Reply to: Non-invasive tests and advanced chronic liver disease in NAFLD: two steps forward and one step back?

We appreciate the interest in our study by Majumdar and Tschochatzis and welcome the opportunity to provide some clarifications.

The literature to date has examined non-invasive test (NIT) algorithms to rule-in and rule-out advanced fibrosis (AF). The main use of such algorithms is to identify those at low risk of AF who can be managed in primary care. We propose an algorithm2 where the rule-out cut-offs remain optimised for AF, whereas the rule-in cut-offs are optimised for cirrhosis. The false-negative (FN) rate of 10% in our proposed algorithm refers to the FN rate for AF and not cirrhosis as Majumdar and Tschochatzis state in their letter. Only 18/570 (3%) of patients with cirrhosis are missed using our proposed algorithm (Table 1).

We also argue3 that patients with NITs above the rule-in cut-off for AF should undergo liver biopsy to identify those with cirrhosis who should undergo screening for hepatocellular cancer (HCC) with 6-monthly ultrasound scans. Our data consist mostly of cases that have undergone liver biopsies to stage fibrosis and do not include patients with overt features for cirrhosis, as these patients do not usually undergo liver biopsy. While we do not have radiology data, liver surface nodularity is not specific to liver cirrhosis, but can be seen in earlier stages of disease.3 Our data show that among the few patients with laboratory parameters suggestive of cirrhosis (platelet count <150×10^9/L, albumin <35 g/L and international normalised ratio (INR) >1.2) most fall above the liver stiffness measurement (LSM) cut-off of 20 kPa (Table 2). Therefore, laboratory features are not helpful in diagnosing cirrhosis in those with LSM <20 kPa.

Majumdar and Tschochatzis suggest that the LSM cut-off of 15 kPa recommended by Baveno VI could identify those with compensated advanced chronic liver disease (cACLD). However, it is not clear how patients with LSM ≥15 kPa should be managed with regard to HCC surveillance. Based on our data, if those with LSM ≥15 kPa are entered into HCC surveillance, only 44% will have cirrhosis, whereas nearly a quarter will have F0–2 fibrosis (Table 1). We are not aware of any data supporting HCC surveillance in those with LSM ≥15 kPa, and Baveno VI4 makes no recommendations on whether these patients should undergo screening for HCC. Furthermore, screening is generally cost-effective if the annual risk of HCC is ≥1% and currently recommended only in those with Non-Alcoholic Fatty Liver Disease and cirrhosis.5 The risk of HCC is <1% in those with LSM <18 kPa,6 while the presence of cirrhosis rather than high NITs is the main driver of the HCC risk.7 We therefore believe that screening patients with LSM ≥15 kPa for HCC without further disease staging is not justified.

With regard to risk stratification for oesophageal varices, the LSM cut-off of 20 kPa recommended by Baveno VI is only useful as a screening tool with a high negative predictive value that decreases the number of unnecessary endoscopies done to identify varices needing treatment (VNT). This cut-off has not been validated as a diagnostic tool that could replace endoscopy. The positive predictive value of the.Baveno VI criteria for VNT was only 0.18 in one study.8 The patients ruled in as having cirrhosis by the 20 kPa cut-off would therefore still need to undergo endoscopy to identify the minority with VNT.

In conclusion, diagnosis of liver cirrhosis is still important to determine the need for HCC screening. Previously proposed NIT cut-offs are optimised for AF or cACLD on biopsy and not on HCC risk. Long-term outcome data to determine NIT cut-offs that incur a 1% annual risk of HCC are needed before we know which patients will benefit from HCC surveillance without a histological diagnosis of cirrhosis.

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**Table 1** Number of patients with fibrosis stage F0–2, F3 and F4 according to LSM cut-offs recommended by the Baveno 6 consensus (10 and 15 kPa) and our previous paper (8 and 20, and 8 and 28 kPa)

| LSM <10 kPa | LSM≥10 and < 15 kPa | LSM≥15 kPa |
|------------|---------------------|------------|
| F0–2       | 3135                | 508        | 192        |
| F3         | 420                 | 372        | 292        |
| F4         | 53                  | 140        | 377        |
| LSM <8 kPa | LSM≥8 and <20 kPa   | LSM≥20 kPa |
| F0–2       | 2591                | 1174       | 70         |
| F3         | 213                 | 701        | 170        |
| F4         | 18                  | 260        | 292        |
| LSM <8 kPa | LSM≥8 and <28 kPa   | LSM≥28 kPa |
| F0–2       | 2591                | 1218       | 26         |
| F3         | 213                 | 819        | 52         |
| F4         | 18                  | 399        | 153        |

LSM, liver stiffness measurement.

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**Table 2** Number of patients with laboratory features of cirrhosis according to histological and liver stiffness-based classification

| n=1657 | LSM≥15 kPa | LSM≥20 kPa | LSM≥28 kPa |
|--------|------------|------------|------------|
| Pt <150×10^9/L | F4         | 47         | 44         | 25         |
|         | F0–3       | 19         | 9          | 2          |
| Pt <150×10^9/L and Albumin <35 g/L | F4         | 8          | 7          | 6          |
|         | F0–3       | 1          | 1          | 1          |
| Pt <150×10^9/L and Albumin <35 g/L and INR >1.2 | F4         | 5          | 5          | 4          |
|         | F0–3       | 1          | 1          | 1          |

INR, international normalised ratio; LSM, liver stiffness measurement; Pt, platelet count.
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