On the path to detecting significant liver disease

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Rohit Gupta,[1] James O'Beirne [1,2]

The rising prevalence of alcohol-related liver disease (ARLD) and non-alcoholic fatty liver disease (NAFLD) presents a challenge to gastroenterology and hepatology departments. Traditional referral practices from primary care based on raised liver function tests alone can lead to a significant number of referrals of patients without significant liver disease, leading to overdiagnosis and adding to pressure on outpatient services and associated increased costs.[1] Moreover, such referral practices may fail to identify patients with serious liver disease, as it is well known that advanced fibrosis and cirrhosis can be associated with normal liver function tests.

In *Frontline Gastroenterology*, Chalmers *et al* present findings from a commissioned referral pathway designed to focus on risk factors for NAFLD or ARLD rather than abnormal liver enzymes alone.[2] Under the pathway, general practitioners (GPs) were encouraged to identify patients at risk of significant liver disease and to refer these patients for assessment with transient elastography (TE). Patients with a TE reading suggesting significant liver fibrosis (TE >8 kPA) were recommended to be referred for assessment in secondary care, whereas those with lower readings underwent a brief intervention regarding lifestyle by a dedicated nurse in the TE clinic and were referred back to primary care. Criteria for referral to the TE clinic were harmful alcohol use (>50 units/week for men and >35 units/week for women), an aspartate transaminase (AST):alanine transaminase (ALT) ratio of >0.8 in the context of raised liver enzymes or risk of NAFLD (defined by the presence of steatosis on imaging or the presence of obesity, diabetes mellitus or metabolic syndrome). Using these criteria, the study reported that a total of 968 patients were referred and underwent assessment in the clinic over the first 12 months of the pathway. The number of referrals increased over the course of the year, with 129 referred in the last month analysed, suggesting that uptake of the pathway was acceptable to referrers in primary care. When analysing the results of the pathway, the authors found that the majority (60%) of patients were referred either with abnormal liver enzymes (AST:ALT ratio >0.8) or a combination of risk factors. Significantly, nearly a third of patients were referred based on risk factors for fibrosis alone, either due to harmful alcohol intake or risk of NAFLD rather than abnormal liver enzymes. In the group as a whole, the majority of patients had a TE score of less than 8 kPa, essentially ruling out significant fibrosis. Overall, liver stiffness was elevated at >8 kPa in 222 patients, of whom 57 had advanced fibrosis a (TE ≥15 kPa). Compared with using abnormal liver enzymes alone as a referral trigger, the Nottingham pathway identified more patients with advanced chronic liver disease, although the absolute increase in the number of patients identified with advanced chronic liver disease was small (7.4%).

Facilitating rapid access to TE for GPs allows stratification of low-risk disease while also yielding a higher detection rate of significant liver disease. As highlighted in this study, relying only on abnormal liver function tests will miss a proportion of patients with significant liver disease. It is interesting to note that within the pathway, of the patients referred to hepatology services with a TE score of 8–14 (n=165), only four patients were subsequently diagnosed with advanced chronic liver disease, suggesting that the cut-off of 8 kPa may be too low. Nonetheless, the majority of patients treated through the pathway avoided needing assessment in a secondary care clinic, and this reflects the growing realisation that the vast majority of patients with NAFLD are at low risk of liver-related events and can be managed in primary care. Currently, there is much interest in the community or primary care-based risk stratification of NAFLD.[3] Many patients without significant fibrosis can be identified in primary care by the use of simple non-invasive tests calculated from readily available biochemical variables. For example, fibrosis-4 (FIB-4), which comprises age, AST, ALT and platelet count, is easy to perform in primary care and can exclude significant disease with a negative predictive value of greater than 90%.[4] In NAFLD, models using FIB-4 as an initial step followed by a secondary step of stratification using specialised serum-based tests or elastography have shown efficacy in reducing referrals of those with low-risk liver disease with a consequent enrichment of secondary care referrals with advanced liver disease and are likely to be cost-effective.[5 6]

The authors are to be congratulated on their implementation of a commissioned pathway that was developed in partnership with primary care and other stakeholders. This degree of engagement should mean that the model is easily modifiable as new data become available.

How could the pathway be improved? Moving the initial stage of stratification into primary care using FIB-4, with a further step of stratification, using either enhanced liver fibrosis test or TE in the community rather than secondary care would be a major advantage. As technology becomes cheaper and with wider availability of elastography as part of routine liver ultrasound scans, the majority of patients with low-risk liver disease could be reassured and onward referral could be avoided.

These approaches to risk stratification at the primary care level will undoubtedly increase identification of advanced liver disease and reduce secondary care referrals and hence costs. However, for maximum impact, linking such pathways to population-based strategies to reduce alcohol consumption and obesity should be the ultimate aim.

Twitter James O'Beirne @drobeirne

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ORCID iD
James O'Beirne http://orcid.org/0000-0003-3400-2816

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