Errors in modeling miss-represent the utility of the Enhanced Liver Fibrosis test in the management of Non-Alcoholic Fatty Liver Disease

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We read with interest Vali et al.'s(1) meta-analysis and modelling of the performance of the Enhanced Liver Fibrosis (ELF) test for diagnosing liver fibrosis in Non-Alcoholic Fatty Liver Disease (NAFLD) patients. They report excellent performance of ELF in ruling out the presence of advanced fibrosis (F3-4) with accuracy exceeding 90%. Specificity is good (86% at 9.8 and 93% at 10.51) generating a positive predictive value (PPV) of >80% where the prevalence of F3-4 fibrosis is relatively high. However, modelling predicted suboptimal performance in primary care if the prevalence of F3-4 is estimated to be 5%.

Current British Society for Gastroenterology guidance(2) advocates the use of a sequential two-tier fibrosis staging strategy in primary care such that patients with indeterminate FIB4 scores undergo ELF testing or transient elastography. Srivastava et al.(3) evaluated this approach reporting an overall PPV of 30%. We believe evidence derived from clinical studies should carry greater weight than hypothetical modeling. Nevertheless, after the application of FIB4 the prevalence of F3-F4 fibrosis in the FIB4 indeterminate group should rise from 5% to 13%. Applying the authors' model, subsequent ELF testing would yield PPVs for advanced fibrosis of 40.1% and 52.1% at ELF thresholds of 9.8 and 10.51 respectively. This approach would ensure the identification of patients with advanced fibrosis and even if half the referrals to specialist care were "false positives", empirical evidence suggests this would be considerably better than current best practice. Srivastava et al. reported 80% reduction in unnecessary referrals, 5 fold improvement in detection of advanced fibrosis and costs saving from a FIB4-ELF pathway compared to standard care(3).

The authors' concern that the ELF algorithm has undergone multiple revisions merits clarification. The original ELF assay was developed on the Immuno-1 auto-analyser with an algorithm that incorporated patient age(4) that generated both negative and positive ELF scores. Guha et al.(5) found that age could be removed from the algorithm without affecting performance and Nobili et al.(6) subsequently added a factor of ten to the algorithm to generate only positive scores. When the ELF test was transferred to the Centaur analyser great care was taken to ensure that the component assays, in a new Centaur algorithm, would generate scores identical on both platforms as confirmed by Vali et al. This revised algorithm and new platform were utilized for CE marking and have not changed since 2011. These changes, in the public domain, should have informed the harmonization of ELF scores for Vali et al.'s meta-analysis.

Vali et al.'s use of a regression equation to "harmonize" ELF scores in the Guha(5) and Dvorak(7) studies to "Siemens scores", rather than merely adding 10 as described above,(6) introduced serious flaws in their analysis evidenced by the generation of ELF scores ranging from -4.25 and 35.59 which

have never been reported in the literature or encountered in our clinical experience. Revision of the meta-analysis using the correct conversion is warranted.

The authors highlight National Institute for Health and Care Excellence (NICE) Guidance recommending the use of ELF to assess risk of advanced fibrosis in NAFLD based on both cost and performance(8) even though the cost-effectiveness analysis is based on a price for the ELF test nearly three times the true NHS cost. The suggestion that the NICE recommendation was based on one small study in a pediatric population(6) is misleading. Guha et al.(5) used the same algorithm as Nobili et al. (but for the addition of 10) and reported 90% specificity for advanced fibrosis at a threshold of 10.36.

Liver biopsy is a reference test associated with sampling error, that may result in 20% of specimens being under or over-staged, and histopathological inter- and intra-observer variability.(9) Even a perfect diagnostic test compared to liver histology would be restricted to an AUROC of 0.90 (sensitivity and specificity=90%).(10) As a consequence when applied to a population with 5% prevalence of advanced fibrosis, a perfect test for F3-F4 fibrosis would generate a PPV of only 32% when compared to histology, close to Vali et al.'s prediction of PPVs for ELF of 19.4% and 27.5% at the diagnostic thresholds of 9.8 and 10.51 respectively.

While we share the authors' enthusiasm for research into newer and better tests for liver fibrosis we believe there is a duty of care to make best use of the effective tests currently available to identify those patients with NAFLD who have advanced fibrosis, rather than wait for better tests that may not materialize. It would be wrong to infer from Vali et al.'s work that clinicians should wait in hope for these better tests. Consortia such as LITMUS (in Europe, led in by the authors) and NIMBLE (in the USA) may discover better tests but it is likely to be a decade before their potential superiority can be validated against clinically meaningful outcomes rather than the existing reference standard.

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