

Letter to the Editor

Arne Åsberg*, Lena Løfblad and Gunhild Garmo Hov

The likelihood ratios of FIB-4-values for diagnosing advanced liver fibrosis in patients with NAFLD

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To the Editor,

Fibrosis-4 Index (FIB-4) is a non-invasive test for advanced fibrosis (stage F3 [bridging fibrosis] and/or stage F4 [cirrhosis] in patients with non-alcoholic fatty liver disease [NAFLD]) [1]. FIB-4 is calculated from age and three blood tests: $(\text{age} \times \text{AST})/(\text{thrombocytes} \times \text{ALT}^{0.5})$. Its diagnostic accuracy is neither excellent nor bad. In a recent meta-analysis, based on individual data from 5,393 patients in 37 primary studies, the diagnostic accuracy of FIB-4 for advanced fibrosis in patients with NAFLD was measured against histological classification of liver fibrosis [1]. The area under the receiver operating characteristic (ROC) curve was 0.76 [1]. Clinically FIB-4-values are judged against one or two cut-off values, i.e. FIB-4 is used as a qualitative or semiquantitative test [1]. However, we believe an individual risk assessment is more appropriate than just comparing the patient's FIB-4-value against cut-off values, because the patients should be treated according to their individual risk, i.e. their posttest probability of disease.

In order to calculate the posttest probability for an individual patient the physician must know the patient's

pretest probability and the likelihood ratio (LR) of the patient's FIB-4-value [2]. The posttest probability is $(\text{LR} \times \text{pre})/(\text{LR} \times \text{pre} + 1 - \text{pre})$, where pre is pretest probability [2]. LR-values less than 1 makes the posttest probability less than the pretest probability, while LR-values greater than 1 makes the posttest probability greater than the pretest probability. A LR-value of 1 does not change the probability of disease.

Judging the pretest probability is difficult, and requires knowledge of the prevalence of disease in the relevant populations [3, 4]. Finding the LR of the individual patient's FIB-4-value is even more difficult, because FIB-4 is a quantitative measure that can take on many different values. So we need a graph or a table showing the corresponding values of LR and FIB-4. Such a graph may be derived from Figure 2B in the article of Mózes et al. [1].

LR of a certain FIB-4-value is the slope of the tangent of the ROC-curve at the point of the curve that corresponds to the FIB-4-value [5]. Using the online software tool Web-PlotDigitizer (<https://apps.automeris.io/wpd/>), we read the values of sensitivity and specificity from Figure 2B in [1] and constructed the ROC curve (data in the supplementary file). As a check of the reading accuracy we calculated the area under the plot of sensitivity vs. $100 - \text{specificity}$, from a value of 0.18 to 99.52 % for $100 - \text{specificity}$ (the lowest and highest values we were able to read). The area was 0.752, quite close to the value 0.76 given in the article of Mózes et al. [1]. Then we used fractional polynomial regression (mfp-module in Stata, version 16) to smooth the curve. The function of the smoothed ROC curve was $y = 23.82 + 44.05 \times ((x/10)^{0.5} - 0.6723) - 0.3405 \times ((x/10)^2 - 0.2043)$, where y is sensitivity and x is $100 - \text{specificity}$ (Supplementary Figure). Finally, we found the derivative of the smoothed ROC curve using an on-line service from WolframAlpha (<https://www.wolframalpha.com/>). This gave us an expression of LR as a function of $100 - \text{specificity}$: $\text{LR} = 6.965/x^{0.5} - 0.006812 \times x$, where x is $100 - \text{specificity}$ (in percent). From Figure 2B in [1] we know the connection between FIB-4-values and $100 - \text{specificity}$, so we were able to construct a curve (Figure 1A) showing the LR of FIB-4-values up to 5.

*Corresponding author: Arne Åsberg, Department of Clinical Chemistry, St. Olav's Hospital, POB 3250 Torgarden, 7006 Trondheim, Norway, E-mail: arne.aasberg@stolav.no

Lena Løfblad, Department of Clinical Chemistry, St. Olav's Hospital, Trondheim, Norway

Gunhild Garmo Hov, Department of Clinical Chemistry, St. Olav's Hospital, Trondheim, Norway; and Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

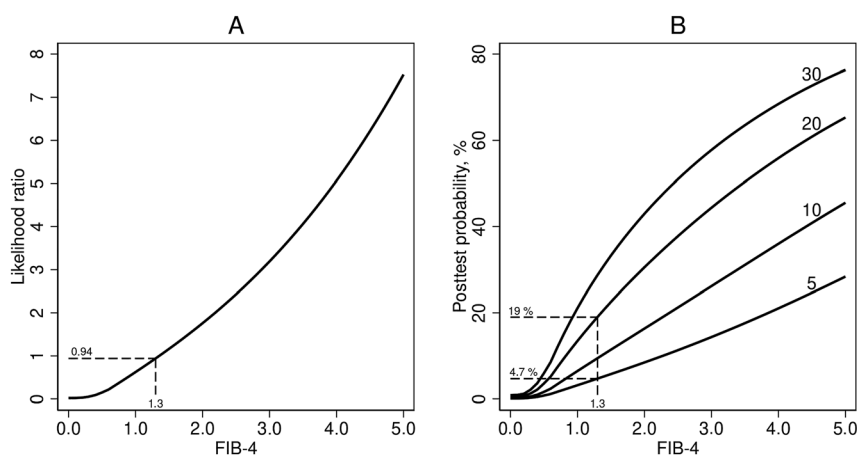


Figure 1: Likelihood ratio and posttest probability. (A) Likelihood ratio for diagnosing advanced liver fibrosis in patients with NAFLD, as a function of FIB-4. (B) Posttest probability of advanced liver fibrosis as functions of FIB-4, for 4 different values of pretest probability: 5 %, 10 %, 20 %, and 30 %.

Very few patients have higher values. Knowing the LR of FIB-4-values, we calculated the posttest probability for advanced liver fibrosis for FIB-4-values up to 5, given four different values of pretest probability (Figure 1B). A more accurate function of LR might possibly be derived directly from the collection of individual data [2]. However, we believe that our figures are sufficiently accurate for the purpose and hope they will be clinically useful, in spite of the difficulties judging pretest probability. For instance, as shown in Figure 1B, in a patient with FIB-4 of 1.3 (corresponding to a LR of about 1), posttest probability is almost the same as the pretest probability. Then, if the pretest probability is 5 %, the posttest probability is also 5 % and perhaps below the threshold for referral to more definitive diagnostic procedures. If the pretest probability is 20 %, the conclusion may be quite the opposite at the same value of FIB-4, illustrating the need for individual assessment.

Admittedly, the LR of a test result may vary with the clinical population; however, theoretically it is independent of the prevalence of disease. This is a general issue using Bayes' theorem in diagnostic medicine. In any case, we should try to use the correct LR and not pretend that quantitative tests (like FIB-4) are qualitative.

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