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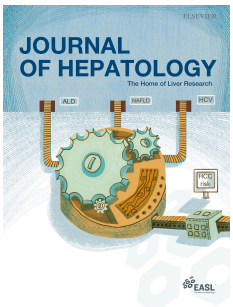

Development and prognostic relevance of a histologic grading and staging system for alcohol-related liver disease

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PII: S0168-8278(21)00402-5

DOI: https://doi.org/10.1016/j.jhep.2021.05.029

Reference: JHEPAT 8294

To appear in: *Journal of Hepatology*

Received Date: 8 July 2020

Revised Date: 18 April 2021

Accepted Date: 11 May 2021

Please cite this article as: Lackner C, Stauber RE, Davies S, Denk H, Dienes HP, Gnemmi V, Guido M, Miquel R, Paradis V, Schirmacher P, Terracciano L, Berghold A, Pregartner G, Binder L, Douschan P, Rainer F, Sygulla S, Jager M, Rautou PE, Bumbu A, Horhat A, Rusu I, Stefanescu H, Detlefsen S, Krag A, Thiele M, Cortez-Pinto H, Moreno C, Gouw ASH, Tiniakos DG, Development and prognostic relevance of a histologic grading and staging system for alcohol-related liver disease, *Journal of Hepatology* (2021), doi: https://doi.org/10.1016/j.jhep.2021.05.029.

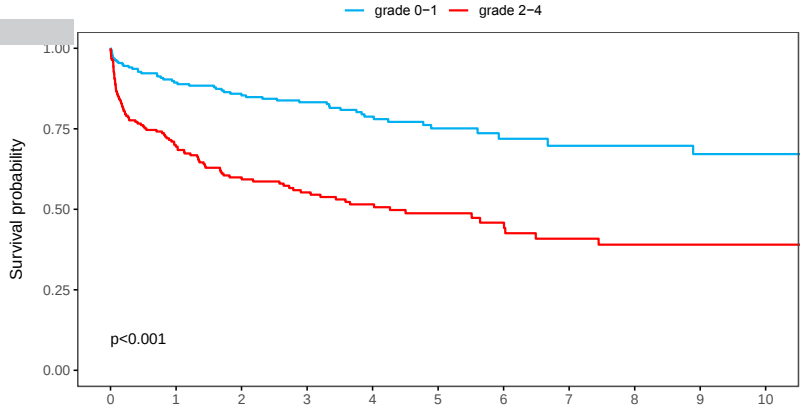
445 patients with alcohol-related liver disease (ALD) from four European centers

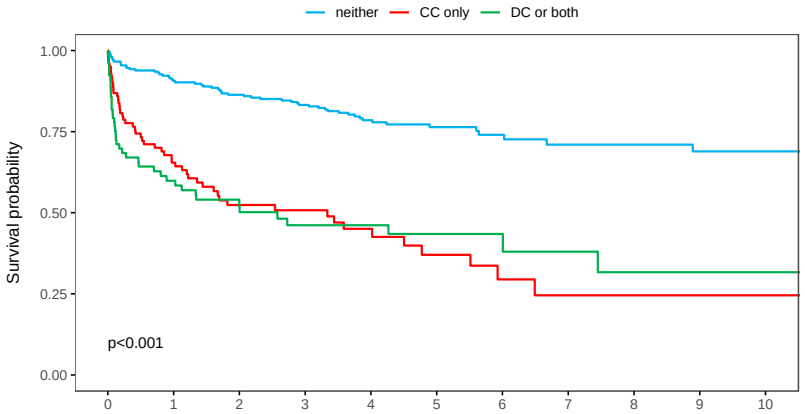
- Compensated ALD (n=159)
  enrolled at Graz and Odense
- Decompensated ALD (n=286)
  enrolled at Graz, Cluj-Napoca, Paris

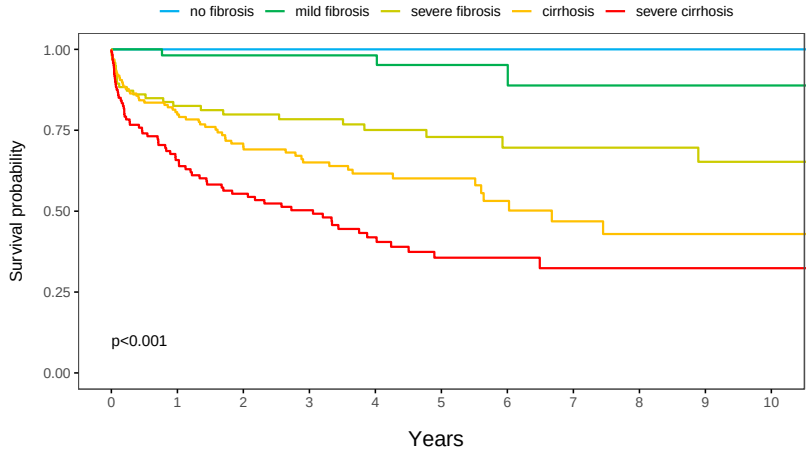
Liver biopsy (percutaneous or transjugular)

Development and validation of an ALD-specific grading & staging system by the SALVE Histopathology Group

Median follow-up 0.5 – 4.1 years







Development and prognostic relevance of a histologic grading and staging system for alcohol-related liver disease

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Electronic word count: 5994 words

Abstract: 266 words

Number of Figures: 3

Number of Tables: 5

Conflicts of interest: None

Financial support: None

Author contributions:

CL, RES, HCP, CM, ASHG, DT: study design, data evaluation, manuscript writing and final review; CL, SD, HD, HPD, VG, MG, RM, VP, PS, LT, IR, SD, SS, ASHG, DT: review of histologic slides and final review; CL, RES, AB, GP: data management, statistical analysis and final review; RES, LB, PD, FR, PER, MJ, HS, AB, AH, MT, AK: patient recruitment, data collection and final review.

Key words:

Alcohol-related liver disease, prognosis, grading, staging, cholestasis

Data availability statement:

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

Abstract

Background & Aims: The SALVE Histopathology Group (SHG) developed and validated a grading and staging system for the clinical and full histological spectrum of alcohol-related liver disease (ALD) and evaluated its prognostic utility in a multinational cohort of 445 patients.

Methods: SALVE grade was described by semiquantitative scores for steatosis, activity (hepatocellular injury and lobular neutrophils) and cholestasis. The histological diagnosis of steatohepatitis due to ALD (histological ASH, hASH) was based on the presence of hepatocellular ballooning and lobular neutrophils. Fibrosis staging was adapted from the Clinical Research Network staging system for NAFLD and the Laennec staging system and reflects the pattern and extent of ALD fibrosis. There are 7 SALVE fibrosis stages (SFS) ranging from no fibrosis to severe cirrhosis.

Results: Interobserver κ-value for each grading and staging parameter was >0.6. In the whole study cohort long-term outcome was associated with activity grade and cholestasis, as well as cirrhosis with very broad septa (severe cirrhosis) (p<0.001 for all parameters). In decompensated ALD, adverse short-term outcome was associated with activity grade, hASH and cholestasis (p=0.038, 0.012 and 0.001, respectively), whereas in compensated ALD, hASH and severe fibrosis/cirrhosis were associated with decompensation-free survival (p=0.011 and 0.001, respectively). On multivariable analysis, severe cirrhosis emerged as an independent histological predictor of long-term survival in the whole study cohort. Severe cirrhosis and hASH were identified as independent predictors of short-term survival in decompensated ALD, and also as independent predictors of decompensation-free survival in compensated ALD.

Conclusion: The SALVE grading and staging system is a reproducible and prognostically relevant method for the histological assessment of disease activity and fibrosis in ALD.

Lay summary

Patients with alcohol-related liver disease (ALD) may undergo liver biopsy to assess disease severity. We developed a system to classify ALD under the microscope by grading ALD activity and staging the extent of liver scarring and validated its prognostic performance in 445 patients from four European centers.

Introduction

Alcohol abuse is a major global health concern, being a frequent cause of chronic liver disease, cirrhosis, hepatocellular carcinoma and indication for liver transplantation. Alcohol-related liver disease (ALD) shows a spectrum of liver pathology ranging from steatosis to steatohepatitis and fibrosis [1]. For the sake of clarity, steatohepatitis related to ALD [2] is referred to as histological alcoholic steatohepatitis (hASH) in this manuscript, to differentiate it from non-alcoholic steatohepatitis and it is not synonymous with the clinical scenario of alcoholic hepatitis (AH).

Clinically, steatosis is associated with few, if any symptoms and has a low risk of progression, whereas hASH is a major driver of fibrogenesis and disease progression. In turn, progression can be associated with clinical abnormalities, development of cirrhosis and hepatocellular carcinoma. Severe symptoms may be due to decompensation of cirrhosis and/or clinical alcoholic hepatitis (AH) the latter being associated with 3-months mortality rates of 20-50% [2,3]. As clinical ALD classifications may correspond poorly with histology [4], EASL Clinical Practice Guideline for the Management of ALD recommends liver biopsy in cases with uncertain diagnosis of ALD in both clinical practice and clinical trials [2].

Standardized and reproducible assessment of disease activity and fibrosis is a prerequisite for histological-based patient stratification, prognosis and monitoring of treatment effects. Several histological grading and staging systems have been developed for use in chronic liver disease including non-alcoholic fatty liver disease (NAFLD) [5, 6] and viral hepatitis [7, 8]. Although ALD is among the most frequent of liver diseases and its morphological features are well described, few proposals for specific grading and staging system have been made [1] and a universally accepted system for the full clinical spectrum of ALD is currently lacking.

As ALD and NAFLD show histological overlap, it has been suggested applying NAFLD grading and staging systems for ALD [9] but several prognostically relevant ALD features, like cholestasis, Mallory-Denk bodies (MDB) and megamitochondria, are not considered in NAFLD grading [10]. Further, the vast majority of ALD patients have cirrhosis at first presentation [11] in contrast to NAFLD patients in

whom it is infrequent [12]. Histological substages of cirrhosis [13, 14] and the extent of pericellular fibrosis (PCF) [15] are prognostically relevant in ALD but are not reflected in current NAFLD staging systems. Finally, ALD is associated with fibro-obliteration of hepatic veins, perivenular fibrosis and sclerosing hyaline necrosis, all predictors of progression and adverse prognosis but are rare in NAFLD [16, 17].

A group of European liver pathologists, members of the EASL-endorsed consortium for the Study of Alcohol-related LiVer disease in Europe (SALVE), comprising the SALVE Histopathology Group (SHG), convened to design a morphological grading and staging system valid for the whole clinical spectrum of the disease and evaluated its prognostic utility.

Patients and methods

Study cohort

A previously described retrospective cohort with clinical and histologically confirmed ALD, the Graz cohort [11], was used to design the morphological grading and staging system and to assess interobserver variation. The prognostic utility of the grading and staging system was then evaluated in the Graz cohort and three additional cohorts from SALVE centres in Odense (Odense University Hospital, Denmark), Paris (Hôpital Beaujon, Clichy, France), and Cluj-Napoca (Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania). Patients in the Graz cohort underwent liver biopsy for diagnosis and/or staging of liver disease. The Paris and Cluj cohorts included consecutive patients undergoing liver biopsy for suspicion of clinical alcoholic hepatitis. The Odense cohort included patients from a prospective diagnostic study on patients with compensated ALD in Southern Denmark [18, 19]. Patients received standard of care or, if needed, intensive care support.

Follow-up data on survival and liver transplantation were available for all patients. Length of survival and cause of death were documented based on data from hospitals, family practitioners and national death registries. Data on abstinence during follow-up were available in 323 out of 445 patients. In addition, data on liver-related events were collected in the subgroup of patients with compensated

ALD. All studies received approval by the local Ethics Committees of all centres. Informed consent was obtained in accordance with the Declaration of Helsinki.

Design of the SALVE grading and staging system

The SALVE grading and staging system was based on (i) characteristic morphological features of ALD, (ii) previously reported independent prognostic parameters of grade [15, 20, 21] and stage [11, 14, 22], and (iii) at least substantial interobserver agreement as documented in the literature or according to the results of studies by the SHG (described below). For the Graz cohort morphological evaluations were carried out by members of the SHG in consensus using a multiheaded microscope. Scanned liver biopsy slides of the Cluj-Napoca, Paris and Odense patients were scored in consensus by groups of at least 3 SHG pathologists using the "share screen" option on a digital platform. One SHG pathologist (CL) attended all virtual scoring sessions to ensure homogeneity of histological evaluation. The observers were unaware of the clinical data.

All studied samples were routinely stained with hematoxylin-eosin and either chromotrope aniline blue or sirius red.

SALVE grading

A semiquantitative evaluation method was defined using numerical scores for macrovesicular steatosis (0-3), hepatocellular ballooning (0-2), MDB (0-2), and lobular neutrophils (0-2). Ballooning was defined as hepatocellular enlargement (at least 2x the size of normal hepatocytes), rounded cellular shape and rarefied cytoplasm (cytoplasmic clarification). Cholestasis was specified as hepatocellular, canalicular, or ductular cholestasis and scored as absent (0) or present (1). The SHG evaluated 30 cases on digitized slides for the assessment of interobserver variation.

Parameters with substantial interobserver agreement ($\kappa>0.6$) namely steatosis, ballooning, MDB, lobular neutrophils, canalicular and ductular cholestasis were selected as descriptors of SALVE Grade defined by scores for steatosis (0-3), activity (0-4), canalicular (0-1) and ductular cholestasis (0-1) (Supplementary Figure 1). Because ballooning and MDB scores showed a strong correlation (Spearman´s rho=0.9), the higher score of either feature rather than their sum was considered, to

avoid overestimation of hepatocellular injury. The activity range of 0-4 was based on cellular injury and inflammation as the sum of scores for ballooning or MDB and lobular neutrophils. The definition of ASH [1] was based on ballooning and neutrophil score of ≥1 each and cases with activity scores of 3 and 4, as well as some cases with score 2 were diagnosed with hASH. The SALVE grading system is shown in Table 1.

SALVE staging

Fibrosis stages were described based on a combination of the NASH Clinical Research Network (CRN) [5] and the Laennec systems [14] with some modifications. The SALVE staging system details 7 SALVE fibrosis stages (SFS) comprising 4 pre-cirrhotic (SFS 0, 1, 2, and 3), similar to the CRN, and 3 cirrhotic stages (SFS 4A, 4B, and 4C), similar to Laennec. For some clinical settings, and also within trials, the presence of severe pericellular fibrosis (PCF) may be included, as described below and in Table 2. Morphological aspects of staging are also illustrated in Table 2 and Supplementary Figures 2, 3 and 4. SALVE fibrosis stage 1 (SFS 1) comprises two distinct morphological patterns: Typically, centrilobular regions are affected by PCF occasionally extending to intermediate lobular areas (Supplementary Figure 2B). Alternatively, there may be predominantly portal-based fibrosis with periportal extension (Supplementary Figure 2C) [10]. SFS 2 is defined by coexisting centrilobular PCF and periportal fibrosis (Supplementary Figure 2D). In SFS 3 portal-based dense fibrous septa develop, linking portal tracts, portal tracts and central veins as well as central veins. This may be accompanied by variable degrees of PCF (see below for when PCF predominates) (SFS 3) (Supplementary Figures 2E and F). The cirrhosis stage, SFS 4 is characterised by destruction of lobular architecture and development of parenchymal nodules surrounded by septa, the thickness of which are used for sub-classification. Septa may be dense and thin (SFS 4A; Supplementary Figure 3A and B), broad (SFS 4B; Supplementary Figure 3C and D) or very broad (SFS 4C; Supplementary Figure 3E and F). The assessment of septal thickness was based on the dimension of the smallest distinct parenchymal nodule as detailed in Table 2.

Expanded SALVE fibrosis staging in consideration of severe forms of pericellular fibrosis

In ALD, PCF can be the predominant pattern of fibrosis, present at all stages and therefore SFS 1, 3, and 4A-C can be further classified as outlined below and in Table 2.

In SFS1 cases the designation *SFS 1P* may be used to indicate the presence of centrilobular PCF only (Supplementary Figure 2B). In some cases of SFS 3, *SFS 3P* denotes that severe PCF may assume a septum-like configuration (centro-central septal PCF) (Supplementary Figure 4A) or involve entire hepatic lobules but with preservation of porto-central relations (Supplementary Figures 2E and 4B). In this setting obliterative venous lesions are frequently noted, and a few dense septa may be seen. In *SFS 4AP* severe PCF is present, destroying portal-central relations resulting in indistinct parenchymal nodules (Supplementary Figure 3B). SFS 4B and 4C with severe PCF and indistinct parenchymal nodules may be referred to as *SFS 4BP* (Supplementary Figure 3D) or *4CP* (Supplementary Figure 3F), respectively.

An algorithm was designed to facilitate and standardize the staging procedure (Figure 1). Two groups of observers of the SHG independently assessed SFS of the first consecutive 140 cases of the Graz cohort using the SALVE Staging Algorithm for interobserver studies.

Assessment of venous lesions of ALD

Perivenular fibrosis, sclerosing hyaline necrosis and fibro-obliteration of hepatic veins are presumed to be of prognostic relevance. Therefore, its presence was evaluated by five SHG observers in 140 cases of the Graz cohort.

Statistical analyses

Continuous variables were reported by median (Q1, Q3) whereas categorical data are presented as relative frequencies. Liver-related mortality at short-term (90 days) or long-term (end of follow-up) was defined as death due to liver failure, complications of cirrhosis or HCC. Patients with non-liver-related death and those undergoing liver transplantation during follow-up were censored and counted as non-event. Decompensation-free survival was defined as absence of liver-related events (new-onset jaundice, ascites, portal hypertensive bleeding, hepatic encephalopathy) or liver-related death during follow-up. The effect of prognostic variables on survival was analysed by the Kaplan-

Meier method and compared by log-rank tests performing Bonferroni correction for pairwise comparisons. The association of clinical, biochemical, and histological variables with survival was analysed by univariable and multivariable Cox regression. Multicollinearity was assessed with variance inflation factors (VIF). Statistical analyses were performed using SPSS Statistics Version 26 (SPSS Inc., Chicago, IL, USA) or R version 3.6.1. A p-value of <0.05 was considered significant.

Results

Clinical, biochemical, demographical, and histological characteristics of the study cohort

The whole study cohort consisted of 445 patients representing the entire clinical spectrum of ALD. Subgroup analysis was performed in patients (i) with compensated ALD defined by lack of clinical symptoms and no evidence of cirrhosis on ultrasonography or biochemistry (n=159), (ii) with decompensated ALD characterized by bilirubin levels >3mg/dl and/or signs of decompensation (new-onset jaundice, ascites, hepatic encephalopathy, portal hypertensive gastrointestinal bleeding) (n=286), and (iii) with decompensated ALD and hASH (n=181). Twenty-eight patients died from non-liver-related causes. Twenty-two patients underwent liver transplantation during follow-up (6 patients within 90 days from liver biopsy). Clinical, biochemical, and demographical characteristics of the study cohorts are shown in Table 3.

Histological characteristics of the study cohort are compiled in Supplementary Table 1. Median biopsy length was 25 mm in transcutaneous and 27 mm in transjugular biopsies. Decompensated patients more often had severe cirrhosis (SFS 4C). In addition, all cirrhotic stages with severe PCF (*SFS 4AP, 4BP* and *4CP*) were more frequent in decompensated than in compensated patients. Individuals with decompensated disease had higher activity grade and presence of hASH than patients with compensated ALD. Canalicular cholestasis was infrequent and ductular cholestasis was nearly absent in compensated patients but present in approximately 57% and 27% of those showing decompensation.

Parameters of SALVE grading and staging in interobserver studies

Substantial interobserver agreement was found for steatosis, ballooning, MDBs, lobular neutrophils, canalicular and ductular cholestasis, whereas agreement was moderate for the interpretation of hepatocellular cholestasis. Interobserver agreement for interpretation of the 7 SFS as well as the SFS with severe PCF was substantial (Table 4).

Association of SALVE grading with survival

Kaplan-Meier analysis in the whole study cohort revealed no prognostic utility for steatosis grade (data not shown). The association of SALVE activity grade with survival is shown in Figure 2A. High activity (grade 2-4) was associated with significantly shorter survival (p<0.001 vs. grade 0-1). An association with shorter survival was also seen for patients with hASH compared to those without hASH (p<0.001; Supplementary Figure 5). Survival of patients with canalicular or ductular cholestasis was significantly shorter than that of individuals without cholestasis (both p<0.001, significance level p=0.016) (Figure 2B).

Patients with decompensated ALD and activity grade 2-4, hASH or canalicular and/or ductular cholestasis had significantly higher 90-day mortality than patients with activity grade 0-1, no hASH or no cholestasis (p=0.038, 0.012 or 0.001, respectively) (Supplementary Figure 6A-C). In the subgroup of decompensated patients with hASH, canalicular and/or ductular cholestasis was associated with lower 90-day survival compared to those without cholestasis (p=0.029) (Supplementary Figure 7).

In patients with compensated ALD, activity grade 2-4 or hASH was associated with a higher incidence of liver-related events during follow-up than activity grade 0-1 or no hASH (p=0.011, respectively) (Supplementary Figure 8A-B).

Association of SALVE staging with survival

SFS staging was aggregated in a five-tiered system based on relation to survival: no fibrosis (SFS 0), mild and moderate fibrosis (SFS 1 and 2), severe fibrosis (SFS 3), cirrhosis with thin or broad septa (SFS 4A and 4B), and cirrhosis with very broad septa (severe cirrhosis; SFS 4C). On Kaplan-Meier analysis the respective mortality rates of patients were 0%, 4%, 23%, 33% and 55%, respectively (Figure 3A).

Long-term mortality was significantly higher for patients with severe cirrhosis vs. pre-cirrhotic stages and vs. lesser cirrhosis (p<0.001 and p=0.003, significance level p=0.016). In contrast, severe cirrhosis showed only a trend in relation to short-term outcome (p=0.162) in patients with decompensated disease and also in the subgroup of decompensated patients with hASH (p=0.070) (Supplementary Figure 9). In compensated ALD, severe fibrosis/cirrhosis was related to the development of liver-related events on long-term follow up (p<0.001) (Figure 3B).

Association of the pericellular fibrosis type with outcome, inflammation, and venous lesions

Stages with severe PCF (*SFS 3P, 4AP, 4BP, 4CP*) had significantly worse long-term outcome than the respective SFS stages without severe PCF (SFS 3, 4A, 4B, 4C) (p=0.042) (Supplementary Figure 10).

Severe PCF was associated with ballooning/MDB, cholestasis and lobular neutrophils (Chi-square test, p<0.001 for all parameters). In the Graz cohort, venous lesions were assessed and associated with severe PCF although no association of any of the venous lesions with long- or short-term prognosis was found.

Independent predictors of survival and liver-related events

Clinical, biochemical and histological variables associated with long- or short-term survival on univariable Cox regression are detailed in Supplementary Table 2. On multivariable Cox regression, sex, MELD, platelet count, hepatic encephalopathy, and severe cirrhosis emerged as independent predictors of long-term liver-related mortality (Table 5). In a subgroup of patients in whom follow-up data on abstinence were available (n=323), sex, MELD, hepatic encephalopathy, abstinence, and severe cirrhosis were independent predictors of long-term liver-related mortality.

In decompensated ALD, MELD, hepatic encephalopathy, hASH, and severe cirrhosis were independent predictors of short-term (90-day) liver-related mortality. In the subgroup of decompensated patients with hASH, MELD, hepatic encephalopathy, and severe cirrhosis independently predicted 90-day liver-related death.

In patients with compensated ALD, decompensation-free survival was independently predicted by MELD, albumin, hASH, severe cirrhosis, and abstinence during follow-up.

Discussion

The aim of our study was to design and validate an ALD specific histological grading and staging system that has hitherto been lacking. This study presents the SALVE grading and staging system, a robust histological method with substantial interobserver agreement and clear associations to clinical outcomes in ALD.

While none of the grading features have been identified as independent prognostic factors for long-term outcome in previous studies [11, 23], ballooning, MDBs or lobular neutrophils have been described as independent predictors of short-term mortality in patients with decompensated ALD [15, 20, 24]. The association of hASH with short-term outcome in decompensated patients in our study confirms these results. Histological diagnosis of hASH in patients with decompensated ALD is clinically important to identify those with worse prognosis. Furthermore, in those with decompensation and hASH, short-term prognosis is predicted by clinical factors along with severe cirrhosis. The results emphasize the clinical utility of liver biopsy in these high-risk situations.

Cholestasis is a distinct feature of severe ALD, which is not described in NAFLD [1, 25]. Ballooning-associated obstruction of bile radicles [26], impaired bile formation and transport in hepatocytes [27] may be involved in canalicular cholestasis. Defective bile secretion via canalicular transporters and/or decreased bile flow have been implicated in sepsis-associated cholestasis [28, 29]. Bacterial infection and sepsis-associated immune paralysis are frequent in advanced ALD and often fatal complications triggering acute-on-chronic liver failure [30]. Ductular cholestasis has been associated with evolving

(subclinical) sepsis and thus may indicate infection at an early stage [15, 20, 24]. Both canalicular and ductular cholestasis convey prognostic information in the whole study cohort, in the decompensated subgroup as well as in decompensated patients with hASH. This supports similar results of others [29, 31] and underscores the prognostic utility of morphological cholestasis as an integral factor of SALVE grading.

Since most patients with ALD exhibit severe fibrosis or cirrhosis at first diagnosis, any stepwise staging method should allow subclassification into prognostically meaningful categories. Based on the SALVE staging system and Kaplan-Meier analyses, two cirrhosis substages with different mortality risk could be defined. Patients with severe cirrhosis (SFS 4C) had worse outcome than patients with lesser grades cirrhosis (SFS 4A and 4B). Moreover, severe cirrhosis emerged as an independent histological predictor for both long- and short-term survival in the whole study cohort, in subgroups of patients with symptomatic/decompensated disease as well as in patients with hASH. Our data are thus in line with results from earlier studies, indicating the prognostic utility of cirrhosis substaging in chronic liver disease [14, 32].

PCF can be a striking feature in ALD. Interestingly, in contrast to SFS with predominant septal fibrosis, (like SFS 3 or 4A/B/C), severe PCF (*SFS 3P* or *4AP/BP/CP)* was associated with morphological features of liver injury, inflammation, fibro-obliterative venous lesions, cholestasis, and significantly shorter long-term outcome. The PCF pattern may indicate active disease and ongoing fibrogenesis. It may represent an immature type of fibrosis because it lacks elastic fibres and clusterin, a potent inhibitor of matrix-degrading metalloproteinases [33] present in mature scar tissue [34]. Data from rodent models of cirrhosis suggest that recent fibrous septa are readily degraded whereas older septa rich in elastin are more resistant [35]. Therefore, it could be speculated that PCF is more sensitive to degradation than dense fibrotic septa. Regression of PCF observed in a paired biopsy on follow-up could indicate decreased or resolved liver injury in phases of abstinence or medical intervention and could be useful to trace early antifibrotic treatment effects to monitor the evolution of fibrosis. Specific stages *SFS 3P, 4AP, 4BP* and *4CP* were introduced in the SALVE staging system as an option to identify cases in which PCF is the predominant fibrosis type and to define these stages that to date

are not represented in other staging systems. If applied with the help of the staging algorithm, interrater agreement is substantial.

Our study has some limitations related to its retrospective design. Although a large panel of expert hepatopathologists reached substantial interobserver agreement, the proposed system should also be validated in a general pathology setting.

In conclusion, the SALVE histopathology group developed and validated an ALD specific grading and staging system based on a large cohort of patients representing the whole clinical spectrum of alcohol-related liver disease. This histological system integrates features of disease activity and fibrosis in a prognostic context. The large patient number has enabled us to evaluate the applicability and prognostic utility of SALVE grading and staging in clinically important subgroups, with compensated and decompensated disease as well as in patients with histological ASH. Activity scores can be used to define the severity of injury and inflammation as well as the diagnosis of steatohepatitis and may, along with SALVE stage, assist patient management.

Abbreviations

ALD, Alcohol-related liver disease

SHG, SALVE Histopathology Group

hASH, Histological steatohepatitis due to ALD

SFS, SALVE fibrosis stage

PCF, Pericellular fibrosis

SALVE, Consortium for the Study of Alcohol-related LiVer disease in Europe

MDB, Mallory-Denk body

Acknowledgement

The authors thank Drs. Elizabeth M. Brunt and Ian R. Wanless for fruitful discussion of the ALD-specific staging system.

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Table 1. SALVE grading

Steatosis (S) grade: Macrovesicular steatosis*; % parenchymal involvement

Score 0: <5%

Score 1: 5-33%

Score 2: 34-66%

Score 3: >66%

Activity (A) grade: Sum of scores for hepatocellular injury (ballooning (B) **OR** Mallory-Denk bodies (MDB))** and lobular neutrophils (LN)

Score 0: None-rare

Score 1: Few[§]

Score 2: Many[§§]

Lobular neutrophils (LN)

Score 0: None-rare

Score 1: Few[§]

Score 2: Many[§§] and/or satellitosis[%]

Cholestasis Type

Canalicular cholestasis (CC)

Score 0: None

Score 1: Present

Ductular cholestasis (DC)

Score 0: None

Score 1: Present

SALVE grade is described by itemization of each of the component scores:

S 0-3**, A (B/MDB** 0-2 **+ LN** 0-2**), CC** 0-1**, DC** 0-1

* Lipid vacuoles in the cytoplasm of hepatocytes larger than the hepatocellular nucleus.

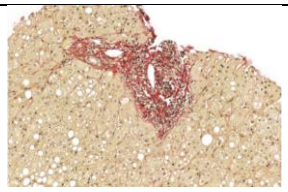
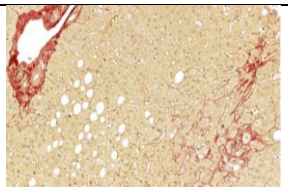
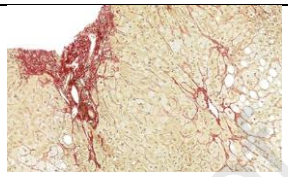
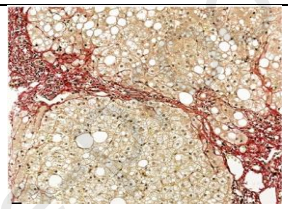
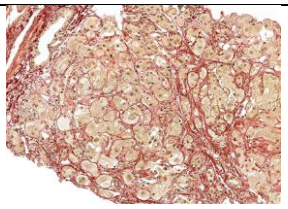
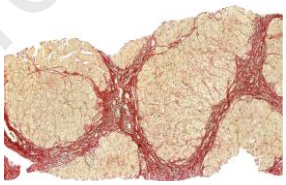
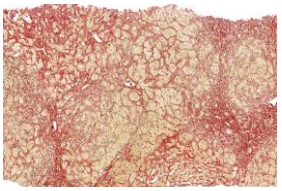
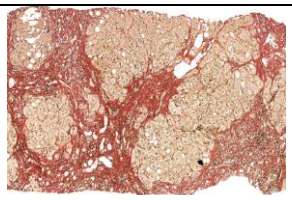
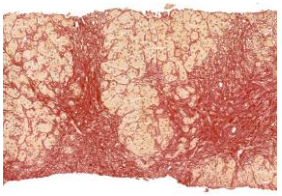
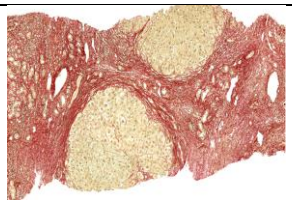
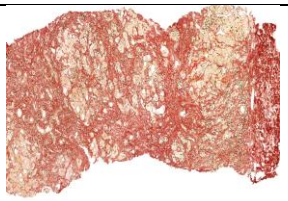
** If scores for ballooning and Mallory-Denk bodies are unequal the higher score is applied.

[§] Feature is appreciated after a reasonable search and is present in few microscopic fields.

[§§] Feature is frequent and easy to find without searching and present in many microscopic fields.

[%] Neutrophils surrounding ballooned hepatocytes.

Table 2. SALVE staging

SFS[a]	Description	Morphological changes[b]	Examples	
0	**No fibrosis**	Fibrosis is absent		
1	**Mild fibrosis**	Periportal fibrosis only or PCF[c] in zone(s) 3±2 ***SFS 1P[d]**: PCF in zone(s) 3±2 only*		
2	**Moderate fibrosis**	Periportal fibrosis and PCF in zone(s) 3±2		
3	**Severe fibrosis**	≥1 complete septum[e] bridging portal tracts and/or central veins, ±PCF ***SFS 3P[d]**: Panlobular PCF and/or complete septal PCF ± few dense septa ± venous lesions*		
4A	**Cirrhosis thin septa**	≥1 parenchymal nodule[f], thin septa[g], ± 1 broad septum[h], ±PCF ***SFS 4AP[d]**: Severe PCF[i] in >50% of parenchyma, indistinct parenchymal nodules[j]*		
4B	**Cirrhosis broad septa**	Parenchymal nodules, >1 broad septum, ± 1 very broad septum[k], ±PCF ***SFS 4BP[d]**: Severe PCF in >50% of parenchyma*		
4C	**Cirrhosis very broad septa**	Parenchymal nodules, >1 very broad septum, ±PCF ***SFS 4CP[d]:** Severe PCF in >50% of parenchyma*		

[a] SALVE Fibrosis Stage

[b] Description of the full range of topographical abnormal fibrosis including the degree of both dense septal and pericellular fibrosis.

[c] Pericellular fibrosis: Collagen fibres surrounding single or small groups of hepatocytes.

[d] **OPTIONAL, the presence of pericellular fibrosis as a dominant fibrosis type may be staged as defined in the grey insets.**

[e] Complete septum: Fibrous band consisting mainly of collagen fibres resembling septa in viral hepatitis or septal PCF crossing biopsy diameter and linking portal tracts, portal tracts and central veins, or central veins.

[f] Parenchymal nodule without evidence of portal-central relations surrounded by dense septa.

[g] Thin septum: Dense septum, <50% of diameter of smallest parenchymal nodule.

[h] Broad septum: Dense septum, ≥50% of the diameter of smallest parenchymal nodule but not thicker.

[I] PCF evaluated at **LOW magnification** (20x or 40x total magnification).

[j] Parenchymal areas of indistinct nodular shape dissected by severe PCF.

[k] Very broad septum: Dense septum, wider than the diameter of smallest parenchymal nodule.

Table 3. Clinical, biochemical and demographic characteristics of the study cohorts.

Centre	*Graz (n=172)*	*Cluj-Napoca (n=92)*	*Paris (n=75)*	*Odense (n=106)*
Period of enrolment	1995-2009	2016-2019	2011-2019	2013-2016
Decompensated ALD, %	69	100	100	0
Age, years	49 (41, 57)	51 (43, 57)	54 (48, 59)	56 (49, 62)
BMI	25 (22, 29)	26 (22, 30)	26 (22, 30)	26 (23, 28)
Sex female, %	31	27	20	26
AST, U/L	45 (26, 77)	140 (99, 188)	146 (96, 197)	39 (27, 55)
ALT, U/L	28 (16, 54)	44 (27, 57)	41 (31, 67)	30 (21, 43)
GGT, U/L	148 (62, 327)	332 (207, 642)	272 (134, 667)	103 (47, 238)
Alkaline phosphatase, U/L	160 (109, 226)	463 (322, 573)	164 (122, 234)	96 (76, 125)
Bilirubin, mg/dl	2.6 (1.1, 8.5)	8.1 (4.0, 19.5)	11.1 (6.7, 19.4)	0.6 (0.4, 0.9)
INR	1.22 (1.03, 1.57)	1.93 (1.65, 2.29)	1.82 (1.58, 2.36)	1.0 (0.9, 1.1)
Creatinine, mg/dl	0.9 (0.8, 1.1)	0.7 (0.6, 0.8)	0.7 (0.6, 1.0)	0.8 (0.7, 0.9)
Albumin, g/dl	3.5 (2.9, 4.3)	2.8 (2.5, 3.1)	2.0 (1.8, 2.4)	4.1 (3.8, 4.3)
Platelet count, G/L	138 (94, 231)	110 (78, 162)	127 (73, 173)	227 (163, 297)
Leucocyte count, G/L	6.8 (5.3, 10.8)	9.8 (7.2, 13.0)	9.9 (7.0, 15.2)	6.7 (5.4, 9.2)
MCV, fl	100 (94, 105)	102 (97, 108)	n.r.	95 (91, 101)
Sodium, mmol/L	138 (135, 141)	136 (133, 139)	132 (128, 136)	139 (138, 141)
Variceal bleeding, %	15	16	n.r.	0
Hepatic encephalopathy, %	21	37	31	0
Ascites, %	44	84	88	0
MELD	14 (9, 20)	22 (19, 26)	23 (19, 27)	6 (6, 8)
Child-Pugh score	8 (6, 10)	10 (8, 12)	12 (11, 13)	5 (5, 5)
Route of biopsy, n (percutaneous/transjugular)	164/8	0/92	0/75	106/0
Length of biopsy core, mm	18 (12, 27)	21 (16, 28)	37 (28, 50)	33 (27, 40)
Survival, years	4.1 (0.9, 8.8)	1.6 (0.4, 3.5)	0.5 (0.1, 1.4)	4.0 (3.5, 4.9)
90-day mortality, %	9	23	27	0
5-yr mortality, %	34	49	44	5

Data are given as median (Q1, Q3).
n.r., not reported.

Table 4. Interobserver variation in scoring of histological features of SALVE grade and stage (Graz cohort).

Item	Scoring system	Kappa value
Steatosis	Score 0: <5%; 1:5-33%; 2:34-66%; 3: >66%	0.88[a]
Hepatocellular ballooning	Score 0: none, 1: few; 2: many	0.66[a]
Mallory-Denk bodies	Score 0: none, 1: few; 2: many	0.78[a]
Lobular neutrophils	Score 0: none, 1: few, 2: many and/or satellitosis	0.67[a]
Hepatocellular cholestasis	0: none, 1: present	0.33[b]
Canalicular cholestasis	0: none, 1: present	0.65[b]
Ductular cholestasis	0: none, 1: present	0.66[b]
SFS* (all substages)	0, 1/1P, 2, 3/3P, 4A/4AP, 4B/4BP, 4C/4CP	0.69[c]
SFS* (main stages)	0, 1, 2, 3, 4A, 4B, 4C	0.80[c]
Pericellular fibrosis	0, 1	0.69[c]

* SFS, SALVE Fibrosis Stage

[a] Kendall's W, 10 raters, 27-29 observations

[b] Fleiss' Kappa, 10 raters, 28-29 observations

[c] Cohen's Kappa, 2 rater groups, 138 observations

Table 5. Clinical, biochemical and histological predictors of outcome in patients with ALD. Multivariable Cox regression.

Variable	Hazard ratio (95% CI)	*P*
Predictors of long-term liver-related mortality in the whole cohort (n=445)		
Severe cirrhosis (SFS 4C)	1.88 (1.32-2.68)	<0.001
Male sex	0.68 (0.47-0.97)	0.036
MELD	1.11 (1.08-1.13)	<0.001
Platelet count	0.997 (0.995-0.999)	0.014
Hepatic encephalopathy	1.58 (1.09-2.27)	0.015
Entered variables: severe cirrhosis (SFS 4C), hASH, ductular cholestasis, sex, MELD, WBC, platelet count, hepatic encephalopathy. Maximal VIF=2.17.		
Predictors of 90-day liver-related mortality in patients with decompensated ALD (n=286)		
Severe cirrhosis (SFS 4C)	2.21 (1.24-3.96)	0.008
hASH present	1.98 (1.02-3.85)	0.043
MELD	1.19 (1.14-1.24)	<0.001
Hepatic encephalopathy	2.44 (1.38-4.30)	0.002
Entered variables: severe cirrhosis (SFS 4C), hASH, ductular cholestasis, sex, MELD, WBC, hepatic encephalopathy. Maximal VIF=1.64.		
Predictors of 90-day liver-related mortality in decompensated patients with hASH (n=181)		
Severe cirrhosis (SFS 4C)	2.16 (1.11-4.18)	0.023
MELD	1.19 (1.13-1.26)	<0.001
Hepatic encephalopathy	2.28 (1.20-4.35)	0.012
Entered variables: severe cirrhosis (SFS 4C), canalicular cholestasis, sex, MELD, WBC, platelet count, hepatic encephalopathy. Maximal VIF=1.51.		
Predictors of decompensation-free survival in patients with compensated ALD (n=159)		
Severe cirrhosis (SFS 4C)	3.26 (1.38-7.69)	0.007
hASH present	2.80 (1.32-5.96)	0.008
MELD	1.22 (1.05-1.42)	0.011
Albumin	0.44 (0.22-0.91)	0.026
Abstinence during follow-up	0.33 (0.12-0.91)	0.032
Entered variables: severe cirrhosis (SFS 4C), hASH, age, MELD, albumin, abstinence during follow-up. Maximal VIF=1.32.		

SFS, SALVE fibrosis stage; hASH, histological steatohepatititis due to ALD; VIF, variance inflation factor

Figure legends

Figure 1. SALVE staging algorithm.

For definitions see Table 2.

[a] SFS, SALVE fibrosis stage

[b] PCF, Pericellular fibrosis

[c] Optional stages to indicate presence of PCF as the predominant fibrosis type

Figure 2. Kaplan-Meier plots of long-term survival by SALVE grade (whole cohort, n=445).

A. Effect of activity grade on survival: 0-1, no or mild activity; 2-4, high activity; $p<0.001$ (log-rank test).

B. Effect of canalicular cholestasis (CC) and ductular cholestasis (DC) on survival; $p<0.001$ (log-rank test).

Figure 3. Kaplan-Meier plots of long-term outcome by SALVE fibrosis stage (SFS).

A. Effect of SFS tiers on long-term survival (whole cohort, n=445): no fibrosis, SFS 0; mild fibrosis, SFS 1-2; severe fibrosis, SFS 3; cirrhosis, SFS 4A-4B; severe cirrhosis, SFS 4C; $p<0.001$ (log-rank test).

B. Effect of SFS on decompensation-free survival during follow-up (compensated ALD, n=159): no/mild fibrosis, SFS 0-2; severe fibrosis/cirrhosis, SFS 3-4; $p<0.001$ (log-rank test).

Figure 1

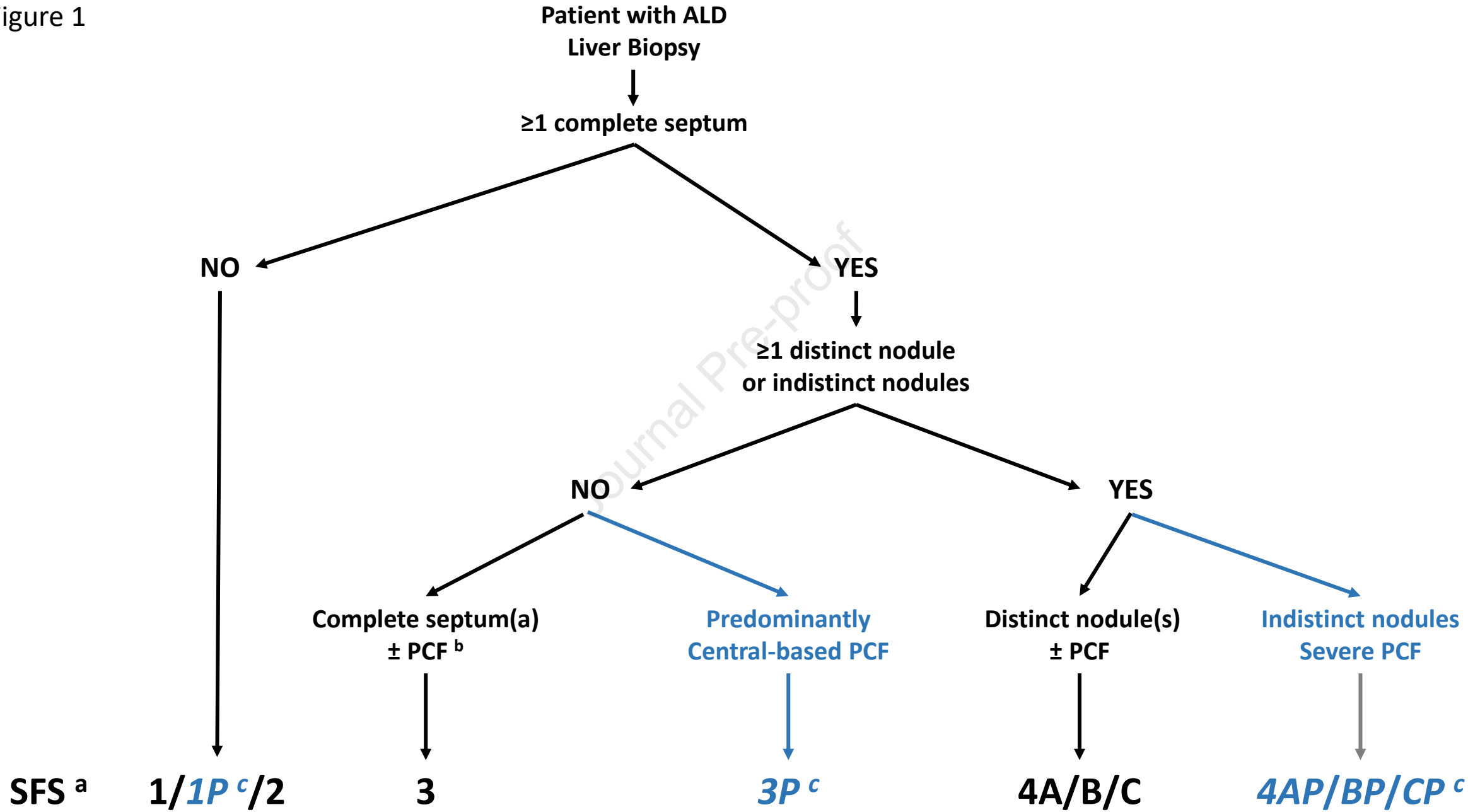


Figure 2A

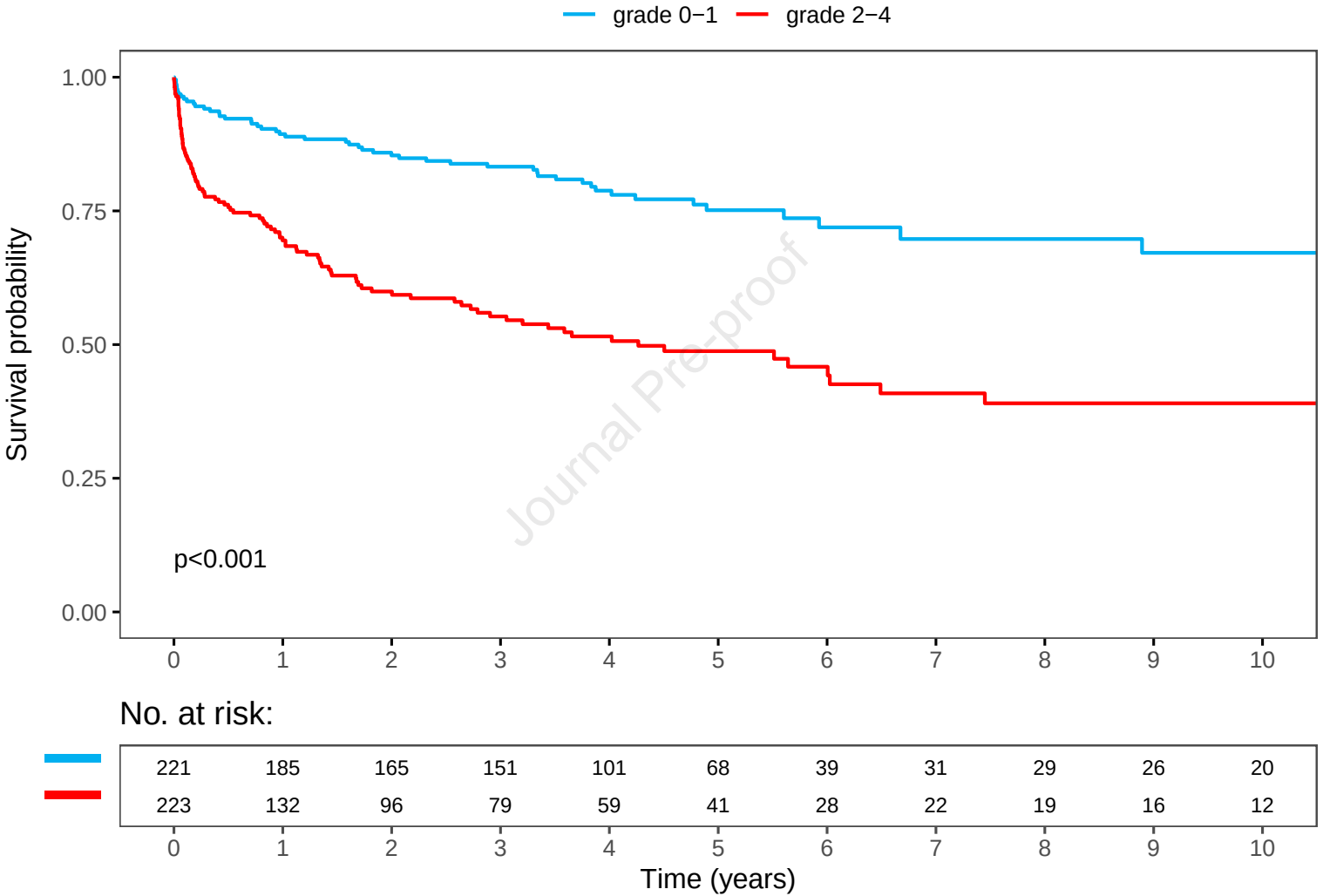


Figure 2B

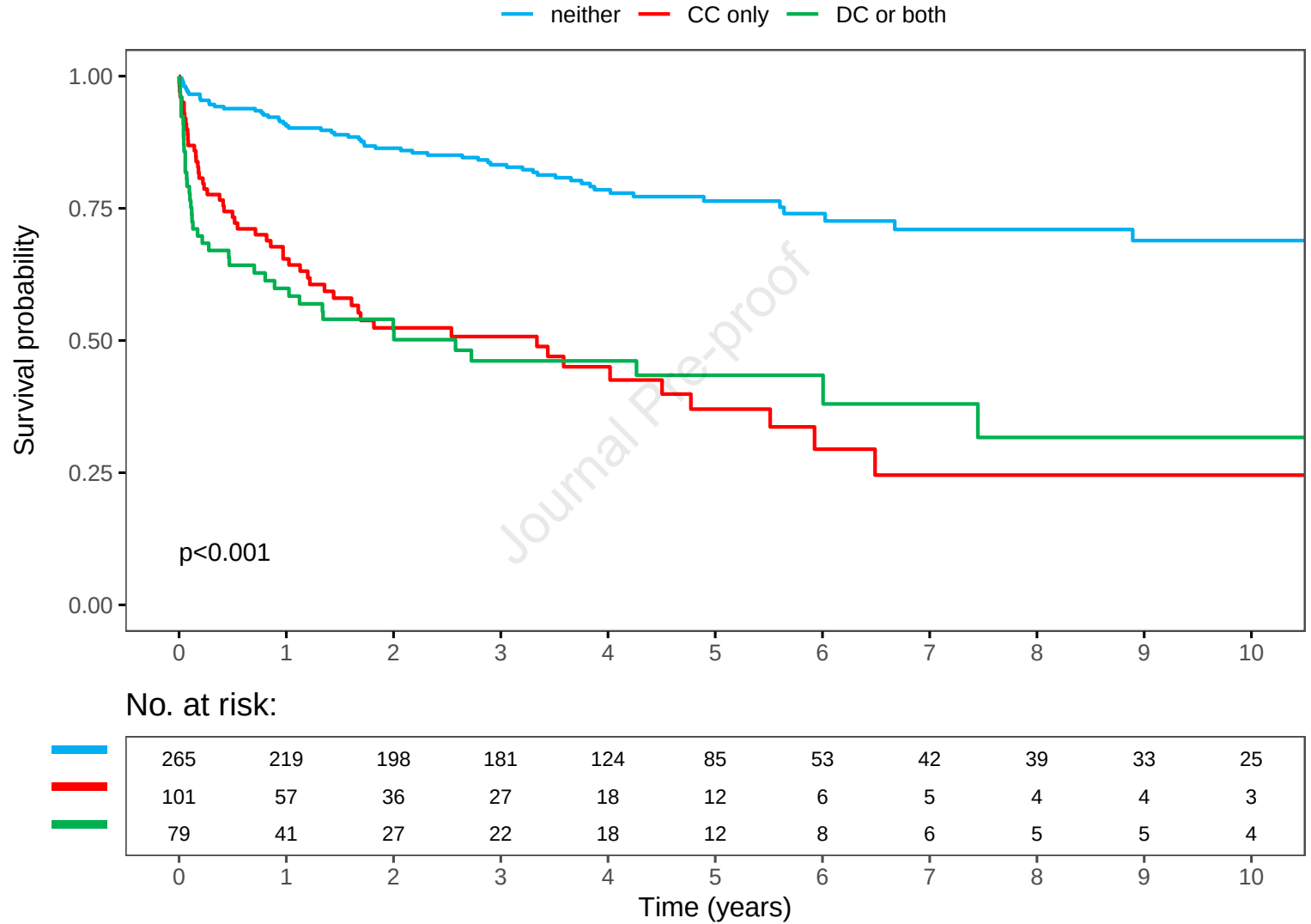


Figure 3A

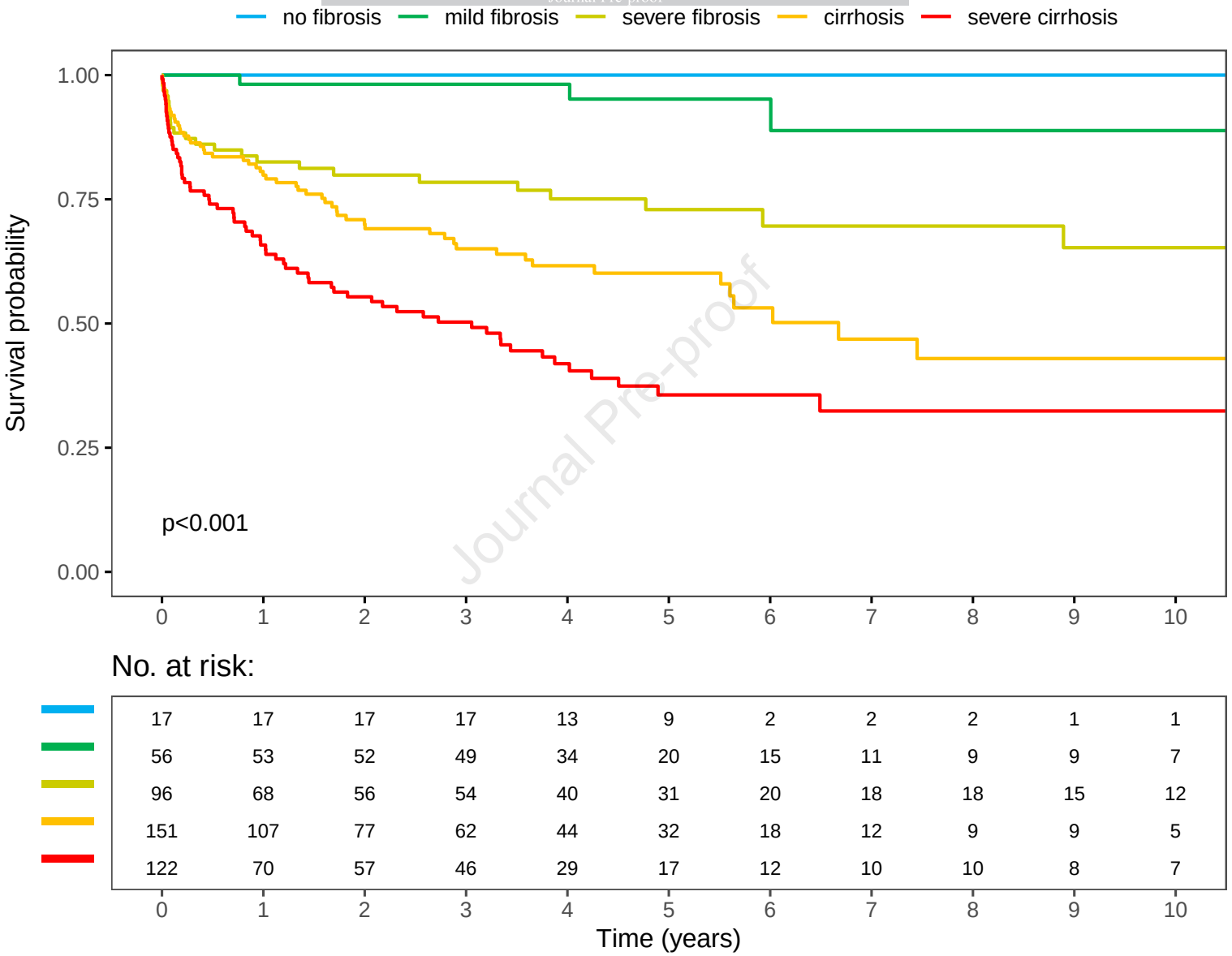
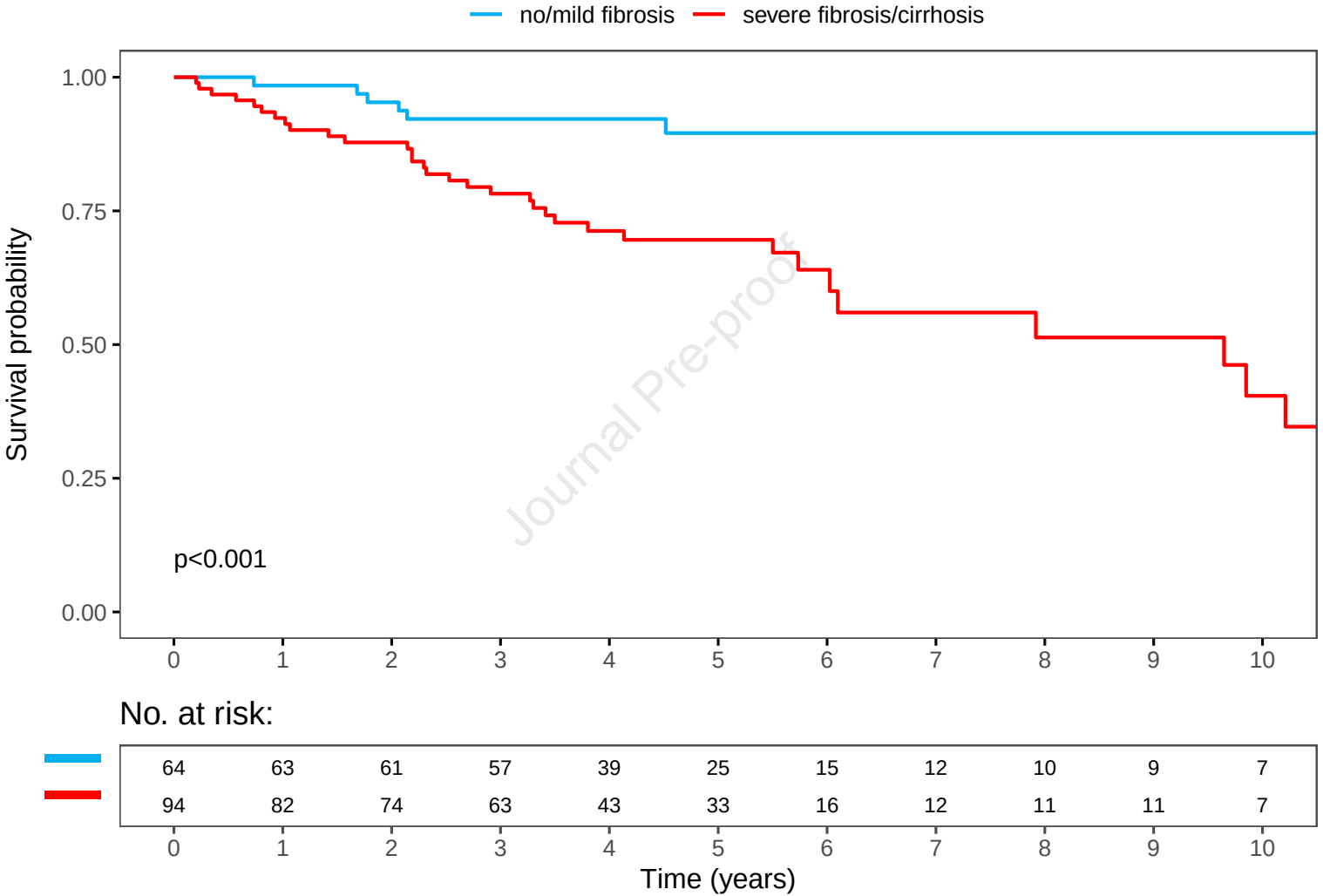


Figure 3B



JHEPAT-D-20-01693

Development and prognostic relevance of a histologic grading and staging system of alcohol-related liver disease

Highlights:

- Alcohol-related liver disease (ALD) is the most frequent cause of cirrhosis in Europe but an ALD-specific histologic grading and staging system is lacking.
- The SALVE Histopathology Group developed a reproducible grading and staging system for ALD
- The prognostic value of the new grading and staging system was evaluated in a large cohort of patients with compensated or decompensated ALD enrolled at four European centers.
- ASH and severe cirrhosis on histology were independent predictors of liver-related events in compensated ALD as well as liver-related death in decompensated ALD.