Research Article

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Contribution of alcohol use disorders on the burden of chronic hepatitis C in France, 2008–2013: A nationwide retrospective cohort study

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Background & Aims: Hepatitis C virus (HCV) patients are at risk of alcohol use disorders (AUDs). We measured the contribution of AUDs on the burden of chronic HCV infection in French HCV patients.

Methods: The hospital trajectory of 97,347 French HCV patients aged 18–65 in January 2008 were tracked and followed until in-hospital death or December 2013. Primary outcome was the frequency of liver-related complications. Secondary outcomes were the frequency of liver transplantation and otherwise cause-specific mortality. Adjusted odds ratios (OR), population attributable risks of AUDs and other cofactors of liver disease progression associated with HCV transmission were measured.

Results: The 28,101 (28.9%) individuals with AUDs had the highest odds for liver-related complications (OR = 7.19; 95% confidence interval [CI], 6.90 to 7.50), liver transplantation (OR = 4.28; 95% CI, 3.80 to 4.82), and liver death (OR = 6.20; 95% CI, 5.85 to 6.58). Alcohol rehabilitation and abstinence were associated with 60% (95% CI, 57% to 63%) and 78% (95% CI, 76% to 80%) reduction of liver-related complications, respectively. The attributable risk of AUDs was 71.8% (95% CI, 66.0 to 76.8) of 17,669 liver-related complications, 67.4% (95% CI, 61.6 to 72.4) of 1,599 liver transplantations, and 68.8% (95% CI, 63.4 to 73.5) of 6,677 liver deaths. The number of liver transplantations remained stable and the number of liver deaths increased, at a faster rate for individuals with AUDs, over the observational period.

Conclusion: In France, AUDs contributed to more than two-thirds of the burden of chronic HCV infection in young and middle-aged adults over 2008–2013.

Lay summary: This study tracked liver-related complications and mortality of all 97,347 young and middle-aged patients (18–65 years old) discharged with chronic HCV infection from French hospitals over 2008–2013. About 30% patients were recorded with alcohol use disorders (AUDs) and had the highest odds for liver-related complications (*i.e.* decompensated cirrhosis and liver cancer). AUDs contributed to more than two-thirds of 1,599 liver transplantations and 6,677 liver deaths recorded in patients with chronic HCV infection over 2008–2013 in France. Alcohol rehabilitation and abstinence were associated with above a 50% risk reduction of liver-related complications. Promoting alcohol abstinence should receive high priority to reduce the burden of chronic HCV infection.

Keywords: Alcohol use disorders; Chronic hepatitis C; Cirrhosis; Hepatocellular carcinoma; End-stage liver disease; Mortality; Natural history; Disease progression; Prognosis; Burden of disease.

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Introduction

Since its discovery in 1989, the hepatitis C virus (HCV) has been recognized as a major cause of liver disease progression to liver-related complications and mortality worldwide.[1] New direct-acting antiviral drug combinations showing up to 100% efficacy to eradicate HCV were marketed in early 2014.[2] Liver disease progression models support widespread screening and treatment to reduce the burden of HCV.[3] The underlying assumptions of these models are usually twofold: 1) chronic HCV infection is the main

factor of liver disease progression; 2) cured patients revert to the risks of liver-related complications and mortality of the general population.[3] However, both assumptions look problematic in light of the frequent comorbidities associated with HCV transmission and the absence of adjustment on potential confounding factors.[4]

In Western countries, injection drug use remains the most common route of HCV transmission.[5] Because injection drug use is associated with heavy drinking and bloodborne infections, alcohol use disorders (AUDs) and coinfections with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) were reported in much higher proportions among individuals screened with chronic HCV infection than in the general population.[6] As these comorbidities carry a sizable risk for liver-related complications and premature mortality,[7–9] their impact on the burden of chronic HCV infection should be taken into consideration[10].

The main aim of our study was to measure the contribution of AUDs and other comorbidities associated with HCV transmission on the burden of chronic HCV infection in a nationwide sample of young and middle-aged adults who should mostly benefit from HCV screening and treatment by avoiding liver transplantation and premature death.[11]

Patients and methods

Data source

The main data source was the French National Hospital Discharge database (Programme de Médicalisation des Systèmes d'Information), which contains all public and private claims for acute inpatient/day-case hospital admissions and post-acute care since 2008. The standardized discharge summary includes: patients' demographics (gender, age, postal code of residency); primary and associated discharge diagnosis codes according to the World Health Organization International Classification of Diseases, tenth revision (ICD-10); medical procedures performed; length of stay, entry and discharge modes (including in-hospital death). 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.[12]

Study population

We selected all individuals residing in metropolitan France, aged between 18–65 years in January 2008, and discharged at least once with a primary or associated discharge diagnosis code of chronic HCV infection (ICD-10 B18.2) in 2008–2013. The ICD-10 code dictionary of all medical conditions and outcomes tracked in this study is provided in Table S1.

Outcome measures

We studied two major outcomes of the burden of chronic HCV infection in 2008–2013: liver-related complications and premature mortality.[1] Liver-related complications require hospital care and included the first record of decompensated cirrhosis or primary liver cancer related to cirrhosis. In patients without liver transplantation, premature death was categorized as a liver death (after liver-related complication) or non-liver death otherwise.

Death was primarily assessed from in-hospital death records. In a sensitivity analysis (see Supplementary materials and methods), we assessed mortality outside hospital based on the morbidity profile of new patients discharged with chronic HCV infection and lost to follow-up from 2008 (17% of 29,013 new patients) to 2013 (93% of 10,100 new patients). We estimated that in-hospital mortality accounted for 97.0% (95% confidence interval [95% CI]: 96.6 to 97.3) of overall mortality in this study cohort. Similar findings were found with use of overall mortality instead of in-hospital mortality and are reported in Supplementary results.

Cofactors of liver disease progression

AUDs were identified by three categories of discharge diagnosis codes: "alcoholic" liver disease (ICD-10: K70); another disease onset that is mainly due to AUDs (for example ICD-10: K86.0 for "alcohol-induced" chronic pancreatitis, see Table S1); and mental and behavioral disorders due to former or current harmful use of alcohol (ICD-10: F10.1-F10.9, Z50.2).[13] There was reasonable agreement between the three categories of discharge diagnosis codes used to identify AUDs (see Table S2). To measure the benefits of alcohol abstinence, individuals recorded with alcohol rehabilitation (ICD-10: Z50.2) or abstinence (ICD-10: F10.20-F10.23) at any point before the first liver-related complication were contrasted with individuals with "uncontrolled" AUDs.

Chronic HBV infection was categorized according to any record of the Delta agent. HIV infection was staged into three categories depending on HIV control level: patients hospitalized for the Acquired Immune Deficiency Syndrome (AIDS) in 2008–2013; patients recorded with former AIDS; and those with no AIDS recorded. Metabolic syndrome is not defined in the ICD-10 coding system, and we used a proxy based on any record of non-alcoholic "fatty" liver disease, diabetes mellitus, obesity (body mass index $\geq$30 kg/m^2), and their interaction. Other primary causes of cirrhosis were identified (congenital malformations; inherited metabolic liver diseases; primary Budd-Chiari syndrome; and autoimmune liver diseases) as well as prior liver transplantation before cohort inception in 2008.

HCV treatment is mostly administered in an outpatient setting and is not recorded in the French National Hospital Discharge database.

Other comorbidities of HCV

Three other comorbidities possibly associated with iatrogenic transmission of HCV were identified: hemophilia; chronic dialysis as defined by ICD-10 codes and dialysis procedures over three months; and prior transplantation other than liver before cohort inception in 2008. Drug addiction and smoking status were identified by any record of mental and behavioural disorders due to former or current use of opioids and tobacco, respectively.

Statistical procedures

Age and categorical variables were compared using Kruskal-Wallis tests and χ^2 tests, respectively. The strength of association of cofactors of liver disease progression with the major outcomes was measured by means of odds ratios (OR) estimated in multivariate logistic regression models adjusted for other comorbidities of HCV, gender, age in 2008 in 5-year categories (<40, 40–44, 45–49, 50–54, 55–59, 60–65), year at first discharge with HCV in six categories (2008 to 2013), and residency area in five main French regions (North-West, North-East, Greater Paris area, South-West, South-East).

Population attributable risks (PAR) denote the fraction of the major outcomes that would have been prevented in 2008–2013 if cofactors of liver disease progression were absent in young and middle-aged French individuals discharged with chronic HCV infection. PARs combine information about prevalence with OR estimates, and we took into account all interactions of AUDs with gender, age categories, and other cofactors of liver disease progression to calculate PARs and asymptotic 95% CI with use of the SAS Macro%PAR. All analyses were performed with SAS 9.4 (Statistical Analysis System, Cary, NC).

Research ethics approval

The study was approved by the French National Commission for Data Protection (CNIL DE-2015–025). The requirement for informed consent was waived because the study used de-identified data.

For further details regarding the materials used, please refer to the CTAT table.

Results

Baseline characteristics

Chronic HCV infection was recorded in 97,347 (0.43%) of 22,410,782 individuals aged 18–65 in 2008 and discharged from French hospitals in 2008–2013 (Table 1). AUDs were the most