and Sons 1981).

RESULTS

Overall, 287 biopsies were available for evaluating agreement between on site and central laboratory METAVIR assessments.

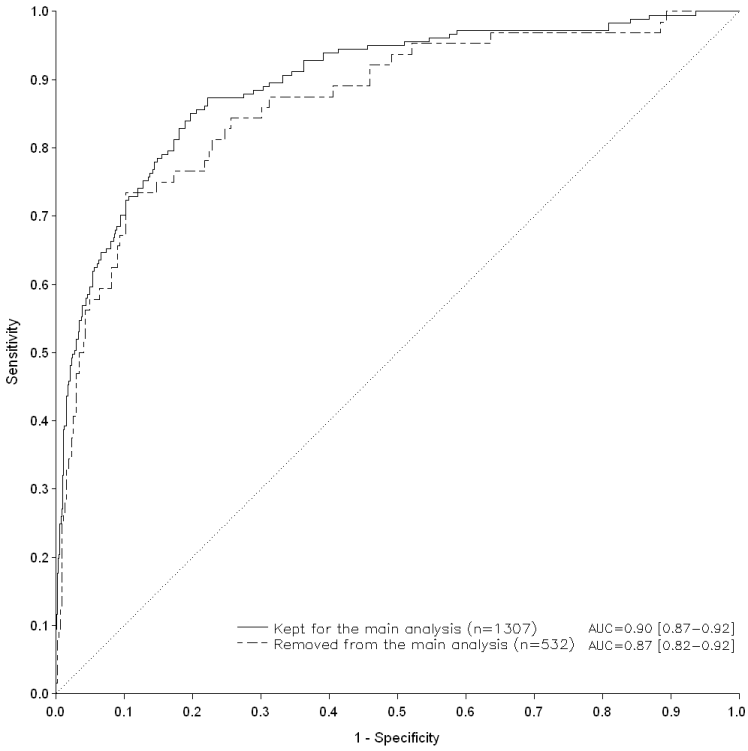
Agreement was substantial when calculated on the five-point score ($\kappa w = 0.72$; 95%CI 0.59-0.85) and for the diagnosis of cirrhosis ($\kappa = 0.74$; 95%CI 0.68-0.80). It was moderate for the diagnosis of presence versus absence of significant fibrosis ($\kappa = 0.51$; 95%CI 0.41-0.61).

APPENDIX 5

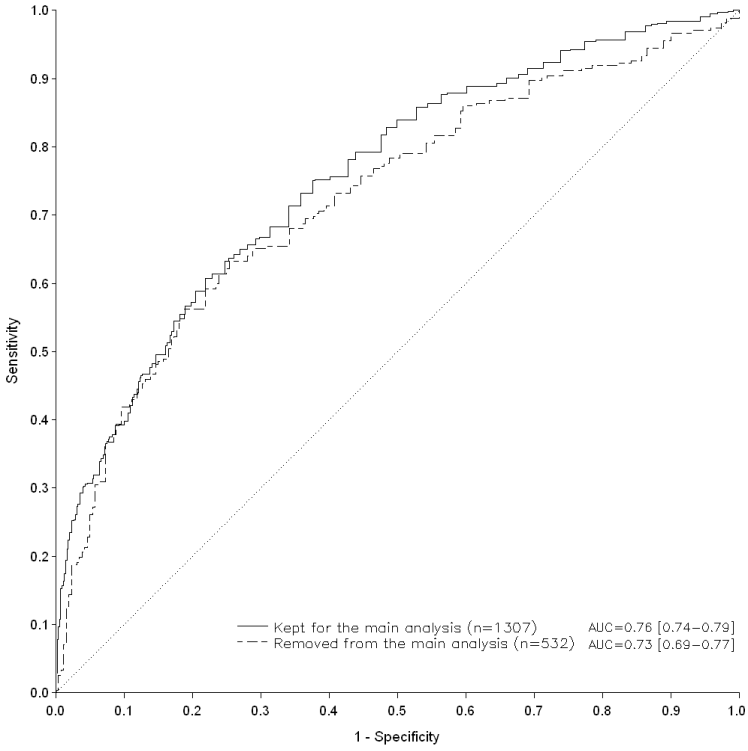
Figures 5.1.1. to 5.3.2. ROC curves of Transient elastography in the diagnosis of cirrhosis and significant fibrosis according to patient subgroups (AUC and 95%CI) (FIBROSTIC study, France, 2006-2008).

5.1. Patients included in the primary analysis vs. not included (patients with protocol deviation, mostly according to eligibility criteria of Fibroscan® examinations)

5.1.1 Diagnosis of cirrhosis

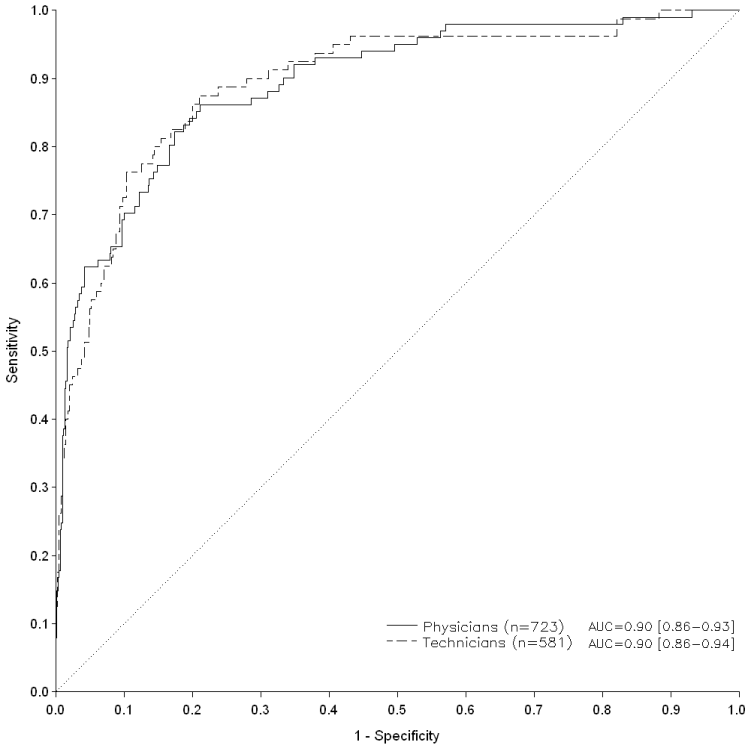


5.1.2 Diagnosis of significant fibrosis

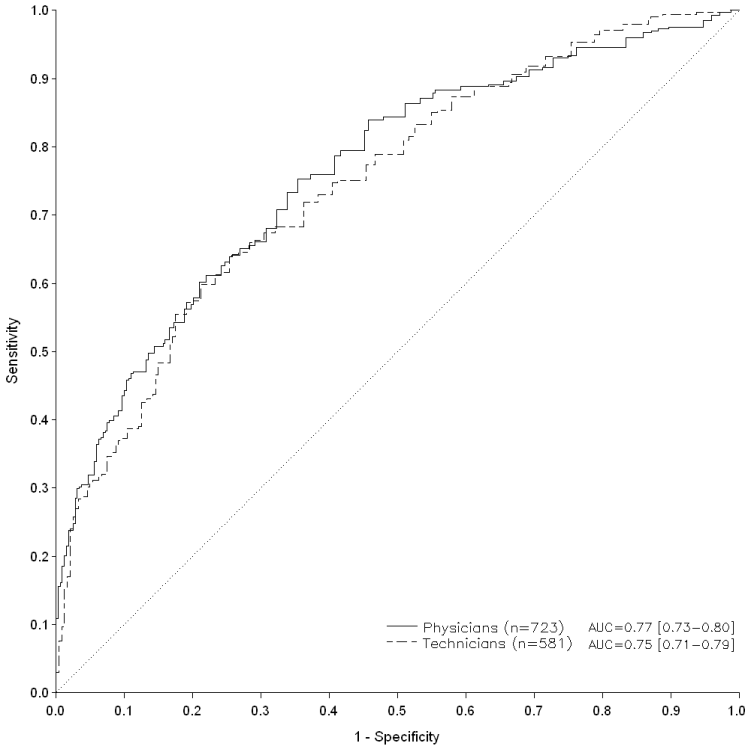


5.2. Operator of Fibroscan® examinations: physician vs. technician*

5.2.1 Diagnosis of cirrhosis



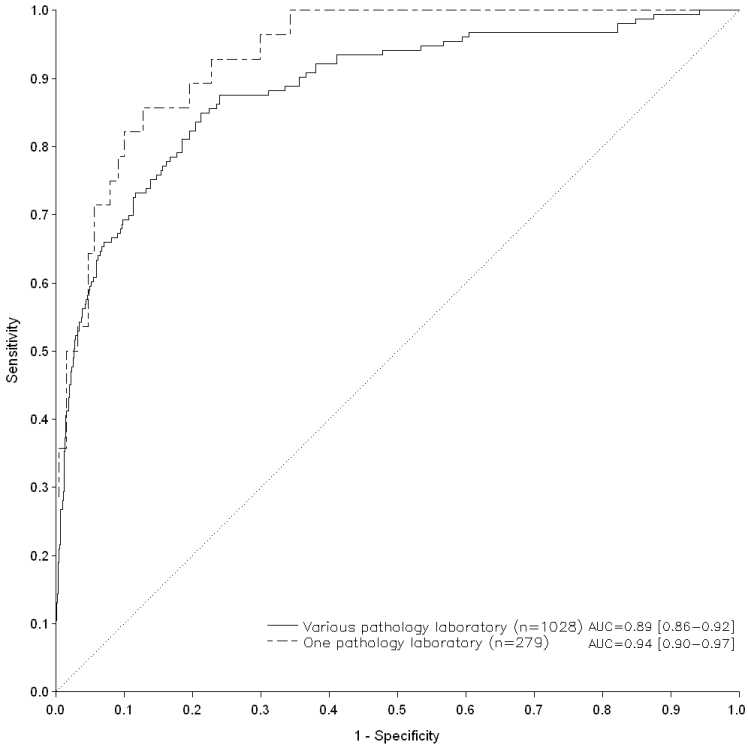
5.2.2 Diagnosis of significant fibrosis



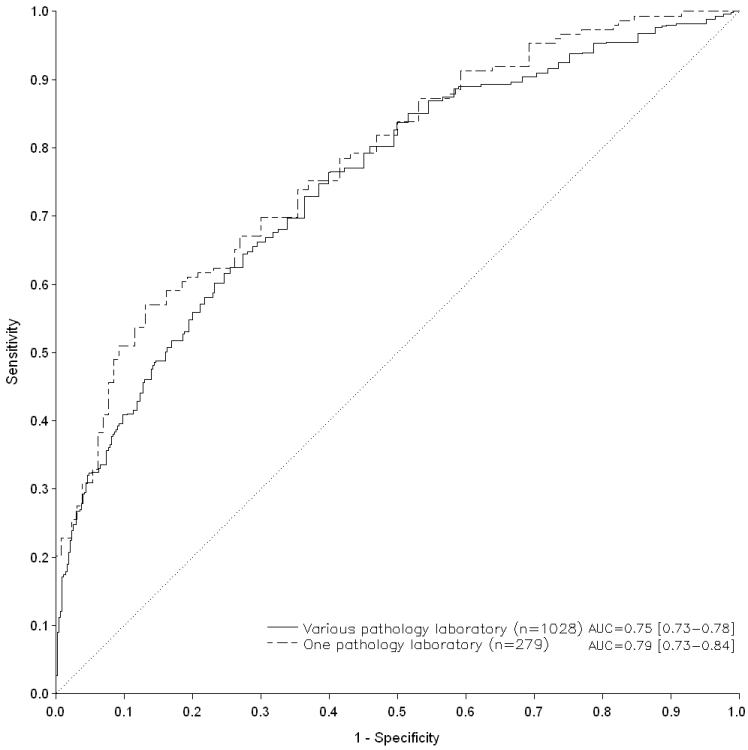
* Transient elastography was carried out by physicians (55% of patients) or trained technicians (45%). Technicians complied with procedure recommendations more often than physicians did (77% vs. 67% of patients).

5.3. Pathology laboratory: on site, various laboratories vs. on site, central laboratory only

5.3.1 Diagnosis of cirrhosis

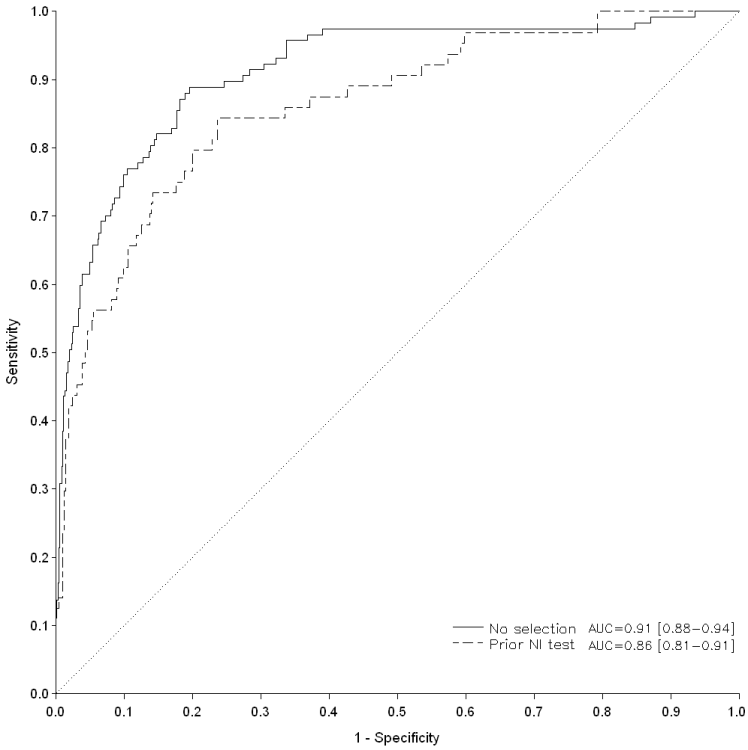


5.3.2 Diagnosis of significant fibrosis

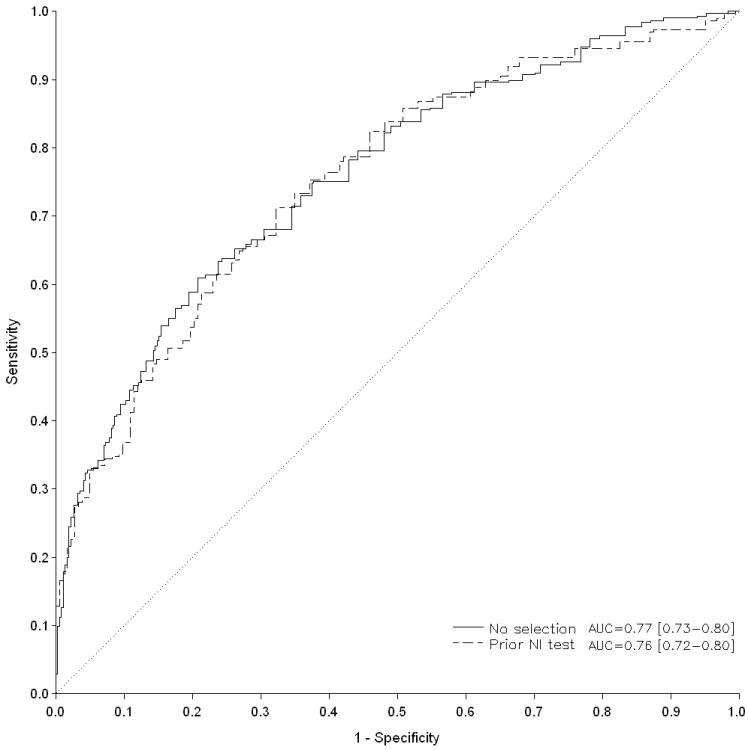


5.4. Selection of patients for liver biopsy (and inclusion in the study): according to previous non-invasive tests of liver fibrosis or not

5.4.1 Diagnosis of cirrhosis

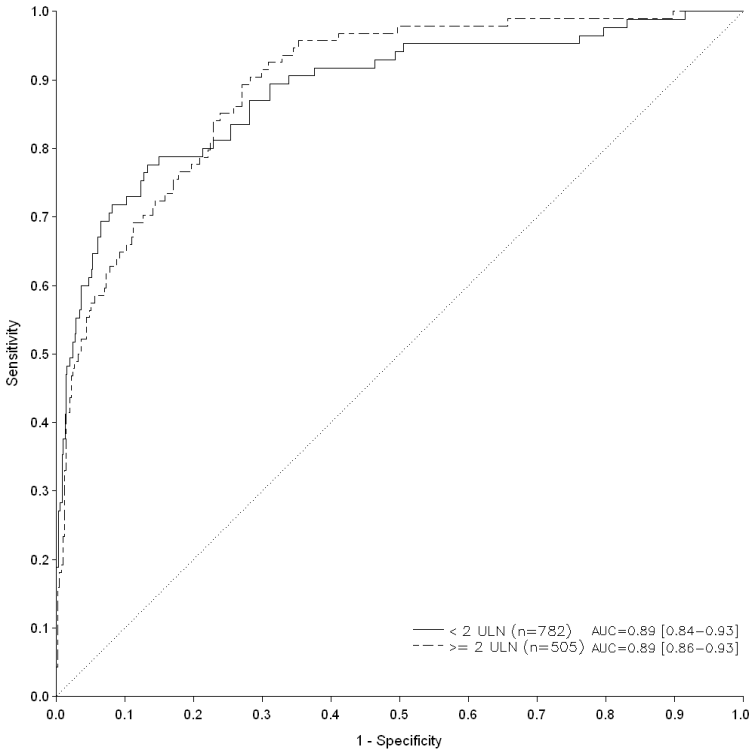


5.4.2 Diagnosis of significant fibrosis

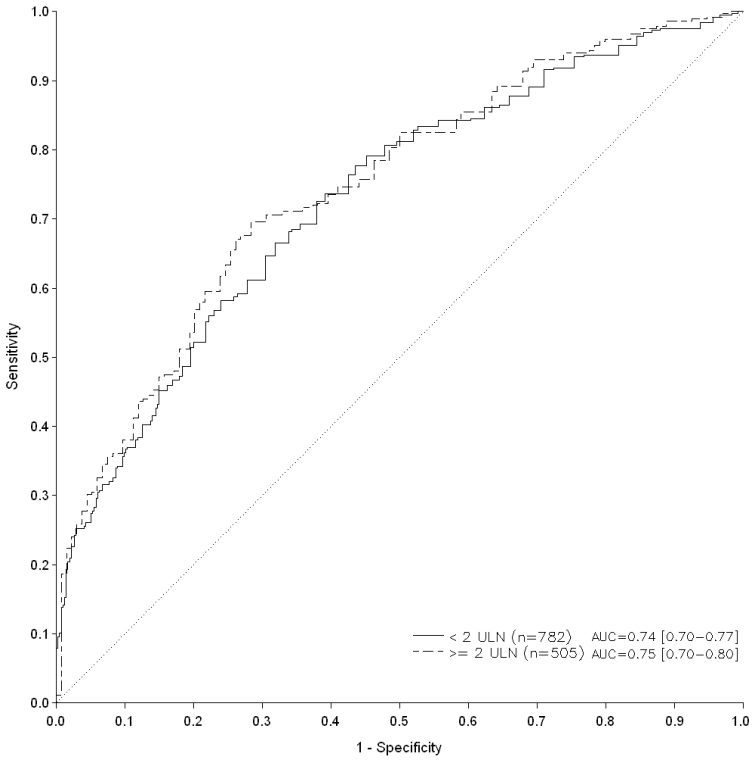


5.5. Patients with high vs. low alanine aminotransferase level (ALT≥ 2 x Upper limit of normal vs. ALT<2 x Upper limit of normal)

5.5.1 Diagnosis of cirrhosis



5.5.2 Diagnosis of significant fibrosis



APPENDIX 6

Cross tabulation between transient elastography results (elasticity above or below the cut-off) and liver biopsy results (METAVIR Fibrosis score) in the diagnosis of cirrhosis and significant fibrosis (FIBROSTIC Study, France, 2006-2008).

Diagnosis of cirrhosis

	METAVIR score		
	= F4	< F4	Total
Elasticity			
≥ 12.9 kPa	127	111	238
< 12.9 kPa	54	1015	1069
Total	181	1126	1307

Diagnosis of significant fibrosis

	METAVIR score		
	≥ F2	< F2	Total
Elasticity			
≥ 5.2 kPa	672	370	1042
< 5.2 kPa	74	191	265
Total	746	561	1307

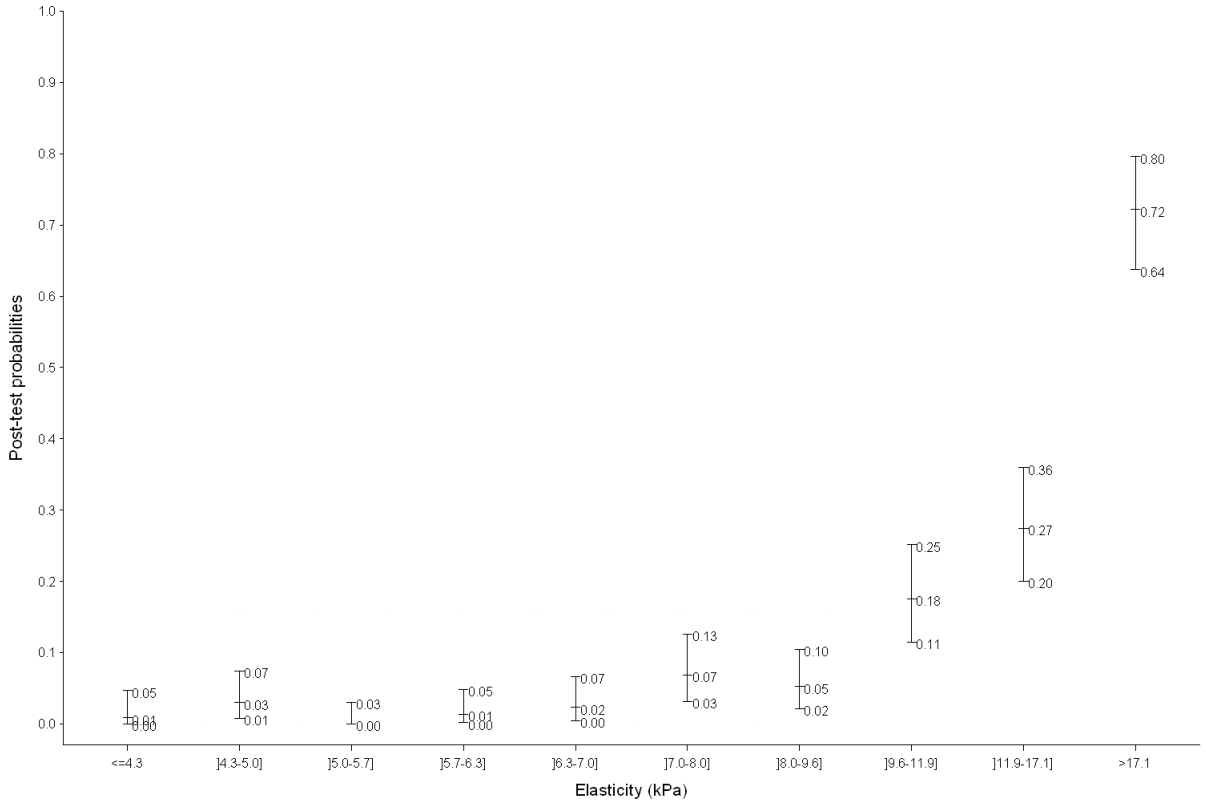
APPENDIX 7

Figures 7.1.1. to 7.5.2. Post-test probability* of the target condition (cirrhosis or significant fibrosis) and 95% CIs (y axis) for the deciles of results (x axis) of five non-invasive tests of liver fibrosis (FIBROSTIC study, France, 2006-2008).

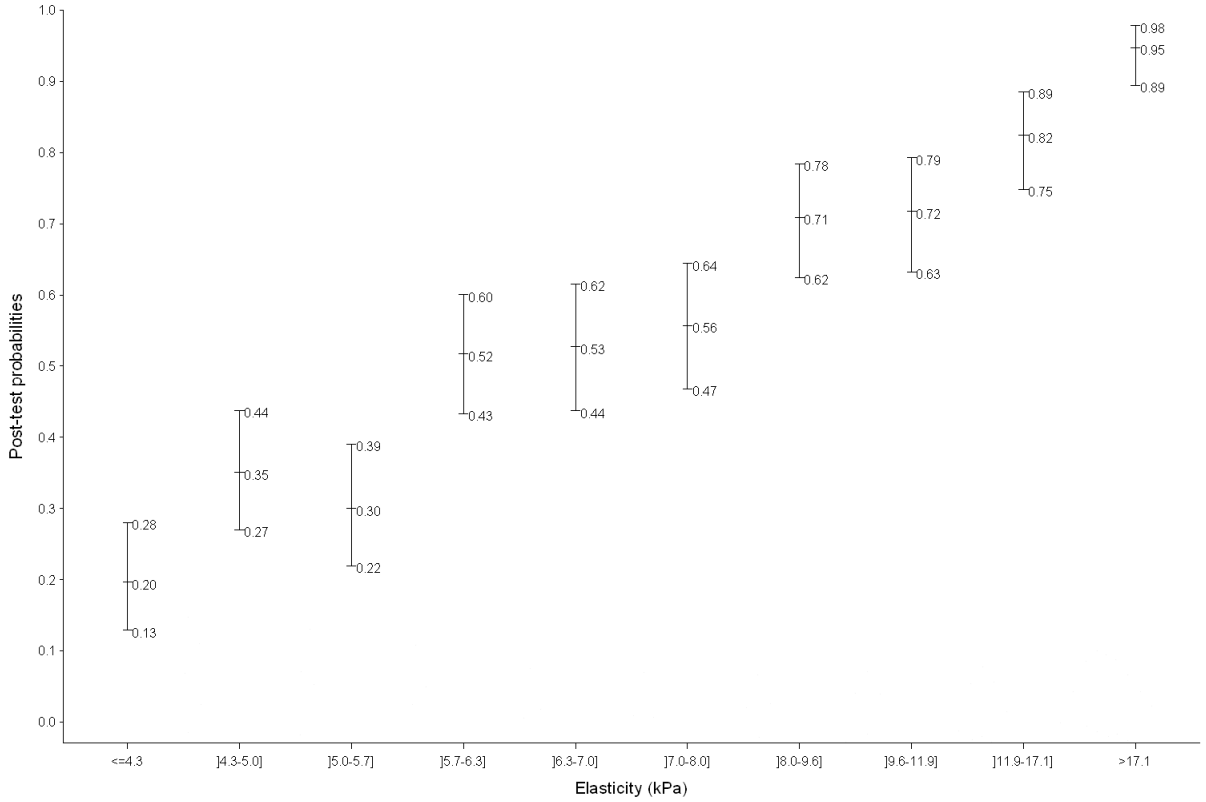
*** Post-test probabilities obtained in a study population with a 13.8% prevalence of cirrhosis and a 57.1% prevalence of significant fibrosis**

7.1. Transient elastography (Fibroscan®)

7.1.1. Diagnosis of cirrhosis

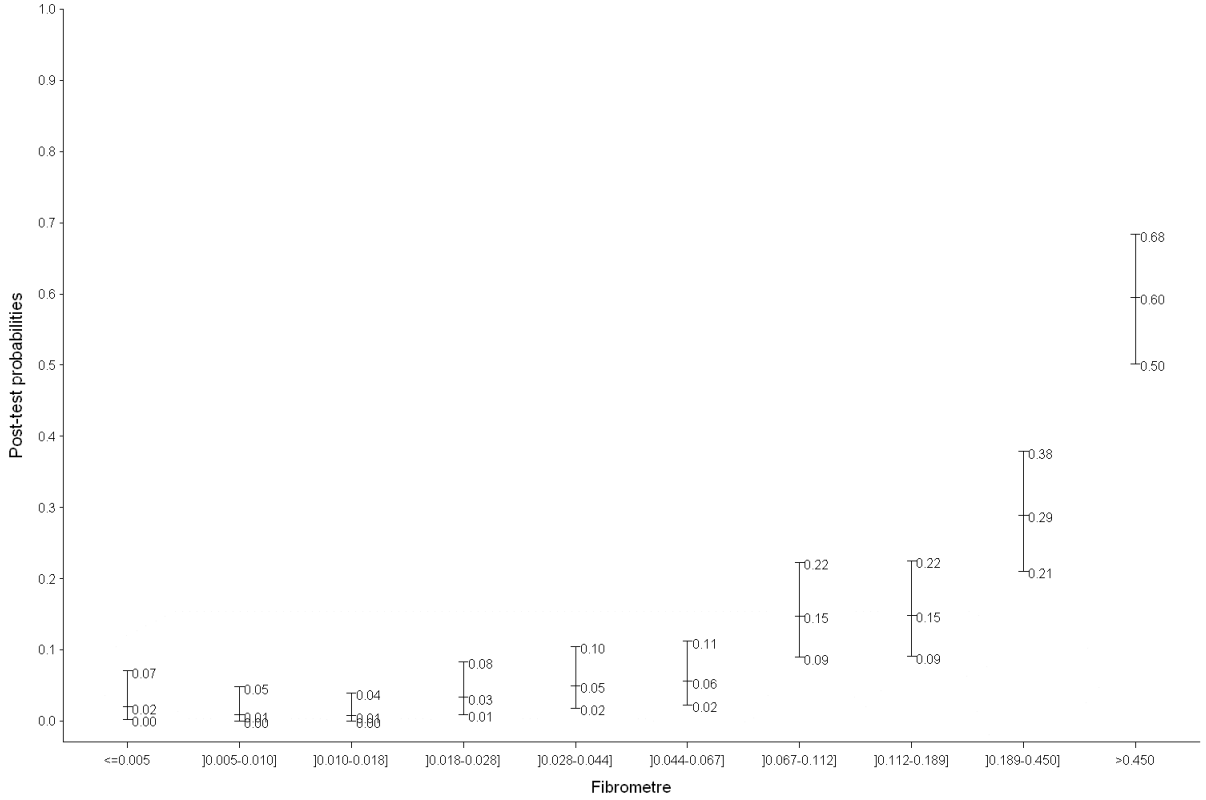


7.1.2. Diagnosis of significant fibrosis

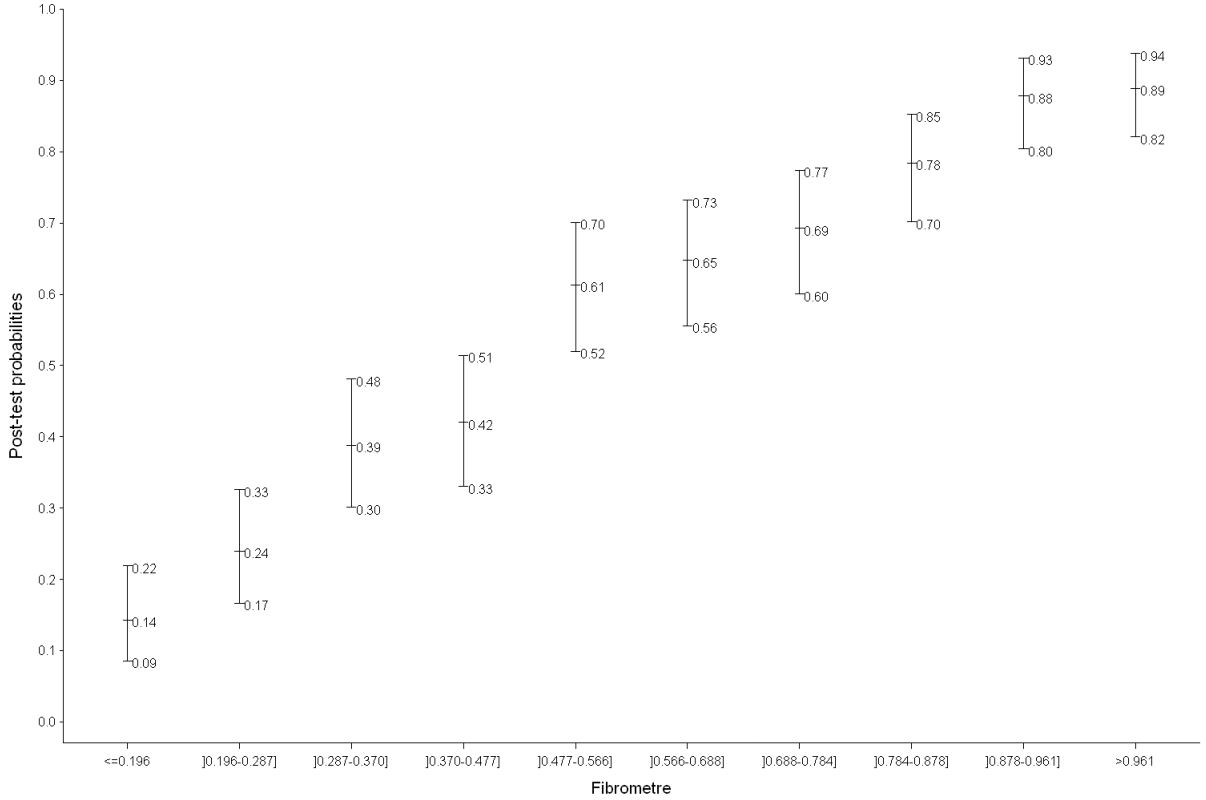


7.2. Fibrometre®

7.2.1. Diagnosis of cirrhosis

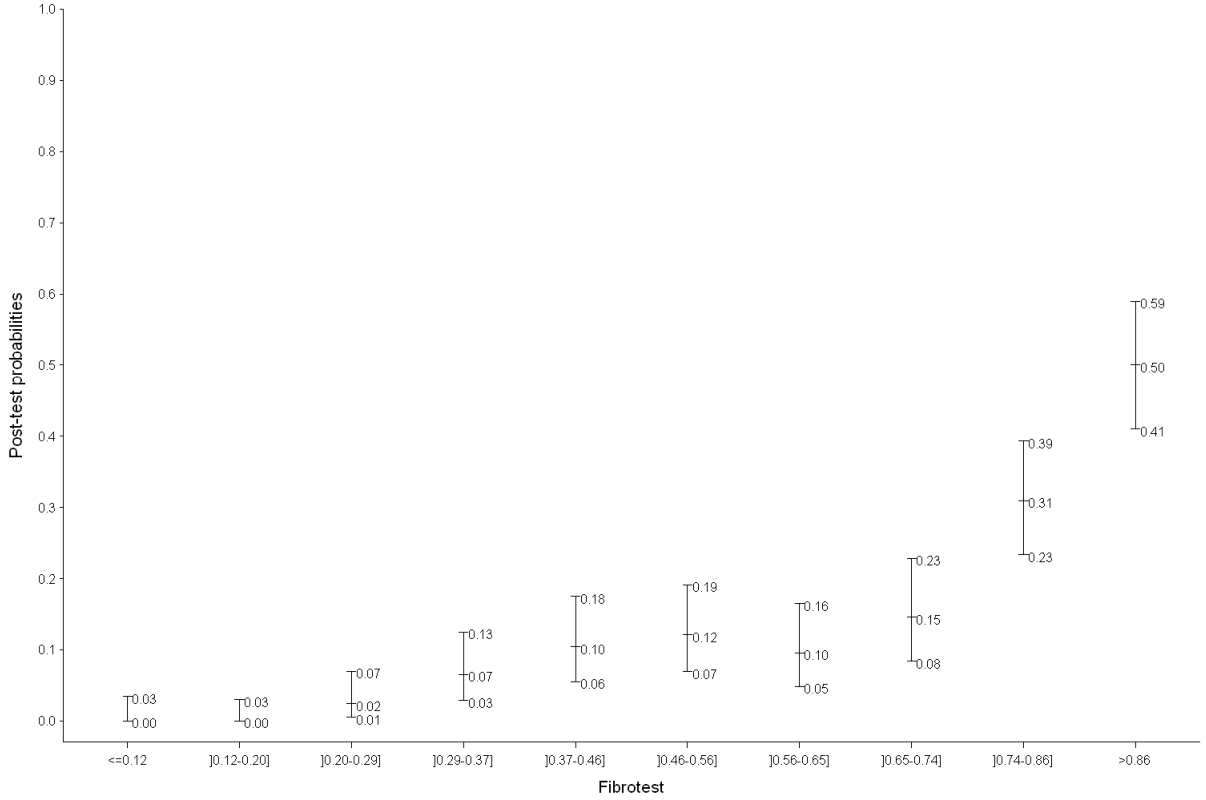


7.2.2. Diagnosis of significant fibrosis

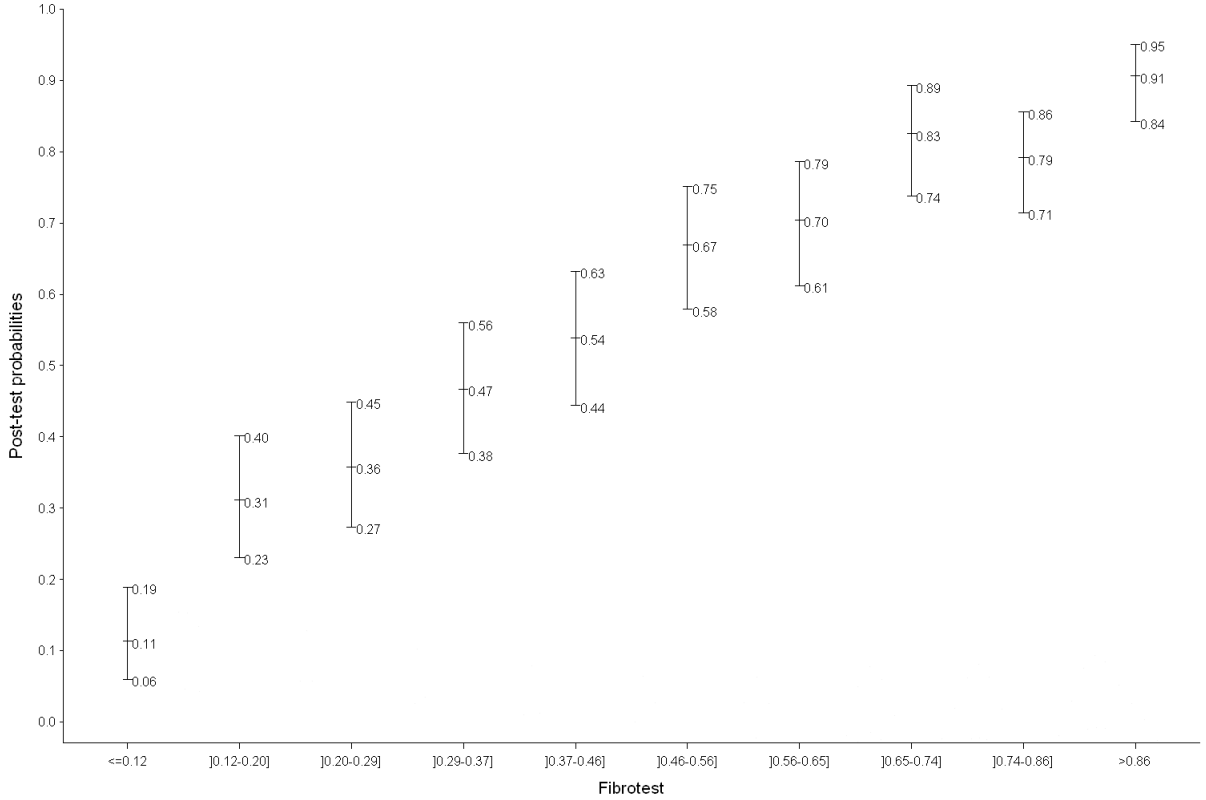


7.3. Fibrotest®

7.3.1. Diagnosis of cirrhosis

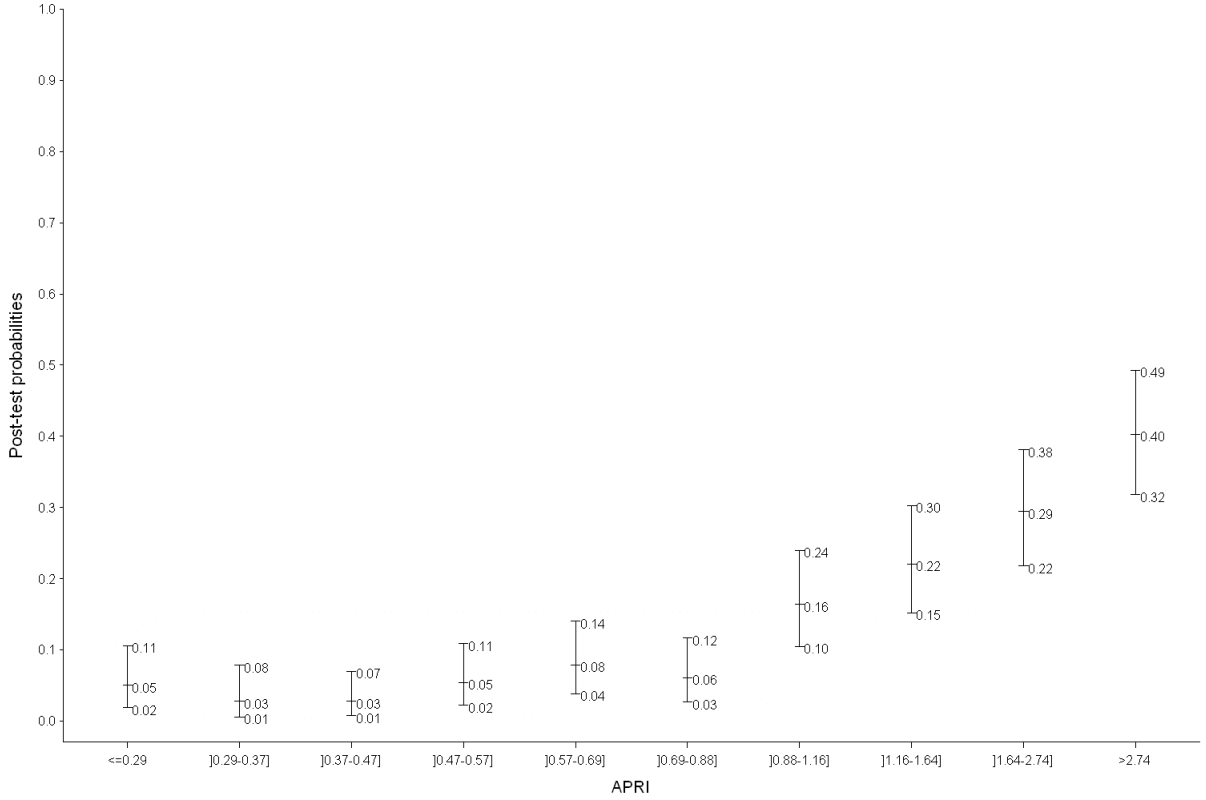


7.3.2. Diagnosis of significant fibrosis

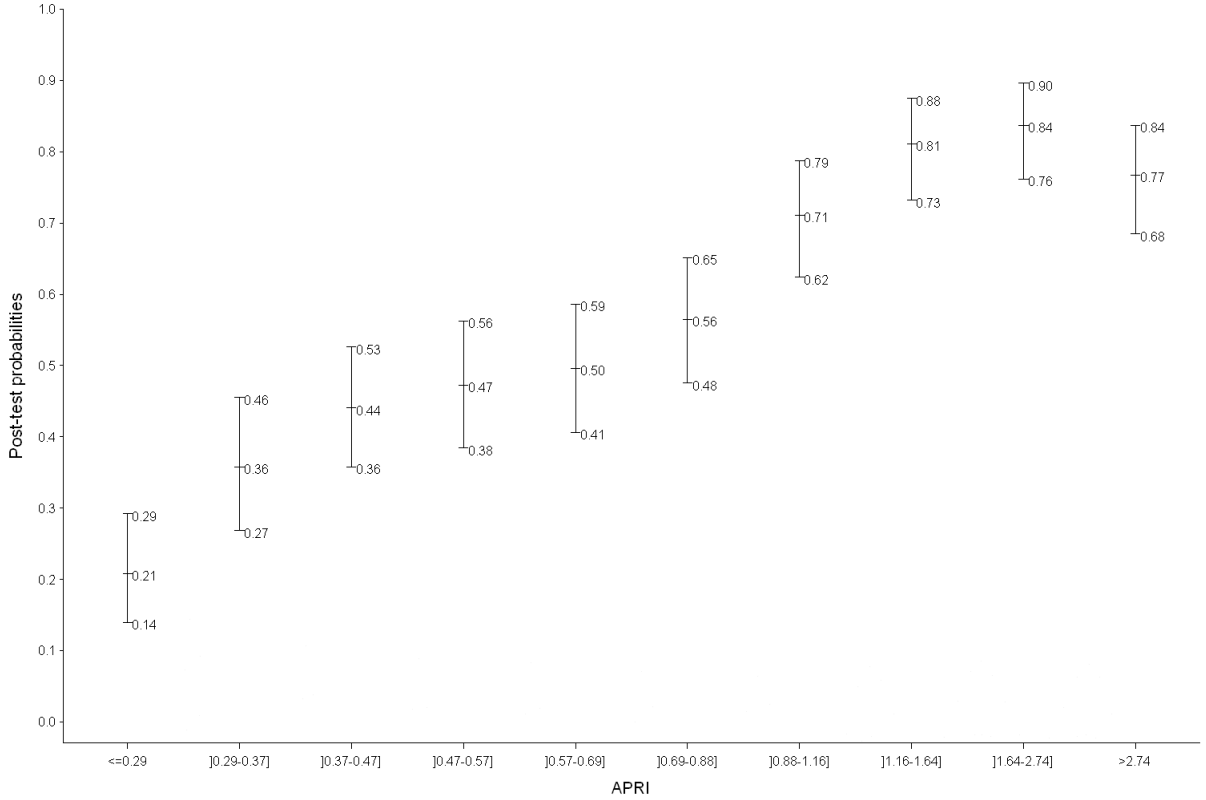


7.4. APRI

7.4.1. Diagnosis of cirrhosis

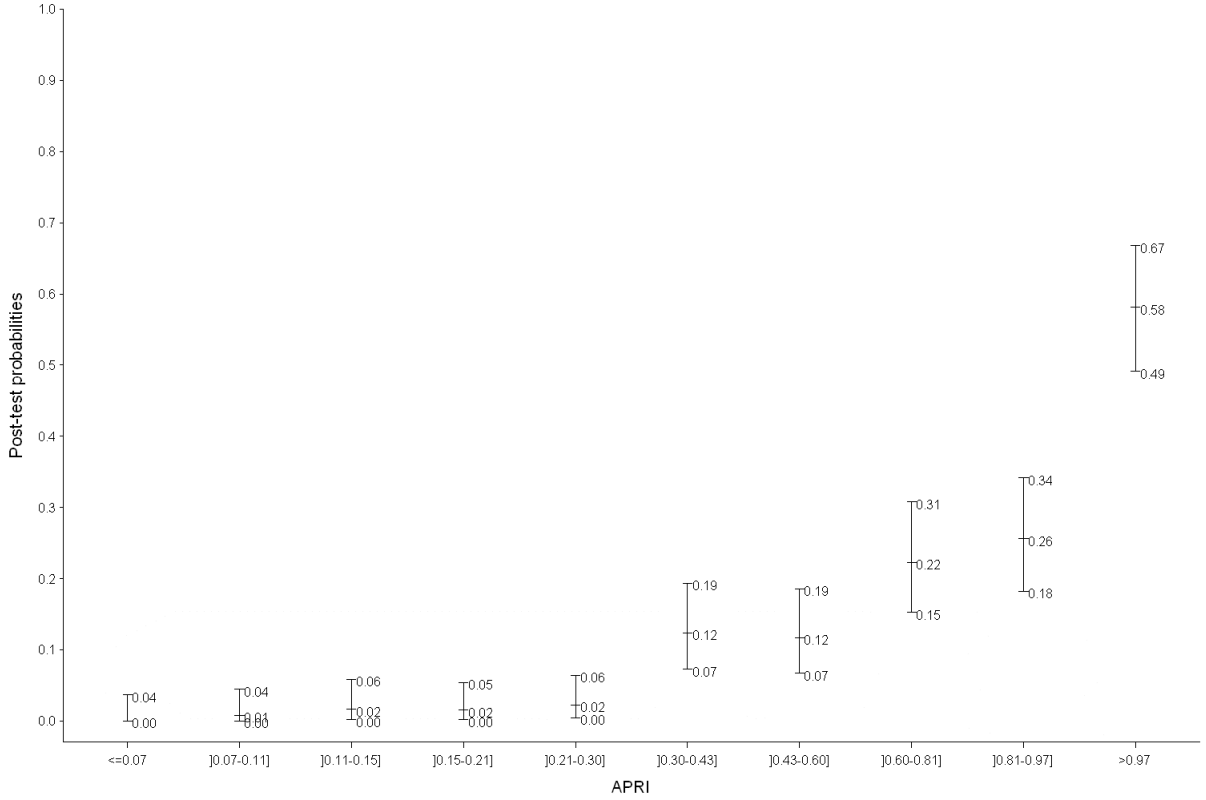
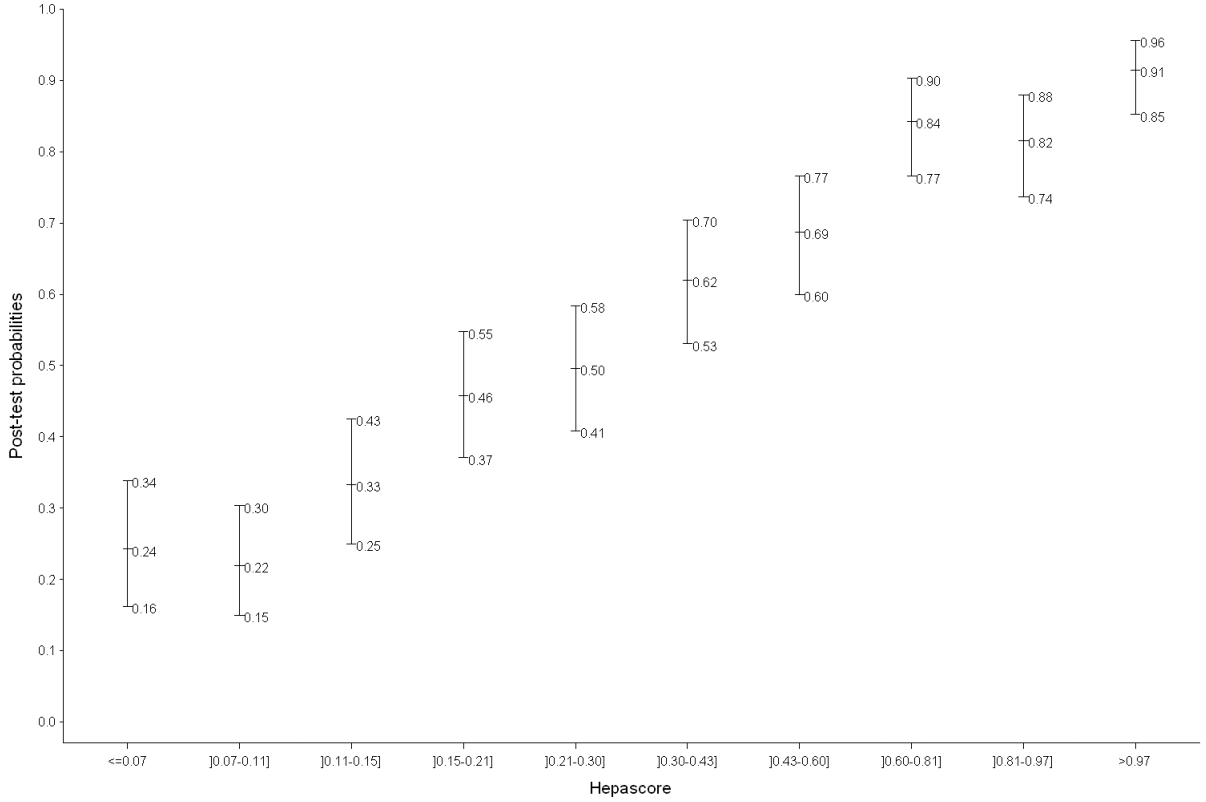


7.4.2. Diagnosis of significant fibrosis



7.5. Hepascore

7.5.1. Diagnosis of cirrhosis



7.5.2. Diagnosis of significant fibrosis