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Keywords:	NAFLD, MASLD, fibrosis, FIB-4 index, liver biopsy

Clinical variables predicting liver-related events in steatotic liver disease diagnosed by liver biopsy

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ABSTRACT

***Objective*:** Identifying high-risk patients with steatotic liver disease is crucial. The liver fibrosis stage is the most reliable marker for liver disease-related mortality. However, non-invasive risk stratification methods are still debated. Therefore, we aimed to analyze the risk of liver-related events in patients who underwent liver biopsy as non-alcoholic fatty liver disease (NAFLD) at our hospital.

***Methods*:** We retrospectively reviewed the clinical courses of patients with steatotic liver disease to identify the occurrence of liver-related events.

Patients: The study included 146 patients diagnosed with steatotic liver disease through liver biopsy.

Results: Liver-related events occurred in 20 patients, and were more frequent in patients with advanced fibrosis compared to those without. However, patients with advanced steatosis showed reduced

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disease progression. Patients with obesity and/or diabetes complications had lower fibrosis stage and better prognosis. The non-invasive fibrosis-4 (FIB-4) index and NAFLD prognosis related to the NAFLD outcome score (NOS) have effectively differentiated patients with disease progression. Standard laboratory data analysis revealed that high total bilirubin and low albumin levels were risk factors. Multivariate analysis with significant factors other than the NOS score revealed that the absence of obesity and/or diabetes complications, high FIB-4 index, and high total bilirubin level were independent factors for liver-related events.

Conclusion: High NOS score, absence of obesity and/or diabetes complications, high FIB-4 index, and high total bilirubin levels are risk factors for disease progression. Patients with lean phenotypes or non-diabetic steatotic liver disease should also be assessed using these non-invasive markers to determine their risks and potential outcomes.

Keywords; NAFLD, MASLD, fibrosis, FIB-4 index, liver biopsy

INTRODUCTION

The prevalence of non-alcoholic fatty liver disease (NAFLD) in adults with one or more cardiometabolic diseases exceeds 60-75% (1). Due to the high prevalence of cardiometabolic diseases associated with NAFLD, their complications have been recognized as significant risk factors for NAFLD. In 2023, a new criterion called metabolic dysfunction-associated fatty liver disease (MASLD) was proposed in a multi-society Delphi statement (2). MASLD was defined as hepatic steatosis accompanied by at least one of five cardiometabolic risk factors.

Large cohort studies have shown that the prevalence of MASLD highly correlates with NAFLD (3, 4). However, MASLD could be matched relatively low frequency as 84% of lean NAFLD. Lean NAFLD has been reported to be milder than non-lean NAFLD (5); however, a recent meta-analysis indicated worse liver outcomes despite similar cardiometabolic outcomes (6). This highlights the need for liver risk assessment in lean NAFLD patients, which does not meet the MASLD criteria. In Western countries, the most common cause of death in NAFLD is cardiovascular disease, whereas liver-related mortality has been shown to be more prevalent in Asians, particularly the Japanese (7). The gold standard for predicting liver-related mortality has been the histologically-proven liver fibrosis in biopsy-confirmed NAFLD cases in Japan (7). Non-invasive tests for assessing the progression of liver fibrosis are promising methods for predicting liver-related mortality.

In this study, we investigated non-invasive factors that predict liver-related events in patients with biopsy-proven steatotic liver disease (SLD).

METHODS

Patients

Hundred forty-six patients diagnosed with SLD by liver biopsy at Okayama University Hospital between 2006 and 2021 were enrolled in the study. All liver biopsy specimens were assessed by two hepatologists (A.T. and T.A.) who were blinded to the study group allocation. The METAVIR scoring system was used to analyze the activity and stage of liver fibrosis. The patients were confirmed to be cancer-free and tested negative for hepatitis B and C viral markers and autoantibodies. The baseline characteristics of the patients are

summarized in Table 1. Patients with obesity and/or diabetic complications were included.

Written informed consent was obtained from each patient before enrolment in the study. The study adhered to the ethical guidelines of the Declaration of Helsinki. This study was approved by the Institutional Ethics Review Committee of Okayama University (EKI1015).

Non-invasive tests for SLD risk stratification

For non-invasive tests, the following data were included in the assessment: the fibrosis-4 (FIB-4) index (age × AST / platelet × √ALT), the LiverRisk score (LRS) including age, sex, fasting plasma glucose level, platelet counts, total cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (gamma-GTP) levels (8), the NAFLD outcomes score (NOS), including age, diabetes complication, albumin, total bilirubin, prothrombin time international normalized ratio (PT-INR), and platelet counts (9). As representative metabolic risk factors, obesity and/or diabetic complications were defined as steatotic liver disease complicated by obesity and/or diabetes (OD-SLD).

Clinical course assessment

The patients were followed up until December 2023, and their clinical courses were assessed. Liver-related events were defined using the following criteria: development of hepatocellular carcinoma (HCC), ascites or edema requiring diuretics, and death from liver-related conditions.

Statistical analysis

The endpoints of liver-related events were calculated from the date of liver biopsy. Differences in the time until liver-related events were analyzed using the Kaplan–Meier method and Wilcoxon test. Factors associated with improved overall survival (OS) were analyzed using univariate and multivariate Cox proportional hazards regression models. The Wilcoxon rank-sum test was used to compare continuous data, while the chi-square test was used for categorical data. Statistical analyses were performed using JMP, version 13 (SAS Institute, Cary, NC, USA), with significance set at $p < 0.05$.

RESULTS

Participants characteristics and the liver-related outcomes

The baseline clinical and laboratory characteristics of the participants are shown in Table 1. The median age was 56 years, with 46.2% being male. The median BMI was 26.8 kg/m^2. Analysis revealed that 64 patients (44.8%) had advanced fibrosis stages (F3-4), 41 patients (28.6%) had severe activity grades (A2-3), and 93 patients (64%) had >30% steatosis. The median observation period was 1202 days post-liver biopsy.

Advanced fibrosis and low steatosis were significantly associated with liver-related events

As expected, advanced liver fibrosis patients showed significantly worse clinical course than others. The liver histological activity grades showed no significant differences in the occurrence of liver-related events. However, patients with lower steatotic levels have poorer outcomes (Figure 1).

Obesity and/or diabetes complications were negatively associated with liver disease-related events

We hypothesized that the cardiometabolic risks from obesity and diabetic complications might result in poor outcomes; therefore, we compared liver-related events in patients with these conditions (Figure 2A). However, these patients had better outcomes than those without complications. To determine why the data were contrary to our predictions, we compared the clinical characteristics of the two groups (Table 2). The obesity and/or diabetes-complicated group showed higher ALT and albumin levels, with a relatively high frequency of low-stage liver fibrosis. These data suggested that these patients were not in an advanced stage.

Non-invasive tests for NAFLD were significantly associated with liver-related events

Next, we investigated the FIB-4 index, LRS, and NOS to determine the best non-invasive tests for predicting liver-related events. The FIB-4 index, a widely accepted fibrosis predictive test, successfully differentiated between high-risk and low-risk groups, as expected (Figure 2B). In contrast, the LRS, which was created based on the general population, did not show significant differences between the high and low LRS groups. However, the NOS, which was created based on the data at specialized hospital, was significantly associated with an increased risk of liver-related events (Figure 2C).

Low albumin and high total bilirubin levels were significantly associated with liver-related events

To determine whether standard laboratory tests could identify the risk of liver-related events, we analyzed the liver function-related data and found that low albumin and high total bilirubin levels were significant risk factors (Figure 2D, E).

Multivariate analysis of the non-invasive markers for risks of liver-related events

Univariate analysis revealed that complications of obesity and/or diabetes, NOS, FIB-4 index, albumin, and total bilirubin were not significant predictors of liver-related events. We then performed a multivariate analysis to determine independent factors with significant univariate factors, excluding those already included in the NOS (Table 3). The analysis revealed that the absence of complications of obesity and/or diabetes, a high FIB-4 index, and high total bilirubin levels were independent risk factors for liver-related events.

DISCUSSION

In this study, we determined the risk of progression of biopsy-proven SLD. Advanced fibrosis stages were significantly associated with a high risk of liver-related events, as expected; however, cardiometabolic risk factors, such as obesity and/or diabetes complications, showed a negative correlation with their progression. The multi-factor NOS score was predictive of disease progression. Multivariate analysis revealed that the absence of complications of obesity and/or diabetes, fibrosis-associated FIB-4 index, or liver reservoir-related total bilirubin level were not significant risk factors for progression.

Recently defined MASLD requires cardiometabolic risk analysis, and non-complicated patients are excluded. However, our analysis showed that representative cardiometabolic factors, obesity, and/or diabetic complications were negative risk factors for liver-related events, which may seem counterintuitive. This discrepancy could be due to our patients with obesity and/or diabetes being at an earlier stage of SLD, with relatively lower fibrosis. In chronic liver disease, patients in advanced stages often show sarcopenia and decreased

cholesterol production, resulting in non-obese conditions (10). Our results indicate that risk assessment in non-obese and non-diabetic individuals with NAFLD should be adequately performed using the FIB-4 index, NOS, and total bilirubin levels because of the possibility of including advanced patients in these cohorts.

Additionally, lean NAFLD, which constitutes 7–25% of NAFLD cases, is relatively common in Asia (11). Of the lean NAFLD cases, approximately 70% are based on visceral adiposity and insulin resistance, while the remaining 30% show hepatic monogenic disease (12). Patients with lean NAFLD have been shown to exhibit a higher risk of liver-related mortality than those with non-lean NAFLD (13). Our data showed that lean non-OD-SLD showed 67% advanced-stage fibrosis, while non-lean OD-SLD showed 42% advanced-stage, indicating that the characteristics of lean NAFLD may affect the results. Genetic studies, such as genome-wide association studies, have shown that genetic polymorphisms affect the risk of developing NAFLD and lean NAFLD. Several Human Leukocyte Antigen (HLA) loci are reportedly associated (14). The risk of fibrosis-related factors should be assessed in patients with monogenic hepatic disease.

In addition to obesity and/or diabetes complications, a high FIB-4 index and elevated total bilirubin levels were significant predictive factors of liver-related events. The FIB-4 index is widely accepted as a reliable marker of fibrosis and liver-related events (15). Total bilirubin is a known liver function-related marker included in the Child-Pugh score. Recently, many approaches have been investigated to predict the stages of liver fibrosis. Imaging modalities such as ultrasound elastography and Magnetic Resonance (MR) elastography provide accurate prediction of liver fibrosis (16). However, a single biomarker is insufficient (17), and a combined

assessment is recommended. Scores derived from laboratory data, such as the FIB-4 index, should be combined with the assessment of fibrosis on imaging, although we could not include such imaging data. In addition, total bilirubin is also an important marker that should be included in patient risk assessments.

Several multifactorial calculations have been reported as non-invasive tests. We examined LRS and NOS scores. The LRS is derived from records of the general population without known liver disease, while the NOS is based on data from patients diagnosed with NAFLD and followed at a specialized hospital. The NOS includes liver function-related parameters such as albumin, total bilirubin, and PT-INR. These differences in background factors may have influenced our findings, resulting in the superior performance of the NOS. Based on this background, the LRS score and the complications of obesity and/or diabetes may be important in analyzing early-stage SLD. Given that SLD includes patients with various stages of the disease, from mild to severe, the risk of progression varies depending on the target patient's background. Our indications for liver biopsy in SLD are specific to cases expected to be in advanced stages. The characteristics of these patients may have influenced our results.

This study has some limitations. First, the number of patients included was limited, and the observation period was not sufficiently long. Second, MASLD could not be diagnosed due to the unavailability of several metabolic factors, such as waist circumference and lipid-related data. The included patients who underwent liver biopsies were primarily those expected to be in advanced stages, which may have introduced selection bias and affected our interpretation.

In conclusion, this study found that metabolic factors, such as complications of obesity and/or diabetes, may not be significant risk factors for liver-related events in patients who underwent liver biopsy. NOS, liver fibrosis-related FIB-4 index, and liver reservoir-related total bilirubin were effective markers to predict their outcome. Given the diverse nature of the SLD population, careful risk assessment is essential.

The authors state that they have no Conflict of Interest (COI).

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Abbreviations

NAFLD: non-alcoholic fatty liver disease

MASLD: metabolic dysfunction-associated fatty liver disease

SLD: steatotic liver disease

FIB-4 index: fibrosis-4 index

LRS: LiverRisk score

AST: aspartate aminotransferase

ALT: alanine aminotransferase

gamma-GTP: gamma -glutamyl transpeptidase

NOS: NAFLD outcomes score

PT-INR: prothrombin time international normalized ratio

OD-SLD: steatotic liver disease complicated by obesity and/or diabetes

HCC: hepatocellular carcinoma

OS: overall survival

HLA: Leukocyte Antigen

MR elastography: Magnetic Resonance elastography

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FIGURE LEGENDS

Figure 1. Liver-related events according to biopsy-proven liver fibrosis stages

(A) Occurrence rate of liver-related events was investigated. Kaplan-Meier curve for the liver-related events of all patients.

(B) Occurrence rate of liver-related events was divided into two groups according to the fibrosis stages (F0-2 vs F3-4) with significant differences.

(C) Occurrence rate of liver-related events was divided into two groups according to the steatosis.

Figure 2. Liver-related events according to non-invasive tests

Rate of occurrence of liver-related events was also investigated. The Kaplan-Meier curves for liver-related events were divided into two groups.

(A) Patients were grouped according to the complications of obesity and/or diabetes (OD-SLD). Patients with OD-SLD had better outcomes.

(B) Patients were grouped according to FIB-4 index. Patients with a lower FIB-4 index have better outcomes.

(C) Patients were grouped according to the NOS index. Patients with lower NOS scores had better outcomes.

(D) Patients were grouped according to their albumin levels. Patients with higher albumin levels had better outcomes.

(E) Patients were grouped according to their total bilirubin (T-Bil) levels. Patients with lower T-Bil levels had better outcomes.

TABLES

Table 1. Baseline characteristics of all patients

Patient Characteristics	Value (Median, Range)
Age, Years	56 (18 - 79)
Sex, Male/Female	68/78 (47% / 53%)
BMI, kg/m^2	26.7 (14.3 - 46.0)
Liver histology	
F0-2 / F3-4	82/64 (56%/ 44%)
A0-1 / A2-3	116/30 (79%/ 21%)
steatosis ≥30%	93 (64%)
NAFL/NASH	34/112 (23% / 77%)
OD-SLD	134 (92%)
T-Bil, mg/dL	0.99 (0.84 - 1.47)
Albumin, g/dL	4.4 (3.1 - 5.1)
PLT, $10^4/\mu L$	22.1 (6.7 - 79.1)
AST, U/L	51 (14 - 215)
ALT, U/L	67 (11 - 219)
GGT, U/L	69 (15 - 1059)
TC, mg/dL	190 (102 - 352)
FPG, mg/dL	107 (80 - 269)
FIB-4 index	1.75 (0.082-15.138)
LRS	7.41 (4.28 - 21.39)
NOS	-1.6 (-4.5 - 1.04)

BMI, body mass index; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis; OD-SLD, obesity and/or diabetes complicated steatotic liver disease; T-Bil, total bilirubin; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; TC, total cholesterol; FPG, fasting plasma glucose; FIB-4 index, fibrosis-4 index; LRS, LiverRisk score; NOS, NAFLD outcomes score

Table 2. The characteristic of obesity and/or diabetes complicated NAFLD

Patient Characteristics	OD-SLD	non OD-SLD	P
	Value (Median, Range)		
n	134	12	
Age, Years	56	52	0.81
Sex, Male/Female	63/71	5/7	0.72
BMI, kg/m^2	27.3	20.3	<0.01*
Liver histology			
F0-2 / F3-4	78 (58%) / 56 (42%)	4 (33%) / 8 (67%)	0.09
A0-1 / A2-3	108 (81%) / 26 (19%)	8 (67%) / 4 (33%)	0.27
steatosis ≥30%	87 (66%)	5 (46%)	0.18
T-Bil, mg/dL	0.88	0.83	0.18
Albumin, g/dL	4.4	4.1	0.03*
PLT, 10^4/μL	22.1	17.4	0.70
AST, U/L	51	64	0.35
ALT, U/L	68	40	0.02*
GGT, U/L	68	149	<0.01*
TC, mg/dL	190	165	0.04*
FPG, mg/dL	107	105	0.18
FIB-4 index	1.70	3.07	0.11
LRS	7.36	8.95	0.01*
NOS	-1.67	-1.66	0.94

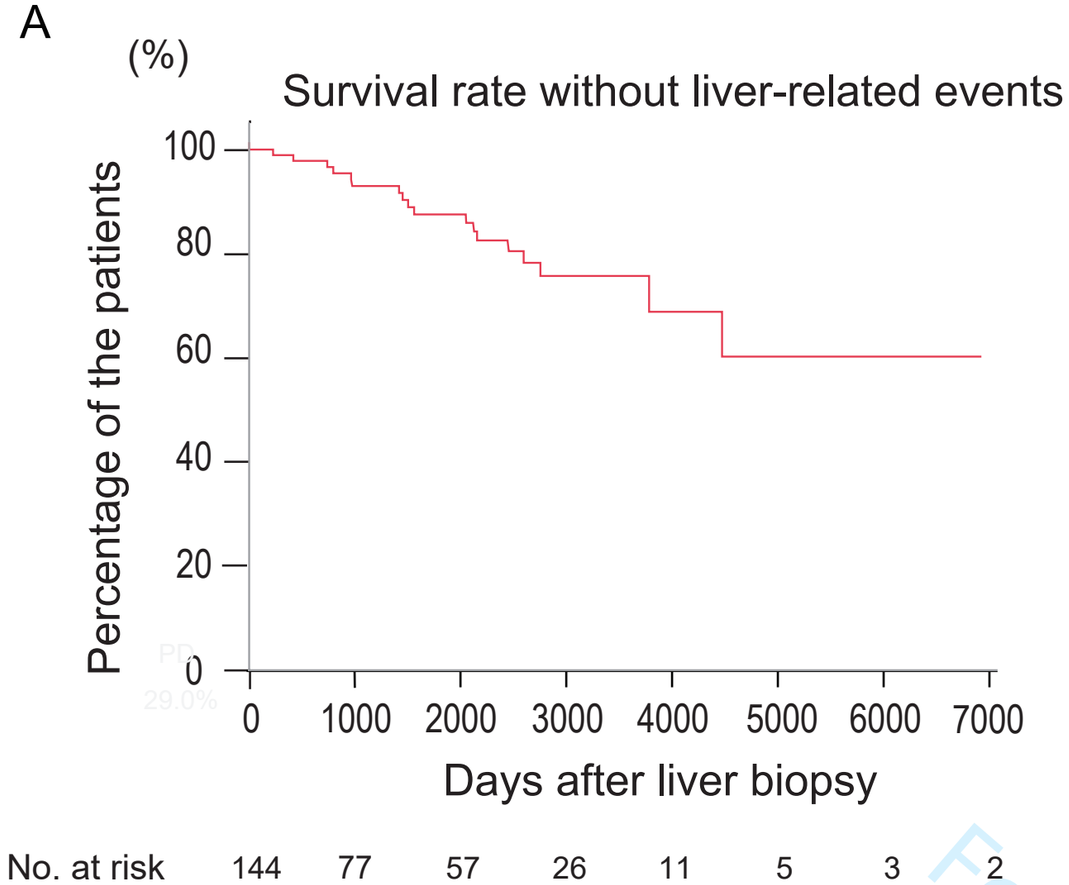
OD-SLD, obesity and/or diabetes complicated steatotic liver disease; BMI, body mass index; T-Bil, total bilirubin; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; TC, total cholesterol; FPG, fasting plasma glucose; FIB-4 index, fibrosis-4 index; LRS, LiverRisk score; NOS, NAFLD outcomes score

Table 3. Cox proportional hazards analyses determining the factors related with the liver-related events risks

Characteristic		Univariate Analysis (Wilcoxon)	Multivariate Analysis (Cox)		
		P value	Hazard Raito	95%CI	*P* value
OD-SLD		< 0.01*	0.20	0.06 – 0.71	0.01*
Albumin	< 4.1	0.01	1.51	0.56 – 4.06	0.41
T-Bil	> 1.5	< 0.01*	3.85	1.10 – 13.52	0.03*
FIB-4 index	> 2.67	0.02*	3.32	1.22 – 9.06	0.01*

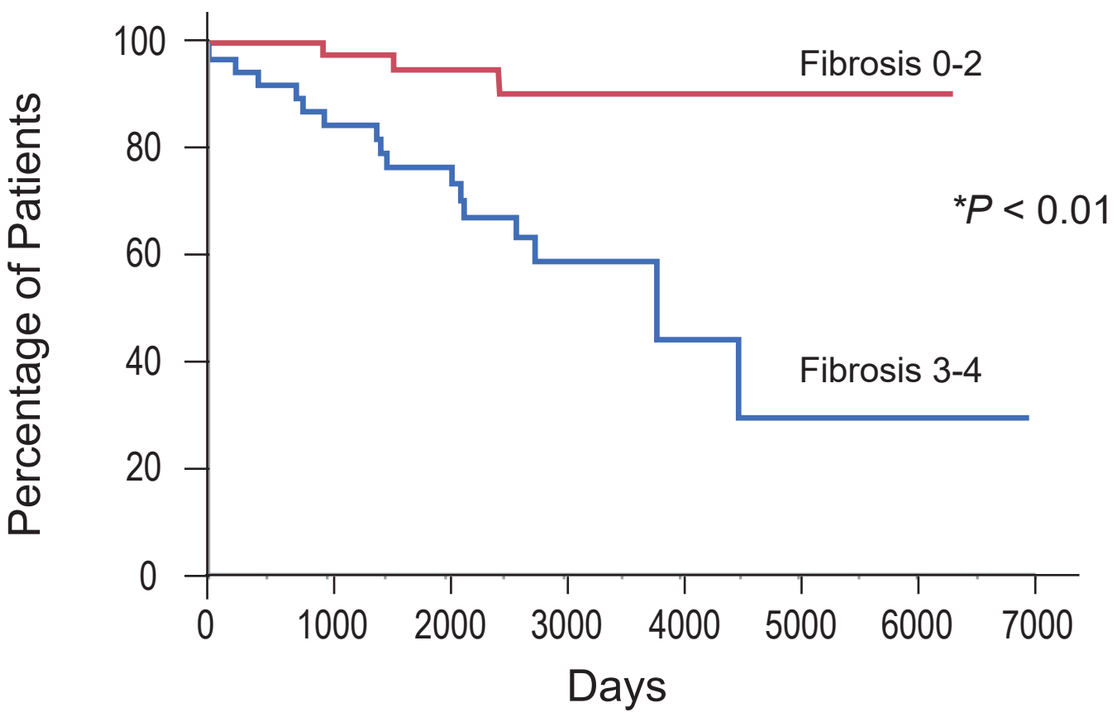
OD-SLD, obesity and/or diabetes complicated steatotic liver disease; T-Bil, total bilirubin; FIB-4 index, fibrosis-4 index

A



No. at risk	144	77	57	26	11	5	3	2

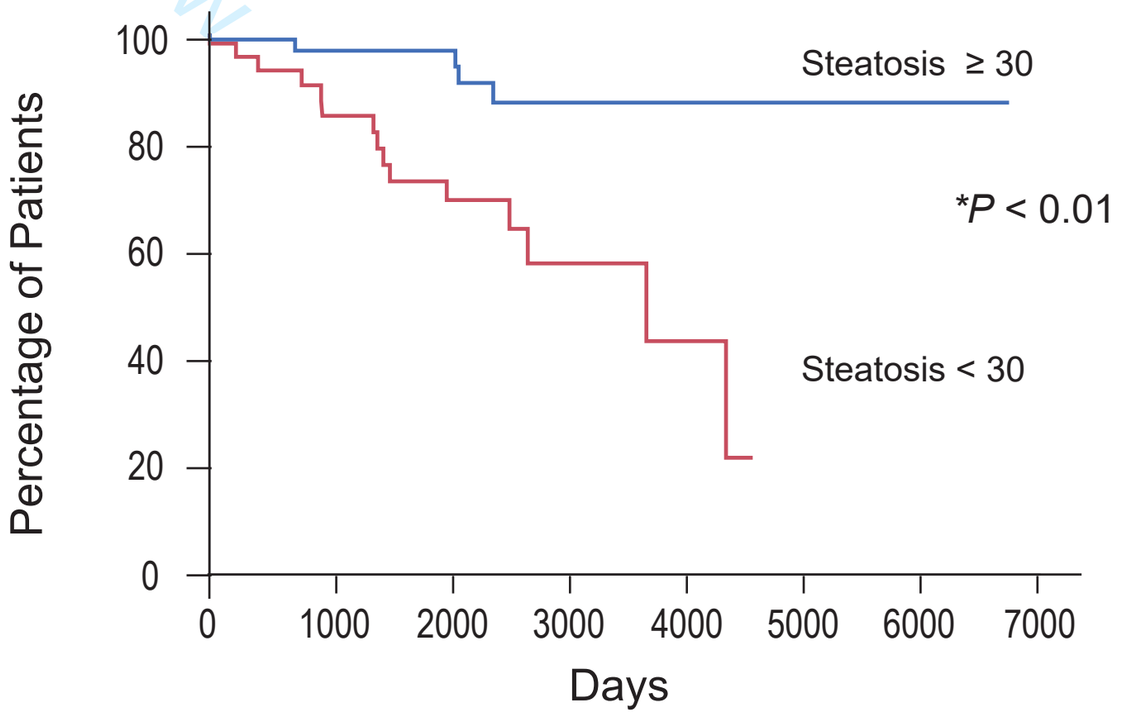
B



No. at risk

Fibrosis 0-2	80	44	31	15	8	4	2	
Fibrosis 3-4	64	34	27	12	4	2	1	1

C



No. at risk

Steatosis < 30	54	31	22	8	4			
Steatosis ≥ 30	90	47	36	19	8	5	3	1