Accuracy of controlled attenuation parameter for assessing liver steatosis in individuals with morbid obesity before bariatric surgery

Federica Tavaglione1,2 | Antonio De Vincentis3,4 | Vincenzo Bruni5 | Ida Francesca Gallo5 | Simone Carotti6,7 | Dario Tuccinardi8 | Giuseppe Spagnolo5 | Ester Ciociola2 | Rosellina Margherita Mancina2 | Oveis Jamialahmadi2 | Rossella D'Alessio5 | Bruna Bottazzi1 | Silvia Manfrini8 | Antonio Picardi1 | Giuseppe Perrone6,9 | Paolo Pozzilli8 | Marco Caricato10 | Umberto Vespasiani-Gentilucci1 | Stefano Romeo2,11,12

1Clinical Medicine and Hepatology Unit, Department of Internal Medicine and Geriatrics, Campus Bio-Medico University, Rome, Italy
2Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, Wallenberg Laboratory, University of Gothenburg, Gothenburg, Sweden
3Internal Medicine Unit, Department of Internal Medicine and Geriatrics, Campus Bio-Medico University, Rome, Italy
4Clinical Lecturer of Internal Medicine, Saint Camillus International University of Health and Medical Sciences, Rome, Italy
5Bariatric Surgery Unit, Campus Bio-Medico University, Rome, Italy
6Research Unit of Microscopic and Ultrastructural Anatomy, Department of Medicine, Campus Bio-Medico University, Rome, Italy
7Predictive Molecular Diagnostic Unit, Department of Pathology, Campus Bio-Medico University Hospital, Rome, Italy
8Department of Endocrinology and Diabetes, Campus Bio-Medico University, Rome, Italy
9Research Unit of Pathology, Campus Bio-Medico University, Rome, Italy
10Unit of Colon and Rectal Surgery, Department of General Surgery, Campus Bio-Medico University, Rome, Italy
11Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden
12Clinical Nutrition Unit, Department of Medical and Surgical Sciences, University Magna Graecia, Catanzaro, Italy

Correspondence
Stefano Romeo, MD, PhD, Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, Wallenberg Laboratory, University of Gothenburg, Bruna Stråket 16, 41345 Gothenburg, Sweden.
Email: stefano.romeo@wlab.gu.se
Umberto Vespasiani-Gentilucci, MD, PhD, Clinical Medicine and Hepatology Unit, Department of Internal Medicine and Geriatrics, Campus Bio-Medico University, Rome, Italy

Abstract
Background & Aims: The ultrasound-based controlled attenuation parameter (CAP) is a non-invasive tool widely validated for assessing liver steatosis across different etiologies. However, few studies, with liver biopsy available, have investigated its performance in individuals with morbid obesity. Herein, we aimed to evaluate the diagnostic accuracy of CAP in participants with morbid obesity from the MAFALDA study before bariatric surgery.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver-operating characteristics curve; BMI, body mass index; CAP, controlled attenuation parameter; FAST, FibroScan-AST; GGT, gamma glutamyltransferase; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; INR, international normalized ratio; LDL, low-density lipoprotein; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis.

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Non-alcoholic fatty liver disease (NAFLD) is becoming the major cause of chronic liver disease worldwide, paralleling the epidemics of obesity and type 2 diabetes. The prevalence of NAFLD in the general population is estimated to be approximately 25% but it reaches over 90% among individuals with severe obesity undergoing weight loss procedures.\(^1\)

NAFLD/non-alcoholic steatohepatitis (NASH) are serious obesity-related complications and their presence qualifies individuals to be eligible for bariatric surgery.\(^2\) Therefore, an accurate diagnosis and staging of NAFLD play an important role in the clinical management of obesity and decision-making on the most appropriate treatment modality (ie, lifestyle changes, pharmacological therapy, or bariatric surgery).

Although the stage of liver fibrosis is the main determinant of liver-related outcomes,\(^3\) the degree of liver fat accumulation has a crucial role in the physiopathology of NAFLD and is causally related to liver damage.\(^4,5\) Consistently, novel drugs under clinical investigation for the treatment of NAFLD primarily target the reduction of liver steatosis.\(^6\)
The aim of this study was to evaluate the diagnostic accuracy of CAP measured by the XL probe to detect liver steatosis in participants with morbid obesity from MAFALDA, a study in which liver biopsy was available. Additionally, we assessed the performance of FibroScan-AST (FAST) score\textsuperscript{24} for detecting progressive NASH (NASH + NAFLD activity score [NAS] ≥ 4 + F ≥ F2) in this cohort.

2 \hspace{0.5cm} METHODS

2.1 \hspace{0.5cm} MAFALDA cohort

The “Molecular Architecture of Fatty Liver Disease in patients with obesity undergoing bAriatric surgery (MAFALDA)” study aims to understand the genetic and molecular architecture of NAFLD in individuals with morbid obesity. The MAFALDA study is composed by two substudies: MAFALDA-1 and MAFALDA-2.

MAFALDA-1 started on 22nd May 2020 and ended on 22nd June 2021. A total of 318 individuals were enrolled and plasma, serum, urine, and blood in EDTA were collected. Among the 318 participants, a total of 264 individuals underwent liver and visceral adipose tissue biopsy and all these individuals had a diagnosis of NAFLD assessed by histology from two pathologists from the Pathology Unit at “Campus Bio-Medico University Hospital” in Rome, Italy.

MAFALDA-2 started on 19th August 2021 and as for the 31st of October 2021 comprises 52 participants and it is still ongoing. In MAFALDA-2 plasma, serum, urine, and blood in EDTA were and will be collected. In this study, NAFLD diagnosis is and will be assessed by vibration-controlled transient elastography including CAP measurement. The MAFALDA study has been approved by the Local Research Ethics Committee (no. 16/20) and it was conducted in accordance with the principles of the Declaration of Helsinki. All participants gave written informed consent to the study.

Consecutive individuals with morbid obesity undergoing bariatric surgery at Campus Bio-Medico University Hospital, Rome, Italy, were recruited. Inclusion criteria were as follows: (1) age ≥18 years; (2) eligibility for bariatric surgery, defined as BMI higher than 40 \text{kg/m}^2 with significant obesity-related comorbidities.\textsuperscript{25}

Exclusion criteria were as follows: (1) chronic viral hepatitis or human immunodeficiency virus infection; (2) excessive alcohol consumption (ie, ≥30 g/day and ≥20 g/day for men and women, respectively\textsuperscript{26}); (3) other causes of chronic liver disease (eg, Wilson’s disease, hemochromatosis, α1-antitrypsin deficiency, autoimmune liver disease, primary biliary cholangitis); (4) drugs known to induce fatty liver (eg, amiodarone, methotrexate, tamoxifen, valproate).\textsuperscript{27}

At the preoperative assessment visit, the following clinical and anthropometric data were recorded: age, gender, BMI, waist and hip circumferences, systolic and diastolic blood pressure, medical history, current pharmacological therapy, lifestyle, and family history of major diseases. BMI was calculated by dividing the weight (kg) by the square of the height (m\textsuperscript{2}). Waist and hip circumferences were measured at the umbilicus level and around the widest portion of the buttocks, respectively, using non-stretchable tape.

For each participant, fasting venous blood samples were collected and processed in the hospital central laboratory for the following biochemical tests: complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), total and fractionated bilirubin, albumin, international normalized ratio (INR), fasting glucose, haemoglobin A1c (HbA1c), fasting insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, creatinine, and ferritin. Additional blood samples and first morning midstream urine samples were also collected. The different blood fractions (plasma, serum, buffy coat) were separated by centrifugation at 3000 \text{g} for 10 \text{min} at room temperature.

Type 2 diabetes was diagnosed according to the American Diabetes Association criteria.\textsuperscript{28} Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (measured on two different days), or treatment with anti-hypertensive drugs. Dyslipidemia was defined as total cholesterol ≥200 mg/dL and/or triglycerides ≥150 mg/dL or treatment with lipid-lowering drugs. Metabolic syndrome was diagnosed according to the International Diabetes Federation criteria.\textsuperscript{29} Insulin resistance (IR) was assessed by the homeostatic model assessment for insulin resistance (HOMA-IR) and defined by a cut-off of ≥2.5.\textsuperscript{30} A hypocaloric diet (1065 kcal, 39% carbohydrates, 25% fats, 38% proteins) was recommended two weeks before the surgery by a dietician.

2.2 \hspace{0.5cm} Collection of tissue biological samples and histopathological evaluation

On the day of surgery, a laparoscopic-guided percutaneous liver core biopsy was obtained by experienced bariatric surgeons, using a 16 gauge-20 mm modified Menghini needle with automatic aspiration (Biomol, HS Hospital Service, Rome, Italy). The liver biopsy was performed during the first part of the surgical procedure, within 10 min after pneumoperitoneum installation, in the left lobe of the liver. Adequacy of the liver biopsy was assessed macroscopically, and an additional core was collected if the specimen was less than 8 mm in length. The biopsy specimen was fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin and picrosirius red for fibrosis evaluation. The slides were analysed by two experienced pathologists (GP and SC) blinded to clinical and laboratory data. Liver biopsy specimens included in histological analysis were at least 8 mm in length and contained at least 7 portal tracts.

Steatosis grade (from 0 to 3), lobular inflammation grade (from 0 to 3), ballooning grade (from 0 to 2), and fibrosis stage (from 0 to 4) were scored according to NAFLD activity score (NAS) classification.\textsuperscript{31} NASH diagnosis was established by the pathological assessment based on Brunt et al criteria.\textsuperscript{32}

If the biopsy specimen exceeded the minimum length required for histological evaluation, part of the exceeding specimen was
immediately snap frozen in liquid nitrogen. Additionally, a wedge visceral fat biopsy was performed at gastric cardia and immediately snap frozen in liquid nitrogen.

2.3 | Vibration-controlled transient elastography including CAP measurement

CAP was acquired simultaneously with liver stiffness measurement (LSM) using the vibration-controlled transient elastography device FibroScan® (Echosens, Paris, France) within three months before the surgery by an experienced operator blinded to clinical and laboratory data, according to the manufacturer's instructions. All individuals were fasted at least three hours before the examination and were placed in the supine position with their right arm fully abducted. Measurements were performed on the right lobe of the liver through an intercostal space using the XL probe. The success rate was calculated as the number of successful measurements divided by the total number of measurements obtained. Only examinations with at least 10 successful acquisitions, with an interquartile range/median (IQR/M) of LSM ≤30%, and with a success rate ≥60% were deemed valid.

2.4 | Statistical analyses

All analyses were performed using the software R, version 4.0.4. Continuous variables were shown as mean (standard deviation [SD]) or median (IQR), as appropriate. Categorical variables were shown as number (percentage). Differences between CAP and steatosis grades were assessed using Kruskal–Wallis test.

The overall accuracy of CAP and FAST score for detecting liver steatosis and progressive NASH, respectively, was estimated by the area under the receiver-operating characteristics curve (AUROC) using the pROC package. The optimal cut-off values of CAP for S ≥ S1, S ≥ S2, and S ≥ S3 disease were chosen at points with the highest Youden index. The population was randomly selected using a bootstrap method, repeating the process 10,000 times.

The impact of covariates on CAP values was assessed by a multi-variable linear regression model. All statistical tests were two-sided. P values <0.05 were considered statistically significant.

3 | RESULTS

From May 2020 to April 2021, 137 consecutive individuals with morbid obesity eligible for bariatric surgery underwent vibration-controlled transient elastography including CAP measurement with the XL probe. Eight individuals were excluded because of unreliable measurements. Nine individuals were excluded because of failure to obtain 10 valid acquisitions. A total of 120 individuals with valid examinations (FibroScan® success rate 88%) were included in the final analyses. All liver biopsy specimens were adequate for histological evaluation. The mean biopsy length (SD) was 1.6 (0.5) cm. The biopsy specimen was at least 1.5 cm long in 65 (54%) individuals. Most specimens (97%) contained more than 10 portal tracts. The clinical characteristics of the overall cohort stratified by steatosis grade are shown in Table 1. The mean (SD) age and BMI were 43.8 (10.1) years and 41.0 (4.0) kg/m², respectively. More than two out of three individuals were women. The prevalence of type 2 diabetes was 19%, whereas those of hypertension and metabolic syndrome were 47% and 72%, respectively. Thirty-five (29%) subjects did not have steatosis (S0), whereas NASH was diagnosed in 54 (45%) individuals. Sixty-four (53%) individuals underwent FibroScan® examination within two weeks before the surgery. A total of 40 (33%) individuals followed the hypocaloric diet recommended before surgery for more than one week. Individuals with higher steatosis have higher transaminases, fasting glucose, HbA1c, triglycerides, and insulin resistance compared to those with lower steatosis. Moreover, these individuals had higher rates of hypertension, metabolic syndrome, and significant fibrosis. Details of liver histology of the cohort according to NAS scoring system are provided in Supplementary Table S1.

3.1 | Accuracy of CAP and impact of covariates on CAP values

The median (IQR) CAP values (dB/m) of individuals with S0, S1, S2, and S3 were 267 (256–292), 325 (295–347), 345 (332–354), and 364 (351–386), respectively. Individuals with higher steatosis grade had higher CAP values compared with those with lower steatosis (P < 0.001, Figure 1).

Overall, the diagnostic accuracy of CAP for detecting S1 or higher, S2 or higher, and S3 disease as assessed by AUROC was 0.91 (95% CI 0.86–0.97), 0.83 (95% CI 0.76–0.90), and 0.86 (95% CI 0.79–0.94), respectively (Table 2, Figure 2).

The best CAP cut-off for S1 or higher disease was 300 dB/m (95% CI 275–316). The negative predictive value to exclude S ≥ S1 was 0.67 (95% CI 0.54–0.93), with a sensitivity of 0.82 (0.67–0.98) and a specificity of 0.89 (0.69–1) (Table 2). The best CAP cut-off for S2 or higher disease was 328 dB/m (95% CI 296–345). The negative predictive value to exclude S ≥ S2 was 0.92 (95% CI 0.84–1), with a sensitivity of 0.87 (0.67–1) and a specificity of 0.73 (0.49–0.89) (Table 2). The best CAP cut-off for S3 was 344 dB/m (95% CI 343–352). The negative predictive value to exclude S = S3 was 0.99 (95% CI 0.96–1), with a sensitivity of 0.94 (0.75–1) and a specificity of 0.77 (0.67–0.88) (Table 2).

We also examined the performance of the recently published CAP cut-offs for the XL probe by Petroff et al among individuals with NAFLD (Table 2). At the S ≥ S1 cut-off of 297 dB/m, sensitivity and specificity were 0.81 (0.73–0.89) and 0.80 (0.66–0.91), respectively. At the S ≥ S2 cut-off of 317 dB/m, sensitivity and specificity were 0.85 (0.72–0.95) and 0.67 (0.57–0.77), respectively. Finally, at the S ≥ S3 cut-off of 333 dB/m, sensitivity and specificity were 0.94 (0.81–1) and 0.63 (0.53–0.72), respectively.
| Clinical data                        | Overall cohort (n = 120) | S0 (n = 35) | S1 (n = 46) | S2 (n = 23) | S3 (n = 16) | P value |
|-------------------------------------|--------------------------|------------|------------|------------|------------|---------|
| Age, years                          | 43.8 (10.1)              | 40.4 (9.2) | 45.1 (10.3) | 47 (9.7)   | 42.8 (10.3) | 0.07    |
| Women, n (%)                        | 93 (78%)                 | 34 (97%)   | 30 (65%)   | 17 (74%)   | 12 (75%)   | 0.06    |
| BMI, kg/m²                          | 41.0 (4.0)               | 40.1 (3.7) | 42 (4.6)   | 40.4 (3.8) | 41.4 (2.8) | 0.25    |
| BMI ≥45 kg/m², n (%)                | 20 (17%)                 | 3 (9%)     | 12 (26%)   | 4 (17%)    | 1 (6%)     | 0.74    |
| Waist circumference, cm             | 123.1 (11.4)             | 119.4 (10.6)| 125.6 (11.7)| 123.1 (12.2)| 124.3 (9.5) | 0.81    |
| Hip circumference, cm               | 132.1 (10.0)             | 132.8 (7.8) | 131.6 (11.6) | 133.3 (11.2) | 130.2 (7.5) | 0.52    |
| Waist to hip ratio                  | 0.9 (0.9–1.0)            | 0.9 (0.8–0.9) | 1.0 (0.9–1.0) | 0.9 (0.9–1.0) | 0.9 (0.9–1.0) | 0.53    |
| Systolic blood pressure, mmHg       | 130 (120–140)            | 120 (120–135) | 138 (123–144) | 130 (120–140) | 135 (120–144) | 0.23    |
| Diastolic blood pressure, mmHg      | 80 (80–90)               | 80 (80–88) | 82.5 (80–90) | 90 (80–90) | 80 (80–90) | 0.46    |
| Metabolic profile                   |                          |            |            |            |            |         |
| Glucose, mg/dL                      | 99 (93–108)              | 93 (90–98) | 100 (95–111) | 101 (95–104) | 114 (101–127) | 1.29 × 10⁻⁴ |
| HbA1c, %                            | 5.6 (5.3–5.9)            | 5.3 (5.1–5.6) | 5.7 (5.4–5.9) | 5.6 (5.4–5.8) | 6.1 (5.7–6.4) | 4.78 × 10⁻⁴ |
| Insulin, uUI/mL                     | 14.8 (11.2–18.8)         | 11.9 (7.7–14.5) | 15.5 (11.9–17.7) | 17.5 (13.4–20.5) | 22.2 (13.9–37.4) | 4.26 × 10⁻⁷ |
| HOMA-IR                             | 3.8 (2.8–4.9)            | 2.5 (1.8–3.4) | 3.8 (3.1–4.5) | 4.5 (3.4–5.2) | 6.5 (4.2–9.3) | 4.78 × 10⁻⁸ |
| Circulating lipoproteins            |                          |            |            |            |            |         |
| Cholesterol, mg/dL                  | 181 (31)                 | 181 (27)   | 177 (32)   | 184 (31)   | 187 (34)   | 0.16    |
| HDL cholesterol, mg/dL              | 45 (9)                   | 49 (10)    | 44 (10)    | 44 (7)     | 44 (7)     | 0.07    |
| LDL cholesterol, mg/dL              | 123 (30)                 | 120 (32)   | 120 (29)   | 128 (31)   | 127 (26)   | 0.09    |
| Triglycerides, mg/dL                | 129 (99–167)             | 111 (82–134) | 132 (105–164) | 154 (123–183) | 154 (103–180) | 2.21 × 10⁻⁴ |
| Liver function tests                |                          |            |            |            |            |         |
| ALT, U/L                            | 32 (20–45)               | 19 (16–27) | 32 (24–44) | 41 (29–60) | 51 (45–72) | 6.06 × 10⁻⁹ |
| AST, U/L                            | 26 (22–32)               | 20 (19.5–25) | 28 (24–32) | 28 (25–35) | 35 (32–41) | 5.85 × 10⁻⁷ |
| ALP, U/L                            | 69 (17)                  | 67 (15)    | 70 (17)    | 69 (18)    | 73 (19)    | 0.43    |
| GGTT, U/L                           | 26 (18–36)               | 20 (14–26) | 25 (18–39) | 33 (23–42) | 36 (28–47) | 4.81 × 10⁻³ |
| Bilirubin, mg/dL                    | 0.6 (0.4–0.7)            | 0.6 (0.4–0.7) | 0.6 (0.4–0.7) | 0.6 (0.5–0.9) | 0.5 (0.4–0.6) | 0.80    |
| Albumin, g/dL                       | 4.3 (0.3)                | 4.2 (0.2)  | 4.3 (0.2)  | 4.2 (0.3)  | 4.3 (0.3)  | 0.20    |
| Platelets, x10³/μL                  | 289.0 (67.5)             | 304.7 (75.5) | 279.6 (67.6) | 287.9 (57.8) | 283.1 (61.3) | 0.76    |
| INR                                 | 0.97 (0.93–1.00)         | 0.97 (0.95–1.00) | 0.98 (0.94–1.02) | 0.96 (0.92–1.02) | 0.95 (0.92–0.98) | 0.06    |
| Ferritin, ng/mL                     | 61.4 (28.4–108.0)        | 36.6 (20.8–64.8) | 70.4 (32.4–105.2) | 96.4 (42.0–140.5) | 86.2 (51.8–133.5) | 0.04    |
| Comorbidities                       |                          |            |            |            |            |         |
| Hypertension, n (%)                 | 56 (47%)                 | 6 (17%)    | 23 (50%)   | 14 (61%)   | 13 (81%)   | 1.02 × 10⁻⁴ |
| Dyslipidemia, n (%)                 | 67 (56%)                 | 15 (43%)   | 25 (54%)   | 17 (74%)   | 10 (62%)   | 0.07    |
| Type 2 diabetes, n (%)              | 23 (19%)                 | 4 (11%)    | 9 (20%)    | 4 (17%)    | 6 (38%)    | 0.13    |
| Metabolic syndrome, n (%)           | 86 (72%)                 | 17 (49%)   | 34 (74%)   | 20 (87%)   | 15 (94%)   | 9.21 × 10⁻⁴ |
| Cardiovascular disease, n (%)       | 4 (3%)                   | 1 (3%)     | 2 (4%)     | 1 (4%)     | 0 (0%)     | 0.54    |

**FibroScan**

| CAP, dB/m                             | 320 (288–351) | 267 (256–292) | 325 (295–347) | 345 (332–354) | 364 (351–386) | 7.39 × 10⁻¹³ |

(Continues)
Next, we estimated by a multivariable linear regression model the effects of covariates on CAP values (Table 3). The only variable that influenced CAP was steatosis grade (estimate 20.60, 95% CI 12.70–28.40, P = 1.05 × 10^{-6}).

Finally, we assessed the performance of the recently designed FibroScan-AST (FAST) score for detecting NASH with significant activity and fibrosis. We found that the diagnostic accuracy of FAST score for detecting progressive NASH (NASH + NAS ≥ 4 + F ≥ F2) as assessed by AUROC was 0.76 (95% CI 0.66–0.86) (Table 4).

At a cut-off of 0.35 (rule-out cut-off), sensitivity was 0.52 (0.30–0.70) with a negative predictive value of 0.88 (0.83–0.92). At a cut-off of 0.67 (rule-in cut-off), specificity was 0.98 (0.95–1), with a positive predictive value of 0.50 (0–1) (Table 4). The impact of covariates on FAST score is provided in supplementary material (Supplementary Table S2).

Herein, we investigate the diagnostic performance of CAP for assessing steatosis in individuals with morbid obesity undergoing bariatric surgery. We provide further evidence that CAP using the XL probe is an accurate non-invasive tool for grading liver steatosis in this high-risk population. Additionally, we demonstrate that steatosis grade is the only factor influencing CAP values in morbidly obese individuals. Finally, we show that the recently developed FAST score has a suboptimal performance for detecting progressive NASH in this bariatric surgery cohort.

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**TABLE 1 (Continued)**

| Overall cohort (n = 120) | S0 (n = 35) | S1 (n = 46) | S2 (n = 23) | S3 (n = 16) | P value |
|-------------------------|------------|------------|------------|------------|---------|
| LSM, kPa | 5.4 (4.6–6.5) | 5.1 (4.6–5.9) | 5.2 (4.6–6.5) | 5.6 (5–6.5) | 6.4 (5.0–7.0) | 0.10 |
| Days between FibroScan® and liver biopsy | 23 (20) | 20 (15) | 23 (19) | 27 (21) | 26 (28) | 0.53 |

| Liver biopsy | | | | | |
|----------------|------------|------------|------------|------------|---------|
| NASH, n (%) | 54 (45%) | 0 (0%) | 15 (33%) | 23 (100%) | 16 (100%) | 0.41 |
| Progressive NASH, n (%) | 23 (19%) | 0 (0%) | 6 (13%) | 11 (48%) | 6 (38%) | 1.17 × 10^{-5} |

| Fibrosis staging, n (%) | | | | | |
|-------------------------|------------|------------|------------|------------|---------|
| F0 | 31 (26%) | 20 (57%) | 9 (20%) | 1 (4%) | 1 (6%) | 6.57 × 10^{-7} |
| F1 | 59 (49%) | 14 (40%) | 25 (54%) | 11 (48%) | 9 (56%) |
| F2 | 27 (22%) | 1 (3%) | 11 (24%) | 9 (39%) | 6 (38%) |
| F3 | 3 (2%) | 0 (0%) | 1 (2%) | 2 (9%) | 0 (0%) |
| F4 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Biopsy length, cm | 1.6 (0.5) | 1.6 (0.5) | 1.5 (0.4) | 1.8 (0.6) | 1.6 (0.6) | 0.48 |
| Biopsy length ≥1.5 cm, n (%) | 65 (54%) | 18 (51%) | 25 (51%) | 15 (65%) | 7 (44%) | 0.84 |

**FIGURE 1** Box plot of CAP vs steatosis grade. Steatosis grade was defined based on NAFLD activity score by Kleiner et al. P value is calculated using Kruskal–Wallis test. CAP, controlled attenuation parameter.

3.2 | Accuracy of FAST score

Finally, we assessed the performance of the recently designed FibroScan-AST (FAST) score for detecting NASH with significant activity and fibrosis. We found that the diagnostic accuracy of FAST score for detecting progressive NASH (NASH + NAS ≥ 4 + F ≥ F2) as assessed by AUROC was 0.76 (95% CI 0.66–0.86) (Table 4).

At a cut-off of 0.35 (rule-out cut-off), sensitivity was 0.52 (0.30–0.70) with a negative predictive value of 0.88 (0.83–0.92). At a cut-off of 0.67 (rule-in cut-off), specificity was 0.98 (0.95–1), with a positive predictive value of 0.50 (0–1) (Table 4). The impact of covariates on FAST score is provided in supplementary material (Supplementary Table S2).

4 | DISCUSSION

Herein, we investigate the diagnostic performance of CAP for assessing steatosis in individuals with morbid obesity undergoing bariatric surgery. We provide further evidence that CAP using the XL probe is an accurate non-invasive tool for grading liver steatosis in this high-risk population. Additionally, we demonstrate that steatosis grade is the only factor influencing CAP values in morbidly obese individuals. Finally, we show that the recently developed FAST score has a suboptimal performance for detecting progressive NASH in this bariatric surgery cohort.
Our findings may have important implications for the management of individuals with morbid obesity referring to bariatric procedures. First, our data support the utility of CAP for the non-invasive assessment of the degree of steatosis among individuals with morbid obesity, providing information that may contribute to identify those eligible for bariatric procedures. Second, our data suggest that being fat accumulation the main determinant of liver damage, the excellent performance of CAP in grading steatosis may help follow-up this disease after bariatric surgery.

To date, there are very few histologically characterized cohort studies investigating the diagnostic accuracy of CAP for assessing liver steatosis in individuals with morbid obesity. \(^{21-23}\) Notably, we found that the performance of CAP for grading liver steatosis using the XL probe was excellent (AUROCs 0.91, 0.83, and 0.86 for \(S \geq S_1, S \geq S_2,\) and \(S = S_3\), respectively). The CAP cut-offs of 300, 328, and 344 dB/m had 82%, 87%, and 94% sensitivity for \(S \geq S_1, S \geq S_2,\) and \(S = S_3\), respectively. The diagnostic accuracy of CAP using the XL probe for predicting steatosis in our cohort was consistent with and even higher than that reported in previous studies including individuals with morbid obesity.\(^{21-23}\) As an example, in a prospective cohort study of 76 individuals, Garg et al reported that the AUROCs of CAP for detecting moderate steatosis and severe steatosis were 0.74 (95% CI 0.62–0.86) and 0.82 (95% CI 0.73–0.91), respectively. Along this line, Naveau et al\(^{22}\) observed that in 194

| TABLE 2 | Diagnostic performance of CAP for steatosis severity |
|----------------|-----------------------------------------------------|
| \(S = S_1\) (\(\geq 5\%\) steatosis) | \(S \geq S_2\) (\(\geq 34\%\) steatosis) | \(S = S_3\) (\(\geq 67\%\) steatosis) |
| AUROC | 0.91 (0.86–0.97) | 0.83 (0.76–0.90) | 0.86 (0.79–0.94) |
| Optimal cut-off, dB/m | 300 (275–316) | 328 (296–345) | 344 (343–352) |
| Sensitivity | 0.82 (0.67–0.98) | 0.87 (0.67–1) | 0.94 (0.75–1) |
| Specificity | 0.89 (0.69–1) | 0.73 (0.49–0.89) | 0.77 (0.67–0.88) |
| Positive predictive value | 0.95 (0.88–1) | 0.60 (0.49–0.78) | 0.39 (0.30–0.53) |
| Negative predictive value | 0.67 (0.54–0.93) | 0.92 (0.84–1) | 0.99 (0.96–1) |
| False positive rate | 0.11 (0–0.31) | 0.27 (0.11–0.51) | 0.23 (0.12–0.33) |
| False negative rate | 0.18 (0.02–0.33) | 0.13 (0–0.33) | 0.06 (0–0.25) |
| Cut-off by Petroff et al.\(^{19}\) | 297 | 317 | 333 |
| Sensitivity | 0.81 (0.73–0.89) | 0.85 (0.72–0.95) | 0.94 (0.81–1) |
| Specificity | 0.80 (0.66–0.91) | 0.67 (0.57–0.77) | 0.63 (0.53–0.72) |
| Positive predictive value | 0.91 (0.85–0.96) | 0.55 (0.47–0.64) | 0.28 (0.23–0.34) |
| Negative predictive value | 0.64 (0.53–0.76) | 0.90 (0.83–0.97) | 0.99 (0.95–1) |
| False positive rate | 0.20 (0.09–0.34) | 0.33 (0.23–0.43) | 0.38 (0.28–0.47) |
| False negative rate | 0.19 (0.11–0.27) | 0.15 (0.05–0.28) | 0.06 (0–0.19) |

Note: Results of the receiver operating curve (ROC) analysis are presented based on a bootstrap method (10,000 stratified bootstrap replicates). Optimal cut-offs are based on the maximal sum of sensitivity and specificity (Youden index). Numbers in brackets are 95% confidence intervals.

Abbreviations: AUROC, area under the receiver operating curve.

\( \begin{align*}
S &= S_1 (\geq 5\%\text{ steatosis}) \\
S &= S_2 (\geq 34\%\text{ steatosis}) \\
S &= S_3 (\geq 67\%\text{ steatosis})
\end{align*} \)
Consequently, studies with bariatric cohorts are usually characterized by a control group who does not have steatosis, resulting in fewer grey zone subjects with S1 and S2 and in a better diagnostic performance of CAP in these cohorts. This unexpectedly increased performance of CAP in these cohorts.

On the other hand, the diagnostic performance of CAP was better in individuals undergoing bariatric surgery (AUROCs of 0.80, 0.77, and 0.76 for S ≥ S1, S ≥ S2, and S = S3, respectively). As commented by the authors, “This unexpectedly increased performance of CAP in bariatric cohorts may be due to the highly standardized recruitment of severely obese individuals due to a thick layer of subcutaneous adipose tissue.” Evidently, in our cohort, 35 (29%) participants did not have hepatic steatosis. Notably, this rate was higher than in other bariatric cohorts in which ranged from 8% to 19%. Larger histologically characterized cohort studies in this high-risk population are needed to clarify these findings.

Notably, our CAP cut-offs closely resembled those reported by Garg et al and by Naveau et al (41.0 kg/m$^2$ vs 45.2 kg/m$^2$ vs 44 kg/m$^2$, respectively). For comparison, details on previous bariatric cohort studies examining the accuracy of CAP for steatosis severity are provided in supplementary material (Supplementary Table S3).

Conversely, a recent comprehensive individual patient meta-analysis of 13 biopsy-controlled studies including the XL probe suggested that the diagnostic capability of CAP for grading steatosis in NAFLD should be taken with caution. Indeed, authors reported an AUROC of 0.82 (95% CI 0.77–0.87), 0.75 (95% CI 0.72–0.79), and 0.72 (95% CI 0.68–0.75) for S ≥ S1, S ≥ S2, and S = S3, respectively. On the other hand, the diagnostic performance of CAP was better in individuals undergoing bariatric surgery (AUROCs of 0.80, 0.77, and 0.76 for S ≥ S1, S ≥ S2, and S = S3, respectively). As commented by the authors, “This unexpectedly increased performance of CAP in bariatric cohorts may be due to the highly standardized recruitment and liver biopsy procedure, irrespectively of liver disease severity. Consequently, studies with bariatric cohorts are usually characterized by a control group who does not have steatosis, resulting in fewer grey zone subjects with S1 and S2 and in a better diagnostic performance of CAP in these cohorts.” Consistently, in our cohort, 35 (29%) participants did not have hepatic steatosis. Notably, this rate was higher than in other bariatric cohorts in which ranged from 8% to 19%.

### Table 3: Impact of covariates on CAP values

| Covariate                      | Estimate (95% CI) | P value |
|--------------------------------|-------------------|---------|
| Steatosis grade (0–3)          | 20.60 (12.70 to 28.40) | 1.05 × 10$^{-6}$ |
| Age, per 10 years              | 2.80 (–3.41 to 9.00) | 0.37    |
| Female gender                  | –10.30 (–25.50 to 4.84) | 0.18    |
| BMI, per unit kg/m$^2$         | 1.17 (–0.29 to 2.62) | 0.12    |
| Type 2 diabetes                | –0.24 (–14.80 to 14.30) | 0.97    |
| ALT, per ln(U/L)               | 20.0 (–1.07 to 41.0) | 0.06    |
| AST, per ln(U/L)               | –0.60 (–33.60 to 32.40) | 0.97    |
| Fibrosis stage (0–4)           | 1.86 (–6.58 to 10.30) | 0.66    |
| Biopsy length ≥1.5 cm          | –1.15 (–12.70 to 10.40) | 0.84    |
| Pre-surgery diet >7 days       | –11.0 (–23.90 to 1.82) | 0.09    |
| FibroScan® > 14 days before biopsy | 6.99 (–5.63 to 19.60) | 0.28    |

Note: Estimates with 95% CIs are calculated by a multivariable linear regression model. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval.

### Table 4: Diagnostic performance of FAST score for progressive NASH

| Progression of NASH (NASH + NAS ≥ 4 + F ≥ F2) | Diagnostic performance of FAST score (NASH = 0, NAS < 4) |
|-----------------------------------------------|--------------------------------------------------------|
| Prevalence, n (%)                             | 23 (19%)                                               |
| AUROC (95% CI)                                | 0.76 (0.66–0.86)                                       |
| FAST ≤0.35 (rule-out zone)                    |                                                        |
| n (%)                                         | 88 (73%)                                               |
| Sensitivity                                   | 0.52 (0.30–0.70)                                       |
| Specificity                                   | 0.79 (0.71–0.88)                                       |
| Positive predictive value                     | 0.38 (0.25–0.52)                                       |
| Negative predictive value                     | 0.88 (0.83–0.92)                                       |
| False positive rate                           | 0.21 (0.12–0.29)                                       |
| False negative rate                           | 0.48 (0.30–0.70)                                       |
| FAST ≥0.67 (rule-in zone)                     |                                                        |
| n (%)                                         | 4 (3%)                                                 |
| Sensitivity                                   | 0.09 (0–0.22)                                          |
| Specificity                                   | 0.98 (0.95–1)                                          |
| Positive predictive value                     | 0.50 (0–1)                                             |
| Negative predictive value                     | 0.82 (0.80–0.84)                                       |
| False positive rate                           | 0.02 (0–0.05)                                          |
| False negative rate                           | 0.91 (0.78–1)                                          |

Note: Results of the receiver operating curve (ROC) analysis are presented based on a bootstrap method (10,000 stratified bootstrap replicates). Cut-offs are those published by Newsome et al. Numbers in brackets are 95% confidence intervals. Abbreviations: AUROC, area under the receiver operating curve; CI, confidence interval; FAST, FibroScan-AST; NAS, NAFLD activity fibrosis score; NASH, non-alcoholic steatohepatitis.
their adapted CAP-XL cut-offs were close to those of the M probe and lower than those of our study and of other bariatric cohorts (Supplementary Table S3).

Consistently, we performed a multivariable analysis showing that steatosis grade was the strongest factor affecting CAP values. Conversely, BMI and type 2 diabetes were not associated with CAP. The lack of association with (a) BMI is likely due to the low BMI variability in our cohort, resulting in no difference in BMI between steatosis grades; (b) type 2 diabetes might be explained by the low prevalence of type 2 diabetes in bariatric surgery cohorts (Supplementary Table S3) as compared to non-bariatric NAFLD cohorts, mostly due to the young age of individuals referring to bariatric procedures.

Finally, we showed that the performance of the recently designed FAST score,[24] which combined LSM, CAP, and AST for detecting progressive NAFLD (ie, NASH + NAS ≥ 4 + F ≥ F2) was suboptimal in our cohort (AUROC 0.76, 95% CI 0.66–0.86). Our findings are in line with those published by Newsome et al,[24] reporting an AUROC range of 0.74–0.95 in the validation cohorts. In our cohort, at the rule-out cut-off of 0.35, we found a lower sensitivity compared with Newsome et al (0.52 vs 0.89–0.90). Conversely, at the rule-in cut-off of 0.67, we found a higher specificity (0.98 vs 0.90–0.92). These findings might be explained by the lower prevalence of progressive NASH in our cohort compared with that in Newsome et al (19% vs 27%–50%, respectively).

The main strength of our study is the use of standardized procedures for clinical data and biological samples collecting, processing, and storage. Furthermore, the mean biopsy length of our cohort was higher than 1.5 cm. Limitations include (1) the small sample size of the cohort, (2) the lack of an external validation, and (3) the inability to test the performance of LSM for advanced fibrosis due to the low prevalence of F3–F4 fibrosis in our cohort (only three subjects, 2%). However, we validated the model internally using 10,000 bootstrap samples and we provided a confidence interval for the optimal cut-offs unlike the standard ROC methods. The performance of LSM for significant fibrosis (F ≥ F2) and the impact of covariates on LSM values are described in supplementary material (Supplementary Tables S4 and S5).

To conclude, CAP measured by the XL probe represents a powerful non-invasive tool for grading liver steatosis in individuals suffering from morbid obesity. Assessing liver steatosis by CAP may help detect hepatic steatosis in individuals with morbid obesity, thus rendering them eligible for bariatric procedures, and may help the follow-up of this disease after bariatric surgery.

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CONFLICTS OF INTEREST
The authors declare no financial or other relationships with drug manufacturers that could lead to a conflict of interest.

AUTHOR CONTRIBUTIONS
UVG and SR contributed to study concept and design. FT, UVG, and SR contributed to drafting the manuscript. FT and ADV contributed to perform the statistical analysis. All authors contributed to analysis and interpretation of data, critically revised the manuscript for important intellectual content and approved the final version for submission. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT
The data supporting the findings of this study are available within the article and its supplementary materials.

ORCID
Federica Tavaglione https://orcid.org/0000-0002-1720-4355
Antonio De Vincentis https://orcid.org/0000-0003-0220-0500
Simone Carotti https://orcid.org/0000-0002-3164-1500
Rossella Margherita Mancina https://orcid.org/0000-0002-1126-3071
Marco Caricato https://orcid.org/0000-0002-5610-1615
Umberto Vespasiani-Gentilucci https://orcid.org/0000-0002-1138-1967
Stefano Romeo https://orcid.org/0000-0001-9168-4898

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