Validation of NIAAAm-CRP criteria to predict alcohol-associated steatohepatitis on liver histology

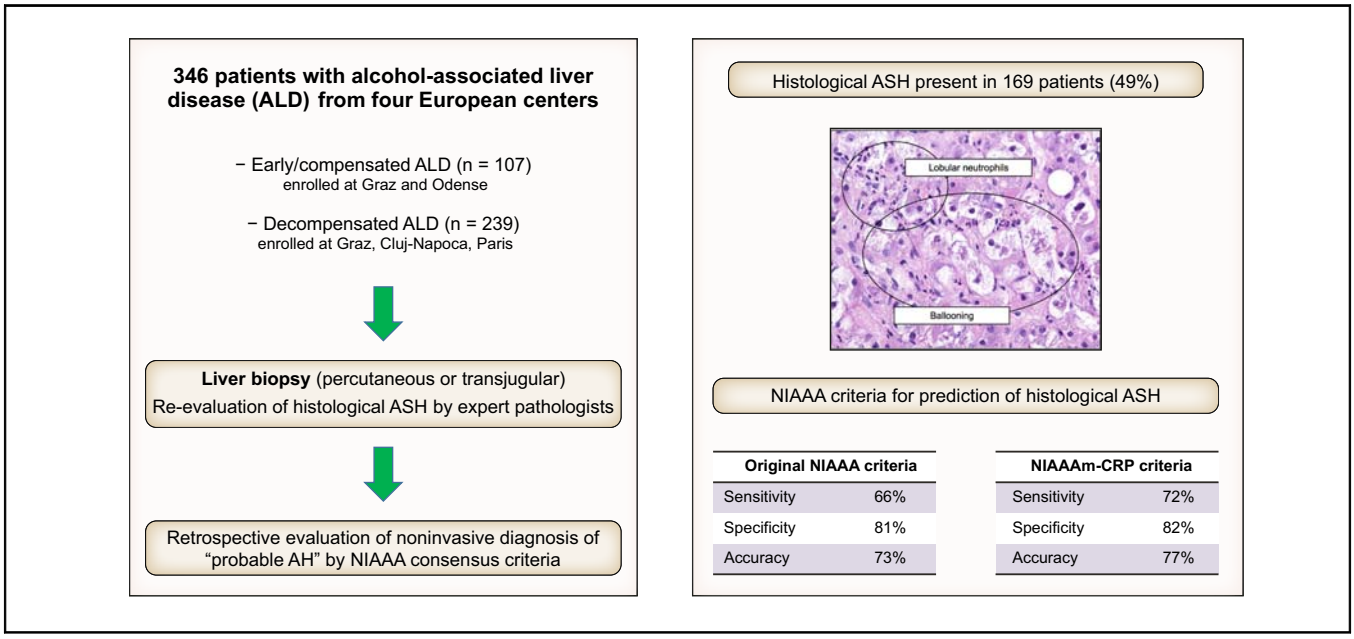
Authors

Rudolf E. Stauber, Pierre-Emmanuel Rautou, Horia Stefanescu, Adelina Horhat, Maja Thiele, Carolin Lackner

Correspondence

rudolf.stauber@medunigraz.at (R.E. Stauber).

Graphical abstract



Highlights

- Alcohol-associated steatohepatitis is defined by histology, but biopsy is not always feasible.
- Non-invasive criteria for probable alcohol-associated hepatitis were proposed at a NIAAA consensus conference.
- A recent study developed modified NIAAAm-CRP criteria with improved yet suboptimal accuracy.
- In the present study we validate slightly superior but still suboptimal diagnostic accuracy of the new NIAAAm-CRP criteria.

Impact and Implications

Alcohol-associated steatohepatitis (ASH) is diagnosed on liver histology but liver biopsy is not always feasible. Non-invasive diagnosis based on clinical findings has been proposed using the National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria and recently improved using NIAAAm-CRP criteria. Our findings validate slightly better but still suboptimal performance of NIAAAm-CRP criteria for the presence of histological ASH. Clinical trials of novel drugs should focus on histologically proven ASH.

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Short communication JHEP|Reports

Validation of NIAAAm-CRP criteria to predict alcohol-associated steatohepatitis on liver histology

Rudolf E. Stauber,[1,*] Pierre-Emmanuel Rautou,[2,3] Horia Stefanescu,[4] Adelina Horhat,[5,6] Maja Thiele,[7] Carolin Lackner [8], SALVE Histopathology Group

[1]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria;* [2]*Université Paris-Cité, Inserm, Centre de recherche sur l'inflammation, UMR 1149, Paris, France;* [3]*Service d'Hépatologie, AP-HP, Hôpital Beaujon, DMU DIGEST, Centre de Référence des Maladies Vasculaires du Foie, FILFOIE, ERN RARE-LIVER, Clichy, France;* [4]*Liver Unit, Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania;* [5]*Service d'Hépato-Gastro-Entérologie, Hôpital La Pitié Salpêtrière, Paris, France;* [6]*"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania;* [7]*Center for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, and Department of Clinical Research, University of Southern Denmark, Odense C, Denmark;* [8]*Institute of Pathology, Medical University of Graz, Graz, Austria*

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Background & Aims: In clinical practice, the diagnosis of alcohol-associated hepatitis (AH) is mostly based on non-invasive criteria, which were defined at a consensus conference by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). These criteria were recently modified by adding C-reactive protein (CRP) and termed NIAAAm-CRP criteria, which showed superior diagnostic accuracy for presence of alcohol-associated steatohepatitis (ASH) on liver histology. The aim of our study was to validate the diagnostic accuracy of both original NIAAA criteria and NIAAAm-CRP criteria for presence of ASH on liver histology in an independent cohort.
Methods: Data from a large multinational cohort of 445 patients with alcohol-associated liver disease (ALD) that served to establish a novel grading and staging system of alcohol-associated liver disease were analyzed retrospectively. Diagnosis of ASH was based on presence of hepatocyte ballooning plus lobular neutrophil infiltration and established in virtual consensus meetings of multiple expert liver pathologists.
Results: Complete data including CRP values were available in 346 patients. Overall diagnostic accuracy for prediction of ASH was 73% for NIAAA criteria and 77% for NIAAAm-CRP criteria. In a subgroup with suspected severe AH (MELD >20, n = 123), overall diagnostic accuracy for prediction of ASH was 69% for NIAAA criteria and 74% for NIAAAm-CRP criteria.
Conclusion: Our findings confirm recent data on suboptimal diagnostic accuracy of original NIAAA criteria and validate slightly better but still suboptimal performance of NIAAAm-CRP criteria for presence of ASH.
Impact and Implications: Alcohol-associated steatohepatitis (ASH) is diagnosed on liver histology but liver biopsy is not always feasible. Non-invasive diagnosis based on clinical findings has been proposed using the National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria and recently improved using NIAAAm-CRP criteria. Our findings validate slightly better but still suboptimal performance of NIAAAm-CRP criteria for the presence of histological ASH. Clinical trials of novel drugs should focus on histologically proven ASH.

Introduction

Alcohol-associated hepatitis (AH) is a serious condition associated with high short-term mortality and increasing incidence in young adults.[1] Prednisolone treatment has been shown to improve prognosis,[2] especially in patients with histologically proven alcohol-associated steatohepatitis (ASH).[3] However, a more recent large randomized trial using non-invasive criteria to diagnose ASH failed to demonstrate a significant benefit of steroid treatment.[4]

In clinical practice, the diagnosis of AH is mostly made by non-invasive criteria of "probable AH" based on expert opinion, which were defined at a consensus conference by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).[5] These criteria include onset of jaundice within prior 8 weeks; ongoing alcohol consumption of >40 (female) or >60 (males) g/day for 6 months or more, with less than 60 days of abstinence before the onset of jaundice; aspartate aminotransferase (AST) >50 U/L, AST/alanine aminotransferase (ALT) ratio >1.5, both AST and ALT <400 U/L, bilirubin >3.0 mg/dl; absence of potential confounding factors such as ischemic hepatitis, drug-induced liver injury, uncertain alcohol use assessment, or atypical laboratory tests like ANA (antinuclear antibodies) >1:160 or SMA (smooth muscle antibodies) >1:80. Non-invasive criteria for "probable AH" were adopted by both EASL[6] and AASLD[7] guidelines on the management of alcohol-related liver disease (ALD) and have been deemed sufficient for inclusion into clinical trials of AH treatment.

Keywords: Alcohol-associated liver disease; noninvasive; histology.
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* Corresponding author. Address: Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria.
E-mail address: rudolf.stauber@medunigraz.at (R.E. Stauber).

Table 1. Patient characteristics (n = 346).

Group	Histological ASH n = 169	No histological ASH n = 177	*p* value[†]
Age (years)	51 (45, 59)	53 (46, 59)	0.253
Male	68%	76%	0.068
Ascites	73%	32%	<0.001
Hepatic encephalopathy	29%	17%	0.009
Gastrointestinal bleeding	15%	11%	0.231
MELD	22 (17, 26)	11 (7, 19)	<0.001
MELD >20	53%	19%	<0.001
Bilirubin (mg/dl)	8.8 (3.4, 18.2)	1.5 (0.6, 5.1)	<0.001
Creatinine (mg/dl)	0.7 (0.6, 1.0)	0.9 (0.7, 1.0)	<0.001
INR	1.71 (1.32, 2.15)	1.15 (1.00, 1.57)	<0.001
Albumin (g/dl)	2.8 (2.2, 3.2)	3.8 (2.9, 4.2)	<0.001
Platelet count (10^9/L)	142 (96, 218)	158 (98, 250)	0.205
White blood cell count (10^9/L)	10.1 (7.1, 13.9)	6.6 (5.3, 8.9)	<0.001
C-reactive protein (mg/L)	34.4 (15.3, 53.9)	5.0 (2.0, 15.5)	<0.001
SALVE fibrosis stage (SFS) [‡]			0.001
SFS 0-3	27%	44%	
SFS 4a-4b	44%	28%	
SFS 4c	29%	28%	

Continuous variables are shown as median (Q1, Q3).
ASH, alcohol-related steatohepatitis; INR, international normalized ratio; MELD, model for end-stage liver disease.
[†] Mann-Whitney test or Chi-square test as appropriate.
[‡] see Ref. 9.

However, in a recent study of 268 patients with ALD, NIAAA criteria for "probable AH" have shown limited diagnostic accuracy against histological ASH as reference standard.[8] The authors also developed and evaluated a new model including C-reactive protein (CRP) (NIAAAm-CRP) based on modified criteria (active alcohol consumption or abstinence <120 days, AST ≥50 U/L, AST/ALT ratio ≥1, bilirubin ≥2.5 mg/dl, CRP ≥10 mg/L), which performed slightly better than the original NIAAA criteria.[8] Our aim was to evaluate the diagnostic accuracy of both models in an independent cohort of patients with ALD against histological ASH according to the ALD-specific grading and staging system developed by the EASL-endorsed consortium for the Study of Alcohol-related LiVer disease in Europe (SALVE).[9]

Patients and methods

A total of 445 patients with early/compensated or decompensated ALD from four European SALVE centers were analyzed retrospectively. This cohort had served to develop the SALVE histological grading and staging system for ALD as previously published.[9] All studies received approval by the local Ethics Committees of all centres. Informed consent was obtained in accordance with the Declaration of Helsinki. Indications for biopsy were diagnosis of ASH if clinically suspected (decompensated ALD and/or jaundice) as well as staging of ALD (compensated ALD) and/or differential diagnosis. Diagnosis of ASH was based on presence of hepatocyte ballooning plus lobular neutrophil infiltration (score ≥1 each) and established in virtual consensus meetings of at least 3 members of the SALVE Histopathology Group, who are all expert liver pathologists.[9] Clinical and laboratory data for NIAAA and NIAAAm-CRP criteria were extracted from the charts. Statistical analyses were performed using IBM SPSS Statistics 28.

Results

Complete data including CRP values were available in 346 patients. Patient characteristics of our cohort (Table 1) are comparable to those reported by Avitabile *et al.*[8] Both cohorts are well comparable in terms of disease severity (median model for end-stage liver disease [MELD] score 17 *vs.* 16) and prevalence of ASH (49% *vs.* 39%). Diagnostic accuracy of both non-invasive models is shown in Table 2. In the whole cohort, diagnostic accuracy of the original NIAAA criteria was moderate and similar to the findings of Avitabile *et al.*[8] Applying the novel NIAAAm-CRP criteria slightly improved diagnostic performance but overall accuracy remained below 80%.

In a subgroup of 123 patients with severe AH (MELD >20, ASH present in 90/absent in 33), slightly lower overall accuracy due to low specifity/NPV was found. The novel NIAAAm-CRP criteria

Table 2. Diagnostic accuracy of noninvasive criteria for "probable AH" as predictors of histological ASH in 346 patients with ALD and in a subgroup of patients with severe disease (MELD >20).

	NIAAA original criteria		NIAAAm-CRP	
	Whole cohort (95% CI)	MELD >20 (95% CI)	Whole cohort (95% CI)	MELD >20 (95% CI)
Number of patients	346	123	346	123
Disease prevalence	49% (43-54)	73% (64-81)	49% (43-54)	73% (64-81)
Sensitivity	66% (58-73)	84% (75-91)	72% (64-78)	89% (81-95)
Specificity	81% (74-86)	27% (13-46)	82% (75-87)	33% (18-52)
PPV	77% (69-83)	76% (66-84)	79% (72-85)	78% (69-86)
NPV	71% (64-77)	39% (20-61)	75% (68-81)	52% (30-74)
Overall accuracy	73% (68-78)	69% (60-77)	77% (72-81)	74% (65-81)

MELD, model for end-stage liver disease; NPV, negative predictive value; PPV, positive predictive value.

again performed slightly better but still suboptimally. Information about infection at admission was available in 119 out of 123 patients with severe AH. Among those, serum CRP concentrations were similar in patients with (n = 54) or without (n = 65) infection (median CRP 39 *vs.* 40 mg/L, p = 0.523 by Mann-Whitney test). In contrast, patients with ASH showed higher CRP concentrations than those without ASH (median CRP 41 *vs.* 20 mg/L, p <0.001 by Mann-Whitney test).

Discussion

Our results confirm the suboptimal diagnostic accuracy of original NIAAA criteria for ASH in a large cohort of patients with ALD of varying severity. We found a remarkably similar overall diagnostic accuracy compared to the results published by Avitabile *et al.* (73% *vs.* 72%), however, specificity was lower in the subgroup of severe clinical AH (MELD >20) (27% *vs.* 55%).[8] This difference may be due to heterogeneity of our cohort and/or different assessment of ASH. The diagnostic accuracy of non-invasive criteria for ASH is of special relevance in severe AH (MELD >20) where corticosteroid treatment shows beneficial effects on short-term survival especially in patients with histologically proven ASH.[3] Low specificity of non-invasive criteria for ASH in severe AH treated with steroids may thus be deleterious as promotion of bacterial infection may outweigh beneficial effects on steatohepatitis. Both in the whole cohort and in the subcohort with severe AH (MELD <20) we found slightly better yet still suboptimal diagnostic performance of NIAAAm-CRP criteria, thus validating the findings of Avitabile *et al.*[8]

A recent sub-analysis of the STOPAH trial reported high concordance of clinical and histological ASH criteria (ASH present in 87% of patients with adequate liver biopsy, in 80% of patients with MELD 21-24, and in 91% of patients with MELD ≥25).[10] However, these findings are prone to selection bias since liver biopsy was performed in only 17% of the patients enrolled, with adequate specimens available in 15%. It should be noted that the inclusion criteria for the STOPAH trial comprised a higher degree of hyperbilirubinemia, *i.e.* >80 μmol/L (>4.7 mg/dl), as compared to the NIAAA criteria (>3.0 mg/dl) or NIAAAm-CRP criteria (≥2.5 mg/dl) which may in part explain the high sensitivity for presence of ASH reported by Forrest *et al.*[10] On the other hand, Mookerjee *et al.* found presence of ASH in only 50% of patients with acute deterioration of alcohol-related cirrhosis and clinically suspected AH due to positive systemic inflammatory response syndrome criteria.[11] Importantly, liberal corticosteroid treatment of clinically diagnosed severe AH may be deleterious by promoting infection.[12]

A limitation of this and other retrospective studies is selection bias which plays an important role on pre-test probability and hence test performance. Besides, information was lacking on some of the confounding factors contained in the original NIAAA criteria (*i.e.* missing data on ischemic hepatitis or drug-induced liver injury). On the other hand, the well-defined reference standard with assessment of ASH by the SALVE Histopathology Group is an important strength of our study. Notably our patient characteristics compare very well to the cohort studied by Avitabile *et al.*[8]

In conclusion, our findings confirm recent data on suboptimal diagnostic accuracy of original NIAAA criteria and validate slightly better but still suboptimal performance of NIAAAm-CRP criteria for presence of ASH. This may be of special relevance in patients with severe AH who are candidates for pharmacological treatment. Clinical trials of drugs in development for AH should aim to enrol patients with histologically proven ASH.

Abbreviations

AH, alcohol-associated hepatitis; ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; ASH, alcohol-associated steatohepatitis; AST, aspartate aminotransferase; CRP, C-reactive protein; MELD, model for end-stage liver disease; NIAAA, National Institute on Alcohol Abuse and Alcoholism; SALVE, Study of Alcohol-related LiVer disease in Europe.

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Conflict of interest

None of the authors have any conflict of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: RES, PER. Data curation: RES, PER, HS, AH, MT, CL, SALVE Histopathology Group. Formal analysis: RES. Writing of manuscript draft: RES. Review & editing: all authors.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SALVE Histopathology Group

Susan Davies[1], Helmut Denk[2], Sönke Detlefsen[3], Hans Peter Dienes[4], Viviane Gnemmi[5], Annette S. H. Gouw[6], Maria Guido[7], Rosa Miquel[8], Valerie Paradis[9], Ioana Rusu[10], Peter Schirmacher[11], Luigi Terracciano[12], Dina Tiniakos[13,14]

1 Department of Histopathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

2 Institute of Pathology, Medical University of Graz, Graz, Austria

3 Department of Pathology, Odense University Hospital, Odense, Denmark; Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

4 Department of Pathology, Medical University of Vienna, Vienna, Austria

5 Université Lille, Canther, Inserm, UMR-S 1277, CHU Lille, Service de Pathologie, Lille, France

6 Department of Pathology and Medical Biology, University Medical Center Groningen, Groningen, Netherlands

7 Department of Medicine - DIMED, University of Padova, Padova, Italy

8 Liver Histopathology Laboratory, Institute of Liver Studies, King's College Hospital, London, United Kingdom

9 Assistance Publique-Hôpitaux de Paris, Service d'Anatomie et de Cytologie Pathologiques, Hôpital Universitaire Beaujon, France; Université Paris Diderot, CNRS, Centre de Recherche sur l'Inflammation (CRI), Paris, France; Département Hospitalo-Universitaire (DHU) UNITY, Clichy, France

10 Pathology Unit, Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania

11 Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany

12 Anatomic Pathology Institute, Humanitas University Research Hospital, Rozzano (Milano), Italy

13 Department of Pathology, Aretaieio Hospital, Medical School, National & Kapodistrian University of Athens, Athens, Greece
14 Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK

Supplementary data

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Author names in bold designate shared co-first authorship

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