Fibrosis-4 (FIB-4) score at the primary care level: an analysis of over 160 000 blood samples

We read with interest the recent article by Newsome *et al* which provides guidelines for general practitioners on the management of abnormal liver blood tests based on the clinical recognition pattern of elevated liver enzymes and recommendations on non-invasive laboratory based liver fibrosis scores such as Fibrosis-4 (FIB-4) to exclude advanced fibrosis.[1] Patients with low FIB-4 values should be managed in primary care, those with intermediate test results receive further diagnostics by an enhanced liver fibrosis test or ultrasound based elastography methods while those with high FIB-4 score are directly referred to secondary care. Newsome's recommendations are especially relevant for non-alcoholic fatty liver disease (NAFLD), the most common aetiology of elevated liver enzymes in the primary care setting in the Western world.[2] In NAFLD, the key predictor for

Table 1 Baseline characteristics of the study cohort

	All patients (n=162 412)
Sex (female)	88 974 (54.8%)
Age	54.4±18.0
18–24	9712 (6.0%)
25–34	15 690 (9.7%)
35–44	22 020 (13.6%)
45–54	34 601 (21.3%)
55–64	30 222 (18.6%)
65–74	23 585 (14.5%)
75–84	20 310 (12.5%)
85–94	6002 (3.7%)
95–104	270 (0.2%)
ALT (U/L)	21 (15 to 32)
Elevated	20 730 (12.8%)
AST (U/L)	24 (20 to 30)
Elevated	13 227 (8.1%)
ALT or AST elevated	24 460 (15.1%)
Platelets (10^9/L)	258 (217 to 303)
Low (<150)	5177 (3.2%)
High (>450)	2846 (1.8%)
HbA1c (%), available from 35 063 patients	5.9 (5.4 to 6.7)
Elevated (>6.5)	9555 (27.3%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, glycated haemoglobin.

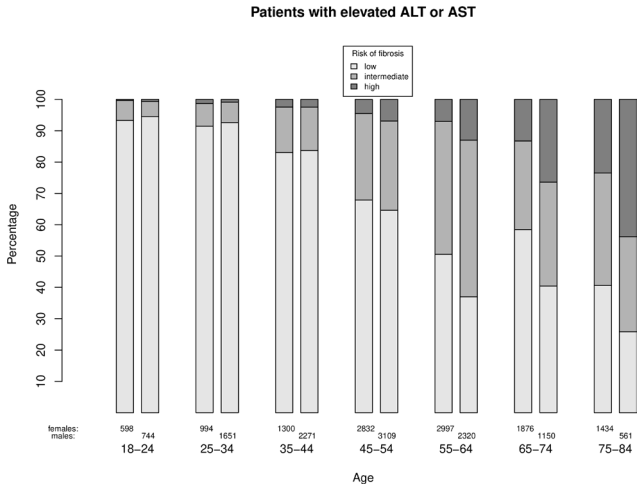

Figure 1 Age and sex specific risk of hepatic fibrosis according to the Fibrosis-4 score in patients with elevated ALT or AST values. The lower cut-off for excluding advanced fibrosis is 1.3 for patients ≤65 years and 2.0 for the age >65 years, the higher cut-off to predict advanced fibrosis is 3.25 for both age groups. ALT,alanine aminotransferase; AST, aspartate aminotransferase.

liver related outcome and mortality is liver fibrosis.[3 4] In Germany by the year 2030, 17 million NAFLD patients will present without fibrosis, but only 0.8 million and 0.5 million with pre-cirrhosis or cirrhosis, respectively.[5] It is therefore crucial to define screening strategies to identify those at risk for cirrhosis and guide referrals from the primary to the secondary care level. The recommended FIB-4 score may be a valuable screening tool, however, FIB-4 data from the primary care setting are scarce. We therefore analysed blood samples sent in from general practitioners to a large central laboratory:

Alanine and aspartate aminotransferases (ALT and AST) were analysed according to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) criteria (upper limit of normal 35 U/L for women and 50 U/L for men). Analyses were restricted to the first blood sample from each patient (table 1). The FIB-4 lower cut-off for excluding advanced fibrosis was 1.3 for patients ≤65 years and 2.0 for age >65, the higher cut-off to predict advanced fibrosis was 3.25 for both age groups.[6]

According to the overall FIB-4 results, a low or high risk of fibrosis was present in 75.4% and 3.3% of cases, respectively, while indeterminate results requiring a guideline recommended subsequent diagnostic were observed in 21.3% of patients. Under the age of 45 years, >95% of patients present with low FIB-4 values.

In those with elevated aminotransferases (whom general practitioners are supposed to schedule for screening), FIB-4 values >3.25 are present in 1.6% under the age of 45 years. In patients aged 45 to 74, the prevalence of indeterminate FIB-4 values was 35.1%, and 9.8% presented with values >3.25 and are thus candidates for direct referral to secondary care (figure 1).

For those without elevated aminotransferases, the prevalence of FIB-4 values >3.25 is only 0.7% under the age of 75 years.

In summary, guidelines recommend the application of non-invasive tests at the primary care level,[1] however, the evidence is limited so far.[7 8] In addition to the publications of Grattagliano and Srivastava, our study provides data on the impact of the FIB-4 score in the largest data set from unselected primary care physicians analysed so far. Analysis of the FIB-4 score at the primary care levels may be a valuable approach to guide subsequent referral strategies. The test is probably a better screening tool for general practitioners than the NAFLD fibrosis score,[9] because the latter demands additional analysis of albumin in serum, which increases the costs and is therefore not attractive for budgetary reasons.[10]

Our results are limited by the absence of clinical data in addition to the laboratory parameters. Cross validation with other non-invasive laboratory or ultrasound based methods or even with liver biopsies is missing as well. Our findings have to be proved in prospective settings with appropriate clinical data.

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