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OCT and CMR for the Diagnosis of Patients Presenting With MINOCA and Suspected Epicardial Causes

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Title: A Model to Identify Heavy Drinkers at High Risk for Liver Disease Progression

SHORT TITLE: A model to predict ALD progression

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CONFLICT OF INTEREST

None: CD, PB, AL, FD, LCNW

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PM was paid speaking at symposiums for Abbvie, Gilead Sciences, Ipsen, Eisai, MSD, Bayer Healthcare pharmaceutical companies. He is member of the French boards of experts in Hepatology for Abbvie, MSD, Gilead Sciences, Ipsen, Eisai and Bayer Healthcare pharmaceutical companies. He is consulting for the MSD, Ipsen, Eisai, Abbvie, Sanofi, Gilead Sciences, Servier, Bayer Healthcare.

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AUTHOR CONTRIBUTIONS

PM and SDB had the idea of the study. CD, PB, AL, PM and SDB contributed to the conception and design of the analysis. CV, GP and SN gave access to the raw data. CD performed the analysis. All authors contributed to the interpretation. CD, PB, AL, PM and SDB drafted the work. All authors revised it critically for important intellectual content and

approved the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abstract:

Background & Aims: Alcohol-related liver disease (ALD) causes chronic liver disease. We investigated how information on patients' drinking history and amount, stage of liver disease, and demographic feature can be used to determine risk of disease progression.

Methods: We collected data from 2334 heavy drinkers (50 g/day or more) with persistently abnormal results from liver tests who had been admitted to a hepato-gastroenterology unit in France from January 1982 through December 1997; patients with a recorded duration of alcohol abuse were assigned to the development cohort (n=1599; 75% men) or the validation cohort (n=735; 75% men), based on presence of a liver biopsy. We collected data from both cohorts on patient history and disease stage at the time of hospitalization. For the development cohort, severity of the disease was scored by the METAVIR (due to the availability of liver histology reports); in the validation cohort only the presence of liver complications was assessed. We developed a model of ALD progression and occurrence of liver complications (hepatocellular carcinoma and/or liver decompensation) in association with exposure to alcohol, age at the onset of heavy drinking, amount of alcohol intake, sex and body mass index. The model was fitted to the development cohort and then evaluated in the validation cohort. We then tested the ability of the model to predict disease progression for any patient profile (baseline evaluation). Patients with a 5-y weighted risk of liver complications greater than 5% were considered at high risk for disease progression.

Results: Model results are given for the following patient profiles: men and women, 40 y old, who started drinking at an age of 25 y, drank 150 g/day, and had a body mass index of 22 kg/m² according to the disease severity at baseline evaluation. For men with baseline F0–F2 fibrosis, the model estimated the probabilities of normal liver, steatosis, or steatohepatitis at baseline to be 31.8%, 61.5% and 6.7%, respectively. The 5-y weighted risk of liver complications was 1.9%, ranging from 0.2% for men with normal liver at baseline evaluation to 10.3% for patients with steatohepatitis at baseline. For women with baseline F0–F2 fibrosis, probabilities of normal liver, steatosis, or steatohepatitis at baseline were 25.1%, 66.5% and 8.4%, respectively; the 5-y weighted risk of liver complications was 3.2%, ranging from 0.5% for women with normal liver at baseline to 14.7% for patients with steatohepatitis at baseline. Based on the model, men with F3–F4 fibrosis at baseline have a 24.5% 5-y weighted risk of complications (ranging from 20.2% to 34.5%) and women have a 30.1% 5-y weighted risk of complications (ranging from 24.7% to 41.0%).

Conclusions: We developed a Markov model that integrates data on level and duration of alcohol use to identify patients at high risk of liver disease progression. This model might be used to adapt patient care pathways.

KEY WORDS: prognostic factor, alcohol-associated liver disease, intermediate-term outcome, ASH

Need to Know

Background: Alcohol-related liver disease (ALD) causes chronic liver disease worldwide but it is a challenge to identify patients at high risk for disease progression.

Findings: A Markov model was developed using data from 2334 heavy drinkers, collected at time of hospitalization on duration of alcohol exposure and clinical and demographic factors to identify patients at highest risk of disease progression in the following 5 years.

Implications for patient care: This tool might be used by general practitioners or hepatologists to identify heavy drinkers at high risk for ALD progression. The patient care pathway could be adapted using this tool.

INTRODUCTION

Alcohol use is a leading cause of disease and mortality worldwide¹. The daily amount of alcohol, duration of exposure to excessive drinking, environmental and individual factors are key drivers of the consequences of alcohol-induced liver injury, including fatty liver, fibrosis and alcoholic steatohepatitis (ASH). ASH, steatosis and the severity of fibrosis influences the progression of fibrosis with the highest risk of disease progression in heavy drinkers with ASH²⁻⁴. Determining the respective contribution of these factors to disease progression is crucial to predict individual risk based on patient characteristics. This approach can help identify patients with a higher risk of progression to cirrhosis and this subgroup should be the target population for therapeutic intervention aimed at reducing disease progression.

Liver biopsy is the gold standard to assess disease stage in ALD⁵. Its limitations, including invasiveness, poor acceptability and cost, explain the difficulty of getting large cohorts with liver samples. The Liver Unit of the Antoine-Béclère Hospital, Clamart, France, has collected a unique cohort of around 1,600 heavy drinkers with histological assessments for each⁶. This cohort makes it possible to develop a predictive model by providing relevant information on cofactors of disease progression. Markov modelling has often been used in these settings to model the natural history of chronic diseases and estimate state-specific progression rates⁷⁻⁹. It allows including cofactors that affect the state-specific transition rates¹⁰. Once this model becomes available it can be used to simulate patient outcome at an individual level. Since a liver biopsy cannot be offered to all patients who are heavy drinkers, an accurate baseline evaluation using non-invasive methods such as blood tests or transient elastography^{5, 11, 12} can

be used as entry data for the Markov model. This approach provides new perspectives for the prediction of patient outcome.

The aims of this study using the Antoine-Béclère cohort were to a/ describe steatosis, fibrosis, ASH progression and liver complications in heavy drinkers, b/ identify independent disease progression cofactors, c/ predict expected disease progression, and d/ propose a medical decision-making tool to predict individual risk based on a Markov model.

MATERIALS AND METHODS

The Markov model

The progression of ALD to liver complications was modelled according to the severity of fibrosis according to METAVIR score and the development of ASH (Figure 1 and Supplementary Methods). The 7 relevant defined stages of ALD were: stage 1, normal liver (no steatosis and no fibrosis); stage 2, steatosis and F0 to F2; stage 3, ASH and F0-F2; stage 4, steatosis and F3-F4; stage 5, ASH and F3-F4; stage 6, liver complications without ASH; and stage 7, liver complications and ASH. Liver complications were defined as the presence of hepatocellular carcinoma (HCC) and/or liver decompensation (defined as bilirubin ≥ 50 $\mu\text{mol/L}$ and/or gastrointestinal haemorrhage and/or ascites).

We hypothesized that all patients had a normal liver when alcohol abuse began and we assessed the progression of ALD from one biopsy from each patient in relation to the known duration of exposure to excessive alcohol consumption. Recovery from lesions or the disappearance of ASH were considered to be impossible. The effects of potential covariates on the progression of ALD were evaluated (more details below).

Data

The initial cohort included all patients admitted to the Hepatogastroenterology Unit of the Antoine Bécère Hospital between January 1982 and December 1997 in Clamart, France ⁶. For the aim of our study, we identified 2,334 heavy drinkers (≥ 50 g/d) having persistently abnormal liver test results and a recorded duration of alcohol abuse during their first admission. None of them had known chronic viral hepatitis. All data were collected during hospitalization using a standardized questionnaire. The population was divided into two groups according to the availability of the histological assessment which was systematically

offered to each patient and performed during routine practice and not for the purpose of a research study (Supplementary Figure 1).

A first group included 1,599 patients who underwent a liver biopsy during their first admission. These patients were used to estimate the model parameters and formed the Development cohort. The METAVIR score was not available in 795 of these patients but 542 of them had an available disease stage (normal liver, pure steatosis, compensated cirrhosis without ASH, compensated cirrhosis with ASH, complicated liver disease with ASH, complicated liver disease without ASH) that could be translated into a METAVIR score. For the remaining 253, the METAVIR score was imputed by predictive mean matching by sex, age, BMI, alcohol consumption and the absence/presence of ASH (Supplementary Table 1).

The second group included 735 patients who did not undergo liver biopsy, but were classified at hospitalization according to the presence of liver complications. This cohort was used as a Validation cohort to determine the adequacy of the model for the prediction of liver complications.

Covariates

Covariates were incorporated into the model through the proportional hazards assumption.

We tested four covariates likely to be associated with the progression of the disease based on the literature^{3, 6, 13-19} and available in our database: sex; age when alcohol abuse began in years; body mass index (BMI in kg/m²); and daily alcohol consumption (g/d) over the 5 years before hospitalization. Missing BMI and daily alcohol intake values were imputed using predictive mean matching by sex and age. Variations in alcohol intake and BMI over time







