External validation of the Fatty Liver Index and Lipid Accumulation Product indices, using ^{1}H-Magnetic Resonance Spectroscopy, to identify hepatic steatosis.

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Short title: Validation of FLI and LAP using ^{1}H-MRS

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Abstract

Background and Aims. Simple clinical algorithms including the Fatty Liver Index (FLI) and Lipid Accumulation Product (LAP) have been developed as a surrogate marker for Non-Alcoholic Fatty Liver Disease (NAFLD). These algorithms have been constructed using ultrasonography, a semi-quantitative method. This study aimed to validate FLI and LAP as measures of hepatic steatosis, as measured quantitatively by proton magnetic resonance spectroscopy (^{1}H-MRS).

Methods. Data were collected from 168 patients with NAFLD and 168 controls who had undergone clinical, biochemical and anthropometric assessment in the course of research studies. Values of FLI and LAP were determined, and assessed both as predictors of the presence of hepatic steatosis (liver fat >5.5 %) and of actual liver fat content, as measured by ^{1}H MRS. The discriminative ability of FLI and LAP was estimated using the area under the Receiver Operator Characteristic curve (AUROC). Since FLI can also be interpreted as a predictive probability of hepatic steatosis, we assessed how well calibrated it was in our cohort. Linear regression with prediction intervals was used to assess the ability of FLI and LAP to predict liver fat content.

Results. FLI and LAP discriminated between patients with and without hepatic steatosis with an AUROC of 0.79 (IQR= 0.74, 0.84) and 0.78 (IQR= 0.72, 0.83), although quantitative prediction of liver fat content was unsuccessful. Additionally, the algorithms accurately matched the observed percentages of patients with hepatic steatosis in our cohort.

Conclusions. FLI and LAP may be used clinically, and for metabolic and epidemiological research, to identify patients with hepatic steatosis, but not as surrogates for liver fat content.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as a major public health concern, being highly prevalent in the general population, particularly in individuals with features of the metabolic syndrome[1]. NAFLD encompasses a disease spectrum, ranging from simple steatosis, through to an inflammatory state (non-alcoholic steatohepatitis, NASH) and culminating in fibrosis and liver cirrhosis[2]. In addition to the known association with liver-related morbidity and mortality, NAFLD patients have an increased risk of type 2 diabetes mellitus and cardiovascular disease[3, 4].

Liver transaminases and abdominal ultrasonography are insensitive in detecting NAFLD, with liver function tests normal in up to 79% of patients and ultrasonography requiring a moderately high liver fat for NAFLD to be recognised[5]. Only histological examination or proton magnetic resonance spectroscopy (^{1}H MRS) can quantitatively assess liver fat (more exactly, hepatocellular lipid content)[3, 4].

Non-invasive algorithms based on metabolic and anthropometric variables, such as the fatty liver index (FLI), lipid accumulation product (LAP), the hepatic steatosis index (HIS) and the Finnish Diabetes Risk Score (FINDRISC)[6-11], have been used as a screening test for hepatic steatosis, and identify potential patients for further clinical investigation or for epidemiologic studies. They have been applied in various clinical populations to assess prevalence of NAFLD [12] and to provide prognostic information about incident risk of metabolic syndrome and type 2 diabetes, cardiovascular disease and risk of mortality in various sub-groups[13-18].

The original studies to propose FLI and LAP were validated using ultrasonography [2, 7, 19], as well as the SteatoTest, an alternative biochemical surrogate marker of liver steatosis[20]. Liver biopsy is an invasive method. The only study to validate FLI using ^{1}H-MRS, which is supposed to be the next best method as compared with liver biopsy, involved only 25 subjects, with the results suggesting a nonlinear relationship between FLI and hepatocellular lipid content[21].

This study aimed to evaluate the ability of FLI and the LAP to discriminate between patients with and without hepatic steatosis, based on simple clinical and biochemical variables; and to evaluate their ability to predict liver fat content based on our non-invasive measurement of liver fat by ^{1}H-MRS. Here we combined data from several large cohorts of participants with detailed characterisation of clinical, metabolic and anthropometric parameters, in whom ^{1}H MRS measurement of liver fat had been performed for several different research projects.

Materials and Methods

Study participants. We analysed data from participants recruited into human metabolic studies from four research centres (University of Liverpool, University of Surrey, Charite University Berlin and German Institute of Human Nutrition, Potsdam-Rehbruecke). We recruited healthy controls and individuals with components of the metabolic syndrome including being overweight/obese (body mass index (BMI) >25kg/m^2), with a waist circumference >80 cm in females and >94 cm in males, and with at least one additional feature of the metabolic syndrome according to International Diabetes Federation criteria[22]. Clinical characteristics of the cohorts

have been presented previously in detail[23, 24]. All participants gave written informed consent and ethical approval was obtained from the respective local ethics committee.

Exclusion criteria. We excluded participants with a history of type 1 or 2 diabetes mellitus, pregnancy, any significant history of endocrine, cardiovascular, renal or hepatic disease, and standard MR contraindications. Other causes of chronic liver disease were excluded by taking a careful alcohol and drug history and performing an auto-immune liver screen and hepatitis serology.

Anthropometric assessments. Trained physicians performed all anthropometry measurements. Body mass index (BMI) was calculated in kg/m^2; waist circumference, was measured midway between the lower rib margin and the iliac crest.

Biochemical assessment. All participants underwent a biochemical assessment and fasting triglycerides (fTG), alanine transferase (ALT) and gamma-glutamyl transferase (GGT) were measured. Routine laboratory markers were measured from venous blood samples using standard methods in the research laboratories of respective centres (University Hospital Aintree, Liverpool, Royal Surrey County Hospital and in the German Institute of Human Nutrition).

Proton magnetic resonance spectroscopy (^{1}H-MRS). Lipid content in the liver was measured by localized ^{1}H MRS, using an Intera 1.5T Achieva (Philips Medical Systems, Best, The Netherlands) for the Surrey participants[25], a Magnetom 1.5T Symphony MR (Siemens

Healthcare, Erlangen, Germany) for the Liverpool participants[26], and a Magnetom 1.5T Avanto (Siemens Healthcare, Erlangen, Germany) for the German participants. Single voxel spectroscopy was used: for the German studies, STEAM with VOI 30 x30x30 mm, 32 acquisitions, TR = 4000 ms, TM = 15 ms, TE = 10 ms; for the UK studies, PRESS with VOI 20x20x20 mm (3 voxels, results averaged), 64 acquisitions, TR = 1500 ms, TE 135 ms[25]. Spectra were quantified using the AMARES algorithm included in the jMRUI software package, incorporating standard prior knowledge. For the German studies signal integrals of water (H_2O at 4.8 ppm) and lipids (CH_2 and CH_3 at 1.25 ppm and 0.95 ppm) were quantified manually in fixed frequency intervals (water: 3.1 – 6.2 ppm, lipids: 0.5 – 1.8 ppm); for the UK studies these signal amplitudes were obtained directly from the AMARES fit. Liver fat is expressed as % of CH_2 lipid signal amplitude relative to water signal amplitude after correcting for T_1 and T_2[25]. Liver fat content (%) was quantified but also coded ordinally as none (≤5.5%) or present (>5.5%).

Calculations

FLI was calculated using BMI (kg/m^2), serum triglyceride (mg/dl) and GGT (u/L) concentrations and waist circumference (cm) according to Bedogni *et al* [7] to obtain a score between 0 to 100:

$$\square\square\square = \frac{\square\square\square(\square)}{1 + \square\square\square(\square)} \times 100$$

where

$$\square = 0.953 \times \square\square(\square\square\square\square\square\square\square\square\square\square\square\square\square) + 0.139 \times \square\square\square + 0.718 \times \square\square(\square\square\square) + 0.053 \times \square\square\square\square\square \ \square\square\square\square\square\square\square\square\square\square\square\square\square - 15.754.$$

LAP was calculated using serum triglycerides (mmol/l) and waist circumference (cm) using sex-specific calculations[9]:

$$\square\square\square_{\square\square\square} = (\square\square\square\square\square \ \square\square\square\square\square\square\square\square\square\square\square\square\square - 65) \times \square\square\square\square\square\square\square\square\square\square\square\square\square$$

$$\square\square\square_{\square\square\square\square\square} = (\square\square\square\square\square \ \square\square\square\square\square\square\square\square\square\square\square\square\square - 58) \times \square\square\square\square\square\square\square\square\square\square\square\square\square$$

Statistical Analysis. Baseline demographic variables are reported as means and standard deviations or median and interquartile range depending on their distribution. Distributional assumptions were assessed using Q-Q plots. Categorical variables are reported as frequencies and percentages. Statistical comparisons of patients with and without hepatic steatosis were undertaken for all demographic variables; Chi-squared tests were used for categorical variables and unpaired *t*-tests or Mann-Whitney U tests for continuous variables, depending on whether relevant distributional assumptions were met.

To assess the ability of a variable to discriminate between patients with and without hepatic steatosis, Receiver Operator Characteristic (ROC) curves were constructed for FLI, LAP, BMI, waist circumference and ALT. In addition, for FLI and LAP, we measured a number of other

diagnostic statistics: the sensitivity, specificity, positive likelihood ratio and negative likelihood ratio at various cut-points.

Since FLI can also be interpreted as a predictive probability for hepatic steatosis, we assessed how well calibrated FLI was in our patient cohort using a calibration plot[27]. To do so we grouped patients into deciles based on measured FLI, and within each decile calculated the proportion of patients with hepatic steatosis. If a variable is well-calibrated, the observed percentages should be close to the 'line of equality' which represents perfect calibration: roughly 50% of patients should have hepatic steatosis at an FLI of around 50 etc.

Linear regression with 95% prediction intervals (PI) was used to determine whether liver fat content could be predicted using FLI or LAP alone. PIs are to be interpreted as the range of values for liver fat we would assign to a new patient with a given FLI/LAP with 95% 'confidence'. Linear regression assumptions were assessed using plots of residuals versus fitted values and Q-Q plots of the residuals. It was necessary to logarithmically transform both liver fat and LAP for these purposes; the linear regression line and prediction intervals, while linear on the log scale, are non-linear, non-constant and asymmetric on the original scale. For simplicity we evaluated their predictive performance at the mean FLI/LAP.

Results

Characteristics of the participants

Table 1 reports the clinical, biochemical and anthropometric characteristics of the participants

(178 males [53%] and 158 females). Participants were sub-divided into two groups, healthy controls or hepatic steatosis, according to their liver fat measured by proton-magnetic resonance spectroscopy (liver fat <5.5%, healthy controls; >5.5% NAFLD). Using this threshold, 50% of participants (*n*=168) had hepatic steatosis (116 males [66%]) and 50% (*n*=168) were healthy controls (61 males [34%]). The two groups were mean-matched for age.

Participants with hepatic steatosis were more obese, with significantly greater weight, BMI and waist circumference, than the healthy controls. Those with hepatic steatosis demonstrated multiple components of the metabolic syndrome with significantly greater serum fasting glucose [4.8 mmol/l (IQR= 4.5, 5.1) vs. 5.0mmol/l (IQR=4.7, 5.4)], triglycerides [1.0 mmol/l (IQR= 0.8, 1.3) vs. 1.6mmol/l (IQR=1.1, 2.3)] and lower HDL concentrations [1.4 mmol/l (IQR= 1.2, 1.7) vs. 1.2mmol/l (IQR=1.1, 1.4)] than the healthy control group (Table 1).

The median liver fat significantly differed in the healthy control group 1.84% (IQR= 1.00, 3.13) as compared with the hepatic steatosis group 16.58% (IQR= 9.10, 30.70). The distribution of liver fat within the hepatic steatosis group is shown in Figure 1. Measurements of liver fat were reflected in the liver biochemistry with significantly greater liver transaminases (AST and ALT) and serum GGT in the hepatic steatosis group. Patients with hepatic steatosis had significantly higher FLI [56.21 (IQR= 31.43, 72.75) vs. 18.77 (IQR= 8.00, 37.60)] and LAP [72.75 (IQR= 47.53, 99.24) vs. 39.96 (IQR= 25.11, 53.64)] than participants in the control group.

Receiver operating characteristic (ROC) curves (Figure 2)

Receiver Operating Characteristic (ROC) curves were constructed and AUROC with NAFLD defined as liver fat >5.5% on MRS. Both LAP and FLI were able to discriminate between patients with and without hepatic steatosis. The AUROC for LAP was 0.78 (IQR= 0.72, 0.83) and for FLI was 0.79 (IQR= 0.74, 0.84). There was no evidence that AUROC for LAP and FLI differed (*P*=0.49). We also considered the AUROC for BMI, waist circumference, ALT, triglycerides and GGT, which were 0.64 (IQR= 0.58, 0.70), 0.73 (IQR= 0.67, 0.79), 0.83 (IQR= 0.79, 0.88), 0.74 (IQR= 0.69, 0.79) and 0.73 (IQR= 0.67, 0.78), respectively. We conducted exploratory pairwise comparisons between all seven of these variables and found evidence that both FLI and LAP were superior to waist circumferences and BMI. FLI was also superior to GGT (*P*=0.03) but not to triglycerides (*P*=0.10). The reverse was true for LAP, which was superior to triglycerides (*P*=0.01) but not GGT (*P*=0.12). Interestingly, ALT had a similar AUROC to both FLI and LAP.

Sensitivity, specificity, positive likelihood ratios and negative likelihood ratio of FLI and LAP

Table 2A gives the sensitivity, specificity, positive likelihood ratios and negative likelihood ratios for a range of 10-unit intervals for FLI. The intervals chosen were those used by Bedogni *et al*[7]. A cut-off of FLI ≥ 10 gives a sensitivity of 95 % and a LR- of 0.15 i.e. an individual without hepatic steatosis is around seven times more likely to have an FLI < 10. A cut-off of FLI ≥ 60 gives a specificity of 91% and a LR+ of 5.10 i.e. an individual with hepatic steatosis is around five times more likely to have an FLI ≥ 60.

Table 2B gives the sensitivity, specificity, positive likelihood ratios and negative likelihood

ratios for a range of 10-unit intervals for LAP. A cut-off of LAP ≥ 20 gives a sensitivity of 99% and LR- of 0.08 i.e. an individual without hepatic steatosis is around ten times more likely to have a LAP < 20. A cut-off of LAP ≥ 80 has a specificity of 94% and LR+ of 4.93 i.e. an individual with hepatic steatosis is around five times more likely to have an LAP ≥ 80.

We report these cut-offs in particular because they yield a LR+ >5 and a LR- < 0.2 and therefore might be used as reasonable 'rule-in' and 'rule-out' criteria respectively.

Calibration of FLI

FLI provides a 'predicted probability' of a patient having hepatic steatosis. The calibration plot in Figure 3 addresses how satisfactory these predicted probabilities were in our cohort. We have established that FLI discriminates between patients with and without hepatic steatosis (using AUROC analysis) and this is evidenced by the horizontal separation of the two clouds of points, clustered at low FLI values for those without steatosis, and at higher FLI values for those with hepatic steatosis.

We further determined how closely an individual's actual FLI corresponds to their probability of having hepatic steatosis and this relates to calibration. We assessed calibration of FLI by grouping patients according to FLI and calculating the proportion of individuals in each group with hepatic steatosis. The proportion of individuals with hepatic steatosis within each decile is plotted in Figure 3 (solid circles) with corresponding confidence intervals.

If these proportions closely match the (dashed) line of equality then FLI is well calibrated and FLI can reliably be used as a predictive probability of hepatic steatosis. The confidence intervals generally include the line of equality and therefore our results indicate that the predicted probabilities of hepatic steatosis given by FLI are consistent with the observed percentages in our cohort i.e. that FLI is reasonably well calibrated. The point estimates being above the line of equality indicate that FLI may underestimate the probability of a patient having hepatic steatosis and perhaps might be considered a pragmatic lower limit.

Predicting hepatocellular lipid content using FLI and LAP

Both FLI and log-transformed LAP were linearly related to log-transformed liver fat (Figure 4). However, the values of log-transformed liver fat varied considerably about the regression line. This variability is the primary contributor to the width of the 95% PIs and hence determines the estimated predictive ability of each algorithm. If we consider the width of the PIs at FLI=30, a patient's liver fat for this score could plausibly be between around 0% and 40%. For LAP=30, the predicted liver fat could plausibly be between around 0% and 45%. Varying the predictive values of FLI and LAP at other values remained uninformative, suggesting FLI and LAP cannot be used to quantitatively determine liver fat content.

Discussion

Here, we provide external validation for the use of two previously reported indices, the FLI and the LAP, to determine any given individual's probability of having hepatic steatosis, based on simple clinical parameters. The validation in the current study was performed on a large cohort

of individuals with varying degrees of obesity, with and without hepatic steatosis, using ^{1}H MRS measurement of liver fat, considered by many to be the gold standard, non-invasive measurement technique.

The predictive models were originally developed using ultrasonography, a semi-quantitative methods capable of defining the degree of steatosis (mild, moderate or severe)[28]. ^{1}H MRS derived measures of liver fat can accurately quantify liver fat, validated against liver biopsy specimens[4] with normal liver fat being <5.5%[4]. The predictive values of FLI in this study compare favourably with those from Bedogni *et al.* [7] to 'rule out' or 'rule in' hepatic steatosis: an FLI cut point of 10 has a 95% vs. 98% sensitivity and a negative likelihood ratio 0.15 vs. 0.10 respectively, whereas a FLI cut point of 60 has a specificity 91% vs. 86% and a positive likelihood ratio of 5.1 vs. 4.3 respectively. Thus in our study an individual without hepatic steatosis was around seven times more likely to have an FLI<10 and an individual with hepatic steatosis was around five times more likely to have an FLI>60. A cut-off of LAP ≥ 20 had a sensitivity of 99% and LR- of 0.08 i.e. an individual without hepatic steatosis was around ten times more likely to have a LAP < 20 while a cut-off of LAP ≥ 80 has a specificity of 94% and LR+ of 4.93 i.e. an individual with hepatic steatosis is around five times more likely to have a LAP ≥80.

The FLI and LAP values are most useful to determine the probability of an individual having hepatic steatosis, but the strength of their relationship with liver fat content is insufficient for accurate prediction. A previous, elegant study by Kotronen *et al*. in a large cohort of Finnish

adults, using ^{1}H MRS measurements of liver fat, developed a NAFLD liver fat score and an equation distinct from FLI, which has been applied to predict NAFLD and liver fat content[29]. However, in contrast to the indices discussed here, that score required measurement of fasting serum insulin concentrations.

To date, FLI has only been validated in a small group of females (*n*=25) using ^{1}H MRS measures of liver fat demonstrating a non-linear relationship between FLI and liver fat content, limiting its predictive ability[21]. Determining the severity of steatosis has arguably only limited clinical utility, mere identification of an individual as having hepatic steatosis, as part of the NAFLD spectrum, being sufficient to trigger prompt assessment and treatment of associated cardio-metabolic complications, and determination of presence of non-alcoholic steatohepatitis or fibrosis either non-invasively or by liver biopsy, to reduce the long term risk of cardiovascular and hepatic complications.

FLI, adopted as a surrogate marker of hepatic steatosis, has been applied in numerous prospective, epidemiological studies, and can predict the risk of incident type 2 diabetes mellitus[30], the incidence of atherosclerosis and cardiovascular disease [18] and of hepatic-related mortality after 15 years[16]. Thus, FLI values have both diagnostic and prognostic significance.

Strengths of this study include the large number of well characterised individuals with liver fat measured by the gold standard, non-invasive method. Furthermore, the study comprised a cross-section of individuals with normal liver fat and with hepatic steatosis (of a mild, moderate or

severe degree). We acknowledge a limitation of the study was that individuals were recruited from three different research sites, thus there was a lack of standardization of the analytical techniques (i.e. biochemical assays and magnetic resonance spectroscopy) between the three centres. However, analysis of the individual data sets from each of the three centres demonstrated similar results. A further limitation, inherent to these algorithms, is that although these values can predict the probability of hepatic steatosis, they have no predictive ability in identifying individuals who may have progressed along the NAFLD spectrum, with non-alcoholic steatohepatitis, NASH or fibrosis.

In summary, we provide an external validation for the use of fatty liver index, FLI and lipid accumulation product, LAP using magnetic resonance spectroscopy. These results provide reassurance about its legitimacy as a surrogate marker for hepatic steatosis.

Declaration of Interest

The authors have nothing to declare.

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Author Contributions

DJC & GJK contributed to the conception and design of the study, drafting and redrafting of the

final manuscript. **DL** contributed to the assembly, analysis and interpretation of data. **MOW, VSS, RD, FSM, MU, AFHP, ELT, JDB** & **HJ** participated in the generation, collection and assembly of data. **VSS, MU** & **HJ** also participated in the drafting and redrafting of the manuscript. All authors approved the final version of the manuscript.

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Figure legends

Figure 1. Distribution of liver fat in those with hepatic steatosis.

Figure 2. Receiver operating characteristics (ROC) analysis of fatty liver index (FLI) to predict presence or absence of non-alcoholic fatty liver disease (NAFLD).

Figure 3. The hollow circles represent individual FLI values for each patient: those circles (patients) at the top of the plot have hepatic steatosis and those at the bottom do not (the points have been artificially separated slightly so that overlapping circles are not obscured).

Solid circles represent the percentage of patients with hepatic steatosis within each decile of FLI (with corresponding confidence intervals).

Figure 4. Linear regression with 95% prediction intervals (PI) to determine whether liver fat content (presented as the natural logarithm of liver fat, y axis) can be predicted using FLI (x axis, upper graph) or LAP (x axis, lower graph).

Table 1. Baseline clinical, anthropometric and biochemical characteristics of participants.

	Controls	**Hepatic steatosis**	***P***
n	168 (50%)	168 (50%)	-
Male	61 (34%)	116 (66%)	<0.0005
Female	107 (67%)	52 (33%)	
Liver fat (%)	1.8 (1.0, 3.1)	16.6 (9.1, 30.7))	0.0001
Age (years)	48.6 (11.9)	50.3 (10.9)	0.19
Weight (kg)	83.3 (72.5, 93.2)	93.4 (84.6, 104.6)	0.29
BMI ($kg.m^{-2}$)	29.2 (26.7, 32.3)	31.2 (28.9, 33.9)	0.0001
Waist (cm)	98.4 (89.9, 104.8)	105.8 (100.5, 113.0)	0.0001
Fasting glucose (mmol/l)	4.80 (4.50, 5.10)	5.00 (4.70, 5.40)	0.0001
Cholesterol (mmol/l)	5.00 (4.55, 5.80)	5.50 (4.87, 6.02)	0.0135
Triglycerides (mmol/l)	1.01 (0.80, 1.30)	1.60 (1.11, 2.32)	0.0001
HDL (mmol/l)	1.40 (1.20, 1.68)	1.20 (1.05, 1.42)	0.0001
LDL (mmol/l)	3.12 (2.64, 3.80)	3.30 (2.80, 3.92)	0.14
Chol:HDL ratio	3.67 (3.00, 4.24)	4.29 (3.81, 5.26)	0.0001
AST (u/L)	21 (18, 24)	28 (23, 35)	0.0001
ALT (u/L)	19 (16, 26	37 (26, 56)	0.0001
GGT (u/L)	20 (13, 29)	37 (21, 58)	0.0001
FLI	18.8 (8.0, 37.6)	56.2 (31.3, 72.8)	0.0001
LAP	40.0 (25.1, 53.6)	72.8 (47.5, 99.2)	0.0001

Categorical variables compared using Chi-squared test. Continuous variables compared using the unpaired t-tests or Mann-Whitney U tests depending on whether data met the relevant distributional assumptions. Categorical variables reported as frequency (percentage) and continuous variables as Mean (SD) or Median (IQR).

Table 2. FLI and LAP cut-point table.

FLI					
Cutpoint	%	SN	SP	LR+	LR-
≥10	0.83	0.95	0.29	1.35	0.15
≥20	0.67	0.86	0.53	1.82	0.27
≥30	0.54	0.75	0.69	2.43	0.36
≥40	0.45	0.66	0.77	2.84	0.45
≥50	0.38	0.56	0.81	3.03	0.54
≥60	0.26	0.44	0.91	5.10	0.61
≥70	0.18	0.29	0.94	4.87	0.75
≥80	0.11	0.19	0.96	4.71	0.85
≥90	0.04	0.06	0.99	9.74	0.94

(% = proportion of patients with an FLI ≥ cut point).

LAP					
Cutpoint	%	SN	SP	LR+	LR-
≥20	0.91	0.99	0.16	1.18	0.08
≥30	0.79	0.93	0.34	1.40	0.22
≥40	0.68	0.86	0.50	1.71	0.29
≥50	0.50	0.70	0.69	2.29	0.43
≥60	0.39	0.59	0.81	3.17	0.50
≥70	0.34	0.54	0.86	3.74	0.54
≥80	0.26	0.43	0.91	4.93	0.62
≥90	0.19	0.33	0.94	5.20	0.72
≥100	0.14	0.24	0.96	5.43	0.80
≥110	0.12	0.2	0.96	5.33	0.83
≥120	0.10	0.18	0.97	5.60	0.85

(% = proportion of patients with a LAP ≥ cut point).