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
Plt <150×10^9/L	F4	47	44	25
	F0-3	19	9	2
Plt <150×10^9/L and Albumin <35 g/L	F4	8	7	6
	F0-3	1	1	1
Plt <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; Plt, platelet count.

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 Tsochatzis[1] 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 algorithm[2] 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 Tsochatzis state in their letter.[1] Only 18/570 (3%) of patients with cirrhosis are missed using our proposed algorithm (table 1).

We also argue[2] 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 Tsochatzis[1] suggest that the LSM cut-off of 15 kPa recommended by Baveno VI[4] 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, while 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 VI[4] 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[4] 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.

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.

Michael Pavlides ,[1,2,3] **Ferenc E. Mózes** ,[1] **Stephen A. Harrison**[1]

1Cardiovascular Medicine, Radcliffe Department of Medicine, Oxford University, Oxford, UK
[2]Translational Gastroenterology Unit, University of Oxford, Oxford, UK
[3]NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust and the University of Oxford, Oxford, UK

Correspondence to Dr Michael Pavlides, Radcliffe Department of Medicine and Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford OX3 9DU, UK; michael.pavlides@cardiov.ox.ac.uk

Contributors MP wrote the manuscript. FEM analysed data. All authors revised the manuscript for significant intellectual content.

Funding MP, FEM and SAH are members of the LITMUS consortium which is funded by the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking under Grant Agreement 777377. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Disclaimer The funder and the authors' institutions had no role in the development of the protocol for this study.

Competing interests MP is shareholder in Perspectum Ltd. SAH has research grants from Akero, Axcella, Cirius, CiVi Biopharma, Cymabay, Galectin, Galmed, Genfit, Gilead Sciences, Hepion Pharmaceuticals, Hightide Therapeutics, Intercept, Madrigal, Metacrine, NGM Bio, Northsea Therapeutics, Novartis, Novo Nordisk, Poxel, Sagimet, Viking. He has received consulting fees from Akero, Altimmune, Alentis, Arrowhead, Axcella, Canfite, Cirius, CiVi, Cymabay, Echosens, Enyo, Fibronostics, Foresite Labs, Fortress Biotech, Galectin, Genfit, Gilead Sciences, Hepion, HIghtide, HistoIndex, Intercept, Kowa, Madrigal, Metacrine, NGM, Northsea, Novartis, Novo Nordisk, Poxel, Prometic, Ridgeline, Sagimet, Terns, and Viking.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

OPEN ACCESS

To cite Pavlides M, Mózes FE, Harrison SA. *Gut* 2022;**71**:1453–1454.

Received 13 October 2021
Accepted 14 October 2021
Published Online First 27 October 2021

Gut 2022;**71**:1453–1454. doi:10.1136/gutjnl-2021-326313

ORCID iDs
Michael Pavlides http://orcid.org/0000-0001-9882-8874
Ferenc E. Mózes http://orcid.org/0000-0002-1361-4349

REFERENCES

1 Majumdar A, Tsochatzis EA. Non-Invasive tests and advanced chronic liver disease in NAFLD: two steps forward and one step back? *Gut* 2022;71:1236–7.
2 Mózes FE, Lee JA, Selvaraj EA, *et al*. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. *Gut* 2022;71:1006–19.
3 Dioguardi Burgio M, Sartoris R, Beaufrere A, *et al*. Liver surface nodularity on non-contrast MRI identifies advanced fibrosis in patients with NAFLD. *Eur Radiol* 2021. doi:10.1007/s00330-021-08261-6. [Epub ahead of print: 17 Sep 2021].
4 de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;63:743–52.
5 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the LiverGalle PR, Forner A, Llovet JM. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182–236.
6 Shili-Masmoudi S, Wong GL-H, Hiriart J-B, *et al*. Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease. *Liver Int* 2020;40:581–9.
7 Kanwal F, Kramer JR, Mapakshi S, *et al*. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. *Gastroenterology* 2018;155:1828–37.
8 Petta S, Sebastiani G, Bugianesi E, *et al*. Non-Invasive prediction of esophageal varices by stiffness and platelet in non-alcoholic fatty liver disease cirrhosis. *J Hepatol* 2018;69:878–85.