SAT-305

Alignment between physician-estimated versus objectively derived fibrosis scores in non-alcoholic steatohepatitis: Real-world evidence suggests clinicians underestimate disease severity in secondary care

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Background

- Non-alcoholic steatohepatitis (NASH) is a chronic liver disease characterised by fatty infiltration and inflammation of the liver with or without fibrosis.[1] NASH can progress to cirrhosis, liver failure and liver cancer[2] and so an accurate diagnosis and risk stratification is important for the further management of patients
- Liver biopsy is currently the reference standard for identifying steatohepatitis and subsequently grading and staging disease; however, use of this technique is limited by cost and expertise to specialist centers.[3] In the real-world setting, physicians do not always have access to or wish to use this invasive diagnostic method
- Alternative non-invasive tests have been developed for the diagnosis of liver fibrosis, including transient elastography by FibroScan. However, FibroScan is subject to some limitations, including potentially reduced accuracy in fibrosis staging in patients who are older, or exhibit obesity, hypertension or type 2 diabetes mellitus (T2DM)[4]
- The results of FibroScan also require interpretation by the supervising clinician and so are open to misinterpretation, through which liver disease severity may be over- or under-estimated

Objective

- To establish the degree of alignment between real-world physician-estimated fibrosis based on available clinical data compared with published FibroScan reference values[5,6]

Methods

Study design and participants

- Data were drawn from the Adelphi Real World NASH Disease Specific Programme™ (DSP) conducted in 2018 in the EU5 (France, Germany, Italy, Spain and UK). The DSP is a point-in-time survey of physicians and their patients presenting in a real-world clinical setting. The DSPs have been described in detail and validated elsewhere[7,8]
- Eligible physicians were hepatologists, gastroenterologists and diabetologists managing ≥10 NASH patients per month. Participating physicians had to be personally responsible for NASH management decisions
- Patients were required to be ≥18 years old, with a physician-confirmed NASH diagnosis (via liver biopsy or non-invasive test approach) but were not allowed to be participating in a clinical trial. Patients included in this analysis had to have both a physician-stated fibrosis stage derived from all available clinical data and a FibroScan test result available
- The study was performed in line with guidelines; ethics approval was obtained from Freiburg Ethics Commission International (FEKI; Approval No. 017/1931). All patients provided written informed consent for use of their anonymised and aggregated data

Sample and data collection

- Physicians completed a questionnaire for the next five consecutive consulting NASH patients, regardless of F0–F4 status, as identified by the physician and who presented for routine care (core sample)
- After completing this task, physicians were then asked to include a further two consecutive consulting patients who presented with F3 or F4 fibrosis as identified by the physician (oversample)
- Questions focused on a range of aspects of patient care, including the diagnostic test used, fibrosis score, and FibroScan reporting

Stated fibrosis staging

- Physicians stated each patient's fibrosis stage as F0, F1, F2, F3 or F4 according to their interpretation of the available clinical data

Derived FibroScan scoring

- Physicians provided FibroScan raw test results as measured by kPa
- A derived FibroScan assessment was then retrospectively performed on FibroScan test results as recommended by Wong et al[5] and Cassinotto et al[6] using the published, optimised, high-sensitivity and high-specificity thresholds shown in Tables 1 and 2

Statistical analyses

- Patients were grouped by fibrosis stage as F0–F2 (early fibrosis) vs F3–F4 (advanced fibrosis NASH [AF-NASH]) by their physicians
- Comparison was made to two reference standards that were retrospectively applied, based on the values published by Wong et al[5] and Cassinotto et al[6]
- All analyses were carried out on the core sample unless otherwise stated

Methods (cont'd)

Table 1. Derived fibrosis scoring according to Wong et al[5]

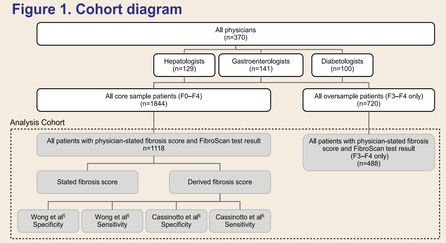
Stage	Cut-off (kPa)	High sensitivity (≥90%)	High specificity (≥90%)
F0-F2	<7.9	✓	
	<9.6		✓
F3-F4	≥7.9	✓	
	≥9.6		✓

Table 2. Derived fibrosis scoring according to Cassinotto et al[6]

Stage	Cut-off (kPa)	High sensitivity (≥90%)	High specificity (≥90%)
F0-F2	<8.2	✓	
	<12.5		✓
F3-F4	≥8.2	✓	
	≥12.5		✓

Results

Figure 1. Cohort diagram



Stated: Physician fibrosis score based on their interpretation of available clinical data. Derived: Retrospective assessment of FibroScan test results derived by application of reference values. Analysis cohort: patients with both a physician-stated fibrosis score and a FibroScan result

Physicians and patients

- Overall, 370 physicians (35% hepatologists; 38% gastroenterologists; 27% diabetologists) provided data on a core sample of 1844 patients with NASH across all severities F0–F4 (Figure 1)
- Of these, distribution of patients across countries was 21% France, 20% Germany, 21% Italy, 20% Spain and 18% UK
- Physicians also provided data on an additional oversample of 720 patients with F3–F4 fibrosis (Figure 1)

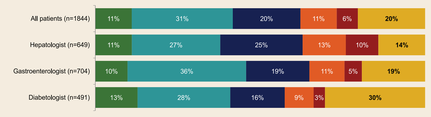
Stated Fibrosis scoring

- Overall, 17% of patients were identified with AF-NASH (F3–F4) as stated by the physician (Figure 2)
- Notably, a considerable proportion of diabetologists did not know their patient's fibrosis score (30%; Figure 2) or did not report their patient's FibroScan result (55%; Figure 3)
- 1118 patients had both a physician-stated fibrosis score and FibroScan result (Figure 1). According to these criteria, 22% of patients were identified with AF-NASH (F3–F4) as stated by the physician (Figure 4)

Demographics

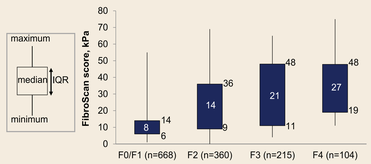
- Almost two thirds of patients were male and more than half were full-or part-time employment; many patients presented with T2DM, obesity, hypertension, or dyslipidaemia (Table 3)

Figure 2. Physician-stated fibrosis scoring according to managing physician specialty (core sample, n=1844)



Results (cont'd)

Figure 3. Median FibroScan score segmented by physician-stated fibrosis stage (core sample, n=1844)



IQR: Interquartile range. Patient's current FibroScan score unknown: hepatologists 28%; gastroenterologists 31%; diabetologists 55%

Table 3. Patient demographic characteristics (core sample)

Characteristic	Core sample patients (n=1844)	Analysis cohort (n=1118)
Mean age, years (SD)	55.7 (11.5)	55.2 (10.9)
Male sex, n (%)	1137 (62)	661 (59)
Mean body mass index, kg/m² (SD)	32.6 (6.5)	32.7 (6.2)
Testing (ever): liver biopsy, n (%)	893 (48)	586 (52)
Employment status, n (%)		
Working full time	770 (42)	490 (44)
Working part time	171 (9)	119 (11)
On long-term sick leave	62 (3)	28 (3)
Retired	452 (25)	235 (21)
Most common concomitant conditions (occuring in >10% of patients overall), n (%)		
T2DM	1083 (59)	630 (56)
Obesity	1060 (57)	623 (56)
Hypertension	892 (48)	549 (49)
Dyslipidaemia	847 (46)	491 (44)
Metabolic syndrome	455 (25)	285 (25)
Sleep disorder	307 (17)	228 (20)
Insulin resistance	291 (16)	160 (14)
Anxiety	263 (14)	183 (16)
Hyperglycaemia	217 (12)	125 (11)

Analysis cohort: patients with both a physician-stated fibrosis score and FibroScan result. SD, standard deviation

Derived fibrosis severity

- When retrospectively applying the FibroScan cut-offs reported by Wong et al[5] and Cassinotto et al[6] to the data, the proportion of patients with AF-NASH increased compared with stated fibrosis scores (22% vs. 46–79%; Figure 4)
- Using the sensitivity derivative, a higher proportion of patients were deemed to have AF-NASH than when the specificity approach was taken (Figure 4)

Alignment of stated fibrosis and derived FibroScan scoring

- When comparing stated fibrosis versus derived FibroScan scoring, scores were aligned in most cases; however, where results were not aligned, physicians were most likely to underestimate the patient's score (Figure 5)
- The degree of underestimation varied between derived approach
  - Wong et al[5] Specificity 42%; Sensitivity 58%; Cassinotto et al[6] Specificity 31%; Sensitivity 47% (Figure 5)
- When the additional sample of the more severe F3 and F4 AF-NASH patients were included, the overall underestimation was reduced
  - Wong et al[5] Specificity 29%; Sensitivity 40%; Cassinotto et al[6] Specificity 21%; Sensitivity 33%
- Although all physician specialties underestimated fibrosis scores, this was most pronounced among diabetologists (Figure 6)

Figure 4. Patient breakdown according to different derived FibroScan scoring systems (core sample, n=1118)

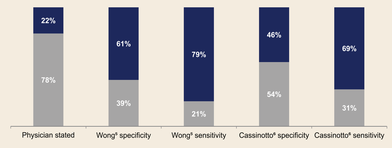
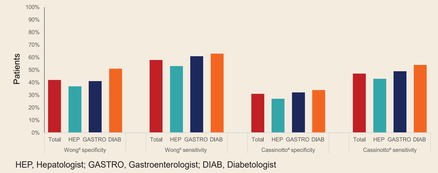
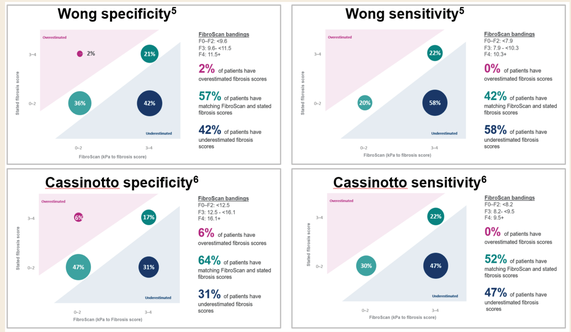


Figure 6. Derived FibroScan score: Degree of underestimation by specialty, by scoring system (core sample, n=1118)



HEP, Hepatologist; GASTRO, Gastroenterologist; DIAB, Diabetologist

Figure 5. Alignment by stated fibrosis score versus derived FibroScan (core sample, n=1118)



All charts do not sum to 100% due to rounding

Conclusions

- In a real-world setting, specialists do not always correctly estimate the fibrosis stage of the patient's NASH compared with established FibroScan reference points
  - As many as one in two patients may be assigned an incorrect, lower fibrosis score
- Underestimation of fibrosis score could result in incorrect patient management and treatment approaches
- Among patients where FibroScan already presents challenges with inaccurate fibrosis staging (ie older, obese, hypertensive or T2DM patients), this misclassification may potentially be magnified
- Further education could help provide physicians with the tools to correctly assign fibrosis classification and enhance optimal, personalised patient management approaches

Limitations

- Identification of NASH patients was based on the judgement of the respondent physician and not a formalised diagnostic checklist, but is representative of physician's real-world classification of the patient
- Although FibroScan was used as the 'reference standard', some physicians may have had access to additional information such as liver biopsy results. Severity assessment in these cases may have been more accurately informed by liver biopsy, providing results with a potentially higher degree of accuracy. This contingency could not be explored further in this analysis and so the discrepancy between physician-stated and derived FibroScan results as reported could be due to the physician being correct as a result of having extra information, such as biopsy results.
- Recall bias, a common limitation of surveys, may have affected physician responses to the questionnaires. However, physicians had access to patient medical records/ charts hence recall bias is unlikely to be a problem

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Acknowledgments

The authors would like to acknowledge critical review by Sam Kozma of Gilead Sciences, UAE and Kate Hallsworth of Newcastle University. Medical writing support was provided by Deirdre Carman of Alispera Communications.

Disclosures

- QMA has received **Research Grant Funding** from Abbvie, Allergan/Tobira, AstraZeneca, GlaxoSmithKline, Glympse Bio, Novartis Pharma AG, Pfizer Ltd., Vertex; **Active Research Collaborations (including research collaborations supported through the EU IMI2 LITMUS Consortium*)** with Abbvie, Antaros Medical*, Allergan/Tobira, AstraZeneca, Boehringer Ingelheim International GMBH*, Ellegaard Gottingen Minipigs AS*, Eli Lilly & Company Ltd.*, Exalenz Bioscience Ltd.*, Genfit SA*, Glympse Bio, GlaxoSmithKline, HistoIndex, Intercept Pharma Europe Ltd.*, IXscient Ltd.*, Nordic Bioscience*, Novartis Pharma AG*, Novo Nordisk A/S*, One Way Liver Genomics SL*, Perspectum Diagnostics*, Pfizer Ltd.*, Sanofi-Aventis Deutschland GMBH*, SomaLogic Inc.*, Takeda Pharmaceuticals International SA*; **Consultancy** with Abbott Laboratories, Acuitas Medical, Allergan/Tobira, Blade, BNN Cardio, Cirius, CymaBay, EcoR1, E3Bio, Eli Lilly & Company Ltd., Galmed, Genfit SA, Gilead, Grunthal, HistoIndex, Indalo, Imperial Innovations, Intercept Pharma Europe Ltd., Inventiva, IQVIA, Janssen, Kenes, Madrigal, MedImmune, Metacrine, NewGene, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk A/S, Pfizer Ltd., Poxel, Raptor Pharma, Servier, Viking Therapeutics and **Speaker** for Abbott Laboratories, Allergan/Tobira, BMS, Clinical Care Options, Falk, Fishawack, Genfit SA, Gilead, Integritas Communications.
- CK, NW, JP and VH are employees of Adelphi Real World
- NL and AH are employees of Gilead
- JB has received consultancy payments from Gilead

Presented at the International Liver Congress (EASL), 10-14 April 2019, Vienna, Austria