ECOLE DOCTORALE PIERRE LOUIS DE SANTÉ PUBLIQUE A PARIS
EPIDÉMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMÉDICALE

Directeur : Pierre-Yves Boëlle
Responsable pour l'Université Paris Cité : Isabelle Boutron

PROPOSITION DE SUJET DE THESE

SIGLE ET NOM DU LABORATOIRE : INSTITUT PIERRE LOUIS D'EPIDEMIOLOGIE ET DE SANTÉ PUBLIQUE (IPLESP)
NOM DE L'EQUIPE : EPIDEMIOLOGIE CLINIQUE DES MALADIES VIRALES CHRONIQUES
DIRECTEUR DE THÈSE : FABRICE CARRAT
ADRESSE : FACULTE DE MEDECINE, 27 RUE CHALIGNY, 75012 PARIS

TITRE DE LA THÈSE : CANCERS AND CARDIOVASCULAR RISKS IN PEOPLE LIVING WITH HEPATITIS B VIRUS IN FRANCE AT DIFFERENT STAGES OF INFECTION - IMPACT OF TREATMENT AND INDIVIDUAL DETERMINANTS.

CO-ENCADRANT ÉVENTUEL :
EQUIPE DU CO-ENCADRANT :
LABORATOIRE :

PRESENTATION DU SUJET

Scientific context

In 2019, according to the WHO, around 296 million people worldwide are living with the hepatitis B virus (HBV), and this infection causes more than 520,000 deaths a year from cirrhosis and hepatocellular carcinoma (HCC) (1,2). The epidemiology of hepatitis B is evolving rapidly, largely as a result of the introduction of vaccination at birth or in childhood, and also due to the large-scale migration of people from highly endemic areas. In France, it is estimated that around 135,000 people were living with HBV in 2016, giving a prevalence of 0.30% [0.13-0.70], of whom 17.5% [4.9-46.4] knew their status (3), and 7% of cirrhosis and 10% of HCC related to HBV (4). Chronic HBV infection can be divided into 5 phases: (1) HBe antigen-positive chronic infection (HBeAg+), (2) HBeAg+ chronic hepatitis, (3) HBeAg- chronic infection, (4) HBeAg- chronic hepatitis and (5) the undetectable HBsAg phase. These phases do not always follow the same chronology and transitions from phase 3 to phase 2 (and also 3 to 1), from phase 4 to phase 3 or even from phase 5 to phase 4 are always possible, depending on viral replication and the intensity of the host immune response. All patients with chronic HBV infection are at risk of progressing to cirrhosis and/or HCC, with different risks depending on the phase of the disease (5), but for patients with chronic hepatitis B and HBeAg viral infection, this risk correlates with the extent of viral replication (6). For patients with HBeAg+ viral infection, the risk is poorly assessed due to the absence of long-term longitudinal cohort studies. In addition, the other risk factors for HCC (obesity, alcohol, diabetes) are poorly assessed in existing cohorts of HBV-infected individuals. In the ANRS CO22 Hepather cohort, we used a structural model to show that age, male sex, metabolic syndrome, alcohol consumption and B viral load had a direct and significant effect on the development

of significant hepatic fibrosis, which in turn predicted the development of HCC (7), and it has now been established that non-alcoholic fatty liver plays a major role in the progression of fibrosis in these patients (8). On the other hand, the risk of HCC is reduced in patients with undetectable HBsAg (9).
In France in 2024, the treatment of patients suffering from chronic hepatitis B is essentially based on the use of antivirals (nucleoside or nucleotide analogues (NUCs)), mainly tenofovir and entecavir. - mainly tenofovir and entecavir, with the main aim of controlling viral replication and limiting its impact on the liver. There is some controversy over the impact of these treatments on the risk of HCC (which is thought to be more significantly reduced with tenofovir than with entecavir (10), a finding that we did not find in the Hepather cohort (11)), and the long-term consequences of these treatments, particularly in terms of renal risk, are not known. A large number of new therapeutic strategies (over 50) are currently being evaluated, with the aim of achieving a functional cure defined by the undetectability of HBsAg (12). Finally, co-morbidities - which may either exacerbate HBV infection (e.g. superinfection with the Delta virus, diabetes) or be a consequence of it (e.g. lymphoma, other cancers, cardiovascular events) - remain very poorly documented, as does the impact of associated metabolic disorders or treatments taken for other indications but which are potentially hepatotoxic over the long term.
In an exploratory study based on the French national health data system (SNDS), we estimated that in 2022, almost 115,000 people in mainland France will be living with HBV, of whom around 20% will require treatment with NUC according to current management recommendations (13).

Objectives

The objectives of this thesis work are to explore the risks of comorbidities (cancer, cardiovascular) in people living with HBV in the SNDS, in the different stages of this infection, and to quantify the impact of therapeutic management and individual determinants on these risks.
In particular, the following will be explored
- The risks of cancer, cardiovascular events and renal failure in people living with HBV infection, compared with a control sample of the general uninfected population matched on age and sex.
- The impact of different treatments (treatment, screening) and individual determinants on the risk of progression of liver disease and co-morbidities.

Data

The main source of data used for this thesis is the National Health Data System / Système National des Données de Santé (SNDS), enriched with data from the Hepather and Hepat-B cohorts linked to the SNDS.
The CLEPIVIR team at IPLESP coordinates the ANRS Hepather cohort, which has been following people living with HBV since 2012 (n=6600). For 85% of the patients in this cohort, data are linked to the SNDS using a deterministic method (reconstitution of the identification number in the NIR register). The Hepather cohort will be extended in 2025 by the ANRS Hepat-B cohort (funding obtained - 4,500 people expected), involving the collection of new data (clinical, behavioural, sociological and biological) and the organisation of follow-up until 2029, as well as an extension of the linkage with SNDS data. All this data is accessible within the team.
We have developed and validated various algorithms for identifying HBV-infected individuals in the SNDS (14), and further work is planned for 2023-2024 (in particular as part of the Health Data Hub's "Bibliothèque Ouverte d'Algorithmes pour le SNDS- BOAS" project) to optimise these algorithms in order to identify the various phenotypes of HBV infection and in particular to distinguish between individuals infected with HBeAg, with HBeAg

hepatitis or with undetectable HBsAg. In addition, our team is currently supervising several theses using SNDS data, in which the assessment criteria concern cardiovascular risk and renal failure - and the present project will be able to benefit from the expertise acquired on the SNDS in these fields. La source principale de données utilisée pour cette thèse est le Système National des Données de Santé (SNDS), enrichie des données des cohortes Hepather et Hepat-B chaînées au SNDS

Methods

The methods used will aim to quantify the effects, taking into account time-dependent confounding factors and the different stages of the disease and, where appropriate, competitive risks, or the effect of time-varying exposures (15). We will use structural marginal models (already used on the SNDS in previous work by the team on people infected with the hepatitis C virus (16)) or multi-state models to take account of the different stages of infection. Depending on the estimated performance of the different algorithms for identifying infection phenotypes, a correction for differential classification errors will be made to the estimates of strength of association (17).

Power and sample size

The cohort of HBV-infected people identified in the SNDS is over 100,000 (>200,000 if a "control" cohort of uninfected people is added), with a follow-up of 10 years; the events studied are not rare and the exposures studied (treatments, metabolic syndrome, diabetes) are frequent: we can assume a power of over 99% for the identification of relative risk, even if relatively low (i.e. RR> 1.2) over the entire cohort.

Provisional agenda

Semester 1 - SNDS training (if necessary), review of the literature on the subject, identification within the SNDS of the different phenotypes of HBV infection.
Semester 2 - analysis of the SNDS - submission of article 1
Semester 3 - publication of article 1 and characterisation of the pathways and management of people living with HBV in the SNDS
Semester 4 - analysis and submission of article 2
Semester 5 - writing the thesis - publication of article 2
Semester 6 - defense

Articles

Article 1: cancers, cardiovascular events, and renal failure in people living with HBV infection - incidence according to infection status and risk factors.
Article 2: impact of different management (treatment, screening) of people living with HBV infection and individual determinants on the risk of progression of liver disease and associated comorbidities.

References

1. Hsu YC, Huang DQ, Nguyen MH. Global burden of hepatitis B virus: current status, missed opportunities and a call for action. Nat Rev Gastroenterol Hepatol. août 2023;20(8):524-37.
2. Hepatitis B [Internet]. [cité 9 avr 2024]. Disponible sur: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
3. Brouard C, Saboni L, Gautier A, Chevaliez S, Rahib D, Richard JB, et al. HCV and HBV prevalence based on home blood self-

sampling and screening history in the general population in 2016: contribution to the new French screening strategy. BMC Infect Dis. 28 oct 2019;19(1):896.
4. Alberts CJ, Clifford GM, Georges D, Negro F, Lesi OA, Hutin YJF, et al. Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: a systematic review. The Lancet Gastroenterology & Hepatology. 1 août 2022;7(8):724-35.
5. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of Hepatology. 1 août 2017;67(2):370-98.
6. Lee MH, Yang HI, Liu J, Batrla-Utermann R, Jen CL, Iloeje UH, et al. Prediction models of long-term Cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: Risk scores integrating host and virus profiles. Hepatology. 2013;58(2):546-54.
7. Lam L, Fontaine H, Bourliere M, Lusivika-Nzinga C, Dorival C, Thabut D, et al. Predictive factors for hepatocellular carcinoma in chronic hepatitis B using structural equation modeling: a prospective cohort study. Clin Res Hepatol Gastroenterol. sept 2021;45(5):101713.
8. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the Global Burden of Chronic Liver Diseases From 2012 to 2017: The Growing Impact of NAFLD. Hepatology. nov 2020;72(5):1605-16.
9. Zhou K, Contag C, Whitaker E, Terrault N. Spontaneous loss of surface antigen among adults living with chronic hepatitis B virus infection: a systematic review and pooled meta-analyses. Lancet Gastroenterol Hepatol. mars 2019;4(3):227-38.
10. Yip TCF, Wong VWS, Chan HLY, Tse YK, Lui GCY, Wong GLH. Tenofovir Is Associated With Lower Risk of Hepatocellular Carcinoma Than Entecavir in Patients With Chronic HBV Infection in China. Gastroenterology. 1 janv 2020;158(1):215-225.e6.
11. Pol S, ANRS/AFEF study group. Similar 5-year HCC occurrence in Tenofovir- and Entecavir-treated HBV chronic infection in the French AFEF/ANRS CO22 Hepather cohort. Aliment Pharmacol Ther. mars 2021;53(5):616-29.
12. Lim SG, Baumert TF, Boni C, Gane E, Levrero M, Lok AS, et al. The scientific basis of combination therapy for chronic hepatitis B functional cure. Nat Rev Gastroenterol Hepatol. avr 2023;20(4):238-53.
13. Lam L, Carrat F. Nationwide analysis of mortality and economic burden among chronic HBV-infected patients in France: a real-world study. 2023 International HBV meeting.; 2023 sept; Kobe, Japan.
14. Lam L, Fontaine H, Lapidus N, Bellet J, Lusivika-Nzinga C, Nicol J, et al. Performance of algorithms for identifying patients with chronic hepatitis B or C infection in the french health insurance claims databases using the ANRS CO22 HEPATHER cohort. J Viral Hepat. mars 2023;30(3):232-41.
15. Abrahamowicz M, Beauchamp ME, Sylvestre MP. Comparison of alternative models for linking drug exposure with adverse effects. Stat Med. 20 mai 2012;31(11-12):1014-30.
16. Lam L, Pol S, Cohen A, Carrat F. Direct-Acting Antivirals and the Risk of Arrhythmias and Conduction Disorders in Patients with Chronic Hepatitis C: A French Nationwide Cohort Study. Drugs. sept 2023;83(13):1207-13.
17. Tang L, Lyles RH, King CC, Celentano DD, Lo Y. Binary regression with differentially misclassified response and exposure variables. Stat Med. 30 avr 2015;34(9):1605-20.

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SPECIALITE DE LA THESE

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AVIS FAVORABLE ☒

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