# The Canadian Hepatitis B Network:

# A Nationwide Retrospective Cohort Study on the Epidemiology of Chronic Hepatitis B Virus Infection

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**Abstract**

Published epidemiologic data on hepatitis B virus (HBV) infection in Canada include single-centre studies in large urban centres, or are focused on indigenous populations. **Aim:** To characterize the epidemiology, liver disease status and antiviral treatment in hepatitis B patients in Canada. **Methods**: Data were collected by the Canadian Hepatitis B Network involving 15 academic and community centres in 8 provinces, with support from the National Microbiology Laboratory (NML) / Public Health Agency of Canada (PHAC). In this retrospective, cohort study, data from known mono-infected hepatitis B patients were collected from existing administrative and/or clinical databases. Parametric and non-parametric statistical methods were used for analyses with significance level of <0.05. **Results**: In 9386 unique patient records reviewed, the median age was 48 y, 55% male, 74% Asian, 11.5% Black, and 11.5% Caucasian. The majority (~80%) tested were HBeAg negative, and had minimal liver fibrosis. In 1076 subjects with genotype data, 56% were genotype B or C. In 3041 patients that were known to be previously treated, most received tenofovir disoproxil fumarate (55%), lamivudine (48%) and entecavir (18%). There were interprovincial differences in treatment regimen, ethnicity, genotype and HBeAg status, especially in Ontario and British Columbia vs. national averages**. Interpretation**: Canadian hepatitis B patients are predominantly Asian, HBeAg negative and genotype B. There were significant provincial variations in demographics, genotypes and antiviral treatment, likely reflecting regional migration patterns and disparities in provincial drug reimbursement programs. Hepatitis B afflicts as many as one in four people worldwide, yet HBV is grossly under-appreciated in Canada. This is the largest nationwide study to date highlighting the impact and magnitude of hepatitis B.

## Introduction

The hepatitis B virus (HBV) is a major human pathogen with 257 million chronic HBV (CHB) carriers worldwide, especially in Asia and sub-Saharan Africa, who remain at risk for cirrhosis, liver failure and hepatocellular carcinoma (HCC)[1, 2]. There are 8 major HBV genotypes with a specific geographic and ethnic distribution, which have been linked to disease outcomes and response to antiviral therapy[3]. Hepatitis B is a reportable disease to the Canadian Notifiable Disease Surveillance System (CNDSS)[4], yet reliable epidemiologic data are limited due to the lack of standardized reporting practices. A 2013 Public Health Agency of Canada (PHAC) report on hepatitis B lacks data from two provinces (i.e., Newfoundland and Labrador; Prince Edward Island) and two territories (i.e., Northwest Territories; Nunavut)[5]. PHAC also reported a lower estimate of CHB prevalence and incidence rate in British Columbia (BC) than the BC Center of Disease Control (BCCDC) due to disparate reporting practices[6]. A recent report from the Canadian Liver Foundation estimated that 250,000-460,000 Canadians have CHB, with highest rates found in larger urban centres[7]. Overall, the prevalence of CHB has declined in Canadian born individuals with the advent of universal childhood vaccination in the mid 1990s. A recent sero-survey of Artic indigenous populations, historically considered to be hyperendemic for CHB, found a non-endemic prevalence of 1.2%, yet a significant number were found to have lower than expected vaccine based immunity (hepatitis B surface antibody titres), with unknown clinical characteristics[8].

In 2016, the Statistics Canada long-term census survey reported significant ethnocultural diversity within Canada, with 1 in 5 Canadians (21.9%) either a landed immigrant or permanent resident. Importantly, the majority of newcomers are from Asia (61%), with Africa as the second highest source continent (13.4%) for recent immigrants, especially from highly HBV endemic countries[9]. Most new Canadians live in established communities from their home country in large urban centres (i.e., Toronto, Montreal, Vancouver). Interestingly, there is increasing settlement in less populous regions (e.g., prairie and Atlantic provinces) due to economic factors

(i.e., job growth in energy sector) or under special provincial nominee programs to encourage population growth, i.e., Manitoba "*growing through immigration*" (www.immigratemanitoba.com). This evolving Canadian demographic landscape highlight the need for updated, large scale, epidemiological data on HBV infection-associated disease burden in Canada.

The current work illustrates the key demographics, clinical, virological outcomes and treatment of hepatitis B patients followed in diverse academic and community care clinics nationwide. This study is the largest and most comprehensive research ever conducted on hepatitis B epidemiology in Canada.

**Methods**

Study Design: The Canadian Hepatitis B Network (CanHepB)

CanHepB was formed in 2016, and received official endorsement by the Canadian Association for the Study of the Liver (CASL) in 2017. It currently includes 21 academic and community clinical care centers for hepatitis B patients in eight Canadian provinces, supported by provincial as well as national reference laboratories (National Microbiology Laboratory, PHAC). The mission is (1) To improve treatment and control of hepatitis B in Canada; (2) To advance the understanding of HBV infection-associated diseases and their natural history; (3) To promote collaboration on national hepatitis B studies and databases and, (4) To enhance and inform research and educational opportunities on HBV infection and its consequences.

In this retrospective cross-sectional cohort study, data on HBV surface antigen (HBsAg) positive patients for a minimum of 6 months (i.e., chronic HBV carriers) were collated from information submitted by participating sites through an online web-based portal following local site chart review, or submitted directly to the central data coordinating centre (University of Calgary) from existing clinical databases. Additionally, in Alberta administrative data on demographics and laboratory data were collected for 3 participating sites from the Alberta Health Services (AHS) data repository, as previously described[10]. In total, 15 sites submitted

data from 8 provincial health jurisdictions. A waiver of consent was obtained from local research ethics board and / or under section 50, Health Information Act of Alberta Study or if possible, patients provided signed informed consent to participate. All data received were anonymous and collected under an approved University of Calgary (U of C) Conjoint Ethics Research Board Approved Protocol (Ethics ID# REB16-0041), following consultation with the U of C privacy office, with sub-site ethics and legal agreements for data sharing between sites within the Canadian HBV Network.

Data Elements

In total 9,386 unique patient records were reviewed from available records of adult patients with known chronic hepatitis B infection. Patients were excluded from analysis if co-infected with hepatitis C virus (HCV), hepatitis delta virus (HDV) or human immunodeficiency virus (HIV). Available retrospective data elements included demographics (age, sex, and in some, ethnicity), and most recent tests for HBV DNA, HBV e antigen (HBeAg), HBV genotype, alanine aminotransferase (ALT), liver stiffness measurement via transient elastography (TE, FibroScan®) and, antiviral therapy. HBV serological testing (HBsAg, HBeAg) was done by standard commercial immunoassays (i.e., Abbott Architect) offered by provincial and/or accredited hospital diagnostic labs. HBV DNA testing was done through provincial diagnostic laboratories using commercial real-time polymerase chain reaction (PCR) (i.e., TaqMan®) assays (i.e., Abbott Architect, sensitivity <10 IU/mL and Roche Cobas Amplicor, sensitivity <20 IU/mL; 1 IU/mL equivalent to ~5 virus genome copies/mL). HBV genotype was available retrospectively (including a data subset from a previously published study[11]) or was determined prospectively at the National Microbiology Laboratory, Public Health Agency of Canada by in-house direct population sequencing and phylogenetic analysis and/or reverse hybridization assay (Inno-LiPa, Innogenetics).

**Statistical Analysis:**

Data were transferred into GraphPad Prism software for analysis. Continuous variables were expressed as mean and SEM or median and range and compared with two-tailed *Mann-Whitney* tests. Categorical variables were expressed as number and frequencies or percentages and compared with Fisher's exact tests. P-values less than 0.05 were considered statistically significant. Missing variables were not included in the group analysis.

**Results**

**Comparison of patient characteristics, demographics and genotypes across Canada**

Clinical and demographic data was submitted on 9,386 patients nationwide from 15 hepatology or infectious disease clinics within 8 provinces. The majority of patients were male (55%), median age 48y. In 7885 patients with ethnic data, 74% Asian, 11.5% Caucasian and 11.5% Black, and 3% other (including indigenous/First Nations) (Table 1). Among 1,076 with available HBV genotyping analysis, most had HBV genotype B or C infection (Figure 1), as expected given the predominant Asian origin. There was interprovincial demographic variation in that more patients were of Asian descent and HBV genotype B in British Columbia compared to national averages. This data is likely a reflection of interprovincial migration patterns, as many patients tend to settle in urban centers with established cultural communities, especially those affiliated with specific sponsorship (i.e., religious, economic) programs.

**Comparison of HBV disease status, fibrosis and antiviral therapy nationwide**

The majority of patients with available data (N=6802) tested HBeAg negative (82%), and 58% had HBV DNA levels <2000 IU/mL (10,000 virus genome copies/mL) at their last test (Table 2, Figure 2). A significant proportion had documented stage 2 or greater fibrosis (~18%, Metavir score) based on liver stiffness measurement via transient elastography on most recent testing. In 3041 patients that had available treatment data, 32% were treated with more than one drug

over time. The most common treatment was tenofovir disoproxil fumarate (TDF) (55%), lamivudine (48%) and entecavir (18%) (Table 2). Interprovincial differences were also noted in antiviral treatment regimen, with higher proportion of patients in British Columbia (58%) and Ontario (62%) receiving first generation nucleos(t)ide analogs (i.e., lamivudine) compared to other provinces.

**Comparison of clinical characteristics, according to specific HBV genotype across Canada**

In 1,076 patients with HBV genotype data, we noted significant differences in ethnicity as well as hepatitis B disease status according to genotype (Table 3). There was higher proportion of Asian ethnicity in persons with genotype A, B, and C infection. Overall, patients with HBV genotype C were more likely to be HBeAg+, have HBV DNA > 20,000 IU/mL, higher mean ALT levels, more advanced liver fibrosis (>Stage 2) and to receive antiviral therapy compared to all other genotypes.



**Interpretation**

There are limited epidemiological data on hepatitis B in Canada, and no nationwide clinical study has ever been reported. In this large scale, cross-sectional retrospective multi-ethnic cohort study of 9386 patients from the Canadian Hepatitis B Network, we report that the majority of patients followed nationwide are older age, male, Asian, serum HBeAg-negative and have HBV genotype B or C infection. A significant proportion of patients show HBV DNA >2000 IU/mL and greater than stage 2 fibrosis, which are important clinical indicators regarding need for antiviral therapy. In those with known treatment data, many received long-term oral antiviral therapy, but there were significant interprovincial differences between NA use (i.e., LAM vs. TDF/ETV), likely due to historic disparities in access to second generation potent NA therapy. These therapeutic differences will enable future studies characterizing potential differences in

disease natural history. In >1000 patients with available genotype data we also noted significant differences between HBV genotype C clinical characteristics (i.e., higher fibrosis stage and viral load) compared to other genotypes. These data are consistent with reported studies of HBV genotype epidemiology and more severe liver fibrosis in HBV genotype C (vs. B) from large Asian cohort studies[12]. The data also provides important and unique comparisons across all reported genotypes in one country, that is not feasible in jurisdictions with less ethnic diversity. As expected, the majority of the data were contributed on patients residing in larger urban centres and from tertiary referral clinics in regions with high rates of immigration. However, regions with increasing immigration due to improving economy[10], as well as with provincial nominee programs also reported increasing patient numbers. Universal childhood vaccination in Nunavut has led to a significant decline in the prevalence of chronic infection in Inuit populations[8] and mirrors the current study which did not find a significant number of hepatitis B patients in Canadian indigenous populations (<1% reported, data not shown).

The baseline demographic and clinical data reported in the current study are similar to those reported by the North American Hepatitis B Research Network (HBRN) funded by the National Institutes of Health (NIH), USA. The HBRN is a consortium of 21 academic centres in the USA and includes one Canadian site (Toronto, Ontario) that collected prospective data in untreated HBV adult and pediatric patients. Published data from HBRN also show that 50% of adults were male, median age 42 years and 74% of the cohort were HBeAg negative[13]. Additionally, similar HBV genotype data were reported by the HBRN with mainly B (39%) and C (33%), followed by A (18%), D (8%), and E (3%), which also reflected the largely foreign-born population of Asian and Africans [13]. However, the HBRN did not include treatment information, and all fibrosis data were based on liver histopathology or serum based markers of liver fibrosis (i.e., FibroTest® or AST-to-Platelet index, APRI), as transient elastography is a relatively recently approved test in the US.

Under the Canada Health Act, universal health care is publically funded and all Canadians should have reasonable access to medically necessary services [14]. However, medically necessary is not specifically defined in the Canada Health Act and health care spending and services are implemented by provincial / territorial government health care boards. Historically, this has led to significant variation in public access to prescription medications, and even in childhood HBV immunization schedules across Canada. For example, Alberta and Quebec have included second generation nucleos(t)ide analogs (i.e., TDF and ETV) as first line therapy for hepatitis B for almost a decade, yet these drugs were not approved on public drug benefits list in Ontario until recently and are still not covered by BC pharmacare, unless patients have advanced fibrosis, despite availability of less-costly generic TDF in 2017. There is a safe and effective HBV vaccine approved for decades yet many regions have imperfect vaccination programs. The WHO recommends that all infants should receive their first dose of vaccine as soon as possible after birth due to an abundance of epidemiological evidence that the greatest risk of developing chronic infection is within the first 5 years of life[1]. Only 4 provinces (British Columbia, Quebec, Prince Edward Island and New Brunswick) and the territories offer universal neonatal / infant vaccination, all others provide pre-adolescent vaccination. Universal HBV screening during pregnancy is mandatory in many provinces while it is only "strongly" recommended in Ontario, although widely implemented as good clinical practice[15]. Thus, whilst infants born to mothers with known hepatitis B may receive birth immunoprophylaxis, there are often cases of missed opportunities reported especially if the father or other close family members are infected. Our data also highlighted regional variations in HBV management that can inform policy makers of areas to implement best practice.

Chronic hepatitis B is a silent disease, over 250 million people worldwide are infected although less than 10% have been diagnosed. Most people do not have access to current therapy, and there is no cure for the millions of people already infected. In Canada, although there has been significant public health focus on people living with HCV and HIV, hepatitis B

remains an orphan disease that is unnoticed and underfunded. There is underappreciation of disease burden, complexity of management and need for better treatments. According to the Ontario Burden of Infectious Diseases Study, the hepatitis B virus was the fifth-ranked pathogen causing significant health adjusted life years lost[16]. Modelling data show that immigrants with CHB lost an average of 4.6 life years with higher lifetime risk of end-stage liver disease[17]. Immigrants and their descendants play a significant role in shaping and enriching Canadian sociocultural fabric and economic development. Current immigration trends and aging of Canadian population mean that it is imperative that uniform, structural programs are developed for identification (screening), education and access to care for Canadians at risk for HBV infection and possible life-threatening consequences.

In the current study, the majority of patients (~82%) tested were HBeAg negative. The HBeAg negative state may be due to the presence of pre-core and basal core promoter mutations in the viral genome which are linked to development of cirrhosis and/or hepatocellular carcinoma in Asian cohort studies[18], and hence would be an area for future evaluation in a multiethnic Canadian population. HBV data included standard clinical tests – i.e., HBV DNA and HBeAg status, as analysis for mutations associated with HBeAg negative disease is not available or needed in routine clinical practice to assess need for treatment. Additionally, there are limited genotype data to date from participating sites in Ontario, British Columbia and Quebec, which have large HBV patient populations. However, ongoing robust prospective data collection by Canadian Hepatitis B Network investigators will help address these data gaps in future studies. Whilst the data completeness may be affected by under-reporting and referral bias (i.e., patients identified with advanced fibrosis are more likely to be referred for treatment by their primary care provider), all study investigators highlight very consistent or increasing patient numbers in their clinical practice. For the first time, we report unique data from 8 provincial health care jurisdictions, both specialist academic and community clinics, and from regions (i.e., Atlantic provinces) in which limited historic data have been published. The

Canadian HBV Network is continuing to conduct longitudinal, prospective epidemiological studies on HBV infection in Canada. Our network is working to establish global partnerships such as “The International Coalition to Eliminate HBV (ICE-HBV, www.ice-hbv.org)”, which includes more than 50 scientists from 21 countries. Recent exciting research on the HBV lifecycle has uncovered potential new antiviral targets, with ~50 new treatments in the pipeline (www.hepb.org/treatment-and-management/drug-watch). The data from this current study, will inform global research on the impact of HBV, even in wealthy countries such as Canada, and the search for a HBV cure.

In conclusion, the current study is one of the largest and most comprehensive nationwide ever published on HBV epidemiology to date, and provides an important snapshot of demographics, clinical features, virology and antiviral treatment in persons living with hepatitis B in Canada. Hepatitis B is an ongoing and important cause of morbidity and mortality in Canada. Country specific epidemiological data will inform the development of programs to improve prevention, diagnosis and access to treatment for hepatitis B in Canada.

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Table 1: Comparison of demographics of patients with chronic hepatitis B across Canada

| Province (N) | Median Age | Male (%) | Asian (%) | Caucasian (%) | Black (%) |
|---|---|---|---|---|---|
| British Columbia (N=1536) | 53 y * | 56 % | 94 % * | 3 % * | 1 % * |
| Alberta (N=1814) | 44 y * | 51 % * | 74 % | 6 % * | 18 % * |
| Saskatchewan (N=179) | 41 y * | 59 % | 60 % * | 15 % | 21 % * |
| Manitoba (N=1051) | 46 y * | 53 % | 70 % * | 6 % | 21 % * |
| Ontario (N=4640) | 48 y * | 57 % | 71 % * | 15 % * | 11 % |
| Quebec (N=132) | 47 y | 61 % | 11 % * | 68 % * | 12 % |
| Nova Scotia (N=19) | 36 y * | 68 % | 73 % | 0 % | 13 % |
| Newfoundland and Labrador (N =13) | 50 y | 77% | 60% | 0% | 20% |
| National averages and total known, (not all clinical data is complete) | 48 y (n=9386) | 55% (n=9386) | 74 % | 12 % | 12 % |
| | | | 5808/7885 | 914/7855 | 914/7855 |

Note: Based on available clinical data from 9,386 patients reported. * P<0.05

Table 2: Comparison of HBeAg status, viral load, liver biochemistry, liver fibrosis and antiviral therapy used across Canada.

| Province | %HBeAg + | % HBV DNA >2,000 IU/mL | Mean most recent ALT (U/L) | % > F2 Fibrosis | % F3 – F4 Fibrosis | Antiviral Therapy (N=3041 known) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | % LMV | %TDF | % ETV |
| British Columbia | 28% * | 27% * | 33 * | 17% | 7% | 58% * | 56% | 12% * |
| Alberta | 19% | 51% * | 38 | 29% * | 13% * | 10% * | 57% | 28% * |
| Saskatchewan | 18% | 29% * | 37 | 12% | 8% | 5% * | 89% * | 0% * |
| Manitoba | 9% * | 38% * | 51 | 17% | 9% | 30% * | 76% * | 20% |
| Ontario | 17% * | 53% * | 48 * | 15% * | 5% * | 62% * | 51% * | 17% |
| Quebec | 23% * | 72% * | 44 * | 17% | 8% | 5% * | 81% * | 3% * |
| Nova Scotia | 20% | 39% | 30 | N/A | N/A | N/A | N/A | N/A |
| Newfoundland and Labrador | 50% | 100% * | N/A | N/A | N/A | N/A | N/A | N/A |
| National averages | 18% | 42% | 42 | 18% | 8% | 48% | 55% | 18% |
| n (total known) | 6802 | 1880/4496 | 4038 | 779 /4263 | 324 /4263 | 1446/3041 | 1658/3041 | 550/3041 |

*P<0.05

Table 3: Comparison of demographics, HBeAg status, viral load, liver biochemistry, liver fibrosis and antiviral therapy (nucleos(t)ide analog vs. interferon) used between HBV genotypes (N=1076) in Canada.

| Genotype | Asian | Caucasian | Black | % HBeAg+ | % HBV DNA>20,000 (IU/mL) | Mean ALT (U/L) | %>F2 | %>F3 | %NA | %IFN |
|---|---|---|---|---|---|---|---|---|---|---|
| A | 62% | 5 % * | 33% * | 15% | 4% * | 35 | 17% | 6% | 49% | 7% |
| B | 71% * | 27% | 2% * | 19% | 41% | 37 | 14% | 6% | 95% | 12% |
| C | 58% | 37% * | 5% * | 35% * | 47% * | 79 * | 30% * | 12% * | 138% | 23% |
| D | 30% * | 26% | 21% | 12% * | 26% | 40 | 9% * | 4% | 84% | 7% |
| E | 5% * | 3% * | 90% * | 17% | 23% | 52 | 22% | 11% | 39% | 0% |
| Total | 54% | 24% | 18% | 22% | 35% | 42 | 19% | 8% | 92% | 14% |
| N (total known) | 400/736 | 176/736 | 135/736 | 180/833 | 273/775 | 685 | 66/352 | 27/352 | 243/263 | 36/263 |

*P<0.05

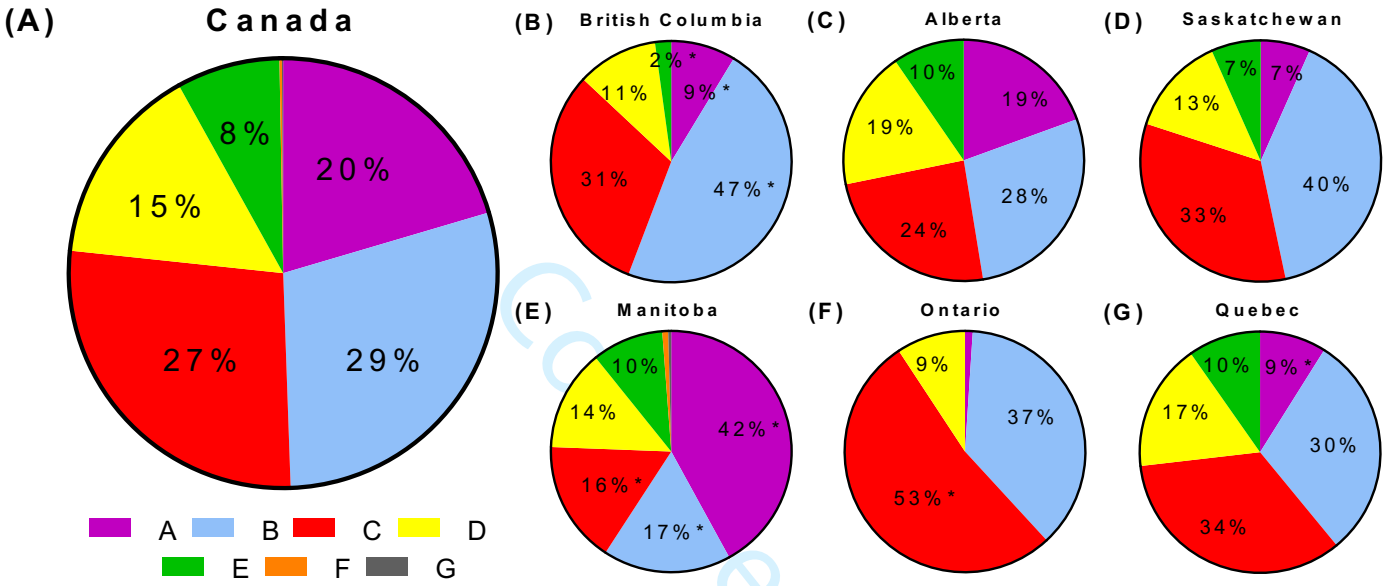


**Figure 1**: Comparison of HBV genotypes in Canada. (A) National total (n=1076). (B) British Columbia (n=138). (C) Alberta (n=447). (D) Saskatchewan (n=15). (E) Manitoba (n=250). (F) Ontario (n=97). (G) Quebec (n=123). *P<0.05

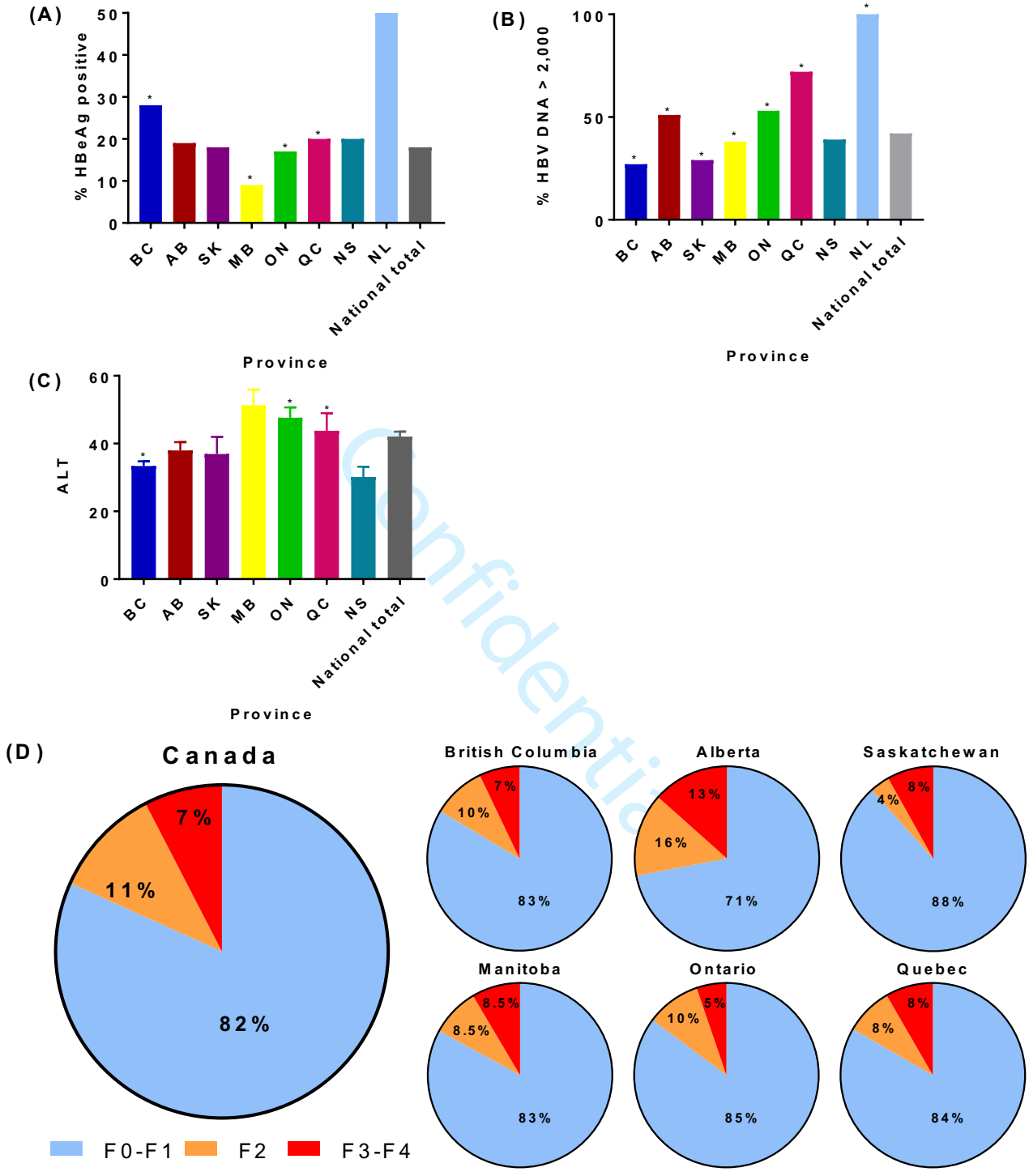


**Figure 2**: Comparison of HBeAg positivity, viral load, ALT and liver fibrosis stage, by province vs. national totals across Canada. (A) HBeAg (n=6802). (B) HBV DNA > 2,000 IU/mL (n=4496).

(C) ALT (mean ± SEM, n=4038). (D) Percent of patients with F0-F1 vs. F2 or F3-F4 liver fibrosis (n=2910). *P<0.05