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Non-Alcoholic Steatohepatitis Patient Characterization and Real-World Management Approaches in Italy

Elisabetta Bugianesi[1], Luca Miele[2,3], Giovanna Donnarumma[4], Katrine Grau[5], Mariarosaria Mancuso[4], Preethy Prasad[5], Andrea Leith[6], Victoria Higgins[6]

[1]Division of Gastroenterology, Department of Medical Sciences, University of Torino, AOU Città della Salute e della Scienza, Torino, Italy; [2]Dipartimento di Scienze Mediche e Chirurgiche Addominali ed Endocrino Metaboliche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [3]Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy; [4]Novo Nordisk SpA, Rome, Italy; [5]Novo Nordisk A/S, Søborg, Denmark; [6]Adelphi Real World, Bollington, Cheshire, UK

Correspondence: Elisabetta Bugianesi, Email elisabetta.bugianesi@unito.it

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Background: Although the estimated prevalence of non-alcoholic steatohepatitis (NASH) in Italy is 4–6%, little is known about patient characteristics and care pathways.

Aim: To describe patient characteristics and management approaches for patients with NASH or suspected NASH in Italy.

Methods: Data were drawn from the Adelphi Real World NASH Disease Specific Programme™, a cross-sectional survey of endocrinologists and gastroenterologists in Italy from January to March 2018. Physicians completed questionnaires for their next five consecutively consulting patients with NASH or suspected NASH. Analyses were descriptive.

Results: Seventy-six physicians provided data on 380 patients. The mean age was 58.5 ± 11.1 years and the mean body mass index was 31.8 ± 5.5 kg/m^2. A total of 231 patients (61%) had no/non-advanced fibrosis as evaluated by liver biopsy or non-invasive tests. Common diagnostic assessments were cholesterol, hemoglobin A1c, absence of viral hepatitis, and alcohol assessment. At diagnosis, 87% (n=322/372) and 45% (n=169/372) of patients received an ultrasound and liver biopsy, respectively. Overall, 88% of patients were referred from primary to secondary care. Obesity (81%) and type 2 diabetes (62%) were the most commonly recorded comorbidities, with 70% of patients having ≥3 comorbidities. Vitamin E (13%) and GLP-1 receptor agonists (13%) were the most prescribed guideline-recommended treatments for all patients.

Conclusion: Patients with NASH in Italy had high levels of obesity and comorbidities, while diagnosis and treatment frequently were not according to guidelines. Our data show an unmet need for more targeted diagnosis and treatment in Italian patients with NASH, in order to optimize outcomes.

Plain language summary: Fat buildup in the liver, known as fatty liver disease, affects around 4-6% of people in Italy, and can lead to complications if left untreated. However, little is known about how doctors manage people with this disease. Fatty liver disease can only be diagnosed by a liver biopsy, but we found this is only performed in 45% of people, making accurate diagnosis difficult. We also found that 28% of people receive a recommended medication. Overall, increasing doctor awareness of fatty liver medical guidelines may help improve the diagnosis and treatment for people living with fatty liver disease in Italy.

Keywords: NASH diagnosis, NASH treatment, NASH resource utilization

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, with approximately 30% of the general adult population potentially affected.[1] In Italy, the prevalence of NAFLD and its progressive form, non-alcoholic steatohepatitis (NASH), has been examined in several studies. A study using vibration-controlled transient elastography (VCTE), conducted in the Palermo region, revealed a NAFLD prevalence of 48%, with

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possible advanced fibrosis in 6.5% of cases.[2] A population-based nested case-control study of all individuals aged ≥18 years registered at Italian primary care services revealed a NAFLD prevalence of 9%, with high regional variability.[3] A Markov model, based on the adult prevalence of obesity and type 2 diabetes mellitus (T2DM), predicted that the prevalence of NAFLD in Italy will increase from 25.4% in 2016 to 29.5% in 2023; with the corresponding values for NASH being 4.4% and 6.3%, respectively.[4]

Most patients with NAFLD are asymptomatic.[5] The symptoms of NASH may be non-specific, thus making diagnosis challenging. Symptoms include fatigue, abdominal pain, and sleep difficulties.[6] A definitive diagnosis of NASH is only possible with a liver biopsy indicative of steatosis, hepatocyte ballooning, and lobular inflammation.[7] However, the use of liver biopsy is restricted by cost, patient refusal, and requirement for specialist pathologist interpretation.[8] Several non-invasive approaches may assist with the diagnosis of NASH or suspected NASH and liver fibrosis, including predictive models, serum biomarkers, and imaging techniques.[9]

The primary goals of NASH management are to reduce progression to cirrhosis or hepatocellular carcinoma and to reduce mortality due to NASH.[7] Currently, there are no NASH-specific therapies approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA), although many therapies are currently in development.[10] Any pharmacotherapies used in NASH are off-label and include insulin sensitizers, antioxidants such as vitamin E, and lipid-lowering agents.[7,11] The most established approach to NASH management currently consists of weight loss through a combination of diet and exercise[12,13] though weight loss through the use of glucagon-like peptide-1 (GLP-1) receptor agonists has also been found to be effective.[14]

A prospective study conducted in Cuba on 293 patients with histologically proven NASH revealed that the greatest rates of reduction in fatty liver disease activity score, fibrosis regression, and NASH resolution occurred in patients with weight loss ≥10%.[12] However, initiating and sustaining the necessary lifestyle changes may be challenging.[15]

Although clinical practice guidelines developed by European liver, diabetes, and obesity associations are available,[7] awareness and uptake of these guidelines are limited and management approaches differ between regions and are inconsistent.[16,17] Recently, the Italian liver, diabetes, and obesity societies have developed clinical practice guidelines for the diagnosis and management of NASH in Italy.[11,18,19] However, the uptake of these guidelines in real-life practice in Italy has not been examined.

Despite the high prevalence of NAFLD in Italy, there is a lack of real-world data on the NASH patient population and care pathway. A better understanding of the clinical and treatment landscape of NASH in Italy may lead to improved identification, diagnosis, management, and ultimately patient outcomes, reducing the societal and healthcare burden of the disease. We aimed to describe the patient characteristics, diagnostic approaches, referral pathways, disease management approaches, compliance, and healthcare resource utilization for patients with NASH or suspected NASH attending secondary care centers in Italy.

Materials and Methods

Data Source

Data were extracted from the 2018 Adelphi Real World NASH Disease Specific Programme (DSP)™ conducted in Italy from January to March 2018. DSPs are large, multinational surveys conducted in routine clinical practice that describe patient demographics and clinical presentation, disease management, any associated treatments prescribed, and healthcare resource utilization. Although not longitudinal in nature, each survey provides independent cross-sectional insights with retrospective data capture, which can be used to explore patterns over time. The DSP methodology has been previously described,[20,21] validated,[22] demonstrated to be representative and consistent over time,[23] and has been employed in a previous publication on NASH.[16]

Patients and Physicians

Specialist physicians (endocrinologists, gastroenterologists without a subspecialty in hepatology, and gastroenterologists with a subspecialty in hepatology) were eligible to participate. For this analysis, physicians were categorized as either i) an endocrinologist or ii) a gastroenterologist (gastroenterologists and gastroenterologists with a subspecialty in

hepatology were grouped). Physicians were required to have been personally responsible for the management and treatment decisions of patients with biopsy-proven or suspected NASH and must have consulted ≥10 patients per month. Physicians completed questionnaires for their next five consecutively consulting patients with NASH or suspected NASH, with all types of physicians completing the same standardized questionnaire for all patients. The questionnaire collected information on patient demographics, clinical characteristics, disease management, and patient healthcare resource use.

Eligible patients for analysis had biopsy-confirmed NASH or suspected NASH as identified by the physician, were ≥18 years of age and were not participating in NASH clinical trials at time of data capture.

Fibrosis severity was categorized by the physician as no or non-advanced fibrosis (F0-F2) or advanced fibrosis (F3-F4) according to liver biopsy or non-invasive tests (NITs) depending on the physician's clinical practice, and according to the physician's routine clinical judgement.

Ethics

The DSP is noninterventional and solely employs retrospective data collection. Data were collected in such a way that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt for research and publication in scientific journals. Data collection was consistent with the European Pharmaceutical Marketing Research Association guidelines,[24] and had ethics approval obtained from Freiburg Ethics Commission International (FEKI; Approval No. 017/1931).

Statistical Analysis

Results are presented as descriptive analysis; mean ± standard deviation (SD) for continuous variables and frequency (%) for categorical variables are shown. Base sizes may change due to incomplete data or targeted analyses on certain subgroups. Base sizes are reported per variable.

Results

Patients and Physicians

A total of 76 specialist physicians (58 gastroenterologists [15 with subspecialty in hepatology] and 18 endocrinologists) provided data on 380 patients (endocrinologists, 90 patients; gastroenterologists, 290 patients) with NASH or suspected NASH. Physician details are reported in Supplementary Table 1, most physicians (87%) were hospital-based (endocrinologists, 61%; gastroenterologists, 95%). Overall, NASH patients represented 3% and 8% of all patients seen by endocrinologists and gastroenterologists, respectively. Mean patient age was 58.5 ± 11.1 years, and most patients were male (63%). Approximately, a third of patients never smoked (37%). Mean body mass index was 31.8 ± 5.5 kg/m^2. Obesity (81%) and T2DM (62%) were the two most common comorbidities; most patients (n=267/379, 70%) had ≥3 comorbidities. Most patients (61%) had no or non-advanced fibrosis (fibrosis stage F0-F2). Fifty-eight gastroenterologist-managed patients had advanced fibrosis (fibrosis stage F3-F4; 20%) compared with 16 (18%) endocrinologist-managed patients; of these patients with advanced fibrosis, n=35/58 (60%) and n=6/16 (38%) had ever had a liver biopsy, respectively (Table 1).

Clinical Characteristics and Testing at NASH Diagnosis

Mean time since diagnosis was 1.1 ± 1.4 years. Most patients (56%) were diagnosed by a gastroenterologist, with a third (33%) of patients having a physician-confirmed NAFLD diagnosis prior to NASH diagnosis. Most patients (n=212/372, 57%) had no or non-advanced fibrosis at diagnosis. Gastroenterologists reported 26% of patients (n=81/315) to have advanced fibrosis at diagnosis. For endocrinologists, this was 19% of patients (n=11/57). Among patients with advanced fibrosis at time of diagnosis, half (n=40/81) of gastroenterologist-diagnosed patients and 18% (n=2/11) of endocrinologist-diagnosed patients had a liver biopsy.

General weakness (n=166/301, 55%), fatigue (n=134/301, 45%), and sleep disturbance (n=128/306, 43%) were the most common signs reported by all diagnosing physicians at diagnosis. Sleep disturbance was reported for 45% (n=115/

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Table 1 Patient Demographics and Clinical Characteristics

	Total (N=380)			Endocrinologist (n=90)			Gastroenterologist[a] (n=290)		
	Total (N=380)	**No LB (n=204)**	**LB (n=176)**	**Total (n=90)**	**No LB (n=58)**	**LB (n=32)**	**Total (n=290)**	**No LB (n=146)**	**LB (n=144)**
Patient age, years, mean ± SD	58.5 ± 11.1	57.8 ± 10.9	59.4 ± 11.2	59.8 ± 8.4	58.8 ± 8.5	61.7 ± 7.9	58.1 ± 11.8	57.4 ± 11.8	58.9 ± 11.8
Sex, n (%)									
Male	240 (63)	122 (60)	118 (67)	51 (57)	31 (53)	20 (63)	189 (65)	91 (62)	98 (68)
Employment status, n (%)									
Working full-time/part-time	178 (47)	91 (45)	87 (49)	43 (48)	28 (48)	15 (47)	135 (47)	63 (43)	72 (50)
Not working [b]	195 (51)	106 (52)	89 (51)	45 (50)	28 (48)	17 (53)	150 (52)	78 (53)	72 (50)
Do not know	7 (2)	7 (3)	0 (0)	2 (2)	2 (3)	0 (0)	5 (2)	5 (3)	0 (0)
Smoking status, n (%)									
Current smoker	78 (21)	45 (22)	33 (19)	17 (19)	11 (19)	6 (19)	61 (21)	34 (23)	27 (19)
Ex-smoker	131 (34)	57 (28)	74 (42)	30 (33)	15 (26)	15 (47)	101 (35)	42 (29)	59 (41)
Never smoked	142 (37)	84 (41)	58 (33)	38 (42)	27 (47)	11 (34)	104 (36)	57 (39)	47 (33)
Do not know	29 (8)	18 (9)	11 (6)	5 (6)	5 (9)	0 (0)	24 (8)	13 (9)	11 (8)
Alcohol units consumed per week, mean ± SD	(n=84) 5.1 ± 8.4	(n=44) 5.5 ± 10.6	(n=40) 4.7 ± 5.1	(n=13) 7.5 ± 13.4	(n=8) 8.5 ±16.9	(n=5) 6.0 ±5.7	(n=71) 4.6 ±7.2	(n=36) 4.8 ± 8.8	(n=35) 4.5 ± 5.0
Fibrosis stage at survey[c], n (%)									
No/non-advanced fibrosis	231 (61)	129 (63)	102 (58)	63 (70)	40 (69)	23 (72)	168 (58)	89 (61)	79 (55)
Advanced fibrosis	74 (19)	33 (16)	41 (23)	16 (18)	10 (17)	6 (19)	58 (20)	23 (16)	35 (24)
Unknown	75 (20)	42 (21)	33 (19)	11 (12)	8 (14)	3 (9)	64 (22)	34 (23)	30 (21)
BMI at survey, kg/m^2, mean ± SD	31.8 ± 5.5	32.1 ± 6.1	31.4 ± 4.7	33.5 ± 8.1	34.3 ± 8.5	32.0 ± 4.2	31.3 ± 4.3	31.3 ± 3.7	31.3 ± 4.8
BMI classification at survey, n (%)									
<30 kg/m^2	116 (31)	58 (28)	58 (33)	20 (22)	12 (21)	8 (25)	96 (33)	46 (32)	50 (35)
30.0–34.9 kg/m^2	201 (53)	115 (56)	86 (49)	50 (56)	33 (57)	17 (53)	151 (52)	82 (56)	69 (48)
35.0–39.9 kg/m^2	49 (13)	23 (11)	26 (15)	13 (14)	7 (12)	6 (19)	36 (12)	16 (11)	20 (14)
≥40.0 kg/m^2	14 (4)	8 (4)	6 (3)	7 (8)	6 (10)	1 (3)	7 (2)	2 (1)	5 (3)
Top five comorbidities, n (%)									
Obesity [d]	308 (81)	166 (81)	142 (81)	81 (90)	53 (91)	28 (88)	227 (78)	113 (77)	114 (79)
Type 2 Diabetes	235 (62)	132 (65)	103 (59)	70 (78)	47 (81)	23 (72)	165 (57)	85 (58)	80 (56)
Dyslipidemia	206 (54)	124 (61)	82 (47)	46 (51)	35 (60)	11 (34)	160 (55)	89 (61)	71 (49)
Hypertension	195 (51)	106 (52)	89 (51)	49 (54)	35 (60)	14 (44)	146 (50)	71 (49)	75 (52)
Metabolic syndrome	132 (35)	78 (38)	54 (31)	32 (36)	26 (45)	6 (19)	100 (34)	52 (36)	48 (33)

Other selected concomitant conditions, n (%)									
Sleep disorder	118 (31)	75 (37)	43 (24)	22 (24)	15 (26)	7 (22)	96 (33)	60 (41)	36 (25)
ASCVD[e]	99 (26)	59 (29)	40 (23)	15 (17)	12 (21)	3 (9)	84 (29)	47 (32)	37 (26)
CKD	9 (2)	6 (3)	3 (2)	2 (2)	2 (3)	0 (0)	7 (2)	4 (3)	3 (2)
Number of comorbidities [f], n (%)									
0	16 (4)	10 (5)	6 (3)	0 (0)	0 (0)	0 (0)	16 (6)	10 (7)	6 (4)
1	44 (12)	18 (9)	26 (15)	5 (6)	4 (7)	1 (3)	39 (13)	14 (10)	25 (17)
2	52 (14)	25 (12)	27 (15)	20 (22)	10 (17)	10 (31)	32 (11)	15 (10)	17 (12)
≥3	267 (70)	150 (74)	117 (66)	65 (72)	44 (76)	21 (66)	202 (70)	106 (73)	96 (67)

Notes: [a] Gastroenterologist category also includes gastroenterologists or internists with a subspecialty in hepatology. [b] Defined as patients who are homemakers, on long-term sick leave, retired, students, or unemployed. [c] As assessed and reported by physician. F-stage F0-F2 was considered as no/non-advanced fibrosis and F3-F4 as advanced fibrosis. [d] Selected as comorbidity or stated current BMI ≥30 kg/m^{2}. [e] Defined as having at least one of myocardial infarction, peripheral vascular disease, or cerebrovascular disease. [f] Data from 379 patients, data not available from one patient treated by a gastroenterologist.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; LB, liver biopsy; SD, standard deviation.

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257) of gastroenterologist-diagnosed patients and for 30% (n=13/44) of endocrinologist-diagnosed patients. The most common symptoms reported by all physicians at diagnosis were swelling in the legs, ankles, and feet (n=115/301, 38%), swelling of the stomach/abdomen (n=108/301, 36%), and aching/discomfort in upper right abdomen (n=107/301, 36%). Aching/discomfort in upper right abdomen was reported for 36% (n=93/257) of gastroenterologist-diagnosed and for 32% (n=14/44) of endocrinologist-diagnosed patients (Table 2).

Assessment tests commonly conducted for all patients with NAFLD or suspected NASH at NASH diagnosis included cholesterol (high-density lipoprotein, low-density lipoprotein, total), HbA1c, serological tests for viral hepatitis, and evaluation of alcohol intake (thresholds <20 g/day for females and <30 g/day for males, Figure 1A). Notably, the assessment of alcohol intake was conducted for only 56% (n=32/57) of patients diagnosed by endocrinologists (Figure 1A). Ultrasonography was the most common diagnostic test performed by the physicians to diagnose NASH or suspected NASH, accounting for 87% (n=322/372) of cases. The survey did not cover the specific ultrasonography modalities used. Additionally, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also commonly used (Figure 1B). The Fibrosis 4 (FIB-4) index and serum Enhanced Liver Fibrosis (ELF) tests were performed for 5% (n=19/372) and 4% (n=15/372) of patients, respectively.

VCTE was performed on 62% (n=230/372) of patients. Liver biopsy was performed on 45% (n=169/372) of patients; 47% (n=148/315) of gastroenterologist-diagnosed patients and 37% (n=21/57) of endocrinologist-diagnosed patients had liver biopsy (Figure 1B). The mean number of tests performed to aid diagnosis was 8.1 ± 4.7; gastroenterologists performed a mean of 8.2 ± 4.9 tests compared with 7.4 ± 3.6 tests by endocrinologists (Table 2).

Referral and Current Managing Physician

Most patients (87%) were referred from another physician instead of presenting directly to the current managing physician (Figure 2A). For both specialties, patients were commonly referred to their current managing physician by a primary care physician (PCP) (n=145/334, 43%); 58% (n=47/81) of endocrinologist-managed patients and 39% (n=99/253) of gastroenterologist-managed patients were referred by a PCP (Figure 2B). Overall, 85% (n=106/124) of endocrinologist-managed patients were co-managed for NASH with another physician. For gastroenterologist-managed patients, this was 63% (n=152/240). Physicians involved in co-management with an endocrinologist were mostly PCPs (n=58/106, 55%) or other gastroenterologists (n=54/106, 51%, Supplementary Table 2).

Further Testing After NASH or Suspected NASH Diagnosis

The mean number of tests conducted by physicians following the diagnosis of NASH or suspected NASH was 5.8 ± 4.0. Managing gastroenterologists performed a mean of 6.0 ± 4.2 tests and managing endocrinologists performed a mean of 5.2 ± 3.3 tests (Table 3). VCTE was performed on 54% of all patients (Figure 1C). Liver biopsy was performed on 10% of all patients; 9% (n=27/290) of patients managed by gastroenterologists and 13% (n=12/90) of patients managed by endocrinologists had a liver biopsy. Overall, FIB-4 index and serum ELF test were performed for 2% and 1% of patients, respectively.

Physician Attitudes for Role of Liver Biopsy to Manage NASH

Overall, physicians sent on average 37% of their NASH patients to liver biopsy as part of NASH diagnosis. Gastroenterologists and endocrinologists sent 39% and 29% of their patients to liver biopsy, respectively (Figure 3A). Among physicians managing patients who had a liver biopsy (n=54), 88% (n=37/42) of gastroenterologists and 50% (n=6/12) of endocrinologists considered liver biopsy as superior for diagnosing NASH when compared with all other testing options (Figure 3B). Among physicians managing patients who had not had a liver biopsy (n=71), the most common reason for not requesting liver biopsy was invasiveness and discomfort (n=49/71, 69%). This reason was reported by gastroenterologists in 74% of cases (n=39/53, Figure 3C). Liver biopsy was not discussed with 61 patients; the most common reason for physicians not discussing liver biopsy was absence of a currently approved treatment for NASH (n=32/61, 52%, Figure 3D). Liver biopsy was discussed with, and refused by, 24% of patients overall (Figure 3E). For these patients, the most common reason for refusing liver biopsy was fear of procedure (n=68/93, 73%, Figure 3F).

Table 2 Clinical Characteristics and Tests on Diagnosis of NASH or Suspected NASH

	Current managing physician								
	Total (N=380)			Endocrinologist (n=90)			Gastroenterologist[a] (n=290)		
	Total (N=380)	No LB (n=204)	LB (n=176)	Total (n=90)	No LB (n=58)	LB (n=32)	Total (n=290)	No LB (n=146)	LB (n=144)
Years since diagnosis, mean ± SD	(n=299) 1.1 ± 1.4	(n=149) 1.0 ± 1.2	(n=150) 1.3 ± 1.6	(n=62) 1.1 ± 1.5	(n=37) 1.0 ± 1.2	(n=25) 1.3 ± 1.8	(n=237) 1.1 ± 1.4	(n=112) 1.0 ± 1.1	(n=125) 1.2 ± 1.6
Diagnosing physician, n (%)									
Gastroenterologist	213 (56)	98 (48)	115 (65)	13 (14)	9 (16)	4 (13)	200 (69)	89 (61)	111 (77)
Gastroenterologist[a]	102 (27)	64 (31)	38 (22)	28 (31)	18 (31)	10 (31)	74 (26)	46 (32)	28 (19)
Endocrinologist	57 (15)	36 (18)	21 (12)	46 (51)	28 (48)	18 (56)	11 (4)	8 (5)	3 (2)
PCP	2 (1)	1 (0)	1 (1)	0 (0)	0 (0)	0 (0)	2 (1)	1 (1)	1 (1)
Other	3 (1)	2 (1)	1 (1)	2 (2)	2 (3)	0 (0)	1 (0)	0 (0)	1 (1)
Do not know	3 (1)	3 (1)	0 (0)	1 (1)	1 (2)	0 (0)	2 (1)	2 (1)	0 (0)
NALFD diagnosis prior to suspected NASH/NASH diagnosis, n (%)									
Yes	125 (33)	58 (28)	67 (38)	34 (38)	25 (43)	9 (28)	91 (31)	33 (22)	58 (40)
	Diagnosing physician								
	Total (N=372[b])			Endocrinologist (n=57)			Gastroenterologist[a] (n=315)		
	Total (N=372)	No LB (n=198)	LB (n=174)	Total (n=57)	No LB (n=36)	LB (n=21)	Total (n=315)	No LB (n=162)	LB (n=153)
Fibrosis stage at diagnosis[c], n (%)									
No/non-advanced fibrosis	212 (57)	103 (52)	109 (63)	43 (75)	25 (69)	18 (86)	169 (54)	78 (48)	91 (59)
Advanced fibrosis	92 (25)	50 (25)	42 (24)	11 (19)	9 (25)	2 (10)	81 (26)	41 (25)	40 (26)
Unknown	68 (18)	45 (23)	23 (13)	3 (5)	2 (6)	1 (5)	65 (21)	43 (27)	22 (14)
Top six physician-reported signs/symptoms prior to/at diagnosis, n (%)									
n	301[d]	156	145	44	26	18	257	130	127
General weakness	166 (55)	88 (56)	78 (54)	27 (61)	17 (65)	10 (56)	139 (54)	71 (55)	68 (54)
Fatigue	134 (45)	72 (46)	62 (43)	20 (45)	14 (54)	6 (33)	114 (44)	58 (45)	56 (44)
Sleep disturbance	128 (43)	75 (48)	53 (37)	13 (30)	10 (38)	3 (17)	115 (45)	65 (50)	50 (39)
Swelling in the legs, ankles, feet	115 (38)	73 (47)	42 (29)	17 (39)	14 (54)	3 (17)	98 (38)	59 (45)	39 (31)
Swelling of the stomach/abdomen	108 (36)	60 (38)	48 (33)	16 (36)	14 (54)	2 (11)	92 (36)	46 (35)	46 (36)
Aching/discomfort in upper right abdomen	107 (36)	71 (46)	36 (25)	14 (32)	13 (50)	1 (6)	93 (36)	58 (45)	35 (28)
Tests used at diagnosis[e]									
Mean ± SD	8.1 ± 4.7	6.9 ± 3.5	9.3 ± 5.5	7.4 ± 3.6	6.5 ± 2.9	9.0 ± 4.0	8.2 ± 4.9	7.0 ± 3.6	9.4 ± 5.7

Notes: [a] Gastroenterologist category also includes gastroenterologists with a subspecialty in hepatology. [b] All physicians who conducted tests at diagnosis of NASH or suspected NASH. [c] As assessed and reported by physician. F-stage F0-F2 was considered as no/non-advanced fibrosis and F3-F4 as advanced fibrosis. [d] Lower base as only data from patients with current signs or symptoms were captured. [e] Include the following: imaging tests (computed tomography, Magnetic resonance imaging, Proton magnetic resonance spectroscopy and ultrasonography), blood tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], AST/ALT ratio, alkaline phosphatase, gamma-glutamyltransferase, platelets, international normalized ratio, serum albumin, and total bilirubin) and liver-specific (actiTest, BARD Score, fatty liver index, FIB-4 index, VCTE, fibrotest, liver biopsy, NAFLD activity score, NAFLD fibrosis score, NAFLD liver fat score, serum ELF test, steatotest, and steatosis activity fibrosis score).

Abbreviations: LB, liver biopsy; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PCP, primary care physician; SD, standard deviation.

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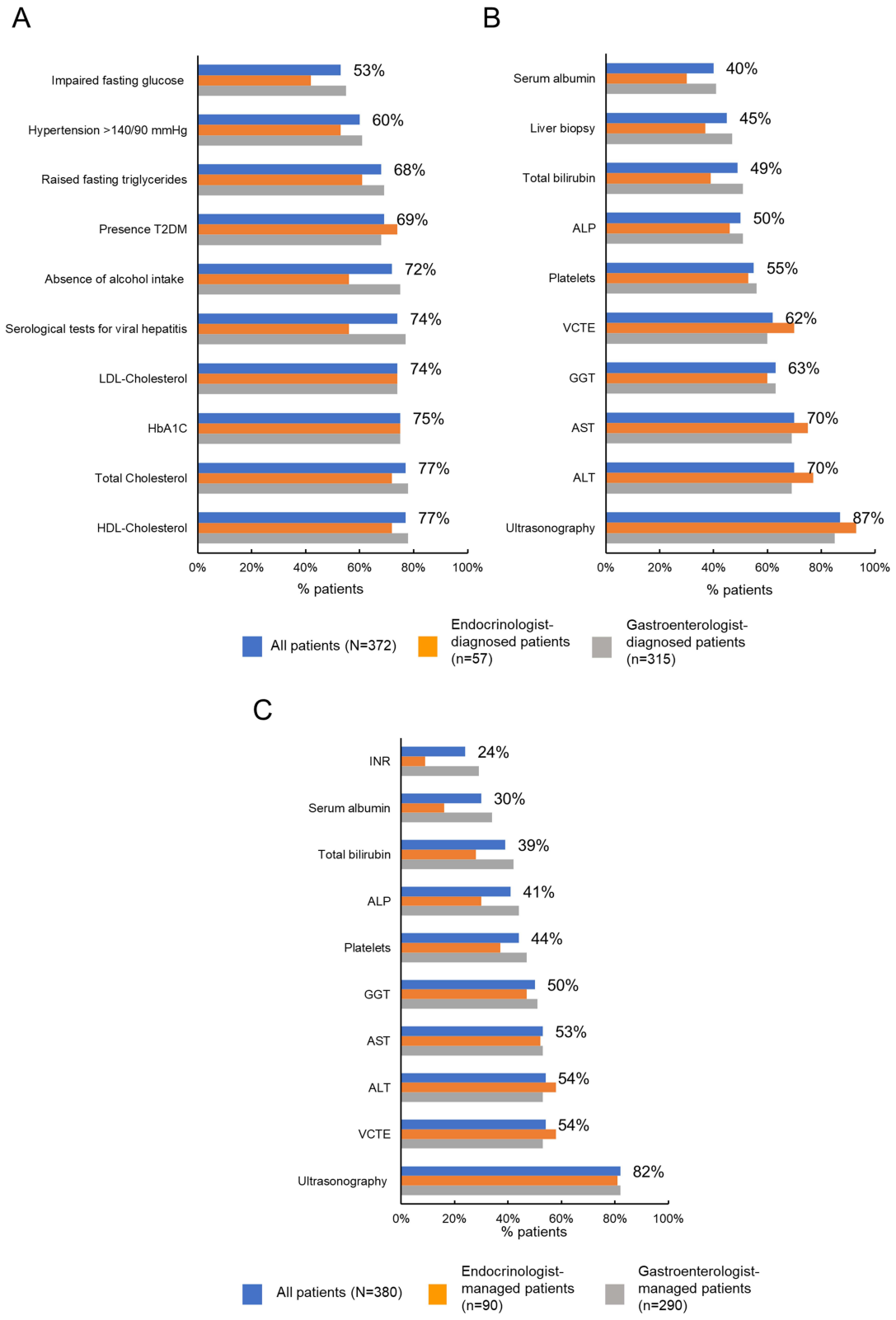

Figure 1 Top ten elimination/assessment tests (**A**) and tests for NASH or suspected NASH (**B**) conducted to aid diagnosis by diagnosing physician. Top ten tests for NASH or suspected NASH conducted after NASH or suspected NASH diagnosis by managing physician (**C**). For all panels, percentage values indicated are for all patients for that particular category. The gastroenterologist category also included gastroenterologists with a subspecialty in hepatology. Tests are categorized by frequency of total percentage, from lowest to highest.

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

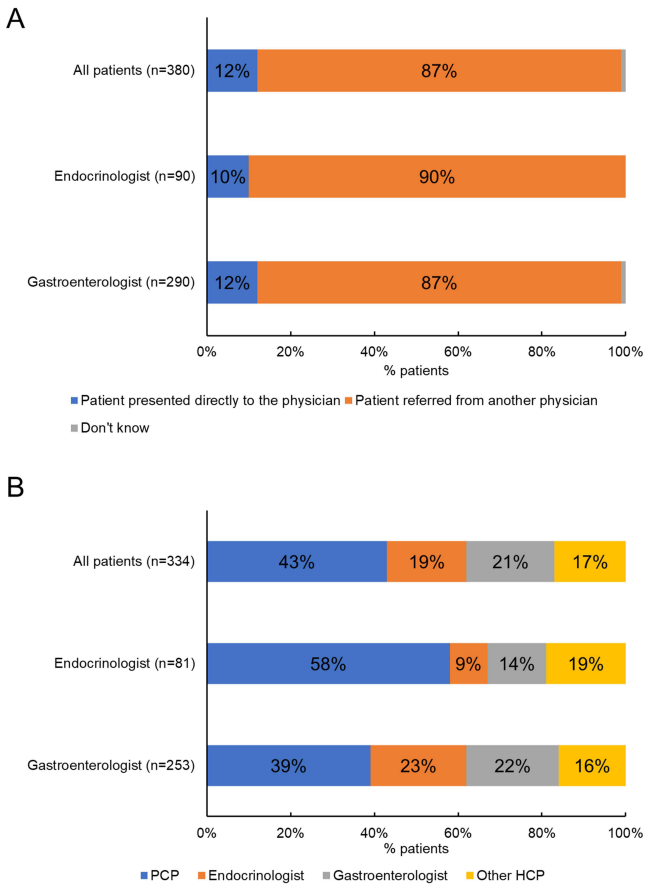

Figure 2 (**A**) Percentage of patients referred either directly to managing physician or referred by another physician. (**B**) Specialty of physician who referred patient. Other infectious disease specialist, cardiologist, specialist nurse, radiologist, surgeon, neurologist, and not specified. For both panels, current managing physician is indicated in the Y-axis label. The specialty of the referring physician is shown by the different colors as defined below panel B. The gastroenterologist category also included gastroenterologists with a subspecialty in hepatology.
Abbreviations: HCP, healthcare provider; PCP, primary care physician.

Patient Management and Treatment After NASH or Suspected NASH Diagnosis

Nearly two-thirds of all patients (58%) were receiving ≥1 treatment to manage NASH (weight-loss treatment, guideline-recommended NASH treatment, or treatment for associated conditions). Fifty-four (14%) patients were receiving or had received weight-loss treatment. For all patients, the most common guideline-recommended NASH treatments were vitamin E (13%) and GLP-1 receptor agonists (13%).[7,11,25] GLP-1 receptor agonists were prescribed to 28% (n=25/90) of patients managed by endocrinologists and only 9% (n=25/290) of patients managed by gastroenterologists. Overall, 5% of patients were currently receiving pioglitazone to manage their NASH or suspected NASH; this was prescribed to 11% (n=10/90) of patients managed by endocrinologists and 3% (n=10/290) of patients managed by gastroenterologists (Table 3). Overall, 31% of patients were using statins, of whom only 3% were clinically diagnosed with T2DM and 18% were not clinically diagnosed with T2DM (Supplementary Table 2). In addition, statins were prescribed for 27% of endocrinologist-managed patients and 32% of gastroenterologist patients.

A total of 62% and 81% of patients with NASH or suspected NASH were also diagnosed with T2DM and obesity, respectively. Among patients with T2DM or obesity (BMI ≥30 kg/m^2), 66% (n=154/235) and 62% (n=192/308, 62%) were receiving ≥1 treatment to manage NASH, respectively. The corresponding values for those without T2DM or without obesity were 45% (n=65/145) and 38% (n=27/72), respectively. GLP-1 receptor agonists were the most common guideline-recommended NASH treatment prescribed to 20% (n=46/235) of patients with T2DM and 3% (n=4/145) of patients without T2DM. Vitamin E was prescribed to patients with T2DM (n=27/235, 11%) or without T2DM (n=22/145, 15%). Pioglitazone was prescribed to 11% (n=8/70) of endocrinologist-managed patients with T2DM to target NASH or

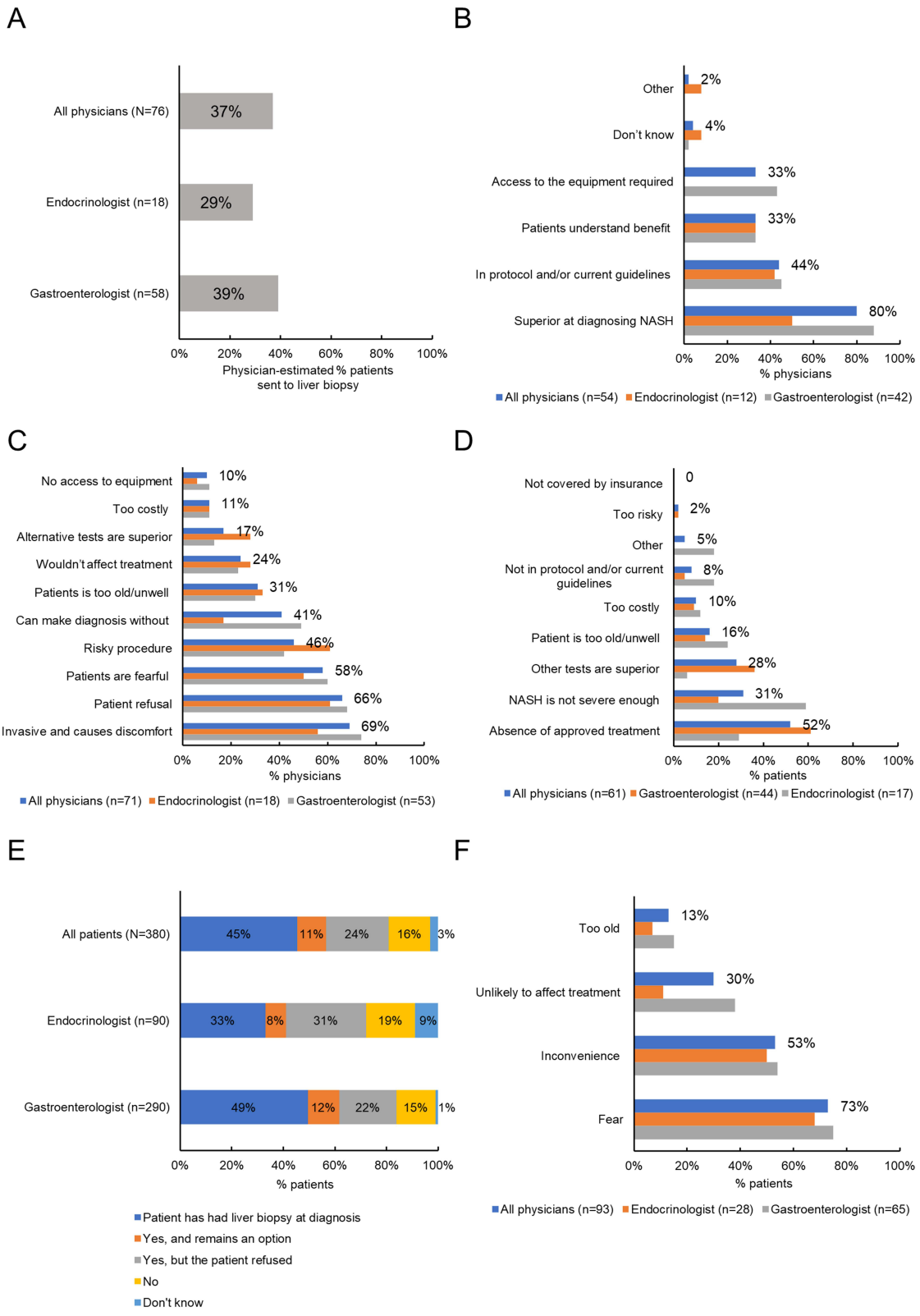

Figure 3 (**A**) Physician-estimated proportion of patients sent to liver biopsy. (**B**) Reasons why physicians sent patient to liver biopsy. Percentage values indicated are for all physicians for that particular category. (**C**) Top ten reasons why physicians did not send patient to liver biopsy. Percentage values indicated are for all physicians for that particular category. (**D**) Reasons why physician did not discuss liver biopsy with patient. Percentage values refer to proportions of patients treated by all physicians for that particular category. (**E**) Discussion of liver biopsy with patient. (**F**) Reasons why patients refused liver biopsy. Percentage values refer to proportions of patients treated by all physicians for that particular category. Physician survey data shown in panels **A–C**; data from physician-reported patient record forms shown in panels **D–F**.

Table 3 Patient Management and Treatment After NASH or Suspected NASH Diagnosis

	Total	Current managing physician	
	(N=380)	Endocrinologist (n=90)	Gastroenterologist[a] (n=290)
Receiving ≥1 treatment to manage NASH at time of survey, n (%)[a]	219 (58)	61 (68)	158 (54)
Treatments received for NASH at time of survey as recommended by Italian guidelines, n (%)[b]			
Any guideline-recommended treatment	106 (28)	40 (44)	66 (23)
Vitamin E	49 (13)	10 (11)	39 (13)
GLP-1	50 (13)	25 (28)	25 (9)
Pioglitazone	20 (5)	10 (11)	10 (3)
Treatments received for NASH-associated conditions, n (%)[c]	179 (47)	52 (58)	127 (44)
Any anti-hypertensive treatment[d]	237 (65)	58 (64)	179 (66)
Any anti-diabetic treatment[e]	148 (39)	42 (47)	106 (37)
Metformin	141 (37)	40 (44)	101 (35)
DPP-4	12 (3)	4 (4)	8 (3)
SGLT-2	12 (3)	4 (4)	8 (3)
Any weight-loss treatment[f]	54 (14)	20 (22)	34 (12)
Prescription anti-obesity medication	23 (6)	11 (12)	12 (4)
Non-prescription weight-loss drug	38 (10)	10 (11)	28 (10)
Previous weight-loss surgery	4 (1)	2 (2)	2 (1)
Top five reasons why patient has never received drug treatment for NASH, n (%)	n=153	n=29	n=124
No approved medicines	81 (53)	12 (41)	69 (56)
Recent diagnosis/currently undergoing evaluation	35 (23)	9 (31)	26 (21)
Patient refused treatment	24 (16)	3 (10)	21 (17)
Cost/insurance	17 (11)	2 (7)	15 (12)
Patient has other health problems	6 (4)	2 (7)	4 (3)
Top five reasons for reduced drug compliance, n (%)[g]	n=79	n=31	n=48
Change of routine	37 (47)	12 (39)	25 (52)
Does not always carry medication with them	18 (23)	5 (16)	13 (27)
Does not feel ill, medication unnecessary	16 (20)	8 (26)	8 (17)
Confused as so many drugs in total	15 (19)	8 (26)	7 (15)
Lack of family/friend support	12 (15)	1 (3)	11 (23)
Tests used after diagnosis[h]			
Mean ± SD	5.8 ± 4.0	5.2 ± 3.3	6.0 ± 4.2

Notes: [a] Defined as having at least one of the following: currently on treatment with a guideline-recommended treatment (vitamin E, pioglitazone, or GLP-1), currently on anti-diabetic treatment (metformin, DPP-4, or SGLT-2), or currently on weight-loss treatment (had weight-loss surgery, currently on prescription weight-loss drug, or currently on non-prescription (over the counter) weight-loss drug). [b] Defined as currently on treatment with a guideline-recommended treatment (vitamin E, pioglitazone, or GLP-1). Use of GLP-1 is recommended in the context of T2DM. Refer to: Eat Weight Disord 2022;27:1603–19. [c] Defined as having at least one of the following: currently on an anti-diabetic drug (metformin, DPP-4, or SGLT-2), or currently on weight-loss treatment (had weight-loss surgery, currently on a prescription weight-loss drug, or currently on non-prescription (over the counter) weight-loss drug). [d] Defined as currently on anti-diabetic treatment (angiotensin II receptor inhibitors, angiotensin receptor-neprilysin inhibitors, angiotensin-converting-enzyme inhibitors, alpha blockers, beta blockers, calcium channel blockers, diuretics, renin inhibitors, vasodilators or other anti-hypertensive medication). [e] Defined as currently on anti-diabetic treatment (metformin, DPP-4, or SGLT-2). Note: excludes GLP-1 as included as guideline treatment for NASH. [f] Defined as having at least one of the following: had weight-loss surgery, currently on prescription weight-loss drug, or currently on non-prescription (over the counter) weight-loss drug. [g] Physician-reported. [h] Includes the following: imaging tests (computed tomography, magnetic resonance imaging, proton magnetic resonance spectroscopy and ultrasonography), blood tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), AST/ALT ratio, alkaline phosphatase, gamma-glutamyltransferase, platelets, international normalised ratio, serum albumin and total bilirubin) and liver specific (actiTest, BARD Score, fatty liver index, FIB4 index, VCTE, FibroTest, liver biopsy, NAFLD activity score, NAFLD fibrosis score, NAFLD liver fat score, serum ELF test, SteatoTest, and steatosis activity fibrosis score).

Abbreviations: DPP-4, dipeptidyl peptidase 4 inhibitor; GLP-1, Glucagon-like peptide-1 receptor agonist; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2 inhibitor.

suspected NASH compared with 4% (n=7/165) of patients managed by gastroenterologists (Supplementary Table 3). The most common reason for patients not receiving drug treatment for NASH was the absence of approved treatments (n=81/153, 53%). The most common reason for lack of patient compliance with drug treatment was patient change of daily routine (n=37/79, 47%) (Table 3).

Healthcare Resource Use

Among all patients with available hospitalization data (n=231), 15% had been hospitalized in the past 12 months for any reason. Of these, 51% were hospitalized for a NASH-associated condition and 37% for NASH. A total of 16% (n=30/184) gastroenterologist-managed patients and 11% (n=5/47) of endocrinologist-managed patients were hospitalized for any reason in the last 12 months (Supplementary Table 4).

A total of 28% (n=8/29) of patients with advanced fibrosis were hospitalized in the last 12 months; 63% (n=5/8) of patients with advanced fibrosis were hospitalized in the last 12 months for a NASH-associated condition. The corresponding values for those with no or non-advanced fibrosis were 18% (n=25/142) and 48% (n=12/25), respectively (Supplementary Table 4).

Discussion

This real-world survey of patients with NASH or suspected NASH in Italy revealed that these patients are often obese and have a high burden of comorbidities. Ultrasonography was performed on most patients for diagnosis, with liver biopsy performed on slightly less than half of patients. VCTE was a NIT commonly performed by diagnosing and managing physicians. Common clinical investigations or biochemical tests performed included cholesterol, HbA1c, serological tests for viral hepatitis, and assessment of alcohol intake.

Most patients were referred by another physician instead of presenting directly to the current managing physician for NASH management. Although nearly two-thirds of all patients were receiving at least one treatment to manage NASH, treatment according to current guidelines appears suboptimal. Pathologic diagnosis remains a key standard for establishing diagnosis of NAFLD, with radiological modalities also being widely used. However, radiological modalities such as ultrasonography, computerized tomography and magnetic resonance imaging lack the ability to detect or characterize NASH from steatosis alone, or are able to detect the different forms of NAFLD.[26,27]

These modalities can also produce nonspecific findings, which may lead to a significant variability in interpretation among radiologists. It is therefore important to be able to distinguish a clear prognosis of patients with NAFLD, with better clinical, radiological and serological markers of fibrosis, which highly supports the role of liver biopsy in staging liver disease in NAFLD.[28] In this study we do not specify which radiology modality is used by our physicians. In addition, this study contains descriptive analysis, and as such we did not compute any data to identify any independent predictor of the decision of performing liver biopsy.

Gastroenterologists tended to evaluate alcohol intake more frequently than endocrinologists. To the best of our knowledge, data on the attitudes towards alcohol assessment among gastroenterologists and endocrinologists in the context of NASH management is limited. It may be possible that liver health and associated assessments are more likely to be standard of care among gastroenterologists. The emphasis on liver health and alcohol assessment may also be reflected, in the proportion (approximately a quarter) of physicians with a subspecialty in hepatology, among the gastroenterologists recruited in this study. As >60% of the patients in this study had T2DM, it is possible that the managing endocrinologists were more focused on addressing T2DM and were less aware of or focused on liver health.

Patients currently managed by endocrinologists were frequently referred by a PCP, suggesting that there is already an effective referral pathway in Italy from PCPs to endocrinologists, but not to gastroenterologists. Endocrinologists may be more likely to reach the general population through their connection with PCPs. Another possibility may be that PCPs are referring to endocrinologists due to the high prevalence of T2DM in this population, as there may be a lack of liver indicators due to the asymptomatic nature of NASH. Hence, through routine T2DM assessment, endocrinologists may be subsequently identifying suspected NASH. These results indicate that a similar pathway between gastroenterologists and PCPs in Italy has not been established and development of such a pathway is warranted.

The FIB-4 for liver fibrosis is recommended as a first-line non-invasive assessment of liver fibrosis for PCPs and endocrinologists due to its simplicity, high negative predictive value, and minimal cost.[25,29–31] Despite this recommendation, FIB-4 was used for <10% of all patients by both diagnosing and managing physicians in this analysis. The minimal use of FIB-4 may be due to requirement for manual calculation or lack of awareness of the assessment or relevant cut-offs for NASH. Use of FIB-4 may be increased by automating and reimbursing this assessment (FIB-4 is currently only reimbursed in Italy in the context of T2DM) and providing cut-off values on every lab report. Reimbursement and provision of cut-off values should be considered for the serum ELF test also, which was used for <10% of patients in this analysis. A study on FIB-4 in the community setting suggested that FIB-4 can facilitate early identification of patients at high risk for advanced liver fibrosis.[32] A systematic review and meta-analysis of ELF in patients with NAFLD revealed a high negative predictive value of ELF, suggesting that ELF can exclude advanced fibrosis in this population.[33] Accordingly, increased use of FIB-4 and ELF may assist in the risk stratification of patients in a primary care setting and expedite referral to specialist management if appropriate.

Current Italian guidelines state that NITs do not have acceptable accuracy for NASH diagnosis and that liver biopsy is the reference standard.[11] The proportion of patients (nearly 50%) who received a liver biopsy to aid diagnosis was perceived to be high for real-world clinical practice, with the possibility that this procedure could have been performed as part of a clinical trial and not in real-world clinical practice, although this could not be verified. It was also not possible to determine if liver biopsy was performed before or after NITs. Broad use of liver biopsy in real-world settings for NASH diagnosis may be restricted by cost, patient refusal, and requirement for specialist interpretation.[8] The current Italian guidelines also state that FIB-4 and VCTE can be used instead of liver biopsy to exclude patients at high risk of advanced fibrosis.[11] Half of diagnosing and managing physicians used VCTE in this analysis. VCTE was performed on over two-thirds of patients diagnosed by endocrinologists, although the rationale for VCTE and whether it was already performed or if it was requested by the diagnosing endocrinologist are unknown. An increased awareness of, access to, and reimbursement for VCTE (along with FIB-4 and ELF, discussed above) may improve risk stratification and referral.

Approximately a third of patients in our cohort received statins. Patients with NAFLD are frequently characterized by the presence of cardiometabolic diseases including type II diabetes, obesity and/or dyslipidemia (collectively known as metabolic syndrome), which may both hasten the progression to more severe forms of NAFLD and increase cardiovascular risk in NAFLD patients.[34,35] For this reason, NAFLD patients should be prescribed statins to reduce cardiovascular risk. However, due to concerns over statin treatment safety in NAFLD patients,[36–38] many patients are not given statins, which leads to increased cardiovascular risks.[39] However, evidence supports that statins not only reduce cardiovascular risk but can display beneficial effects on the liver.[40–43]

There is currently no available FDA- or EMA-approved therapy specific for NASH. Although specific treatment guidelines (including Italy-specific guidelines)[7,8,11,25] are available for NASH, the results from this analysis suggest that uptake of these guidelines in current practice remains suboptimal in Italy. Vitamin E and pioglitazone were used by <15% and <10% of patients, respectively. Despite a recommendation against its use in the context of T2DM, vitamin E was used by 11% of patients with T2DM.[8] GLP-1 therapies were used by 20% of patients with T2DM. While the challenges associated with implementation of clinical practice guidelines into real-world practice have been acknowledged,[44] increased use of current guideline-recommended treatments for NASH may improve outcomes in this population until approved NASH treatments are available.

This analysis has some limitations. Sex (biological structure) and gender (social constructs) differences may be key modifiers of health, disease and medicine.[45] More specifically, it has been recognized that sex differences do exist for NAFLD,[46] including sex hormones/menopausal status, age and other reproductive factors. However, the current cohort is not of sufficient size to allow sub-group analysis with sufficient statistical power. Future work to address these factors may help in providing better targeted treatment to diverse patient groups.

Participating physicians were more likely to have an interest in NASH management and as such are currently identifying patients with NASH or suspected NASH. Accordingly, their patients may receive different treatment or management options than those managed by physicians with less of a specialist interest. This may be reflected in the preponderance of hospital-based physicians in this analysis. When compared with gastroenterologists, VCTE was commonly performed for patients diagnosed or managed by endocrinologists, possibly suggesting that the

endocrinologists included in this analysis had an interest in NASH. Despite this finding, there may still be limited awareness of NAFLD among endocrinologists, given the recent recommendation that endocrinologists and associated societies should develop strategies to address NAFLD.[47] NASH patients were identified based on the judgement of the respondent physician and not on a formalized diagnostic checklist. However, this is representative of physician's real-world classification of patients. Recall bias, a common limitation of surveys, may have affected physician responses to the questionnaires. However, physicians had access to patient medical records or charts; recall bias is unlikely a problem. Some data, such as fibrosis stage, may be unknown due to testing being done by a previous treating physician, prior to the start of patient management by the physician reporting on the patients.

Conclusions

In conclusion, this real-world study provides valuable insights into the patient and clinical characteristics and management approaches of patients with suspected NASH or established NASH in Italy. Increased awareness and uptake of currently available guidelines may optimize resource use and improve outcomes in this highly comorbid population.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DSP, Disease Specific Programme; EMA, European Medicines Agency; ELF, Enhanced liver fibrosis; FEKI, Freiburg Ethics Commission International; FIB-4, Fibrosis 4; FDA, Food and Drug Administration; GLP-1, Glucagon-like peptide; HDL, High density lipoprotein; LDL, low density lipoprotein; NASH, non-alcoholic steatohepatitis; NAFLD, Non-alcoholic fatty liver disease; NITs, Non-invasive tests; PCP, Primary care physician; SD, Standard deviation; T2DM, Type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

Data Sharing Statement

All data, ie, methodology, materials, data and data analysis, that support the findings of this survey are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Andrea Leith at Andrea.Leith@adelphigroup.com. Andrea Leith is an employee of Adelphi Real World.

Ethics Approval and Informed Consent

The DSP is noninterventional and solely employs retrospective data collection. Data were collected in such a way that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt for research and publication in scientific journals. Data collection was consistent with the European Pharmaceutical Marketing Research Association guidelines and had ethics approval obtained from Freiburg Ethics Commission International (FEKI; Approval No. 017/1931). Patients provided informed consent to take part in the survey using a checkbox.

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Author Contributions

Elisabetta Bugianesi was responsible for clinical oversight and guidance as lead author.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

EB is on advisory board of Boehringer Ingelheim, Gilead, Inventiva, MSD and Novo Nordisk and received grant from Gilead Sciences. LM provides advisor/consultancy services to Alfa-Sigma, Boehringer Ingelheim, BMS, Echosens, Galmed, Gilead Sciences, IBSA, Intercept, MEDA, MyGenomics, MSD-Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Promethera, Resalis Pharma, Rottapharm-Madaus, Siemens Healthineers and Synageva; and provides support for research for Gilead, Intercept and Siemens Healthineers. GD, KG, MM and PP are employees of Novo Nordisk and own stocks in the company. AL and VH are employees of Adelphi Real World. The authors report no other conflicts of interest in this work.

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