Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo
www.spedmjournal.com

Artigo Original

FIB-4 Index should Guide the Referral of Patients with Metabolic Syndrome to Gastroenterology: The Perspective of a Portuguese Cohort

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INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2023-04-21
Accepted/Aceite: 2023-07-10
Publicado / Published: 2023-10-18

Keywords:
Metabolic Syndrome;
Non-alcoholic Fatty Liver Disease.

A B S T R A C T

Introduction: Data regarding the referral of patients with metabolic syndrome (MetS) to hepatologists is scarce. Most authors agree that at-risk patients (including the ones with diabetes or MetS) should be screened for non-alcoholic fatty liver disease (NAFLD) and referred to hepatologists when needed. Existing data highlights that referral of patients with NAFLD to specialists remain low among endocrinologists.
Our aim was to evaluate a Portuguese cohort of patients with MetS followed in Endocrinology outpatient setting regarding their need to referral to hepatologists.
Methods: Secondary analysis including the patients from microDHNA cohort (adult patients with MetS followed for any cause in Endocrinology outpatient setting). The recruitment includes anamnesis, physical examination, blood drawing for several predefined analyses and hepatic elastography. Our main outcome was referral to gastroenterology due to hepatic fibrosis (every patient with a median value on elastography ³7kPa was referred). We tested the discriminatory accuracy of hepatic biochemical parameters and indexes [FLI (Fatty Liver Index) score, a predictor of hepatic steatosis; and BARD (Body Mass Index, AST/ALT Ratio, and Diabetes), APRI (Aspartate Aminotransferase to Platelet Ratio Index), NFS (NAFLD Fibrosis Score) and FIB-4 (Fibrosis-4 Index) scores, predictors of hepatic fibrosis] for the need to referral of patients using ROC curve analyses.
Results: We included a total of 65 participants; of those, 53.8% were female and the average age was 61.2±9.6 years old. Eight patients (12.3%) were referred to gastroenterology after performing hepatic elastography, none of which was already referred. Our analysis showed that the best parameter in this cohort was FIB-4 index. A cut-off value of 2.11 associates to an area under the curve of 0.80 and has a sensitivity of 62% and specificity of 98% for predicting the need for referral.
Conclusion: Our results highlight that the use of scores as the FIB-4 index should be included in the evaluation of patients with MetS in the Endocrinology outpatient setting. Further studies are needed to validate FIB-4 best cut-off value in our population.

Palavras-chave:
Doença Hepática Não Alcoólica;
Síndrome Metabólica.

O Índice FIB-4 deve Orientar a Referenciação de Doentes com Síndrome Metabólica para a Gastrenterologia: A Perspetiva de uma Coorte Portuguesa

R E S U M O

Introdução: Os dados sobre a necessidade de referenciação dos doentes com síndrome metabólica (SM) para a consulta de Hepatologia são escassos. A maioria dos autores concorda que os doentes

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https://doi.org/10.26497/ao230023

de risco (incluindo doentes com diabetes ou SM) devem ser rastreados para doença hepática não alcoólica (DHNA) e referenciados para a consulta de Hepatologia/ Gastroenterologia sempre que necessário. A evidência atual reporta uma baixa taxa de referenciação dos doentes com DHNA para hepatologistas. O nosso objetivo foi fazer uma avaliação de uma coorte de doentes com SM seguidos em consulta externa de Endocrinologia relativamente à necessidade da sua referenciação para Hepatologia/ Gastroenterologia.

Métodos: Análise secundária incluindo os doentes da coorte microDHNA (adultos com SM seguidos em consulta externa de Endocrinologia por qualquer causa). O recrutamento inclui anamnese, exame objetivo, estudo analítico e elastografia hepática. O resultado principal desta análise foi a necessidade referenciação para Gastroenterologia por fibrose hepática (todos os doentes com um valor ³7kPa na elastografia hepática foram referenciados). Foi testada a capacidade discriminatória de vários parâmetros bioquímicos e índices ([FLI (*Fatty Liver Index*), preditor de esteatose hepática; BARD (*Body Mass Index*, AST/ALT *Ratio, and Diabetes*), APRI (*Aspartate Aminotransferase to Platelet Ratio Index*), NFS (NAFLD *Fibrosis Score*) e FIB-4 (*Fibrosis-4 Index*), preditores de fibrose hepática]) relativamente à predição da necessidade de referenciação dos doentes, utilizando análises de curvas ROC.

Resultados: Foram incluídos no total 65 doentes, sendo 53,8% do sexo feminino e a média de idade de 61,2±9,6 anos. Oito (12,3%) doentes tinham critérios de referenciação para a consulta de Gastroenterologia após realização de elastografia hepática, nenhum dos quais tinha sido previamente referenciado. A nossa análise mostrou que o melhor parâmetro para predizer a tomada de decisão de referenciação dos doentes com SM foi o índice FIB-4. Um valor limiar de FIB-4 de 2,11 associou-se a uma área sob a curva de 0,80, sensibilidade de 62% e especificidade de 98%, como preditor da necessidade de referenciação.

Conclusão: Os nossos resultados demonstram que a utilização de índices como o FIB-4 deve ser incluída na avaliação dos doentes com SM, nas consultas de Endocrinologia. São necessários mais estudos para validar o limiar de FIB4 que deve guiar.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently the primary cause of chronic liver disease. It comprehends a wide spectrum from simple steatosis to steatohepatitis (NASH) and fibrosis, which may lead to cirrhosis and hepatocarcinoma.[1] It has been termed a "barometer of metabolic health" due to its metabolic recognized origins.[2] Many epidemiological studies show an association between NAFLD and metabolic syndrome (MetS).[3,4] Although traditionally NAFLD is considered as the hepatic counterpart of MetS, growing evidence supports a bidirectional relationship between the two, being insulin resistance the common central pathophysiological process.[5,6]

Endocrinologists frequently follow people with MetS at risk of NAFLD, namely in its severest forms and should, therefore, be aware and promptly refer patients at high-risk of cirrhosis to the hepatologist to achieve a timely diagnosis and treatment.[7]

NAFLD is typically asymptomatic at initial stages. The biochemical evaluation of liver enzymes and its usage in predictive scores is of paramount importance at this time. There are several scores which can be easily used to predict hepatic steatosis and fibrosis, each with acknowledged strengths and limitations.[8]

There are no firm recommendations regarding which individuals should be screened for NAFLD. Most authors agree that at-risk patients (including the ones with diabetes or MetS)[9-12] should be screened, but also disclose that there are no cost-effectiveness studies to support this decision.[10]

Data regarding MetS patient's referral to hepatologists is scarce, namely in tertiary Portuguese patients' cohorts. Existing data highlights that referral of patients with NAFLD to specialists remain low among endocrinologists.[13,14] In this analysis, we aimed to evaluate a Portuguese well defined cohort of patients with MetS, followed in Endocrinology outpatient setting, regarding their need to referral to hepatologists and draw attention to this imminent need.

Methods

This study was reviewed and approved by the ethical committee of Centro Hospitalar Universitário de São João, Porto, Portugal. Written informed consent for participation was obtained from each patient included. Privacy of the included patients was preserved throughout the study.

1. Study Design

This is a secondary analysis including the patients from microDHNA cohort. This is a cohort of adult patients with MetS followed in Endocrinology outpatient setting for any cause. In brief, the inclusion criteria are: 1) being diagnosed with MetS; 2) being 18 to 75 years old. The exclusion criterion was not being able to consent. The recruitment includes anamnesis, filling of quality-of-life questionnaires (Short-Form Health Survey, SF-36, and Chronic Liver Disease Questionnaire), physical examination (including anthropometric and blood pressure evaluation), blood drawing for several predefined analyses and hepatic elastography (performed by the same operator, in 58 from the total 65 individuals). After these steps, all results are reviewed by the authors and patients with hepatic fibrosis (defined as a median value on elastography ³7kPa[15-17] [are referred to the hepatology clinic. We included all 65 patients from microDHNA cohort in this analysis.

2. Clinical Definitions

We used FLI (Fatty Liver Index) score as a predictor of hepatic steatosis and BARD (Body Mass Index, AST/ALT Ratio, and Diabetes), APRI (Aspartate Aminotransferase to Platelet Ratio Index), NFS (NAFLD Fibrosis Score) and FIB-4 (Fibrosis-4 Index) scores as predictors of hepatic fibrosis. These were built based on the following formulas:

1) **FLI score:** FLI = ey/(1+ ey) x 100, where y = 0.953 x ln (triglycerides, mg/dL) + 0.139 x BMI, kg/m^2 + 0.718 x ln (GGT, U/L) + 0.053 x waist circumference, cm – 15.745.

FLI scores <30 indicate low risk of hepatic steatosis, 30 to 60 intermediate risk and ≥60 high risk.[18]

2) **BARD score:** BMI≥28 = 1 point; AST/ALT ratio≥0.8 = 2 points, presence of diabetes = 1 point. Low fibrosis risk patients are scored 0 to 1 points and higher risk patients are scored 2 to 4 points.[19]
3) **APRI score:** (AST/AST upper limit normal)/(platelet count [10^9/L]) × 100[20];
4) **NFS score:** 1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × diabetes (yes = 1, no = 0) + (0.99 × AST/ALT ratio) (0.013 × platelet [×10^9/L]) (0.66 × albumin [g/dL]).[21]
5) **FIB-4:** (age [years] × AST [U/L])/([platelets (10^9/L)] × ÖALT [U/L]).[22]

3. Outcomes and Statistical Analysis

Continuous variables are presented as mean (standard deviation, SD), if normally distributed, or as median (25^{th} to 75^{th} percentiles), if non-normally distributed. Variables with skewed distribution were transformed to their natural logarithm. Categorical variables are presented as absolute and relative frequencies.

Our primary outcome was patients' referral to gastroenterology due to hepatic fibrosis (defined as a median value on elastography ³7kPa).

Logistic regression analyses were performed to evaluate the associations of hepatic biochemical parameters and hepatic steatosis and fibrosis indexes with our main outcome.

The diagnostic accuracy of each hepatic biochemical parameter or index in discriminating between the referral of patients was evaluated using ROC curve analysis calculating the optimal cut-off value (based on Liu index[23]), and the AUC, specificity, and sensitivity at the estimated optimal cut-off value.

Statistical analyses were conducted using Stata software, version 14.1 (StataCorp). We considered a two-sided *p* value less than 0.05 to be statistically significant.

Results

1. Baseline Population Characteristics

Table 1 shows the demographic and clinical characteristics of the included population (total n=65) per group (referred versus not referred to gastroenterology). A total of 8 patients (12.3%) were referred to gastroenterology after performing hepatic elastography, none of which was already referenced.

The groups are significantly different considering GGT, total and direct bilirubin levels, FLI, NFS, APRI and FIB-4 indexes, controlled attenuation parameter, and, as expected, regarding hepatic elastography median (our group defining variable).

2. Logistic Regression Analyses

Table 2 displays the logistic regression models for hepatic biochemical parameters and for hepatic steatosis and fibrosis predictor indexes, regarding our main outcome (patient referral to gastroenterology). Patients with higher total bilirubin levels, and higher APRI and FIB-4 scores had higher odds of being referred to gastroenterology.

3. ROC Curve Analyses

Table 3 displays the ROC curve analysis testing the discriminatory ability of each parameter to patients' referral. Considering such analysis, one should note that a FIB-4 value of 2.11 associates to an area under the curve of 0.80 and has a sensitivity of 62% and specificity of 98% at this cut-off point.

Table 4 shows ROC curve analysis for other FIB-4 cut points previously addressed in the literature. The usage of 3.25 denotes a specificity of 100%, at the expense of a 25% sensibility. The lower

Table 1. Clinical and demographic characteristics of the population included (n=65).

	Not referred (n=57)	Referred (n=8)	*p* value
Age, years	61.8 ± 9.6	62.1 ± 10.4	0.82
Female sex, n (%)	31 (54.4)	4 (50.0)	0.94
Body Mass Index, kg/m²	29.5 ± 5.3	32.9 ± 7.0	0.11
Waist circumference, cm	102.3 ± 12.5	110.4 ± 16.1	0.10
Waist-to-Hip Ratio	0.96 ± 0.09	0.98 ± 0.08	0.46
Systolic blood pressure, mmHg	141.2 ± 20.8	137.6 ± 16.1	0.65
Diastolic blood pressure, mmHg	75.2 ± 13.6	74.1 ± 13.1	0.84
Glycated haemoglobin, %	7.0 ± 1.4	7.0 ± 0.6	0.96
AST, U/L	23.0 [19.0, 30.0]	26 [15.5, 44.0]	0.88
ALT, U/L	24.0 [18.0, 31.0]	20.5 [14.0, 31.0]	0.51
GGT, U/L	25.0 [17.5, 43.0]	58.0 [28.5, 247.5]	**0.029**
Total bilirubin, mg/dL	0.55 [0.44, 0.71]	0.83 [0.54, 1.73]	**0.06**
Total cholesterol, mg/dL	165.5 ± 49.4	145.8 ± 35.9	0.28
HDL cholesterol, mg/dL	49.9 ± 10.4	42.2 ± 8.4	**0.05**
LDL cholesterol, mg/dL	83.0 [66.0, 101.0]	68.5 [49.0, 103.0]	0.32
Triglycerides, mg/dL	117.5 [85.0, 180.0]	136.5 [97.8, 175.5]	0.69
FLI	69.2 [47.0, 82.8]	93.7 [74.0, 96.9]	**0.039**
BARD	3.0 [3.0, 4.0]	4.0 [2.5, 4.0]	0.57
NFS	-0.9 [-2.0, -0.3]	0.3 [-1.5, 1.6]	**0.046**
APRI	0.4 [0.3, 0.5]	0.6 [0.3, 0.9]	**0.07**
FIB-4	1.2 ± 0.5	2.1 ± 1.4	**<0.001**
CAP, dBm	274.4 ± 56.8	315.6 ± 44.4	**0.06**
IQR/median	15.0 [12.0, 21.0]	21.5 [18.5, 26.5]	**0.019**
Elastography median, kPa	5.2 ± 1.6	12.8 ± 4.8	**<0.001**
IQR/median	29.0 [22.0, 49.0]	29.5 [26.0, 39.0]	0.97

Values are shown as mean ± standard deviation or as median [percentile 25 – percentile 75]. AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; FLI, fatty liver index; BARD, body mass index, AST/ALT ratio, and diabetes; NFS, NAFLD fibrosis score; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4 index; CAP, controlled attenuation parameter; IQR, interquartile range.

Table 2. Logistic regression analyses for the main outcome (referral to gastroenterology).

	Odds ratio	95% confidence interval	*p* value
AST, U/L	1.02	0.97, 1.07	0.477
ALT, U/L	0.99	0.94, 1.04	0.630
GGT, U/L	0.02	0.01, 0.03	**0.007**
Total bilirubin, mg/dL	7.53	1.30, 43.5	**0.024**
FLI	0.03	-0.01, 0.07	0.125
BARD	1.12	0.51, 2.45	0.786
NFS	0.80	0.06, 1.53	**0.034**
APRI	4.51	0.91, 8.11	**0.014**
FIB-4	1.36	0.34, 2.39	**0.029**

AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; FLI, fatty liver index; BARD, Body Mass Index, AST/ALT Ratio, and Diabetes; NFS, NAFLD Fibrosis Score; APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, Fibrosis-4 Index.

Table 3. ROC curve analyses for the main outcome (referral to gastroenterology).

	Empirical optimal cut point	Sensitivity/ specificity at cut point*	AUC at cut point*
AST, U/L	37	0.38 (0.09, 0.76) / 0.89 (0.77, 0.96)	0.63 (0.45, 0.82)
ALT, U/L	29.5	0.38 (0.09, 0.76) / 0.72 (0.58, 0.84)	0.55 (0.36, 0.74)
GGT, U/L	52	0.62 (0.25, 0.92) / 0.85 (0.72, 0.93)	0.74 (0.55, 0.92)
Total bilirubin, mg/dL	0.665	0.71 (0.29, 0.96) / 0.69 (0.55, 0.90)	0.70 (0.51, 0.90)
FLI	84.1	0.75 (0.35, 0.97) / 0.77 (0.63, 0.88)	0.76 (0.59, 0.93)
BARD	3.5	0.62 (0.25, 0.92) / 0.56 (0.41, 0.69)	0.59 (0.40, 0.78)
NFS	-0.21	0.71 (0.29, 0.96) / 0.79 (0.64, 0.90)	0.75 (0.56, 0.94)
APRI	0.73	0.50 (0.16, 0.84) / 0.96 (0.87, 0.99)	0.73 (0.54, 0.92)
FIB-4	**2.11**	**0.62 (0.25, 0.92) / 0.98 (0.9, 1.0)**	**0.80 (0.62, 0.98)**

* Values are shown as value (95% confidence interval).

AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; FLI, Fatty Liver Index; BARD, Body Mass Index, AST/ALT Ratio, and Diabetes; NFS, NAFLD Fibrosis Score; APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, Fibrosis-4 Index.

Table 4. ROC curve analyses for different FIB-4 (Fibrosis-4 Index) cut points.

Cut point	Sensitivity/ specificity at cut point*	AUC at cut point*
1.30	0.63 (0.25, 0.92) / 0.58 (0.43, 0.71)	0.60 (0.41, 0.79)
1.45	0.63 (0.25, 0.92) / 0.67 (0.53, 0.80)	0.65 (0.46, 0.84)
2.11	0.62 (0.25, 0.92) / 0.98 (0.9, 1.0)	0.80 (0.62, 0.98)
3.25	0.25 (0.03, 0.65) / 1.00 (0.93, 1.00)	0.62 (0.46, 0.79)

* Values are shown as value (95% confidence interval).

cut points of 1.3 and 1.45 just slightly augment the sensibility to 63%, at the expense of bearing a lower specificity.

Discussion

This is a secondary analysis of a Portuguese well defined cohort of patients with MetS followed in Endocrinology outpatient setting regarding their need to referral to hepatologists. Data on this subject is scarce and needed. We showed that around 13% of patients were referred to gastroenterology due to hepatic stiffness (none of which had already been referenced), and that FIB-4 was the better predictor of referral among the studied parameters.

Current literature is scarce and not consensual. The American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings states that clinicians must screen patients with features of MetS for NAFLD and advanced fibrosis.[24] These authors agreed that a FIB-4 score >1.3 should lead to further workup, for example, hepatic elastography.[24]

The clinical practice guidelines for NAFLD/NASH from the joint committee of Japanese Society of Gastroenterology and the Japanese Society of Hepatology (2020) propose a screening method for NAFLD with hepatic fibrosis by a general physician and, if liver fibrosis is indicated, referral for gastroenterology specialist should be considered.[25] Regarding FIB-4, these authors consider that a value of <1.3 do not need further assessment and that values above this should undertake elastography.[25]

On the other hand, the Practice guidance from the American Association for the Study of Liver Diseases (2016) considered that patients with a FIB-4 score <1.45 are unlikely and that those with values above 3.25 are likely to have advanced fibrosis.[1,26]

In our study, we show that a FIB-4 value of ≥ 2.11 has a specificity of 98% for significant liver stiffness, suggesting that these range of FIB-4 values warrant urgent gastroenterology referral. In our population, the lower cut points of 1.3 and 1.45 just slightly augment the sensibility but considerably diminishes the specificity. The usage of 3.25 denotes a specificity of 100%, at the expense of a 25% sensibility.

FIB-4 has been validated in ethnically different NAFLD populations, with consistent results.[11,24] FIB-4 score seems to be better than BARD and APRI for predicting advanced fibrosis in patients with biopsy-proven NAFLD.[1,27] This index has been shown to predict overall mortality, cardiovascular and liver-related mortality.[11] The performance of such index is dependent on the population studied, being better at hepatology clinics, where pretest probability of liver fibrosis is higher.[24] Of note, this it is not a perfect surrogate marker and physicians must be aware of its weaknesses when interpreting it. For instance, age is one of the factors included in the index and, as such, higher index values in older individuals do not necessarily mean true liver stiffness.[25]

This study has limitations that must be acknowledged. Firstly, the low number of participants may be a drawback given the lack of power to detect small differences. Also, this is a retrospective secondary analysis, and we may have missing confounders. Finally, we used hepatic elastography as our group defining variable and we do not have histological diagnosis of either hepatic steatosis or fibrosis. However, to the best of our knowledge, this is the first study on a tertiary Portuguese cohort, and we believe that the importance of our results fairly overcome the limitations.

Our results highlight that the use of FIB-4 index should be included in the evaluation of patients with MetS in Endocrinology outpatient setting, which are high risk patients for liver fibrosis. It is worth to think about including it as an automatic calculated result when ordering AST, ALT and platelets. Timely patients' referral is of paramount importance to avoid progression of NAFLD to cirrhosis. Further studies are needed to validate FIB-4 best cut-off value in our population.

Contributorship Statement / Declaração de Contribuição:

MBC, JSN, ARL, MvH and CV: Responsible for the study conception and design.
MBC, RL, ARL, JCC, IML and MvH: Contributed to data collection.

MBC, JSN and ARL: Responsible for data analysis and interpretation, and statistical analysis.
MBC prepared the first version of the article.
All authors provided critical revision and approved the final version to be published.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

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