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Clinical practice gaps and challenges in non-alcoholic steatohepatitis care: An international physician needs assessment

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Abstract

Background and aims: Even as several pharmacological treatments for non-alcoholic steatohepatitis (NASH) are in development, the incidence of NASH is increasing on an international scale. We aim to assess clinical practice gaps and challenges of hepatologists and endocrinologists when managing patients with NASH in four countries (Germany/Italy/United Kingdom/United States) to inform educational interventions.

Methods: A sequential mixed-method design was used: qualitative semi-structured interviews followed by quantitative online surveys. Participants were hepatologists and endocrinologists practising in one of the targeted countries. Interview data underwent thematic analysis and survey data were analysed with chi-square and Kruskal-Wallis tests.

Results: Most interviewees ($n = 24$) and surveyed participants (89% of $n = 224$) agreed that primary care must be involved in screening for NASH, yet many faced challenges involving and collaborating with them. Endocrinologists reported low knowledge of which blood markers to use when suspecting NASH (56%), when to order an MRI (65%) or ultrasound/FibroScan® (46%), and reported sub-optimal skills interpreting alanine aminotransferase (ALT, 37%) and aspartate aminotransferase (AST, 38%) blood marker test results, causing difficulty during diagnosis. Participants believed that more evidence is needed for upcoming therapeutic agents; yet, they reported sub-optimal knowledge of eligibility criteria for clinical trials. Knowledge and skill gaps when managing comorbidities, as well as skill gaps facilitating patient lifestyle changes were reported.

Conclusions: Educational interventions are needed to address the knowledge and skill gaps identified and to develop strategies to optimize patient care, which include implementing relevant care pathways, encouraging referrals and testing, and

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate transaminase; CME, Continuing Medical Education; HCPs, Health Care Providers; MRE, Magnetic Resonance Elastography; MRI-PDFF, Magnetic Resonance-Proton Density Fat Fraction; NAFLD, Non-alcoholic Fatty Liver Disease; NASH, Non-alcoholic Steatohepatitis; PCPs, Primary Care Providers.

multidisciplinary collaboration, as suggested by the recent Global Consensus statement on NAFLD.

KEYWORDS
clinical practice gaps, continuing professional development continuing medical education, needs assessment, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis

1 | INTRODUCTION

Obesity has reached proportions that some authors have qualified as epidemic (estimated at 650 million adults globally[1]) and that translates to an increased prevalence of abdominal/visceral adiposity. Both adipocyte dysfunction and increased delivery of free fatty acids to the liver contribute to insulin resistance and predisposition to the development of Type 2 diabetes mellitus (T2DM).[2] Patients with obesity, especially those with T2DM, are at increased risk of non-alcoholic fatty liver disease (NAFLD) and the more serious form of this disorder, non-alcoholic steatohepatitis (NASH), which is characterized by lobular inflammation, ballooning degeneration of hepatocytes and may progress to advanced liver disease.[3] NAFLD is known to be associated with metabolic syndrome, characterized by dyslipidaemia, hyperglycaemia and hypertension.[4] Among people with T2DM, the prevalence of NAFLD and NASH is 55% and 37% respectively.[5] Studies have shown an increased risk of atherosclerotic cardiovascular disease, especially in those with advanced liver fibrosis[6,7] associated with NAFLD.

The definitive diagnosis of NASH currently requires a liver biopsy and histological analysis of tissue[8] demonstrating steatosis, usually accompanied by lobular inflammation, ballooning degeneration of hepatocytes, and variable degrees of fibrosis.[9] There is active research in development of non-invasive tests (NITs) to replace liver biopsy, but currently, such methods have not been approved by regulatory authorities as a substitute for the histopathological diagnosis of NASH.[10] Other approaches, such as the use of imaging tests like magnetic resonance-proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE) and FibroScan®, to assess progression of hepatic steatosis and fibrosis are limited by cost and availability.[11]

Despite the prevalence and public health burden of NAFLD and NASH, awareness of the conditions among public and healthcare providers (HCP) remains limited and practice challenges related to the condition persist.[12,13] There remains a lack of approved therapeutic agents while the incidence of NASH is increasing globally. Development of pharmacological treatments has been hindered by slow disease progression, lack of easily measurable surrogate endpoints, and the variable placebo response, given the effect of lifestyle modification and other non-pharmacological therapies in clinical trials.[14–16] Arguably, showing improvements in mortality rates would require enrolling patients with early-stage NASH who could participate in a decades-long study.[17] The primary current treatments for NASH remain lifestyle and diet changes.[18,19] Pharmacological options vary in efficacy and include (1) off-label treatments to manage the impact of NASH that have shown some benefit in clinical trials, but are not yet approved (e.g. pioglitazone, vitamin E)[20] and (2) treatments to manage blood sugar (e.g. metformin, thiazolidinediones and GLP-1 receptor agonists), cholesterol (i.e. statins), and reduce body fat (e.g. orlistat, GLP-1 receptor agonists).[17] Bariatric surgery is an option for certain patients to manage weight gain, though regular monitoring following the procedure must be carried out to detect decompensated liver disease or fibrosis progression.[21]

As NASH is linked to other common diseases like T2DM and cardiovascular disease, there is a need to better understand potential challenges that HCPs face and how it impacts patient care, especially in the absence of clear pharmacological options. The objective of this study was to assess and categorize clinical practice gaps and challenges of hepatologists and endocrinologists experienced in the management of patients with NASH in selected countries. Current guidelines for NAFLD care exist, such as those of the European Association for the Study of the Liver (EASL),[20] the Italian Association for the Study of the Liver (AISF),[22] the American Association for the Study of Liver Diseases (AASLD)[9] and the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) guidelines for Non-Alcoholic Fatty Liver Disease: Assessment and Management.[23] The aim is to inform complementary context-specific and up-to-date continuing medical education (CME), which is needed to improve knowledge, skills, and to assist HCPs in developing strategies to optimize patient care despite current and persistent barriers.

2 | MATERIALS AND METHODS

This study employed a sequential mixed-methods approach where a qualitative methodology (in-depth semi-structured interviews) was first used to explore the current challenges (and their causalities) facing hepatologists and endocrinologists in Germany, Italy, the UK and the USA.[24] These data informed a quantitative methodology (surveys) to assess the magnitude and frequency of the qualitatively reported challenges by measuring participants' attitude and self-reported knowledge, skill and confidence levels. All data were triangulated with the results of a brief exploratory review of literature (i.e. a single search strategy with keywords "[NASH or NAFLD] and Liver and [Challenges or Gap or Continuing Medical Education]",

restricted to English or French, complemented with articles recommended by clinical subject matter experts - co-authors JWT, KVK, PM and RDS) conducted by searching recent publications (i.e. published no more than two years prior to date of data collection, March 2020) for indications of key issues and current state of research in NASH care, including patient communication challenges, current evidence for treatment recommendations including clinical trials, care models for different patient profiles and the HCP competencies and resources needed to optimize care. This review was used as both a starting point (by informing development of data collection tools) and contextualization (by exploring if the identified challenges and barriers corresponded with previously reported gaps or were associated with regional or national policies, or documented educational and implementation issues). Results were interpreted collaboratively between educational experts (including co-authors PL, GJ, and SM) and clinical subject matter experts (co-authors JWT, KVK, PM and RDS).[25]

An ethics review board, VERITAS IRB (Montreal, QC, Canada), reviewed and approved all components of this study (March 25, 2020). All participants provided their informed consent prior to study participation. Compensation was provided to those who completed the study based on the nature of their participation (interview or survey), their country of practice and their profession (105–250 USD for interviews; 46–63 USD for survey), in correspondence with conventions of research ethics and best practices.[26]

We sought a diversity of perspectives from within a group of specialists experienced in the management of patients with NASH from several countries. Participants were selected using maximum variation purposive sampling.[27] Eligible participants were either hepatologists or endocrinologists/diabetologists with a minimum of three years of clinical practice experience and were currently practising in Germany, Italy, the UK or the USA. Hepatologists were required to have a caseload of at least six patients per month with NASH, while endocrinologists/diabetologists were required to see at least four patients per month with NASH. All data collection was done in the predominant language of the participant's country.

2.1 | Research design

The first phase involved qualitative interviews (45–60 minutes) with 24 participants. They were asked open-ended questions about their experiences, challenges, practice gaps and any barriers they may have encountered while caring for patients with NASH.

In the second phase, quantitative data were collected through an online survey ($n = 224$). This survey contained distinct sections in which participants self-reported their level of agreement with certain statements, rated their knowledge and skill levels with a 5-point Likert-type scale, indicated their confidence levels using a 0–100 visual analogue scale and answered a multiple-choice query of their preferred clinical guidelines.

2.2 | Analysis

A qualitative analysis of transcribed interview data used NVivo software (QSR International Pty Ltd, Version 12, 2018). A hybrid deductive and inductive approach was employed, drawing from the tenets of both thematic[28] and directed content analysis.[29] Data were first organized into themes based on the pre-determined areas of exploration, and then new themes were added during the coding process. The results were systemically analysed to identify similarities and divergences between participants in NASH-related care experiences of participants.[30]

SPSS software (version 26.0, IBM Corporation, Armonk, NY) was used to analyse quantitative survey data collected during the second phase of this study. Data were organized into frequency tables and subject to chi-square tests for frequency and Kruskal-Wallis tests for variance.[31] When participants selected either 1-low, 2-basic or 3-intermediate out of 5 on a five-point Likert scale (where 4-advanced, 5-expert), knowledge or skill levels were described as "sub-optimal" and indicative of a need for educational intervention. For analysis, the responses to agreement items were regrouped from the 5-point Likert scale into three categories: "disagree or strongly disagree," "neither agree nor disagree" and "agree or strongly agree." Each item also had the response option "not relevant to my current practice." When selected, this response was excluded from the analysis to avoid skewing the results.

Data from both qualitative and quantitative phases, as well as results of the literature review, were triangulated to identify commonalities and concordant themes that emerged. Following this, a collaborative review by clinical and educational subject matter experts ensured that final findings were interpreted from both perspectives and clinical processes were described accurately.

3 | RESULTS

Participants included 125 hepatologists and 123 endocrinologists from Germany, Italy, the UK, and the USA. Of those, 47% had between 11 and 20 years of practice experience and 45% practiced mainly in an academic-based or -affiliated hospital setting (Table 1). The most frequently used guidelines, reported by 66% of participants, were the joint guidelines co-written by the European Association for the Study of Liver (EASL), the European Association for the Study of Obesity[20] and the European Association for the Study of Diabetes (EASD),[20] followed by the guidelines from the American Association for the Study of Liver Diseases (AASLD)[9] (51%) and those from the UK National Institute for Health and Care Excellence (NICE)[23] (37%).

Results of this study indicated that hepatologists and endocrinologists experience challenges related to (1) conducting screening and diagnosis for NASH; (2) making treatment decisions when faced with limited options; (3) monitoring and managing comorbidities; (4) integrating new and emerging treatments; (5) supporting healthy lifestyle modifications; and (6) inter-disciplinary management of NASH.

TABLE 1 Description of the sample by phase (qualitative and quantitative) and specialty

	Hepatologists ($n = 125$)	Endocrinologists ($n = 123$)	Total ($n = 248$)
Country			
Germany	23% (29)	23% (28)	23% (57)
Italy	22% (28)	24% (29)	23% (57)
UK	22% (28)	23% (28)	22% (56)
US	32% (40)	30% (38)	31% (78)
	Qualitative ($n = 24$)	**Quantitative ($n = 224$)**	**Total**
Years of practice			
3–10 years	13% (3)	28% (62)	26% (65)
11–20 years	50% (12)	47% (106)	47% (118)
21+ years	38% (9)	25% (56)	26% (65)
Practice setting			
Hospital: academic-based or affiliated	42% (10)	46% (103)	46% (113)
Hospital: community-based, non-academic affiliated	4% (1)	13% (30)	12% (31)
Multi-specialty physician group practice	12% (3)	11% (24)	11% (27)
Single-specialty physician group practice	–	17% (38)	15% (38)
Solo practice	25% (6)	8% (19)	10% (25)
Community clinic	13% (3)	4% (10)	6% (13)
Other	4% (1)	2% (5)	2% (6)

3.1 | Challenges conducting screening and diagnosis for NASH

Participants (89%) agreed that "primary care providers (PCPs) must be involved to a greater extent in the screening of patients with NASH than they currently are" (Table 2). Despite this, participants perceived low awareness among general practitioners (GPs) of the indicators for screening and the importance of doing so.

> "… in some cases, they've had elevated liver values for 20 years and were never referred […] you do have to educate GPs on which fatty liver patients should be referred …"- Hepatologist, Germany

Participants expressed concern about a lack of consensus regarding the optimal screening practices for NASH. Some were concerned that current protocols are seen as impractical in a clinical setting.

> "It's not clear that everybody agrees on when and how you should do liver biopsies. I think there's a fair amount of controversy in screening …"- Endocrinologist, United States"… some advice came out some years ago, which was about screening people. And basically, anyone who's fat or diabetic basically need to be screened very regularly […] It's undoable on an individual hospital basis, and I don't think we're able to do it locally. So, it would need some kind of national screening program."- Hepatologist, United Kingdom

These barriers may impact diagnosis and timely care: 77% of hepatologists and 78% of endocrinologists in this study agreed that "patients with a suspicion of NASH often experience a significant delay in seeing a specialist" (Table 2).

When patients do manage to see a specialist, challenges in diagnosis tend to persist. Overall, 37% of respondents agreed or strongly agreed that "There are no standards for diagnosing patients with a suspicion of NASH". Most endocrinologists (56%) reported sub-optimal knowledge of "which blood marker(s) to use when NASH is suspected" (Table 3) and reported sub-optimal skills interpreting results from alanine aminotransferase (ALT) (37%) and aspartate transaminase (AST) (38%) blood marker-level tests (Table 4). The level of these challenges was significantly different by specialty area ($p < .001$). Half of the respondents agreed or strongly agreed that "current diagnostic tools and biomarkers for NASH are unreliable" (with differences by country, Table 2) and that the utility of these results may be limited:

> "… the liver function test, like raised ALT, sometimes it will be normal despite the patient having high clinical risk factor. […If] we think clinically the patient does have this condition, then we don't rely on that [the liver function test]. We have to look for more tests that have higher specificity."- Endocrinologist, United Kingdom

Endocrinologists reported sub-optimal knowledge of "when to send patients with a suspicion of NASH for an MRI" (65%) and "when to prescribe an ultrasound, including a FibroScan®" (46%). In addition,

TABLE 2 Responses to agreement statements

Statement	Country				Sig.
	Germany	Italy	UK	US	
Primary care providers must be involved at a greater extent in the screening of patients with NASH than they currently are					
Agree or strongly agree	92%	90%	98%	80%	$p < .05$
Neither agree nor disagree	0%	8%	2%	11%	
Disagree or strongly disagree	8%	2%	0%	8%	
Current diagnostic tools and biomarkers for NASH are unreliable					
Agree or strongly agree	53%	33%	60%	53%	$p < .05$
Neither agree nor disagree	22%	49%	22%	28%	
Disagree or strongly disagree	25%	18%	18%	19%	
There is a lack of safe and effective drugs specifically developed for NASH					
Agree or strongly agree	88%	80%	67%	89%	$p = .016$
Neither agree nor disagree	4%	14%	25%	6%	
Disagree or strongly disagree	8%	6%	8%	6%	
Existing patient education materials provide a practical, well-balanced perspective about NASH					
Agree or strongly agree	31%	20%	30%	51%	$p < .05$
Neither agree nor disagree	47%	49%	42%	31%	
Disagree or strongly disagree	22%	31%	28%	18%	

Statement	Specialty		Sig.
	Hepatology	Endocrinology	
Patients with a suspicion of NASH often experience a significant delay in seeing a specialist			
Agree or strongly agree	77%	78%	$p = .976$
Neither agree nor disagree	14%	14%	
Disagree or strongly disagree	9%	8%	
There are no standards for diagnosing patients with a suspicion of NASH			
Agree or strongly agree	31%	43%	$p < .05$
Neither agree nor disagree	26%	34%	
Disagree or strongly disagree	43%	23%	

Statement	Setting		Sig.
	Community	Academic	
Current diagnostic procedures for NASH are too invasive for my patient			
Agree or strongly agree	53%	37%	$p < .05$
Neither agree nor disagree	29%	34%	
Disagree or strongly disagree	18%	29%	

they reported low skills when "interpreting FibroScan® results" (74%). Current diagnostic procedures for NASH are seen as less than ideal: 45% of participants agreed that they are too invasive. Skills when differentiating NASH from other conditions were reported as sub-optimal by endocrinologists (60%) in particular. This process was also seen as time-consuming:

> "… I have to differentiate whether it is caused by alcohol toxicity or whether it's metabolic, like NASH, or whether it is a past inflammation. It takes some time to get the right idea about that."- Endocrinologist, Germany

> "… you have to rule out viral things, hepatitis A, B, C, the other viral things that the patients are at risk. You have to rule out autoimmune diseases, Wilson's, hemochromatosis."- Hepatologist, United States

Endocrinologists reported sub-optimal skills "establishing the need for a liver biopsy based on imaging and serologic test results" (67%), alongside lower confidence when "differentiating between simple steatosis and NASH in the absence of a liver biopsy" (42 ± 24), the utility and benefits of biopsy were difficult to communicate, with the procedure is seen as intrusive and costly.

TABLE 3 Self-reported knowledge gaps to selected items

Knowledge item	Specialty		Sig.
	Hepatologists	Endocrinologists	
Which blood marker(s) to use when NASH is suspected ($n = 224$)	29%	56%	$p < .001$
When to send patients with a suspicion of NASH for an MRI ($n = 221$)	30%	65%	$p < .001$
When to prescribe an ultrasound, including a FibroScan® ($n = 223$)	11%	46%	$p < .001$
Side effects and toxicity of Pioglitazone ($n = 224$)	51%	24%	$p < .001$
Eligibility criteria for inclusion of patients in clinical trials pertaining to NASH in my region ($n = 215$)	50%	68%	$p < .05$
Rare comorbidities associated with NASH ($n = 221$)	54%	76%	$p < .001$

TABLE 4 Self-reported skill gaps to selected items

Skill item	Specialty		Sig.
	Hepatologists	Endocrinologists	
Interpreting FibroScan® results ($n = 227$)	20%	74%	$p < .001$
Establishing the need for a liver biopsy based on imaging and serologic test results ($n = 217$)	17%	67%	$p < .001$
Co-creating solutions with patients that will facilitate necessary lifestyle changes ($n = 224$)	31%	31%	$p = .956$ (ns)
Managing common comorbidities associated with NASH ($n = 224$)	29%	32%	$p = .601$ (ns)
Interpreting ALT levels ($n = 224$)	12%	37%	$p < .001$
Interpreting AST levels ($n = 224$)	11%	38%	$p < .001$

TABLE 5 Self-reported confidence levels to selected items

Confidence item	Specialty	*n*	Mean	Std. deviation	Sig.
Differentiating between simple steatosis (NAFLD) and NASH in the absence of a liver biopsy	Hepatologists	113	60	23	$p < .001$
	Endocrinologists	106	42	24	
Establishing a treatment regimen for patients affected by NASH and advanced fibrosis	Hepatologists	113	65	19	$p < .001$
	Endocrinologists	105	45	25	
Advocating for a patient's preference during interdisciplinary discussions	Hepatologists	112	66	21	$p < .05$
	Endocrinologists	110	59	24	

> "Ideally I'd have better safe diagnostics, non-invasive diagnostics, as patients are often asymptomatic and not very enthusiastic about a liver biopsy."- Endocrinologist, Germany

> "We don't have a specific test other than the liver biopsy, which I cannot perform in all patients, because there exist correlated risks. Therefore, I will have to carry out a number of tests and exclude various possibilities, in order to get to NASH. And that is quite costly."- Endocrinologist, Italy

3.2 | Challenges making treatment decisions when faced with limited options

Most respondents (81%) agreed or strongly agreed that "There is a lack of safe and effective drugs specifically developed for NASH," with significant differences by country (Table 2). This poses a barrier to endocrinologists who report low confidence "establishing a treatment regimen for patients affected by NASH and advanced fibrosis" (Table 5). Pioglitazone is an anti-diabetic agent prescribed off-label for NASH in some countries; however, there is a lack of knowledge of the "indications for pioglitazone prescription" among 50% of hepatologists and 35% of endocrinologists (Table 3). In

addition, participants cited concerns about the risk–reward balance of its use:

> "Pioglitazone is a type of drug that actually does reduce NASH in diabetics. [...] In fact, it's a treatment for diabetes, but it has problems. For example, weight gain; pedal oedema; [...] and, in some cases, heart problems. That's not an ideal drug, and it's not FDA approved for NASH. That's important also, which means getting insurance companies to cover it can be problematic."- Hepatologist, US

According to participants, appropriate treatment options for NASH are limited and the presence of common but serious comorbidities can impact how treatment decisions are made. Certain comorbidities are considered serious as NASH itself, which makes decision-making difficult and consequential:

> "... if it comes to the point that insulin needs to be used, weight loss is even more difficult to achieve, because of the challenges in managing a patient who has more important problems than NASH. [...] You may say to them 'Look, you may have cirrhosis in 10 years, and they might answer 'Well, I might become blind in 2 years!'"- Hepatologist, Italy

3.3 | Challenges in monitoring and managing comorbidities

While there is growing awareness of the many potential complications, the skill level when "managing common comorbidities associated with NASH" was reported as sub-optimal by 29% of hepatologists and 32% of endocrinologists (Table 4). A gap in knowledge of "rare comorbidities associated with NASH" was also reported by 54% of hepatologists and 76% of endocrinologists (Table 3). Interview data described the concerns that physicians have for comorbidities and the risks of complications for patients with NASH:

> "... diabetes, alcohol abuse plays a role, of course, that can be a huge risk for increased cirrhosis risk, hyperlipidaemia as well. And of course, you always consider CV [cardiovascular] risk in those patients, because patients don't die of fatty liver, they die of CV complications. So, the comorbidities are extremely important ..."- Hepatologist, Germany

3.4 | Challenges associated with prospective treatments

Statements from specialists indicate a belief that more evidence is needed to support the use of upcoming therapeutic agents for NASH:

> "... I think sometimes when new products come out, we get something that makes a statistically significant difference, but it really takes a while until we know if it really makes a clinically-significant difference".- Endocrinologist, US

> "I've been disappointed because a number of drugs were not very convincing in recently-published clinical trials, e.g., elafibranor has not shown an effect in the RESOLVE-IT trial. It was equal to placebo."- Hepatologist, Germany

While there is a desire for new treatments, there is also a lack of awareness of who to enrol in ongoing clinical trials: 68% of endocrinologists and 50% of hepatologists reported sub-optimal knowledge of "eligibility criteria for inclusion of patients in clinical trials pertaining to NASH in my region" (Table 3).

3.5 | Challenges supporting healthy lifestyle modifications

Communicating the importance of lifestyle changes was reported as difficult, especially in Germany, Italy, and the UK, where significantly fewer agreed or strongly agreed that "existing patient education materials provide a practical, well-balanced perspective about NASH" compared to the USA (Table 2). The skill level when "co-creating solutions with patients that will facilitate necessary lifestyle changes" was reported as sub-optimal by 31% of both hepatologists and endocrinologists (Table 4). When patients are asymptomatic, specialists reported additional challenges relaying recommendations for beneficial lifestyle changes:

> "[...] NASH doesn't give you particular symptoms or make you feel ill in most cases, so people think that the doctor is making it bigger than it is and won't always follow their recommendations. It will also depend on the patient's background".- Endocrinologist, Italy

3.6 | Challenges related to the inter-disciplinary management of NASH

Ensuring patient compliance with treatment plans was a challenge for participants. Collaborating with PCPs was viewed as a concern; 42% of hepatologists and 56% of endocrinologists had sub-optimal skills "collaborating with PCPs to optimize patients' adherence to treatment for NASH." In addition, sub-optimal skills were reported when collaborating with specialists (34% hepatologists, 47% endocrinologists). The skill level of hepatologists (42%) and endocrinologists (55%) was also seen as lacking when it comes to "using

communication tools in place to facilitate interdisciplinary collaboration" (Table 4). According to participants, navigating the complexity of NASH requires an improved multidisciplinary approach to patient care:

> "… The way the liver interacts with all the different organs that I mentioned, like the heart, the pancreas with insulin, and so forth. I think that's lacking, and I think part of that is because of the fact that we're all so specialized. […] I think that a disease like this really requires a lot of interdisciplinary cooperation."- Hepatologist, United States

Consideration of the patient's own preference regarding their care pathway is also important. Despite this, there was a low confidence level reported among hepatologists (66 ± 21) and endocrinologists (59 ± 24) when "advocating for a patient's preference during interdisciplinary discussions."

4 | DISCUSSION

This study identified self-reported deficits in knowledge, skills and confidence among specialists treating patients with NASH which impacts their delivery of care. The core finding of this study is that a lack of specific knowledge related to several of the items surveyed was reported by HCPs despite NASH's prevalence and impact in high-risk populations. Even specialists who treat associated conditions (obesity, diabetes, dyslipidaemia) must consider that their patients may also be at risk of NAFLD or NASH, even if it is not their primary area of concern. This corroborates other published studies that indicate a need to increase overall awareness in the prevention of NAFLD globally,[32,33] an effort that is obstructed by a lack of data, as acknowledged in the recent Global Consensus Statement on NAFLD.[34] This study's insights should serve to inform the prioritization of educational needs for the two specialties involved in this study.

The challenges identified in this study, particularly those related to selecting patients to screen for NASH, highlight the underestimation of the disease severity, lack of availability of treatment options and the perception that diagnostic and staging tools are unreliable. It is suggested that these issues are exacerbated by a lack of consensus on screening practices and the under-emphasis of efficient collaboration with PCPs.[35–37] Echoing this concern, endocrinologists and hepatologists in the current study reported challenges collaborating with PCPs, despite the critical role that PCPs play in detection and referral to these specialists.[34]

The results of this study show significant consideration of the invasiveness of biopsy and perceived unreliability of biomarker testing to detect NASH and monitor disease progression, especially when even common comorbidities are shown to complicate decision-making, and no treatments are approved. The limitations of these procedures are recognized,[38] especially when facing accessibility issues in remote or non-academic settings. This presents a clinical practice gap, since at the same time, there is a need for specialists to improve their knowledge of, and engagement with, emerging research using non-invasive human modelling, for example,[39] and other technologies currently in development.[40] Addressing this need through educational interventions would ensure that specialists acquire the skills and resources to remain at the forefront of innovative care when treatment breakthroughs occur.[41,42]

Lifestyle modifications (e.g. weight management, exercise) have shown to improve the health of patients with NASH.[43] However, providing patients with the education and support needed to make meaningful and lasting changes remains a challenge. Many participants in this study report a sense of exasperation and scepticism, especially in the absence of effective, approved pharmacological approaches. Though treating patients who have comorbidities is a challenge, a more rounded approach to managing common comorbidities (e.g. diabetes, cardiovascular diseases, etc.) would be improved by increased evidence for, and implementation of, targeted lifestyle interventions.[34] Physicians need to develop novel approaches to encourage lifestyle changes.[44] In addition, they must enhance their knowledge of currently available clinical trials, since, in the absence of licensed therapies, those trials offer the only way to access potentially disease-modifying pharmacotherapy. Specialists may be hesitant to recommend lifestyle changes due to the burden of resources needed to counsel patients.[45] They may also require support to effectively use precision medicine to stratify patients into risk subgroups, and to further validate novel tools and technologies to aid decision-making.[46] Providing that support may establish a strong base for improving skills to select the best strategies within the limited treatment landscape, while also establishing an ability to counsel and educate patients, thereby contributing to a multifaceted approach to patient care.

Diverse skills within a team of HCPs are needed to manage a complex disease like NASH with all its implications for patient health and long-term care. Despite country variation, each region investigated could benefit from specific educational interventions related to interdisciplinary coordination of care. These interventions should include shared responsibility for patient engagement and be designed to improve communication with PCPs. Additionally, these efforts should include patient education and increased monitoring related to disease progression and lifestyle changes[47] as part of a multidisciplinary team, as is suggested by the findings of this study and elsewhere.[48,49] Although an in-depth discussion of proposed models of multidisciplinary practice is beyond the limits of this discussion, a model of care has been developed in a recent review by Lazarus et al. (2021).[34] In addition, others have considered how this model can be applied to encourage individual patient behaviour changes, as well as expand the view so as to play a role in contextualizing care for NAFLD/NASH as a global public health initiative.[34,43,50]

The results of this study reveal gaps in knowledge, skills and confidence when treating patients with this increasingly common condition. A lack of consensus on screening and diagnosis, as well as an absence of approved treatments, has created a situation

where specialists are without the resources needed to provide patients with the best care. Efforts to build the knowledge base and skills of HCPs in counselling and action planning related to lifestyle intervention may be considered outside usual practice; however, they should be considered essential for this patient population. A review of such initiatives has suggested that lifestyle interventions (whether by improving the individual's skill set or involving allied HCPs) can benefit patient outcomes when it comes to a range of common diseases like obesity and certain cancers, as well as have a positive impact on health economics overall.[44] Existing education that focuses on lifestyle decisions could further highlight the importance of monitoring and managing the contributing factors that are related to NASH. In so doing, the focus of the HCP should be on guiding patients in a manner designed to proactively facilitate shared decision-making to ultimately improve the patient's quality of life.

4.1 | Limitations

The use of purposive sampling (including participants with different years of practice and settings), alongside a mixed-method design, was to mitigate potential selection bias and the limited representativeness of lower sample size studies. In addition, the location of participants in high-income countries should be considered a limitation when generalizing the findings more broadly. Several findings indicated the importance of PCPs for NASH but that perspective was beyond the scope of this study.

5 | CONCLUSION

This study identified challenges in screening, diagnosis, treatment and management of NASH, which correspond to the educational needs of physicians involved in the care of patients with this condition. Since evidence-based CME and continuing professional development are increasingly required, these findings should be taken into consideration when developing future interventions. To inform local educational activities/offerings, location-specific needs assessments should be conducted to ensure that unique features/roles of each setting are taken into consideration to maximize the benefits of precise activities for targeted learners. A key finding of this study was the importance of the role of PCPs in patient health and treatment success; therefore, further studies that focus on that group specifically are warranted.

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CONFLICT OF INTEREST

PATRICE LAZURE is an employee of AXDEV Group Inc. JEREMY W. TOMLINSON has been an advisory board member for Novo Nordisk, Pfizer, AstraZeneca, Lumos and Poxel. KRIS V. KOWDLEY received funding from the institution for contracted research Intercept, Gilead, NGM, Madrigal, Pfizer, Enanta, Viking, Celgene, Terns, Corcept, and consulting fees from Intercept, Gilead, Inipharm and honoraria for speaking from Gilead Sciences. PAOLO MAGNI has no conflicts of interest to disclose. RAUL D. SANTOS is recipient of a scholarship from Conselho Nacional de Pesquisa e Desenvolvimento Tecnológico, Brazil, (CNPq) #303734/2018–3 and discloses receiving honoraria related to consulting, speaker or research activities from Abbott, Ache, Amgen, Astra Zeneca, EMS, Esperion, Getz Pharma, Kowa, Novartis, Novo-Nordisk, MSD, Merck, Libbs, PTC Therapeutics, Pfizer and Sanofi. GINNY JACOBS is an employee of AXDEV Global Inc. SUZANNE MURRAY is CEO and Founder of AXDEV Group Inc., AXDEV Global Inc and AXDEV Europe GmbH.

ETHICS APPROVAL STATEMENT

All components of this study were reviewed and approved by VERITAS IRB (Montreal, QC, Canada).

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REFERENCES

1. Haththotuwa RN, Wijeyaratne CN, Senarath U. Worldwide epidemic of obesity. *Obes Obstetr.* 2020;2020:3-8.
2. Burhans MS, Hagman DK, Kuzma JN, Schmidt KA, Kratz M. Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus. *Compr Physiol.* 2018;9(1):1-58.
3. Manne V, Handa P, Kowdley KV. Pathophysiology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *Clin Liver Dis.* 2018;22(1):23-37.
4. Karlsen TH, Sheron N, Zelber-Sagi S, et al. The EASL-lancet liver commission: protecting the next generation of Europeans against liver disease complications and premature mortality. *Lancet.* 2022;399(10319):61-116. doi:10.1016/S0140-6736(21)01701-3
5. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A

systematic review and meta-analysis. *J Hepatol*. 2019;71(4):793-801. doi:10.1016/j.jhep.2019.06.021

6. Lim S, Kim J-W, Targher G. Links between metabolic syndrome and metabolic dysfunction-associated fatty liver disease. *Trends Endocrinol Metabol*. 2021;32:500-514.
7. Santos RD, Valenti L, Romeo S. Does nonalcoholic fatty liver disease cause cardiovascular disease? Current Knowledge and Gaps. *Atherosclerosis*. 2019;282:110-120.
8. Tanaka N, Kimura T, Fujimori N, Nagaya T, Komatsu M, Tanaka E. Current status, problems, and perspectives of non-alcoholic fatty liver disease research. *World J Gastroenterol*. 2019;25(2):163-177.
9. Chalsani N, Younossi Z, Lavine J, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-357.
10. Panel CPG, Berzigotti A, Tsochatzis E, et al. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis–2021 update. *J Hepatol*. 2021;75(3):659-689.
11. Cleveland E, Bandy A, VanWagner LB. Diagnostic challenges of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *Clin Liver Dis*. 2018;11(4):98-104.
12. Arrese M, Feldstein AE. NASH-related cirrhosis: an occult liver disease burden. *Hepatol Commun*. 2017;1(2):84-86. doi:10.1002/hep4.1033
13. Sherif ZA. Unmasking a Stealth Killer: the need for increased awareness of NASH. *Dig Dis Sci*. 2020;65(4):987-989. doi:10.1007/s10620-019-05832-y
14. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med*. 2021;384(12):1113-1124.
15. Patikorn C, Veettil SK, Phisalprapa P, Pham T, Kowdley KV, Chaiyakunapruk N. Horizon scanning of therapeutic modalities for nonalcoholic steatohepatitis. *Ann Hepatol*. 2021;24:100315.
16. Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med*. 2021;385(17):1559-1569.
17. Ofosu A, Ramai D, Reddy M. Non-alcoholic fatty liver disease: controlling an emerging epidemic, challenges, and future directions. *Ann Gastroenterol*. 2018;31(3):288-295.
18. Cardoso AC, de Figueiredo-Mendes CA, Villela-Nogueira C. Current management of NAFLD/NASH. *Liver Int*. 2021;41(S1):89-94. doi:10.1111/liv.14869
19. Takahashi Y, Sugimoto K, Inui H, Fukusato T. Current pharmacological therapies for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol Apr 7*. 2015;21(13):3777-3785. doi:10.3748/wjg.v21.i13.3777
20. European Association for the Study of the liver (EASL), European Association for the Study of diabetes (EASD), European Association for the Study of obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *Diabetologia*. 2016;59(6):1121-1140. doi:10.1007/s00125-016-3902-y
21. Kelly N, Wattacheril J. Nonalcoholic fatty liver disease: evidence-based management and early recognition of nonalcoholic steatohepatitis. *J Nurse Pract*. 2019;15(9):622-626.
22. Lonardo A, Nascimbeni F, Targher G, et al. AISF position paper on nonalcoholic fatty liver disease (NAFLD): updates and future directions. *Dig Liver Dis*. 2017;49(5):471-483.
23. *UK National Guideline Centre. Non-alcoholic Fatty Liver Disease: Assessment and Management*. National Institute for Health and Care Excellence (NICE); 2016.
24. Curry LA, Krumholz HM, O'Cathain A, Plano Clark VL, Cherlin E, Bradley EH. Mixed methods in biomedical and health services research. *Circ Cardiovasc Qual Outcomes Jan 1*. 2013;6(1):119-123. doi:10.1161/CIRCOUTCOMES.112.967885
25. Turner SF, Cardinal LB, Burton RM. Research design for mixed methods. *Org Res Methods*. 2016;20(2):243-267. doi:10.1177/1094428115610808
26. Persad G, Lynch HF, Largent E. Differential payment to research participants in the same study: an ethical analysis. *J Med Ethics*. 2019;45(5):318-322.
27. Martínez-Mesa J, González-Chica DA, Duquia RP, Bonamigo RR, Bastos JL. Sampling: how to select participants in my research study? *An Bras Dermatol*. 2016;91:326-330.
28. Braun V, Clarke V, Terry G. Thematic analysis. In: Rohleder P, Lyons A, eds. *Qualitative Research in Clinical and Health Psychology*. Palgrave MacMillan; 2014.
29. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005;15(9):1277-1288. doi:10.1177/1049732305276687
30. Nowell LS, Norris JM, White DE, Moules NJ. Thematic analysis. *Int J Qual Methods*. 2017;16(1):160940691773384. doi:10.1177/1609406917733847
31. Onwuegbuzie AJ, Bustamante RM, Nelson JA. Mixed research as a tool for developing quantitative instruments. *J Mixed Methods Res*. 2009;4(1):56-78. doi:10.1177/1558689809355805
32. Nath P, Singh SP. Nonalcoholic fatty liver disease: time to take the bull by the horns. *Eur J Hepato-Gastroenterol*. 2018;8(1):47-51.
33. Polanco-Briceno S, Glass D, Stuntz M, Caze A. Awareness of non-alcoholic steatohepatitis and associated practice patterns of primary care physicians and specialists. *BMC Res Notes*. 2016;9:157. doi:10.1186/s13104-016-1946-1
34. Lazarus JV, Anstee QM, Hagström H, et al. Defining comprehensive models of care for NAFLD. *Nat Rev Gastroenterol Hepatol*. 2021;18(10):717-729.
35. Cryer DR. NASH: Connecting the dots with patients in mind. Wiley online Library; 2020, 3.
36. Ratziu V, Goodman Z, Sanyal A. Current efforts and trends in the treatment of NASH. *J Hepatol*. 2015;62(1):S65-S75.
37. Sivell C. Nonalcoholic fatty liver disease: A silent epidemic. *Gastroenterol Nurs*. 2019;42(5):428-434.
38. Iqbal Z, Khalid F, Harrison S, Sanyal A. A disconnect between clinical practice and practice guidelines in the diagnosis and evaluation of NASH: another factor limiting access to care: 2225. *Am J Gastroenterol*. 2015;110:S923.
39. Boeckmans J, Natale A, Rombaut M, et al. Human hepatic in vitro models reveal distinct anti-NASH potencies of PPAR agonists. *Cell Biol Toxicol*. 2021;37(2):293-311.
40. Piazzolla VA, Mangia A. Noninvasive diagnosis of NAFLD and NASH. *Cell*. 2020;9(4):1005.
41. Ocker M. Challenges and opportunities in drug development for nonalcoholic steatohepatitis. *Eur J Pharmacol*. 2020;870:172913.
42. Ramanan SP, Mohamed MWF, Aung SS, Sange I, Hamid P. Treatment of fatty liver disease: the present and the future. *Cureus*. 2021;13(1):e12713. doi:10.7759/cureus.12713
43. Hallsworth K, Adams LA. Lifestyle modification in NAFLD/NASH: facts and figures. *JHEP Rep*. 2019;1(6):468-479.
44. Bodai BI, Nakata TE, Wong WT, et al. Lifestyle medicine: a brief review of its dramatic impact on health and survival. *Perm J*. 2018;22:17.
45. Avery L, Exley C, McPherson S, Trenell MI, Anstee QM, Hallsworth K. Lifestyle behavior change in patients with nonalcoholic fatty liver disease: A qualitative study of clinical practice. *Clin Gastroenterol Hepatol*. 2017;15(12):1968-1971. doi:10.1016/j.cgh.2017.06.011
46. Lonardo A, Arab JP, Arrese M. Perspectives on precision medicine approaches to NAFLD diagnosis and management. *Adv Ther*. 2021;1-29:2130-2158.
47. Cook NS, Nagar SH, Jain A, et al. Understanding patient preferences and unmet needs in non-alcoholic steatohepatitis (NASH):

insights from a qualitative online bulletin board study. *Adv Ther*. 2019;36(2):478-491.
48. Danford CJ, Lai M. NAFLD: a multisystem disease that requires a multidisciplinary approach. *Frontl Gastroenterol*. 2019;10(4):328-329.
49. Moolla A, Motohashi K, Marjot T, et al. A multidisciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health. *Frontl Gastroenterol*. 2019;10(4):337-346.
50. Lazarus JV, Mark HE, Anstee QM, et al. Advancing the global public health agenda for NAFLD: a consensus statement. *Nat Rev Gastroenterol Hepatol*. 2021;18:1-18.

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