An international survey on Patterns Of Practice in Nonalcoholic Fatty Liver Disease (NAFLD) and Expectations for Therapies – the POP-NEXT Project

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ABSTRACT (249/250 words)

Background & Aims. Differences between countries in NAFLD patient care pathways and management need to be understood prior to defining supranational guidelines.

Approach & Results. We conducted an anonymous survey in France, Germany, Hong-Kong, Italy, Romania, Spain, UK, and the USA among physicians providing specialist care for patients with NAFLD. Modalities of patient referral, patterns of practice (diagnosis, staging, monitoring and indications for liver biopsy), therapeutic management and expectations for future NASH pharmacotherapies were assessed. 664 physicians completed the survey. Referral to surveyed physicians (SP) mostly came from primary care. Prior to referral NAFLD was rarely diagnosed and non-invasive tests were not performed. Screening for comorbidities by SP was incomplete and cardiovascular risk not calculated. Elastometry in combination with a serum biomarker was the commonest first-line method for fibrosis staging. Liver biopsy, when performed, was often delayed by at least one year after diagnosis. It was however recommended even if non-invasive methods indicated advanced fibrosis. Frequent, bi-annual monitoring was conducted, including hepatocellular carcinoma surveillance in stage 3 fibrosis. SP rarely implemented and followed dietary and lifestyle changes themselves and local availability of such programs was highly heterogenous. SP favored pharmacotherapy based on mechanism of action adapted to the stage of the disease, including for early stages such as steatohepatitis with mild fibrosis.

Conclusions. This international survey revealed major deficiencies and delays in referral pathways, suboptimal screening for comorbidities or managing lifestyle modifications by SP and limited local availability for non-pharmacological interventions. Monitoring practices are not aligned with current guidelines.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world and nonalcoholic steatohepatitis (NASH), its progressive form, is responsible for a growing number of cases of cirrhosis, hepatocellular carcinomas (HCC) and of indications for liver transplantation. Yet, it is also an underrecognized condition, particularly outside the hepatology field. Underrecognition, coupled with the silent nature of the fibrotic process, may explain why many patients with advanced liver disease are not diagnosed[1]. Inadequate screening tools as well as failure of society guidelines to outline populations appropriate for screening compound the problem[2]. Foremost, the lack of simple and highly performant non-invasive diagnostic tests contributes to a suboptimal referral for specialist care[3]. Algorithms are limited by the lack of noninvasive diagnostic markers, in particular for steatohepatitis, and to the suboptimal performance of current non-invasive fibrosis markers in different population settings[4]. As a consequence, specialists have a large variety of practices further influenced by local conditions and national determinants of their respective healthcare system. Finally, personal perceptions of healthcare providers about the utility of screening, diagnosis and management may be altered by the absence of approved pharmacological therapy. Currently, the recommended therapeutic option is to implement or merely reinforce dietary and lifestyle measures. Yet, there is variability in how this is implemented.

The heterogeneity in practices from screening to therapeutic management needs to be studied in order to better address the gaps in the diagnosis, referral and management of patients with NAFLD. The perception by health care providers of the disease and of its consequences, and their expectations for future diagnostics, pharmacotherapies and management strategies needs to be better understood. We therefore conducted a survey of physicians with a clinical interest in NAFLD in eight different national settings to acquire a wide overview of practices directed to patients with NAFLD. In an attempt to cover a wide spectrum of epidemiological and public health-care burden, we chose five large European countries and the United States to represent countries with a high prevalence of NAFLD, and two other settings traditionally associated with a lesser prevalence or recognition of NAFLD, one from Far-East Asia, Hong Kong and a country from Eastern Europe, Romania.

MATERIALS AND METHODS

Design of the Survey. This international survey was conducted in seven countries and one region: France, Germany, Hong Kong, Italy, Romania, Spain, the U.K., and the USA. A steering committee was formed to lead the project, which included one physician representative from each of the eight countries involved. Based on data from the literature and the clinical expertise of all the steering committee members, an anonymous survey of 15 pages was developed to assess patterns of current practice in NASH and the expectations for forthcoming NASH therapies. The questionnaire was divided into five sections: (1) participant information (data on age, sex, place of practice, medical specialty and percentage of practice dedicated to liver disease; (2) care pathway for patient referral; (3) patterns of practice in terms of initial diagnosis, staging and subsequent monitoring; (4) practices and indications for liver biopsy; (5) current therapeutic management including non-pharmacological versus pharmacological therapies, and expectations for NASH pharmacological therapies. The survey consisted of 47 questions in various formats, and allowing different responses as needed e.g., single-choice vs multiple-choice. The answers were either qualitative (different items to choose from), quantitative (e.g. a 0–100% scale), semi-quantitative (from less important/common to most important/common) or open-ended (choice of words by the participant).

Surveyed physicians. Surveyed physicians (SP) were targeted among those providing specialist care for the liver disease of patients with NAFLD, meaning hepatologists, gastroenterologists or internists. SP were identified through listings provided by professional societies (the German Gastro Association Deutsche Gesellschaft für Gastroenterologie, Verdauungs, und Stoffwechselkrankheiten (DGVS)), the Hong Kong Association for the Study of Liver Diseases (HKASLD), the Romanian Society of Gastroenterology and Hepatology (SRGH), and the Romanian Association for Liver Diseases (RoALD)) or by various specialized medical marketing with a goal to cover a wide field of practice, not limited to academic institutions. The survey was available in English or translated in four local EU languages (French, German, Italian, Spanish). The survey was sent electronically between 1st March 2020 and 31st July 2020 and accessed using a weblink contained in an email. SP were clearly instructed that their answers will stay anonymous. An incentive of €75 (or equivalent) was paid to the physician upon completion of the survey.

Analysis of survey results. All survey results were anonymized and aggregated before analysis. Results are expressed as percent of total respondents for each question, as means (S.D.) or medians for quantitative

variables or by the frequency of distribution for qualitative variables. Whenever notable numerical differences were seen between countries/region, results were reported at the country/region level.

RESULTS

Surveyed physicians. 664 physicians completed the survey (108 from Spain, 105 from Italy, 104 from France, 101 both from the UK and USA, 24 from Romania and 21 from Hong-Kong), which amounts to a 4% response rate (surveys were sent to 15.604 physicians). The characteristics of the SP are listed in **Table 1**. Hepatogastroenterology was by far the most represented specialty. There was a balanced distribution between physicians mainly working in liver disease and those mostly working in gastroenterological, non-liver diseases: only a third exclusively practiced hepatology while 42% of SP had more than half of their practice dedicated to non-liver, gastroenterological diseases. There was also a balance between academic/tertiary care practice and secondary care and private practice. The proportion of physicians not working in tertiary care centers was 50-60% for all countries except three (Italy, Spain and Romania). Around 40% of participants claimed to see more than 20 patients with NAFLD per week, however there was heterogeneity between countries (regions) with Romania and Hong Kong reporting a much lower number of patients than the other Western countries.

Referral patterns for patients with NAFLD.

Most NAFLD patients were referred to SP for abnormal liver enzymes, high serum ferritin and documentation of fatty liver on imaging, without clear differences between countries. Healthcare providers who most frequently referred patients were general practitioners and other liver or gastroenterology specialists with diabetologists/endocrinologists, cardiologists and internal medicine specialists much less frequent sources of referral. The threshold considered for the impact of alcohol consumption on the diagnosis of NAFLD differed among SPs. While 39% of SP considered that 20-30 g of daily alcohol consumption is the threshold to exclude a diagnosis of NAFLD, an equal number (37%) considered such threshold irrelevant since the two conditions (alcoholic and nonalcoholic fatty liver disease) can coexist.

82% of SP said that in more than half of the NAFLD patients referred to them, the diagnosis of NAFLD was not made by the referring physician. Moreover, in many cases the diagnosis of NAFLD was substantially delayed. Two thirds of SP declared that the diagnosis of NAFLD was missed in more than half of referred NAFLD patients despite the availability of historic clinical or lab patient data that should have made the diagnosis possible. There were no clear differences between countries in terms of missed or delayed diagnoses. At the time of referral, the use of non-invasive tests (NIT) was very infrequent: half of the SP reported that less than 5% of NAFLD patients referred to them had an exploration by NIT available when

first seen (**Figure 1**). Only a minority of SPs (11%) declared that more than half of the NAFLD patients referred to them had a NIT result available. For this particular question no distinction was made between serum biomarkers or elastometry methods.

Diagnosis practices. We next tried to determine factors associated with evaluation, specifically if normal ALT values or the absence of metabolic comorbidities are a deterrent towards a more in-depth exploration of a NAFLD patient. Once diagnosed, staging of NAFLD was considered a necessary step for a large majority (80-82%) of SP regardless of normal or abnormal ALT values or of the presence or absence of components of the metabolic syndrome. Staging of fibrosis is performed using a single non-invasive method by 36% of SP and by at least two methods by a larger proportion of 61% - equally divided between those performing a sequential use or a simultaneous use. Fibroscan was by far the most used non-invasive tool in routine clinical practice (89% of participants use it routinely). The other imaging-based elastometry methods had a much lower penetrance: shear-wave elastography is used by 17% of SP, acoustic radiation force imaging by only 9%. Overall, serum-based biomarkers were less used in routine care, the two most widely used being FIB4 (42% of SP) and the NAFLD fibrosis score (NFS) (41%). Proprietary biomarkers such as ELF or Fibrosure were routinely used by only a minority of SP (10 and 24% respectively). Whilst there were no country-based differences for the use of Fibroscan, striking differences for some proprietary serum biomarkers were seen with FibroTest/Fibrosure most used in France (62%), Romania (43%) and USA (31%) and ELF almost exclusively used in the UK (25% of UK SP) and almost never (0-4%) in the USA, France, Romania, Hong Kong or Spain.

The distinction between simple steatosis and steatohepatitis (irrespective of the fibrosis stage) was considered important for information on prognosis (89%), for deciding upon monitoring and follow-up (89%), for deciding if the patient should be returned to primary care for further management (67%) and for the consideration of therapeutic interventions (81%). For all these considerations there was a high level of homogeneity between countries except for the decision to return the patient to primary care for further management, where Italian and French SP were more reluctant to do so based upon the distinction between steatosis and steatohepatitis (52% and 57%, respectively). Most SP used ALT (52%), Fibroscan (60%) or ultrasound (51%) to make this distinction, with only a minority using other serum-based markers including 3% only for serum CK18.

We next aimed to understand the patterns of practice of liver biopsy in routine clinical care. Liver biopsies were rarely (25%) performed by the SP themselves, even when board-certified in hepatogastroenterology: only 21% of surveyed gastroenterologists and 33% of surveyed hepatologists performed the biopsy themselves. Instead, liver biopsies were most frequently performed by radiologists

(42%). There were striking differences between countries: very high in the UK (80%) and US (64%), high in France (50%) and Hong Kong (43%) and lower in Spain (34%), Italy (23%) and Romania (12%). While in 69% of cases the liver biopsy is performed on an outpatient basis, there were 31% of SP who reported performing liver biopsy on an overnight/in-patient basis. The SP were faced with four different situations based on results of non-invasive tests and asked to determine, assuming all other parameters equal, whether they would perform a liver biopsy or not (**Figure 2**). If the non-invasive tests (or combinations thereof) indicate the presence of mild or no fibrosis, 31% would still perform a liver biopsy. If they indicate advanced fibrosis (equivalent to stage 3) 75% would perform a liver biopsy. If the results between non-invasive tests were discordant, 63% of SP would perform a liver biopsy. Finally, if there was indication from non-invasive tests in favor of cirrhosis, a liver biopsy would still be performed by 52% of SP. Notably, liver biopsy was rarely performed in the first year after referral: for a large majority of SP (78%) less than a quarter of their referred NAFLD patients would have a liver biopsy performed within a year of the referral. This was remarkably homogenous across countries (with the highest rate of delaying biopsies beyond one year in the UK (81% and slightly lower in Germany, 62%). Overall, the refusal rate of a liver biopsy was low: for 76% of SP less than 25% of the patients they manage refused to undergo a liver biopsy.

Monitoring practices. In patients with steatohepatitis, the monitoring schedule is largely dependent on the fibrotic severity (**Supplementary Figure 1**). Monitoring is performed every 6 months for a large majority of SP (79%) in case of fibrosis stage 3; every year for 49% of SP in case of fibrosis stage 1; evenly divided between 6 months (42% of SP) and one year (44% of SP) for fibrosis stage 2. In patients with steatosis and without fibrosis (stage 0) 37% of SP would not monitor in their practice but rather refer back to primary care or an adequate health care provider, 29% would still monitor every year and 21% every two years. There were some notable differences between countries: for patients with steatosis and no fibrosis and for patients with steatohepatitis and mild fibrosis, SP from UK were the ones who mostly would not monitor but refer the patient back to primary care. This was also true, with a slightly lower proportion, for Hong Kong SP. In contrast 27%-39% of SP from the other countries would still monitor yearly patients with steatosis and no fibrosis and 42%-59% those with steatohepatitis and mild fibrosis.

The preferred method for monitoring fibrosis is Fibroscan alone for 58% of SP and Fibroscan with a serum biomarker for another 19%. Very few SP (1-3%) would use a serum biomarker only, whether FIB4, Fibrosure/FibroTest or NFS.

Finally, monitoring for hepatocellular carcinoma was performed by virtually all SP in patients with cirrhosis (98%). However, most also recommended surveillance for those with stage 3 fibrosis (81% of SP). Screening for HCC in stage 3 fibrosis patients was remarkably constant across countries with the exception

of a slightly lower percentage in the UK (67%) and the US (73%). It was however higher in SP with higher volume NAFLD practice (>20 NAFLD patients/week, 86%) than those with lower volume of NAFLD practice (10-20 NAFLD patients/week, 79%; <10 NAFLD patients/week, 75%). Forty percent of SP endorsed monitoring for hepatocellular carcinoma in patients with steatohepatitis and stage 2 fibrosis. However, there were clear disparities among countries: SP from UK, US and Hong Kong reported less screening for HCC in F2 patients (22%, 26% and 29%, respectively) than those from Germany, France and Italy (66%, 45%, 45%, respectively).

Patient age was not a limitation for management of NAFLD except for invasive procedures such as liver biopsy. Most SP (71%-82%) would stage at diagnosis, screen for hepatocellular carcinoma, implement dietary and lifestyle interventions and treat with pharmacological agents independent of patient age.

Therapeutic management.

Screening for comorbidities is an important part of management because of the multisystem nature of NAFLD but also a challenge given the numerous medical specialties involved. Here, 75% of SP reported that they screen for extrahepatic comorbidities themselves. Most (72-81%) screen for diabetes, arterial hypertension or dyslipidemia. However, 57% SP would not calculate cardiovascular risk scores. Several other comorbidities are also overlooked by a majority of SP: only 46% screen for kidney disease, 36% for hyperuricemia or gout, 30% for sleep apnea and 20% for depression/anxiety (**Figure 3**). If comorbidities are present, only 19% would manage them themselves while almost half (48%) would have a dedicated specialist manage them and less than a third (32%) refer back to the general practitioner. English and American SP indicated that their patients' comorbidities are managed by the general practitioner (54% and 53%, respectively), while French and Italian SP would have them managed mostly by a dedicated specialist (56% and 78% respectively). Likewise, 52% of SP declared that they rarely or never initiate statin therapy themselves. Less than half of the hepatologists (47%) or gastroenterologists (46%) would prescribe statins themselves vs 80% of the SP who are primarily internists. Here again important differences appeared between countries: American and French SP never or only rarely prescribe statins themselves (73% and 60% respectively). German, Spanish or Italian SP often do (68%, 60% and 51%, respectively). While the majority of SP would not advise against the use of statins in the presence of liver disease, 22% of SP would not recommend if cirrhosis were present.

At the time of referral, 56% of SP declared that less than half of their patients had tried dietary and lifestyle changes to improve their liver or overall health condition prior to referral; for another 37% of SP this was the case of more than half of the NAFLD patients referred to them. In terms of implementing

dietary and lifestyle changes there was a large variety of practices. Overall, more than half of SP (55%) would refer the patient to a specialized health care provider (either within or outside their own center). Most SP (64-79%) declared that their clinic or center already provide services such as weight-loss interventions, lifestyle modification counselling or dietary counselling. However, there were notable differences between countries: high rates of dietary counseling available in the SP institutions was reported for Italy (82%), France (90%) and Hong Kong (91%); high rates of lifestyle modification counseling were reported for the US (77%), France (75%) and Germany (73%). Stronger inter-country disparities were noted for the availability of weight loss interventions in the SP institution: only 33% and 43% of the Romanian and Hong Kong SP, 52%, 57%, 60% and 61% of UK, Spanish, German and American SP and 77% and 78% in Italian and French SP. A minority of SP (15%) would simply describe the necessary dietary and lifestyle changes but do no more. Only 20% declared they would implement and monitor these changes themselves with the highest proportions among the Spanish and German SP (28% and 27%, respectively). The referral rate back to the general practitioner for counseling and monitoring dietary and lifestyle modifications was overall very low, at less than 9%, with only a few countries such as the UK and Germany having slightly higher rates (17% and 12%, respectively).

Other treatment options used by SP specifically for treating NASH are detailed in **Suppl Figure 2**. A majority of SP did not use any of the available but unapproved agents for NASH. Vitamin E was prescribed by 43% of the SP but with striking differences between countries: highest level of prescription in Italy (56%), the US (53%), France (52%), Hong Kong (57%) and Romania (67%). In contrast, only 24% of UK, 29% of Spanish and 34% of German SP declared prescribing vitamin E. Ursodeoxycholic acid prescription was high in France (47%), Italy (39%), Germany (41%) and Romania (67%) but low in the US (15%), UK (20%) and Spain (29%). Only 32% of SP declared enrolling in clinical trials. However, referral for bariatric procedures was quite common (53% of SP) and similar between countries.

A series of questions were designed to understand expectations for future pharmacological therapies for NASH. When asked whether they are willing to perform a liver biopsy if this was necessary to prescribe an approved drug for NASH, only 18% answered “no, they would wait for the biopsy requirement to be lifted” (**Figure 4**). Another 35% agreed only if there is a strong indication on non-invasive tests for fibrosis stage 3, while only 46% of SP agreed, in principle, unconditionally. 67% of American SP are willing to perform a liver biopsy if necessary for drug prescription while only 13% are willing to delay drug treatment until the requirement for biopsy is lifted. German (59%) and French SP (50%) are among the top SP willing to perform a liver biopsy for access to drug therapy. The majority of SP from Italy, UK, Spain and Romania (41-48%) would agree to perform a liver biopsy in order to get access to drug therapy, but

only if there is indication for bridging fibrosis on non-invasive tests. When asked whether a NASH drug should also improve glycemic control or the lipid profile, two thirds of the SP answered that while this would be advantageous, they considered it, in fact, optional. To better understand the adequacy between the stage of the disease and the preferred mechanism of action of an appropriate NASH drug, the SP were given several clinical scenarios (**Figure 5**). They were asked to choose a single treatment, assuming approval and reimbursement. Interestingly, a large majority of SP would consider pharmacological treatment necessary in all scenarios, except for NASH fibrosis stage 0, where only 44% would deem such a treatment unnecessary (highest for Hong Kong, Romania and UK). A drug controlling the metabolic dysfunction ("metabolic drug") would be preferred at early stages (stage 0 and 1) and an antifibrotic drug was deemed necessary by a majority of SP only starting fibrosis stage 3. Interestingly, the choices in fibrosis stage 1 NASH patients were dependent on whether increased ALT and severe metabolic dysfunction were present. As far as fibrosis stage 2, only 2-7% of SP considered pharmacological treatment unnecessary. In cirrhotics an antifibrotic drug would be overwhelmingly preferred, with little or no preference (9% to 16%) for a metabolic or anti-NASH drug.

Finally, there was a very low level of interaction of SP with a patient advocacy group whether specific for NASH (12%) or for associated diseases (e.g. diabetes, 12%).

DISCUSSION

This large international survey had several salient findings pertaining to each aspect of NAFLD management. NAFLD is a disease still largely underrecognized: the diagnosis was often overlooked or significantly delayed, even in patients seeking medical consultation with risk factors for NAFLD. In particular, only a minority of referrals came from specialists mainly seeing patients with cardiometabolic disease such as endocrinologists/diabetologists, nutritionists or cardiologists. Future educational actions should prioritize the dissemination of information regarding NAFLD in order to increase disease recognition among relevant disease specialists while reducing diagnostic delay among general practitioners/primary care providers. Screening for associated comorbidities is also suboptimal: *many relevant comorbid associations are overlooked including those that can worsen the liver disease such as obstructive sleep apnea*[5] *or those that are frequently associated with NAFLD such as chronic kidney disease*[6] while a clear assessment of individual CV risk is not performed. SP from countries such as the USA or France whose clinical practice encompassed primarily liver and gastroenterology, were unfamiliar with prophylactic statin prescription based on individual risk.

While dedicated studies[7] and practice guidelines[8] have tested the applicability of screening for advanced liver injury in primary care, it is striking to see that in 2021 the use of NITs for NAFLD patients in primary care is infrequent. Simple NITs, such as FIB4, are mostly used by specialists. Liver stiffness measured by Fibroscan is unequivocally the first-line tool for fibrosis staging among SP. However, a majority of SP would not use elastometry alone but together with a second, non-proprietary blood-based biomarker (equally FIB4 or NFS), either simultaneously or sequentially. Proprietary biomarkers (ELF, FibroTest, Fibrometer) have a low penetrance globally, although this is highly variable between countries, probably depending on commercial availability. Other ultrasound-based methods of measuring liver stiffness are infrequently used. Elastometry measured by Fibroscan is also the primary method for monitoring patients. Interestingly, irrespective of fibrosis staging, the distinction between steatosis and steatohepatitis is considered overwhelmingly relevant for most SP, particularly for the prognostic information it carries and for deciding on follow-up and therapeutic interventions. While none of the existing methods are appropriate for diagnosing active steatohepatitis, new algorithms are emerging which might prove useful if largely implemented[9-11].

Monitoring of NAFLD patients relies heavily on NITs across all surveyed countries and primarily depends on the fibrosis stage at diagnosis. An unexpected finding of this survey is that the level of monitoring the SP declared adhering to is particularly intense. NAFLD patients at fibrosis stage 3 are monitored every 6 months by a large majority of SPs; those at stage 2 are monitored equally every 6 or 12

months. This stands in contrast with the slow evolving course of this disease[12, 13] and may account for the high level of medical expenditures documented in some real-world administrative claims databases[14, 15]. Remarkable between-country differences were also noted, with some countries such as UK commonly referring patients back to primary care for further monitoring, while in other countries a large proportion of SP monitoring themselves even mild forms of the disease. This highlights the difficulties of designing universal guidelines for patient management and future recommendations should fall short of being too directive given existing discrepancies between health-care systems, even among high-income countries. Also, despite any evidence-based data for a substantially increased risk of HCC in non-cirrhotic NASH[16] or even in some cirrhotic subgroups[17], monitoring for HCC using ultrasound was surprisingly high for stage 3 and even stage 2 patients, with only slight differences between countries and volume of practice of SP. This information is important when designing future guidance for NAFLD management which should focus on providing evidence-based data to avoid an unnecessary waste of medical resources.

An important aspect of this survey was to understand indications and modalities for liver biopsy when managing NAFLD in real-life practice. A first remarkable aspect was that liver biopsy is very often delayed beyond the first year after referral and this was highly homogenous among surveyed countries. We can only hypothesize that this may reflect the time needed for performing NITs and analyzing their results within each particular patient context or, alternatively, the fact that most SP will need to confirm that biochemical abnormalities are persistent or that dietary and lifestyle interventions failed to improve the patient's condition, before proceeding with invasive diagnoses. If future approved drugs require histological documentation for access or reimbursement, current widespread practices could further delay access to pharmacological therapies. Another notable finding was that most SP, despite being hepatogastroenterologists do not perform liver biopsies themselves. Overall, only a fifth of gastroenterologists and a third of those primarily hepatologists performed liver biopsy themselves with, however, very strong disparities between countries. For a third of SP the biopsy was done on an outpatient basis. *We surmise that these* aspects *would* further add to the constraints of liver biopsy if it has to be generalized as a necessary step in real-life management of NAFLD patients.

Despite a large body of evidence in favor of NITs as a substitute for biopsy[4, 18-20] this survey shows that most SP still consider the positive predictive value of current tests insufficient. In fact, in a hypothetical scenario where results of NITs concur in favor of the presence of advanced fibrosis, three quarter of SP would still perform a liver biopsy, while only a minority would do so in case of a clear indication of minimal or no fibrosis. This, together with the impracticability of liver biopsy mentioned above, further reduces the ability to manage seamlessly NAFLD patients in clinical practice. Recent data

showing that patients with advanced disease can be confidently diagnosed with current non-invasive methods[21] and those at risk of adverse liver-related events identified[22], will probably help, *if confirmed,* a more confident implementation of biopsy-free strategies.

Several notable results of this survey describe the current therapeutic landscape and physician expectations for future NASH drugs. Dietary and lifestyle changes are the first-line therapy for patients with NAFLD at large[8, 12]. However, a major finding of this survey is that half of the patients already failed to successfully implement these measures by the time they were referred to the SP. While only a fraction of these may have sufficiently advanced liver disease to qualify for pharmacological therapy, it is important to recognize that further delay in implementing future drugs for NASH, if and when available, will not be helpful or may even be detrimental in these patients. These data could be useful when defining, in future guidelines, the optimal time for introducing pharmacotherapy in addition to dietary and lifestyle measures. The survey also showed that implementation by the SP of dietary and lifestyle changes is all but straightforward. First, only a minority of SP (20%) would personally manage these measures themselves. Second, referral to primary care providers for this specific reason is exceedingly rare (9% overall), even in countries, such as the UK, where primary care facilities are particularly developed (17%). Third, specific weight-loss interventions are unavailable in many of the SP institutions, with only two countries reporting the existence of a structured weight loss intervention program in more than two thirds of their SP institutions. This contributes to the low level of success in implementing and maintaining over the long-term these non-pharmacological interventions and further degrades, through unnecessary delays, their effectiveness. Clearly, investment in these medical capabilities in clinics dealing with liver diseases should be a health-care priority.

The survey revealed that there is a strong expectation for effective drugs in NASH and if such drugs were freely available they would be used in almost all fibrotic NASH patients. Remarkably, less than 10% of SP would consider pharmacological treatment unnecessary in patients with stage 2 fibrosis. They would consider treating even stage 1 fibrosis patients, if increased ALT and severe metabolic dysfunction were present. When specifically asked, very few SP (18%) would postpone treatment initiation if a liver biopsy is mandatory, but this would clearly restrict access to therapy for all but the most advanced patients. For most SP, improvement of comorbidities is considered optional, which reflects the high level of recognition of the liver disease in NASH per se as a contributor to adverse outcomes[23, 24] and as an unmet need. Finally, the perception of future drugs for NASH is largely based on their mechanism of action and its adequacy with the stage of the disease: in early stages of the disease SP expect drugs

treating the metabolic dysfunction at the root of the pathogenesis of steatohepatitis while for later stages more liver directed anti-inflammatory compounds with antifibrotic activity are deemed appropriate.

This study has several limitations: the proportion of responders was low and even if the survey included 664 respondents, the number of responders per country/region was limited and this was particularly true for Hong-Kong and Romania. Respondents were *de facto* motivated to participate, which may introduce bias through convenience sampling and therefore limit generalizability. Recall bias can equally occur for this type of survey without actual audit of real data. Finally, assumptions regarding referrals from primary care were indirectly assessed through answers from SP. Future studies should collect information directly at the primary care level.

In conclusion, this large international survey, provides first-hand information from active practitioners with clinical activity in NAFLD that could be useful for the understanding of the real-life situation of a very frequent but also very often underrecognized chronic liver disease. Practices related to referral, use of NITs, monitoring and implementation of non-pharmacological interventions are largely sub-optimal and often at odds with current evidence-based recommendations, as also recently highlighted[25]. Some differences between surveyed countries are useful for tailoring recommendations to specific national health-care systems or physician practices. Finally, there is a strong expectation among SP for effective pharmacological therapies in most patients with fibrotic steatohepatitis while current difficulties in implementing the necessary dietary and lifestyle changes at the NAFLD practitioner level should not be neglected.

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Table 1. Characteristics of survey participants.

Primary medical specialty, %	
Gastroenterology	52
Hepatology	38
Internal medicine	9
Others	1
Practice dedicated to liver disease, %	
Less than 5% of practice	3
6-25%	15
26-50%	24
51-75%	24
More than 76%	34
Place of practice, %	
Tertiary care or academic hospital	58
General/Secondary care/non-academic hospital	24
Private practice	15
Mixed practice (public and private)	4
Years of practice since completing training, %	
Less than 5	21
5-10	24
11-15	20
More than 15	35
NAFLD patients seen per week, %	
Ten or less	20
11-20	38
21-30	25
More than 30	16

Numbers denote % of survey practitioners within each category of response

LEGENDS TO THE FIGURES

Figure 1. Percentage of patients who already had a non-invasive fibrosis test performed for risk-stratification of liver disease (FIB4, NFS, ELF, FibroTest/FibroSure, FibroMeter, FibroScan, etc).

Figure 2. The need to perform a liver biopsy according to different situations.

Figure 3. Systematic screening for comorbidities linked to NAFLD in clinical practice.

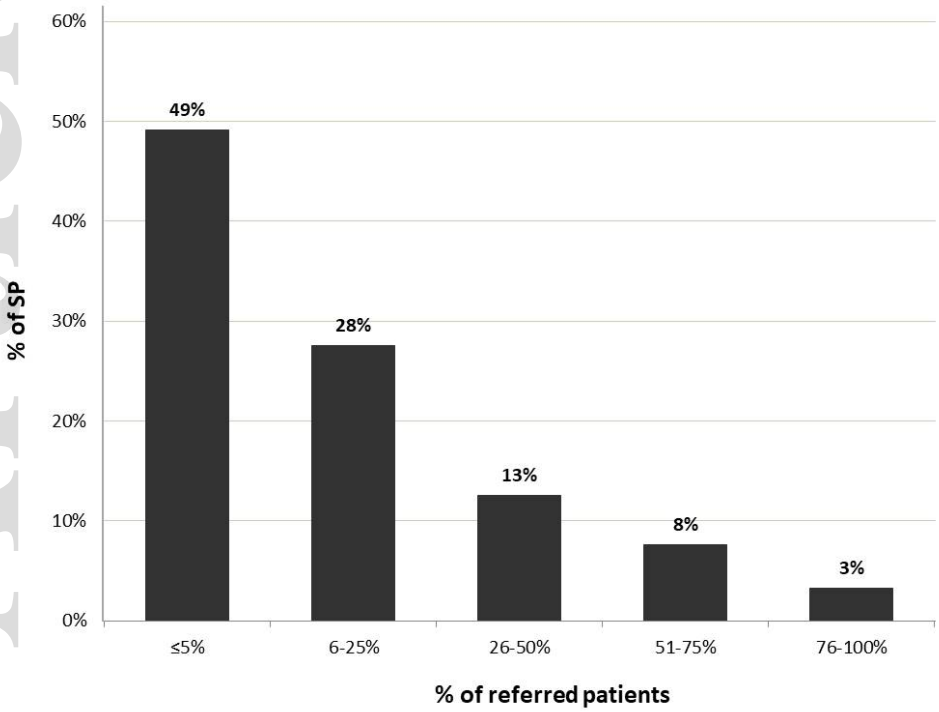
Figure 4. Acceptance by SP to perform a liver biopsy if deemed necessary to prescribe an approved NASH drug.

Figure 5. *Most appropriate pharmacological agent for different clinical scenarios (single choice answer by SP)*

Supplementary Figure 1. Frequency of monitoring patients according to NAFLD stages.

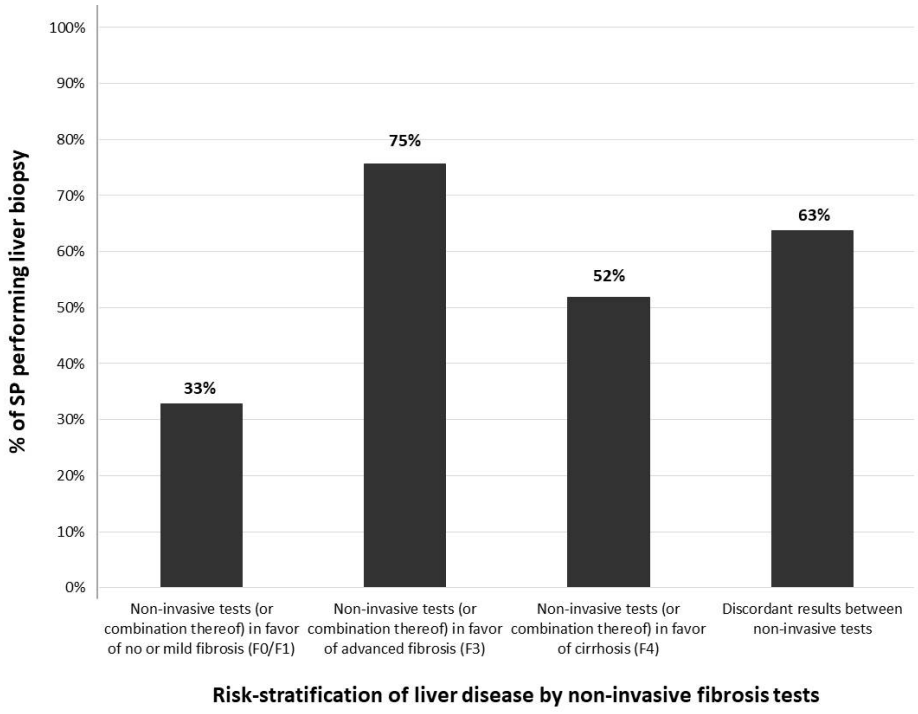
Supplementary Figure 2. Frequency of different prescriptions specifically for liver disease management in NAFLD patients.

Figure 1. Percentage of patients who already had a non-invasive fibrosis test performed for risk-stratification of liver disease (FIB4, NFS, ELF, FibroTest/FibroSure, FibroMeter, FibroScan, etc).



Legend: SP, surveyed participants.

Figure 2. The need to perform a liver biopsy according to different situations.



Legend: SP, surveyed participants.

Figure 3. Systematic screening for comorbidities linked to NAFLD in clinical practice.

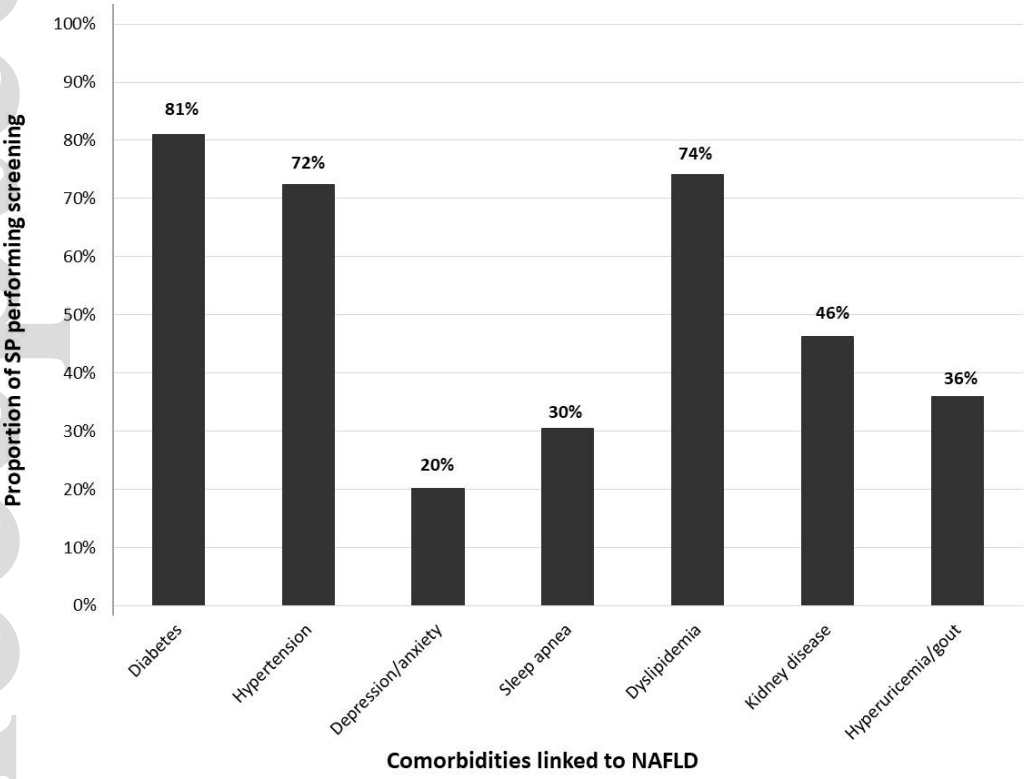


Figure 4. Acceptance by SP to perform a liver biopsy if deemed necessary to prescribe an approved NASH drug.

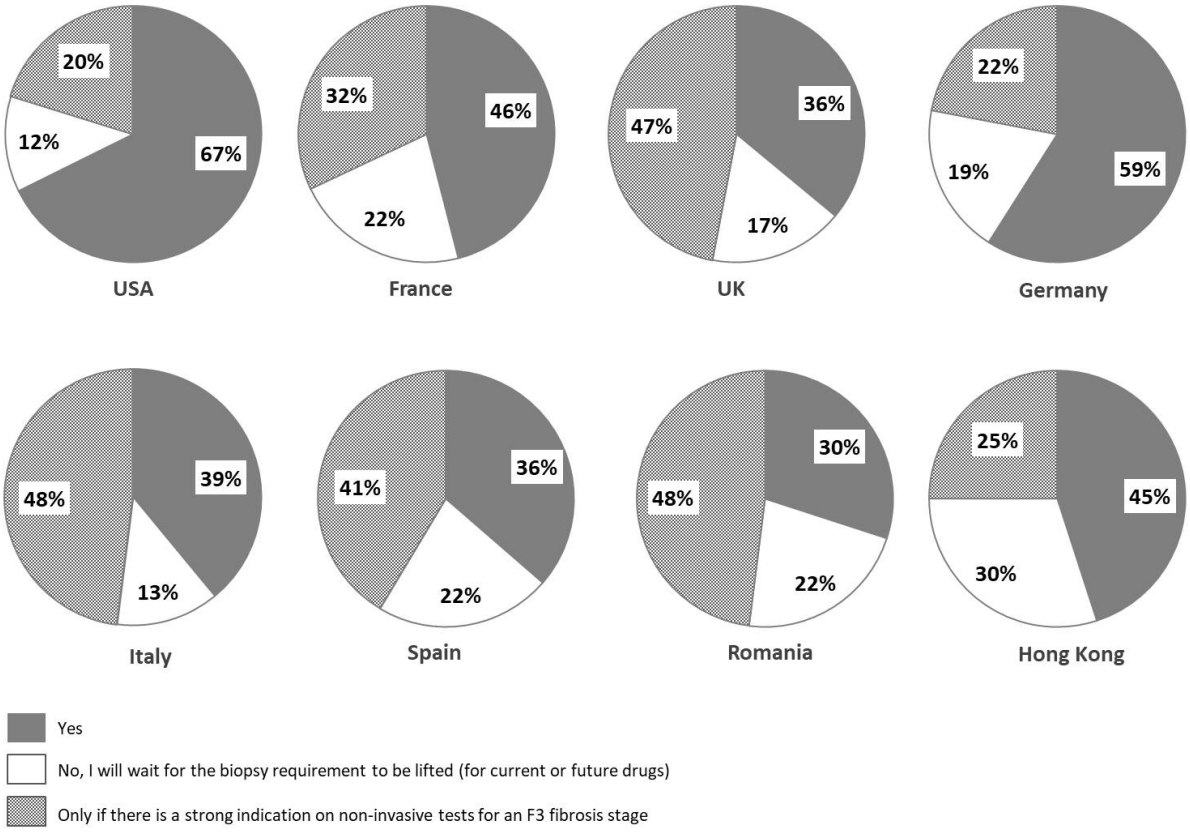
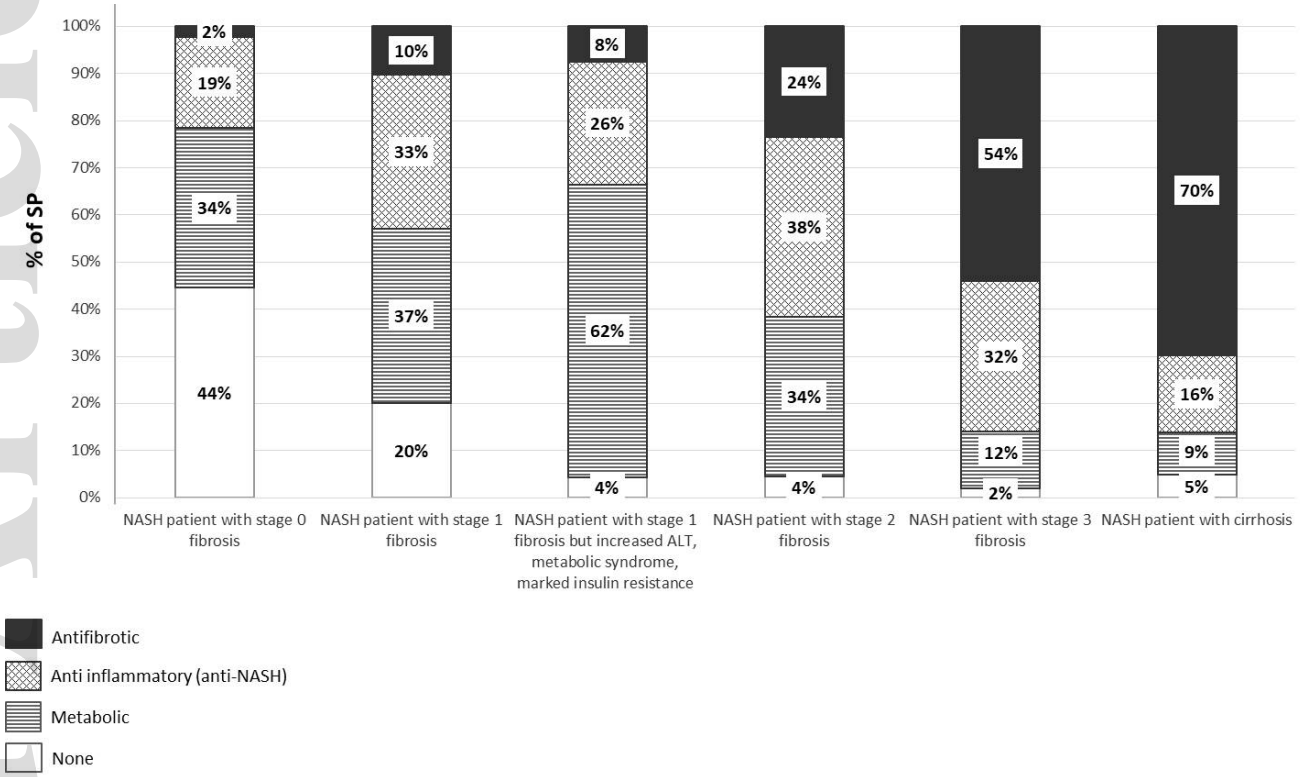


Figure 5. *Most appropriate pharmacological agent for different clinical scenarios (single choice answer by SP).*



Legend: SP, surveyed participants.