Editorial

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Referral pathways for NAFLD fibrosis in primary care – No longer a 'needle in a haystack'

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Non-alcoholic fatty liver disease (NAFLD) is the commonest form of liver disease in primary care, with rates up to 25%.[1] This figure, however, encompasses the whole spectrum of NAFLD from simple steatosis, non-alcoholic steatohepatitis (NASH) through to advanced fibrosis/cirrhosis. Due to the strong association with liver-related morbidity and premature death,[2,3] fibrosis has become the main focus in secondary care for risk stratification, targeted lifestyle and metabolic risk management and drug trial recruitment. Indeed, all recent liver guidelines (EASL-EASD-EASO,[4] AASLD,[5] BSG,[6] NICE)[7] are in agreement in recommending screening for advanced fibrosis (histological stage Kleiner F3-4) in patients diagnosed with NAFLD. The management of patients with NAFLD in primary care, however, lacks consistency and is *ad hoc*, with an excess dependence on secondary care liver services, for what is in the majority a bystander to obesity and diabetes. In the absence of established diagnostic pathways, identification of patients at risk of liver disease progression in primary care is very challenging and is compounded by the fact that only ~1 in 20 patients with NAFLD have advanced fibrosis/cirrhosis in this setting.[8]

A decade has passed since the emergence of non-invasive markers of liver fibrosis, ranging from simple scores (Fibrosis-4 [FIB-4]), NAFLD fibrosis score [NFS]) to more intricate tools (Enhanced Liver Fibrosis [ELF™] test, FibroMeter™, Transient Elastography/FibroScan®) and at large their use remains confined to secondary 'specialist liver' care.[9] Numerous studies around the globe have consistently highlighted that these non-invasive tools have excellent negative predictive values ([NPVs] >90%) for advanced fibrosis/cirrhosis in the hospital setting.[9] Due to the fact that NAFLD has a higher prevalence in the community, but a lower severity (only 5% with advanced fibrosis), the accuracy of these tools for 'ruling out' advanced disease is expected to be even better in the community (NPV >98%) (8). Certainly, standard liver function tests (LFTs) in patients with NAFLD bear no resemblance to the severity of the disease,[9] until it is likely too late and clinically apparent with signs of liver failure. Despite this, there remains a historical and persistent reliance on LFTs (namely elevated liver enzymes) by primary care practitioners (PCPs) to determine who warrants referral to specialist liver services. Not only does this strategy potentiate unnecessary referrals to secondary care, but more importantly it fails to identify those with advanced 'silent' disease in the community.

Srivastava and colleagues are the first to undertake a large, prospective evaluation of a United Kingdom primary care referral pathway (n = 1,452) in patients with NAFLD, designed specifically to identify advanced fibrosis/cirrhosis in the community.[10] The authors should be commended on incorporating a referral pathway into 'real-world' large-scale clinical practice, which in 2013 was a novel approach. In keeping with recent research proposals enlisted in the EASL-EASD-EASO guidelines,[4] their NAFLD pathway utilised a 2-step approach in patients with an elevated alanine aminotransferase (ALT), negative alcohol/liver screen and/or fatty liver on ultrasound. All patients underwent a FIB-4 score and a sequential ELF test was performed in those with an indeterminate FIB-4 (score 1.3–3.25). In doing so, 81% (1,177/1,452) of patients were deemed at low risk of advanced fibrosis (FIB-4 <1.3 [n = 1,022] or ELF <9.5 [n = 155]) and remained in the community, whilst 19% (275/1,452) were recommended for referral to liver services.[10] A significant strength of this study is that they had a large comparator group (n = 1,560), who underwent 'standard of care' either before the introduction (retrospective case-note analysis) or in parallel to the NAFLD pathway (prospective analysis). By doing so, they were able to highlight that the introduction of the NAFLD 2-step pathway reduced unnecessary referrals to liver specialists by 81%, as well as a marked increase (5-fold) in the accurate referral of cases with advanced fibrosis.[10] By reducing unnecessary referrals, this approach may have significant cost-savings, increase specialist clinic capacity, and reduce unnecessary patient anxiety (and potential harm from additional tests) associated with being referred to a hospital specialist. In addition, by identifying patients with advanced disease earlier and subsequently targeting hepatocellular carcinoma/variceal surveillance, intense lifestyle/nutritional management and clinical trial entry, one would predict with time that this may have a

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positive impact on liver-related morbidity and mortality rates. This, however, needs to be proven with further evaluation and longer-term follow-up.

One limitation of the prospective component of the current study (albeit reflecting real-world practice) was that the PCPs were able to decide as to whether to enter the patient into the NAFLD 'two-step' pathway or proceed as per routine standard of care. Interestingly, patients entered into the NAFLD pathway were significantly older (54.4 *vs.* 51.5 years) and had higher prevalence of diabetes (27.6% *vs.* 21%) and ischaemic heart disease (6.7% *vs.* 3.9%) than those under standard of care.[10] This might suggest selection bias, in that the PCPs were more inclined to enter the patient into the NAFLD pathway if they were concerned about the burden of metabolic disease. Furthermore, of the 275 patients (19% of total NAFLD pathway) in which referral to liver services was recommended based on the algorithm, only 152 (55%) were actually referred by the PCP.[10] Even though the authors offer some explanations for this (*i.e.* excess alcohol, already under liver services, lost to follow-up), it highlights the challenges of implementing new liver referral care pathways in primary care and the ongoing need for adequate education for PCPs in the implications and management of NAFLD in the community.

Several organisations have uniformly concluded that at present it is not cost-effective to screen for NAFLD ± advanced fibrosis in unselected populations in the community. However, 2 large-scale analyses from America[11] and Europe,[8] performed as recently as 2015, concluded that screening for advanced fibrosis in patients with an established diagnosis of NAFLD in primary care was more cost-effective with a 2-tier system (*i.e.* NFS ± Fibroscan or FIB ± ELF) than the other options of 'refer all', 'refer none' or 'refer solely based on a simple non-invasive score' (*i.e.* NFS or FIB-4). Srivastava *et al.* highlighted the limitations of the latter option, as performing ELF in cases with an indeterminate FIB-4 rescued 38/45 (84%) patients subsequently found to have advanced fibrosis or cirrhosis, who would otherwise have been falsely reassured by FIB-4 alone.[10]

Utilising non-invasive markers in primary care that were originally designed and validated in secondary (tertiary) care cohorts is not without its challenges. In particular, the current authors highlight that simply adopting secondary care 'cut-offs' for ELF from national guidelines (NICE; <10.5)[7] and/or the manufacturers (<9.8) results in less referrals, but at the expense of missing patients with advanced fibrosis. Similarly, adjusting FIB-4 for patients over the age of 65[12] would have led to false reassurances in 27% cases (12/45) of patients found to have advanced fibrosis.[10] Together, these highlight the importance of validating cut-offs specific to primary care populations and finding the right balance between referral burden versus accurate disease exclusion. Pragmatically, the authors recommend repeat fibrosis assessment with FIB-4 within 3–5 years for those that remain in primary care, but in order to truly understand the NPV of FIB-4 (<1.30) in this setting a confirmatory ELF or Fibroscan would be required.

Finally, it is widely recognised that many patients with NAFLD, including those with cirrhosis, have normal LFTs.[9] Yet, at present the proposed NAFLD pathway is solely reliant on the patient having an abnormal ALT measurement in order to trigger a FIB-4 calculation. In light of the fact that FIB-4 has been shown to have similar accuracy in patients with normal ALT (NPV 92%),[13] is it now time to change the focus from LFTs towards patients at risk of NAFLD with notable metabolic risk factors (*i.e.* obesity, diabetes). In 2017, Guha and colleagues trialled this approach with transient elastography in 899 high risk patients in primary care and subsequently unearthed a 3% rate of cirrhosis in patients, who would otherwise have gone undiagnosed.[14] Interestingly, despite the defined inclusion criteria in the current study, Srivastava *et al.* found that 37/152 patients that were referred to secondary care via the NAFLD pathway actually had normal LFTs at baseline.[10] Even though the numbers are small it would be fascinating to see the breakdown as to how many of these were found to have a clinical diagnosis of advanced fibrosis after specialist review.

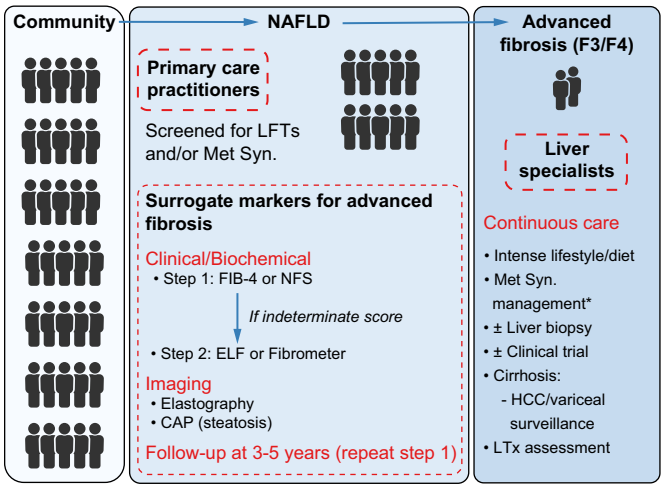

Fig. 1. Primary to secondary care interface in patients with NAFLD. *Optimisation of glycaemic control by an endocrinologist in cases of complex diabetes. CAP, controlled attenuation parameter; ELF, Enhanced Liver Fibrosis test; FIB-4, Fibrosis-4; HCC, hepatocellular carcinoma; LFTs, liver function tests; LTx, liver transplantation; Met Syn, metabolic syndrome; NFS, NAFLD fibrosis score.

NAFLD is an increasing global entity and therefore PCPs have a critical role in the identification and the day-to-day management of these patients. Without clear guidance and robust pathways for risk stratification, a significant proportion of patients with NAFLD and advanced fibrosis will remain undetected and health resources will be focused on the wrong individuals. Widespread integration of non-invasive markers of fibrosis (FIB-4, ELF) into primary care referral pathways (Fig. 1), as described here, paves the way for efficient selection of patients with NAFLD that are most in need of liver specialist services.[15] In parallel, by reducing unnecessary referrals, the non-invasive pathway aids with focusing the clinical support (weight loss strategies, metabolic/cardiovascular optimisation) and services that the vast majority of NAFLD patients need in primary care.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

MJA and GM wrote the manuscript and approved the final version.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.05.010.

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