Research Article

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Prognosis of patients with chronic hepatitis B in France (2008–2013): A nationwide, observational and hospital-based study

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Background & Aims: How risk factors associated with chronic hepatitis B (CHB) modify liver disease progression and mortality has been scarcely reported outside of Asia. We aimed to evaluate these risk factors in a French population between 2008 and 2013.
Methods: All individuals discharged with CHB from acute and post-acute care hospitals in Metropolitan France between January 2008 and December 2013 were selected. Associations between liver- and non-liver-related risk factors and both liver disease progression (end-stage liver disease or hepatocellular carcinoma) and mortality were assessed by multivariate Cox proportional hazard models.
Results: Overall, liver disease progression, liver transplantation and death were recorded in 7479 (15.5%), 433 (8.2%) and 5299 (11.0%) patients, respectively. An additional liver-related risk factor was recorded in 5426 (72.6%) patients with liver disease progression and 2699 (75.5%) patients with liver transplantation or liver death. Adjusted hazard ratios (95% confidence interval) for liver disease progression of hepatitis D virus co-infection, hepatitis C virus co-infection, alcohol use disorders, diabetes mellitus, and other rare causes of chronic liver disease were 1.44 (1.35–1.53), 1.77 (1.68–1.87), 3.37 (3.20–3.55), 1.40 (1.32–1.48), and 2.19 (1.98–2.42), respectively. All liver-related risk factors increased the risk of all-cause mortality, especially after liver disease progression. Adjusted hazard ratios for liver disease progression and in-hospital mortality of HIV co-infection without acquired immune deficiency syndrome (AIDS) were 0.60 (0.52–0.70) and 0.63 (0.51–0.78), respectively.
Conclusions: In France, 2008–2013, liver disease progression among patients with CHB was closely related to other risk factors. HIV co-infected patients without AIDS had better outcomes, suggesting better care in this group of patients.

Lay summary: In France, 2008–2013, about three-quarters of patients with chronic hepatitis B who progressed to a liver-related complication, including liver transplantation and liver-related death, had an additional liver-related risk factor. Despite a higher prevalence of liver-related risk factors, HIV co-infected patients without AIDS had better outcomes.

Prognosis of patients with chronic hepatitis B is closely related to other risk factors. Treatment of patients with chronic hepatitis B, including control of chronic hepatitis B-associated risk factors, is more efficient in HIV co-infected patients.

Introduction

Approximately 3.61% of the global population is chronically infected with hepatitis B virus (HBV) [1]. A fraction of these will progress to a liver-related complication, including end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC), and will contribute to more than half of liver deaths worldwide [2,3].

Male gender, older age, genetic susceptibility, HBV replication level, co-infections with hepatitis D virus (HDV) or hepatitis C virus (HCV), alcohol use disorders, diabetes mellitus, and other rare causes of chronic liver disease have all been associated with liver disease progression in patients with chronic hepatitis B (CHB) [4–9].

Non-liver-related risk factors, including chronic kidney disease (CKD), cardiovascular disease, respiratory disease, and extrahepatic cancer, may alter the course of CHB by increasing the competing risk of death from non-liver causes [10]. Acquired immune deficiency syndrome (AIDS) was historically associated with liver disease progression in patients co-infected with human immunodeficiency virus (HIV) [11], but recent studies conducted in the era of effective antiviral treatment for both HIV and HBV infections suggest that liver outcomes have improved over the past 10 years [12].

Finally, most population studies on CHB were conducted in Asia and it is not clear whether risk factors of liver disease progression identified in these cohorts pertain to Western patients.

Keywords: Hepatitis B virus; Disease progression; End-stage liver disease; Epidemiology; Hepatocellular carcinoma; Prognosis; Risk factors.
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Risks of liver disease progression and all-cause hospital mortality associated with liver- and non-liver-related risk factors were evaluated among all patients discharged with CHB from French hospitals between 2008 and 2013.

Materials and methods

Data source

The Programme de Médicalisation des Systèmes d'Information (PMSI) database contains information on all public and private hospital billing claims for acute and post-acute care in France. Using unique anonymous identifiers, it is possible to trace the hospital trajectory of each selected patient and observe the progression of his/her conditions over time. Standardized hospital discharge summaries include patient demographics, as well as primary and associated discharge diagnosis codes (WHO International Classification of Diseases, 10th revision [ICD-10], French version), medical procedures performed (French Medical Common Procedure Coding System), length of stay, and in-hospital mortality, which accounted for 57.4% of all adult deaths recorded in Metropolitan France during the study period [13].

The study was approved by the French National Commission for Data Protection (CNIL DE-2013-068). The requirement for informed consent was waived because the study used anonymized data.

Study population

The study population comprised all adult patients in Metropolitan France who were discharged with a primary or associated diagnosis of CHB (ICD-10 B18.0 or B18.1 codes) between January 2008 and December 2013. As immunosuppression is a risk factor of liver disease progression in patients with CHB [14], recipients of solid organ transplant (liver, heart, lung, pancreas, or bowel) or allogeneic stem cell transplant before January 2008 were excluded. However, the roles of HIV co-infection and former kidney transplant in CHB progression were evaluated. The codes of the medical conditions and events tracked in this retrospective cohort study are provided in Supplementary Table 1.

Outcome measures

The primary outcome was liver disease progression to a composite outcome of ESLD or HCC before liver transplantation or death. Secondary outcomes included liver transplantation and all-cause in-hospital mortality. In patients without liver transplantation, liver death was defined as death after liver disease progression and competing mortality was defined as death before liver disease progression [15].

Risk factors

Liver-related risk factors included co-infections with HDV or HCV, alcohol use disorders (including alcoholic liver disease), diabetes mellitus, obesity (body mass index $\geqslant 30\ kg/m^2$), and other primary causes of cirrhosis (congenital malformations, inherited metabolic liver disease, primary Budd-Chiari syndrome, or autoimmune hepatitis).

Non-liver-related risk factors were recorded before liver disease progression and included co-infection with HIV, CKD, cancer other than HCC, cardiovascular disease, and respiratory disease [2]. Co-infection with HIV was staged into three categories depending on HIV control: at least one hospitalization for an AIDS-defining condition before liver disease progression; any record of former AIDS (before 2008); and no AIDS recorded otherwise. CKD was staged into three categories at cohort inception: kidney transplant recipient before January 2008; on dialysis; and CKD otherwise. Patients who underwent kidney transplantation during the study period were censored at the time of kidney transplantation. Cardiovascular and respiratory diseases were defined according to causes of death retained in the Global Burden of Disease study [2].

Statistical analysis

Age and categorical variables were compared using Kruskal-Wallis tests and χ^2 tests, respectively. Multivariate associations were analysed by adjusted hazard ratios (aHRs) using Cox proportional hazard models with age as the underlying time variable [16,17]. Follow-up depended on the study outcome. For liver disease progression (ESLD or HCC), follow-up was measured from January 2008 to liver disease progression or last hospital discharge in 2008–2013. For overall mortality, follow-up was measured from January 2008 to in-hospital death or last hospital discharge in 2008–2013. For the composite outcome of liver transplantation or death *vs.* non-liver death, follow-up was measured from January 2008 to liver transplantation, liver death, or non-liver death, whichever came first in the study period. The proportionality of hazards was evaluated by plots of Schoenfeld residuals for all explanatory variables. Accordingly, all multivariate Cox models were stratified by gender, obesity status, and patient residency area across five main French regions. All analyses were performed with SAS 9.4 (Statistical Analysis System, Cary, NC, USA).

Sensitivity analyses

Three sensitivity analyses on selected samples were conducted to explore possible limitations of the main study results on liver disease progression. First, a possible coding bias of CHB was examined and all patients with at least two hospitalizations recording CHB among discharge diagnosis codes were selected. Second, a possible classification bias of ESLD in liver disease staging in 2008-2013 (see Supplementary Table 1) was examined and all patients recorded with cirrhosis were selected. Finally, as CHB treatment is not included in the National Hospital Formulary and therefore CHB treatment is not recorded in the PMSI hospital discharge database, all patients with co-primary discharge diagnosis codes indicating CHB treatment at the hospital before liver disease progression (i.e., administration [ICD-10 Z51.2] or monitoring [ICD-10 Z51.2, Z51.4, Z09.2, Z09.7-9] of treatment for CHB) were selected.

Results

Cohort characteristics

A total of 48,189 patients with CHB constituted the hospital cohort for the main analysis (see Fig. 1). Patients were 58.6% male with a median (IQR) age of 44 (32–57) years at cohort inception. Overall, 29,811 (61.8%) patients had at least one risk factor associated with CHB, including 20,355 (42.2%) and 21,984 (45.6%) patients with liver-related risk factors and non-liver-related risk factors, respectively (see Table 1).

Screening for HBV is mandatory for pregnant women in France and CHB was recorded in 4928 (24.7%) of 19,933 women

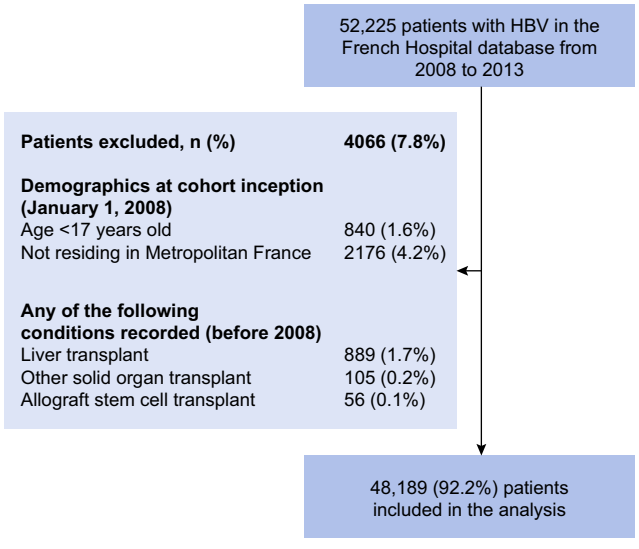

Fig. 1. Study flowchart. HBV, hepatitis B virus.