HOSPITALIZATIONS IN IMMIGRANTS AND NON-IMMIGRANTS WITH CHRONIC HEPATITIS C INFECTION IN QUÉBEC

Rhiannon Kamstra

Department of Epidemiology, Biostatistics and Occupational Health
McGill University, Montréal

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ABSTRACT

Introduction

Chronic hepatitis C (HCV) causes considerable morbidity and mortality in Canada due to liver cirrhosis, liver failure and liver cancer that could be prevented through early screening and treatment. Immigrants are an underappreciated group at risk for HCV, often originating from high prevalence countries. This study examined all-cause and liver-related healthcare utilization in persons diagnosed with HCV in Québec from 1991 to 2007 in order to summarize burden over the study period (**objective 1**). To address the gap in the literature with respect to HCV-infected immigrants, we estimated and compared all-cause and liver-related healthcare utilization in HCV-infected immigrants and non-immigrants (1998 – 2007), identifying predictors of utilization (**objective 2**).

Methods

We performed a retrospective longitudinal cohort study using HCV cases reported to the Québec mandatory disease reporting database (MADO) from 1991 to 2007. Cases were deterministically linked to demographic, hospitalization, and outpatient services databases and followed until death, healthcare non-admissibility, or study completion. Utilization measures included inpatient visits, in-hospital days, and day surgeries. Liver-related events were identified using diagnostic coding for discharges (ICD 9/10) and procedures (CCI/CCA-DTC). Numbers of all-cause and liver-related inpatient stays, in-hospital days, and day surgeries occurring each year from 1991 to 2007 were computed and stratified by immigrant status (**objective 1**). Annual rates using the person-time contribution during each calendar year were calculated to assess the effect of changing cohort size. Mean events per subject and the proportion of subjects with ≥1 event were calculated for each outcome, stratified by immigrant status (**objective 2**). Univariate and multivariate negative binomial regression models were used to model rates of inpatient hospitalizations and in-hospital days, adjusting for immigrant status, age (cont.), and sex.

Results

We identified 22,589 and 20,139 linked cases of chronic HCV from 1991-2007 and 1998-2007 respectively. Nine percent of cases (N=1,821 from 1998-2007) were immigrants. At diagnosis, immigrants were older (47.6 vs. 43.2y, $p<0.05$), more likely to be female (46.7 vs. 31.9%, $p<0.05$), and to have liver cancer (0.2% vs. 0.1%, $p<0.05$). Mean time to HCV diagnosis

after arrival was 9.8 ± 6.9 years. Non-immigrants had a 2-10 fold higher prevalence of HCV-related risk factors, including drug or alcohol abuse, and HIV.

Annual all-cause and liver-related healthcare utilization in subjects diagnosed 1991-2007 increased over the study period, largely driven by increasing cohort size as prevalent cases were diagnosed. Liver-related stays accounted for 18% of inpatient visits (N=5,879). Immigrants contributed 5.5% and 6.2% of all-cause and liver-related stays, respectively.

Non-immigrants were more likely to be hospitalized at least once during follow-up compared to immigrants (43% vs. 28%, $p<0.05$). The most common non-liver primary discharge diagnoses for non-immigrants were mental disorders (27.8%) and injury/poisoning (11.9%) whereas for immigrants they were pregnancy/childbirth-related (13.2%) followed by mental disorders (10.7%). Non-immigrants had a higher burden of all-cause hospitalizations and days in hospital, with more visits (1.35 vs. 0.62, $p<0.05$), in-hospital days (15.49 vs. 7.10, $p<0.05$) and day surgeries (0.25 vs. 0.21) on average per subject and a higher proportion who had been hospitalized (inpatient) at least once (42.6% vs. 28.2%, $p<0.05$). In contrast, the proportion of subjects who had a liver-related hospitalization and the mean numbers of visits and in-hospital days were similar for immigrants and non-immigrants. When hospitalization rates (events/PY) were adjusted for age and sex, immigrant status was associated with lower rates of all-cause and liver-related inpatient visits (All-cause RR: 0.45, 95% CI: 0.40 – 0.51; Liver-related RR: 0.53, 95% CI: 0.40 – 0.70) and in-hospital days (All-cause RR: 0.57, 95% CI: 0.49 – 0.67; Liver-related RR: 0.63, 95% CI: 0.42 – 0.93).

Conclusions

Rising annual healthcare utilization in diagnosed and reported HCV in Québec is attributable to an increase in the number of identified cases, and may underestimate true burden as cases prior to 1998 were not consistently reported. Higher numbers and rates of all-cause hospitalizations in non-immigrants likely reflect more prevalent lifestyle comorbidities. Immigrants had similar numbers and rates of liver-related hospitalization despite having fewer risk factors for disease progression (lower proportion male, less HIV co-infection and alcohol use). We found that the older age of HCV-infected immigrants was a key driver of this, which is also supported by the long delay observed between arrival and HCV diagnosis and higher prevalence of HCC at diagnosis. These results highlight the importance of early HCV screening and treatment in this population. Ongoing analyses will compare utilization by immigrant status

with an uninfected reference cohort to understand drivers of hospitalization in this population including the association between healthcare utilization and HCV status.

RÉSUMÉ

Introduction

L'hépatite C chronique (VHC) est associée à des morbidités et une mortalité considérables au Canada à travers la cirrhose, l'insuffisance hépatique, et le cancer hépatiques qui pourraient être prévenus par un dépistage et un traitement précoces. Les immigrants sont sous-estimés comme groupe à risque de VHC, notamment les originaires de pays ayant une prévalence élevée de VHC. Dans cette étude, nous avons examiné l'utilisation des soins de santé, toute cause et liée aux maladies du foie, chez les individus ayant un diagnostic de VHC au Québec entre 1991 et 2007, et évalué le fardeau de cette utilisation durant cette période (**objectif 1**). Pour adresser le manque de littérature sur les immigrants affectés du VHC, nous avons également comparé l'utilisation des soins de santé toute cause et liée aux maladies du foie chez les immigrants et les non-immigrants ayant un diagnostic de VHC (entre 1998 et 2007) et identifié les prédicteurs (**objectif 2**).

Méthodes

Une cohorte longitudinale rétrospective de cas de VHC rapportés à la banque de données des Maladies à déclaration obligatoire (MADO) du Québec entre 1991 et 2007 a été utilisée. Ces cas ont été reliés d'une manière déterministe aux données démographiques, d'hospitalisation et des cliniques externes, et ont été suivis jusqu'à la survenue d'un décès, d'une non-éligibilité à la couverture universelle ou la fin de l'étude. L'utilisation des soins a été mesurée par l'hospitalisation et le nombre de jours, et les chirurgies d'un jour. Les événements reliés aux maladies du foie ont été identifiés par les codes diagnostiques des congés hospitaliers (CIM9-CM/10-CA) et des procédures (CCADTC/CCI). Le nombre annuel d'hospitalisation toute cause et liée aux maladies du foie, le nombre de jours d'hospitalisation et de chirurgie ont été calculés et stratifiés par le statut d'immigrant/non-immigrant (**objectif 1**). Les taux annuels utilisant la contribution des personnes-temps durant chaque année civile ont été calculés pour estimer l'effet de la variation de la taille de la cohorte. Le nombre moyen d'événements par individus et la fréquence d'individus ayant au moins un événement ont été calculés pour chaque issue et stratifiés par le statut d'immigrant/non-immigrant (**objectif 2**). Des régressions binomiales négatives uni et multivariées ont été utilisées pour modéliser les taux d'hospitalisation et le

nombre de jours d'hospitalisation, ajustés au statut d'immigrant/non-immigrant, à l'âge et au sexe.

Résultats

Nous avons identifié 22,589 cas de VHC entre 1991 et 2007 et 20,139 entre 1998 et 2007, parmi lesquels 9% étaient des immigrants (n = 1821 entre 1998 et 2007). À la date du diagnostic, les immigrants étaient plus âgés (47,6 vs. 43,2 ans, $p<0.05$), ayant plus de probabilité d'être du sexe féminin (46,7 vs. 31,9%, $p<0.05$) et d'être atteint du cancer du foie (0,2% vs. 0,1%, $p<0.05$). Le délai moyen du diagnostic du VHC après l'arrivée au Québec était de 9,8 ± 6,9 ans. Les non-immigrants avaient une prévalence de facteurs de risque de VHC 2 à 10 fois plus élevée, incluant l'abus de drogues et d'alcool, et le VIH.

L'utilisation annuelle des soins, toute cause et liée au foie, a augmenté pendant la durée de l'étude (1991-2007), largement à cause de l'augmentation de la taille de la cohorte. Les hospitalisations liées au foie représentaient 18% de toutes les hospitalisations (n = 5879). Les immigrants avaient contribué respectivement à 5,5% et 6,2% des hospitalisations toute cause et liées au foie.

Les non-immigrants avaient une plus haute probabilité d'être hospitalisés au moins une fois pendant le suivi (43% vs. 28%, $p<0.05$). Leurs principales causes d'hospitalisation non-liées au foie furent les troubles mentaux (27,8%) et blessures/empoisonnement (11,9%), alors que les immigrants l'étaient pour grossesse/accouchement (13,2%) et troubles mentaux (10,7%).

Les non-immigrants portaient un fardeau plus élevé des hospitalisations toute cause, en nombre moyen par individu, avec plus de visites (1,35 vs. 0,62, $p<0.05$), de nombre de jours d'hospitalisation (15,5 vs. 7,1, $p<0.05$) et de jours de chirurgie (0,25 vs. 0,21), ainsi qu'une plus haute fréquence d'au moins une hospitalisation (42,6% vs. 28,2, $p<0.05$). En revanche, la fréquence des hospitalisations liées au foie et le nombre moyen de visites et de jours d'hospitalisation étaient similaires chez les immigrants et les non-immigrants. Lorsque les taux d'hospitalisation (événement/personnes-années) étaient ajustés à l'âge et au sexe, le statut d'immigrant a été associé avec des taux moins élevés d'hospitalisation toute cause et liée au foie (RR toute cause = 0,45, $IC_{95\%}$ = 0,40-0,51; RR lié au foie: 0,53, 95% $IC_{95\%}$ = 0,40-0,70) et de nombre de jours d'hospitalisation (RR toute cause = 0,57, $IC_{95\%}$ = 0,49-0,67; RR lié au foie = 0,63, $IC_{95\%}$ = 0,42-0,93).

Conclusions

L'augmentation de l'utilisation des soins des cas diagnostiqués et rapportés de VHC au Québec est attribuable à une augmentation du nombre de cas identifiés, et pourrait sous-estimer le fardeau comme les cas n'ont pas été rapportés systématiquement avant 1998. Les nombres et taux élevés des hospitalisations toute cause et liées au foie des non-immigrants semblent refléter plutôt des comorbidités liées au mode de vie. Les immigrants avaient un nombre et taux similaires d'hospitalisations liées au foie, bien qu'ils aient moins de facteurs de risque pour la progression de l'hépatite C (moins de mâles, de VIH et d'abus d'alcool). Nous avons identifié l'âge chez les immigrants comme facteur clé, qui est également aligné avec le long délai entre l'arrivée au Québec et le diagnostic, ainsi que la prévalence plus élevée du cancer hépatocellulaire lors du diagnostic. Les résultats de cette étude démontrent l'importance d'un dépistage précoce du VHC et du traitement de la population immigrante. Des analyses sont en cours pour comparer l'utilisation des soins, stratifiée par le statut immigrant/non-immigrant, avec une cohorte de témoins non infectés afin de mieux comprendre les facteurs d'hospitalisation chez la population immigrante, incluant le lien entre l'utilisation des soins et le VHC.

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LIST OF ABBREVIATIONS

CDC – Centres for Disease Control

CNDSS – Canadian Notifiable Disease Surveillance System

EHSSS – Enhanced Hepatitis Strain Surveillance System

EIA – Enzyme immunoassay

FIPA – *Fichier d'inscription des personnes assurées*

GEE – Generalized estimating equations

HCC – Hepatocellular carcinoma

HCV – Hepatitis C virus

IDU – Injection drug use

IgG – Immunoglobulin G (antibodies)

MADO – *Maladies à déclaration obligatoire*

Med-ECHO – *Maintenance et exploitations des données pour l'étude de la clientele*

MIDI – *Ministère d'immigration, diversité et inclusion*

MSM – Men who have sex with men

MSSS – *Ministère de la Santé et des Services sociaux*

NAT – Nucleic acid test

PCR – Polymerase chain reaction

PPV – Positive predictive value

RAMQ – *Regie de l'assurance maladie du Québec*

RIBA – Recombinant immunoblot assay

RNA – Ribonucleic acid

WHO – World Health Organization

CHAPTER 1: INTRODUCTION

1.1. Context

Approximately 220,000 to 240,000 Canadians are estimated to be infected with hepatitis C (HCV), a blood-borne virus that may lead to serious chronic infection, end-stage liver disease and death.[1] Most HCV infections are initially asymptomatic and progress to chronic infection. About 20% of people with chronic HCV will develop liver cirrhosis within 20-30 years.[2, 3] HCV disease progression to long-term complications is slow, so while the incidence of new infections in Canada is decreasing, associated healthcare utilization is expected to rise over the next 20 years as the infected population ages.[4] Annual HCV-related costs in Canada are predicted to increase by at least 60% between 2013 and 2032, eventually reaching $258 million per year.[5] More than 80% of the annual cost in 2032 is expected to be related to health services of patients with cirrhosis or other late-stage liver disease.[5] Until recently, treatments for HCV have been poorly effective and difficult to tolerate. Vastly superior curative therapies are now becoming available, but at prohibitive costs.[6] High-quality information about healthcare utilization in HCV-infected populations will be necessary for informing health policy and planning related to interventions for HCV.

Immigrants are an underappreciated group at risk for HCV. Immigrants make up more than 20% of the Canadian population, more than 70% of whom originate from regions with intermediate and high HCV prevalence, thus accounting for a large potential burden of undiagnosed HCV cases.[7, 8] While ongoing transmission in Canada is primarily related to injection drug use, unsafe medical procedures are a major source of transmission worldwide.[9-11] Unsafe injections alone are estimated to have accounted for 157,592 and 315,120 new HCV infections in 2010.[9, 11] Immigrants are often healthier than their Canadian counterparts on arrival, and typically have a lower prevalence of behavioural comorbidities associated with HCV infection and disease progression such as drug use and alcohol abuse.[12-14] The best current estimates suggest that approximately 35% of people with HCV in Canada are foreign-born.[1]

1.2. Rationale

The predicted healthcare utilization due to HCV is expected to increase as the infected population ages, but few population-based studies have examined HCV-related healthcare utilization in Canada.[4, 15, 16] We will address this gap by examining healthcare utilization in all

diagnosed and reported HCV cases in Québec from 1991-2008 using population-based administrative data. Immigrants account for up to 35% of prevalent HCV cases in Canada and may have different risk factors, health status and care-seeking behaviour compared to Canadian-born cases.[14, 17-19] In addition, immigrants may be a high-risk group for disease progression and hepatocellular carcinoma, a deadly form of liver cancer related to HCV.[12] We examined immigrant healthcare utilization for the first time in a large, population-based Canadian study of HCV cases, which will be important for informing future health services planning in this group.

1.3. Objectives

This study describes healthcare utilization in diagnosed and reported cases of chronic HCV in Québec and compares healthcare utilization between Canadian-born and immigrant cases. We examined annual all-cause and liver-related healthcare utilization from 1991-2008 in persons with diagnosed HCV in Québec in order to summarize burden in our cohort over the study period. We estimated and compared all-cause and liver-related healthcare utilization for immigrants and non-immigrants with HCV diagnosed 1998-2007 to identify predictors of healthcare utilization including age and sex.

CHAPTER 2: BACKGROUND

2.1. Hepatitis C

2.1.1. Identification and biology

Hepatitis C (HCV) was first recognized in the 1970s when serologic tests for hepatitis A and B became available to prevent the transmission of blood-borne hepatitis. It was observed that many cases of post-transfusion hepatitis tested negative for both viruses, which led to a separate classification for non-A, non-B hepatitis.[20] A novel RNA flavivirus, HCV, was finally identified using molecular cloning in 1989 and was found retrospectively to account for up to 90% of non-A, non-B hepatitis.[20, 21] A first-generation serologic assay and systematic blood donor screening soon followed, preventing as many as 40,000 infections in the first year.[20] At this time, it was also discovered that a significant proportion of HCV cases were acquired through community exposures such as injection drug use.[22] Six major HCV genotypes have since been characterized which differ substantially in treatment susceptibility and geographic distribution. Genotype 1 is the most common genotype worldwide, accounting for an estimated 46% of cases, followed by genotypes 3 (30%) and 2 (9%). In high income countries, genotype 1 accounts for more than 75% of cases. However, other genotypes are more frequent in some global regions.[23]

2.1.2. Transmission

HCV is primarily transmitted through parenteral exposure to contaminated blood. Potential sources of infection include unsafe medical procedures, injection drug use (equipment sharing), tattoos, vertical mother-to-child transmission, and occupational exposure (e.g., needle-stick injury).[3] Sexual transmission of HCV is rare. Yearly risk of transmission among heterosexual couples with discordant HCV status is estimated to be less than 0.1%.[24, 25] However, HIV positive men who have sex with men (MSM) have been shown to have a 4-times higher risk of sexual transmission of HCV (Risk difference: 3.3/1000 persons) compared to HIV negative MSMs in a recent meta-analysis.[26] Higher risk of HCV infection in HIV positive MSMs has been specifically linked to sexual behaviours with a high risk of trauma and use of recreational drugs.[27] [28]

In Canada and the United States, screening of blood donors and other safety protocols have nearly eliminated new infections due to medical procedures. Most ongoing transmission in developed countries occurs in people who inject drugs.[29] However, unsafe medical practices

continue to be a major source of infection worldwide. The World Health Organization (WHO) estimates that at least 50% of medical injections are unsafe in developing in countries in Asia and sub-Saharan Africa.[10] In 2010 alone, unsafe medical injections are estimated to have caused between 157,592 and 315,120 new HCV infections (down from nearly 1 million in the year 2000).[9, 11]

2.1.3. Symptoms and sequelae

Acute HCV infection is rarely symptomatic but symptoms can include jaundice, abdominal pain, fatigue, and malaise.[3] Approximately 25% of acute infections resolve on their own, but this proportion has been shown to vary widely depending on a number of factors. The remaining majority persist longer than 6 months and become chronic infections.[30, 31] Chronic HCV infection often remains asymptomatic for many decades but can lead to progressive liver damage, including fibrosis which proceeds to cirrhosis and eventually to decompensated disease and liver failure. Complications of cirrhosis can be life-threatening and include portal hypertension, ascites, and esophageal varices.[3] An estimated 20% of untreated patients develop cirrhosis within 20-30 years of infection.[2, 3] The median time from infection to the development of cirrhosis is about 30 years.[32] In patients with cirrhosis, approximately 30% progress to decompensated disease leading to liver transplant or death.[33] Patients with cirrhosis can also develop hepatocellular carcinoma (HCC), a deadly form of liver cancer. In most studies, the cumulative 5-year incidence of HCC among cirrhotic HCV patients is between 4-14%.[34-37] HCC is the 3rd leading cause of cancer-related death worldwide, with a median survival time of less than 1 year.[38, 39] HCV patients who are at high risk may undergo routine monitoring for disease progression and HCC.[3] Rates of cirrhosis and other sequelae vary substantially depending on many viral and host factors. In particular, HIV co-infection and alcohol abuse have been shown to markedly accelerate liver disease progression in people with HCV.[40, 41]

Although liver-related complications are the most well-characterized, HCV can also cause serious extrahepatic disease.[42-44] Cryoglobulinemia, the production and deposition of abnormal immune complexes (cryoglobulins), occurs in up to 42% of cases.[42] Cryoglobulinemia is typically characterized by arthralgia, fatigue, and palpable purpura, but is also associated with Raynaud's phenomena, vasculitis, renal disease, and peripheral neuropathy. Other conditions associated with HCV include skin and thyroid disorders, diabetes mellitus, and non-Hodgkin's lymphoma.[42-46] Many studies have demonstrated that patients with HCV have a higher risk of

developing diabetes (pooled HR: 1.67, 95% CI: 1.28-2.06)[47] while conversely, patients with HCV and diabetes may be at increased risk of developing cirrhosis, hepatic decompensation, and HCC. [48-51] However, these associations remain controversial as some large population-based studies have failed to produce the same findings.[52] The relationship between diabetes and HCV is likely complex and continues to be investigated.

2.1.4. Case detection

a) Diagnostic tests

The earliest specific tests for HCV were enzyme immunoassays (EIAs) for anti-HCV immunoglobulin G (IgG). First generation EIAs were approved in 1990 and had relatively low sensitivity values (70-80%) and a high rate of false positives (up to 70).[53] Second generation assays were introduced shortly after (1992), with better sensitivity (95%) and slightly improved specificity.[53]The latest third generation EIAs were introduced in 1996 and are highly sensitive and specific (95 - >99%).[53, 54] False-negative results are more likely in people undergoing dialysis and people who are immunocompromised. Typically, a positive EIA test result is confirmed with a second highly specific test such as an immunoblot assay (e.g., RIBA) to rule out the possibility of a false positive. HCV EIAs are limited by a significant delay between infection and a positive test (7-8 weeks), and an inability to discriminate between active and resolved infections.[53-56]

Nucleic acid-based tests (NATs) are now routinely used in the context of HCV diagnosis and management. NATs detect HCV RNA in serum or plasma using PCR (polymerase chain reaction). Qualitative NATs, which have excellent sensitivity and specificity (similar to 3rd generation EIAs), can be used to diagnose active infection (i.e., dichotomous presence or absence of the virus).[57] Unlike anti-HCV IgG, HCV RNA may be present and detectable as early as one week after the initial infection, meaning that qualitative NATs can identify cases in the acute phase. The presence of HCV RNA after 6 months signifies a persistent active infection (i.e., a chronic case). After a patient is diagnosed, quantitative NATs are used to assess viral load. NATs are critical for determining the appropriate course of therapy and, in the case of quantitative NATs, for assessing response to therapy.[55] Despite the advantages of HCV RNA testing, if both the EIA and qualitative NAT are positive, then they do not distinguish between acute and chronic infection.[54-56] A summary of HCV diagnostic test types is given in **Table 2.1**.

Lastly, HCV genotyping is also routinely performed in order to determine the appropriate course of therapy.

Table 2.1 – A summary of the main hepatitis C (HCV) diagnostic test types currently in use.

Diagnostic Test	Biomarker	Use	Sensitivity(Specificity), %
3rd Generation enzyme assay (EIA)	Anti-HCV IgG	-Primary (screening)test -Positive 7-8 weeks after exposure -Indicates past or present infection	>97% (>95%)* [57]
Recombinant immunoblot (RIBA)	Anti-HCV IgG	-Confirmatory test for EIA -Positive 4-24 weeks after exposure	~100% specificity** [55]
Qualitative nucleic acid test (NAT)	HCV RNA	-Detect active infection -Positive >1 week after exposure -Positive >6 months after exposure in chronic active infection	95-99% (98-99%)[57]

*50-60% in low prevalence populations such as blood donors.
** Typically not a primary screening test due to lower sensitivity.

b) Screening and reasons for testing

Most HCV infections worldwide are undiagnosed and an estimated 44% of infected Canadians are unaware of their status.[1] Currently in Canada, screening for HCV is primarily risk factor-based and prevalence data are limited to small seroprevalence surveys, modelled estimates[1, 19], and surveillance data of reported cases[58]. Cases are detected through risk factor-based screening in those with symptomatic liver disease or elevated liver enzymes due to another cause and in patients prior to contraindicated therapies or immunosuppression. In a U.S. CDC survey, nearly half of HCV patients who responded listed clinical indications as the reason for initial testing.[59] Another survey of testing behaviours found that reasons for testing in U.S. HCV patients differed depending on socioeconomic and demographic factors including ethnic group, location, and age group.[60]

In the U.S., the "baby-boomer" generation has the highest HCV prevalence with up to 75% of all U.S. HCV cases born from 1945-1965.[61] While in Canada there is no nationally representative seroprevalence data, more than half all HCV case reports between 1991-2010 occurred in persons born 1946-1965.[62] In 2012, the U.S. CDC recommended that individuals born between 1945 and 1965 undergo one-time screening for HCV regardless of other risk factors.[61] Given that this population is expected to drive rates of HCV sequelae and healthcare

costs over the next several decades, it is important that these cases are diagnosed early to maximize the benefit of any possible interventions. In Canada, screening guidelines are currently being reviewed but no such targeted screening recommendation has been issued as of this time. One barrier to developing evidence-based guidelines for screening in Canada is the lack of strong population-based seroprevalence data.

2.1.5. Treatment

No prophylactic vaccine is available to prevent HCV infection. Since the discovery of the virus, the landscape of HCV therapy has continued to evolve toward safer and more effective treatments. Nonetheless, widespread treatment of HCV has been hampered by the poor efficacy and intolerability of available therapies – until recently.[63] Over the past several years there has been a revolution in HCV therapy promising high cure rates with vastly improved tolerability and an expanded population eligible for treatment.[63] However, the high costs associated with these new drugs represent a serious challenge for patients and policy makers.

The goal of HCV antiviral therapy is sustained virologic response (SVR) which requires that HCV RNA is undetectable in serum at least 6 months after completing therapy.[64, 65] Relapse of infection after SVR (detectable serum RNA) is very rare; the relapse rate in a meta-analysis of 4,228 subjects pooled from 44 studies (follow-up ranging from 0.5-9 years) was 3%[66] and most studies report rates of 0-1%.[67] Patients who achieve SVR experience a large, meaningful reduction in the incidence of cirrhosis, HCC, and both all-cause (adjusted HR: 0.26, 95% CI: 0.14-0.49)[68] and liver-related mortality (adjusted HR: 0.06, 95% CI: 0.02-0.19)[67-70] SVR is also associated with improved scores for health-related quality of life (HRQOL).[71] The normalization of liver histology and biochemistry following treatment have also been demonstrated.[72, 73] Patients in whom liver disease has already progressed to cirrhosis may remain at an elevated risk for liver-related events including HCC even after achieving SVR, underscoring the importance of early HCV detection and therapy. Even after treatment, patients with pre-treatment cirrhosis should be monitored for HCC due to their increased risk.[74]

While treatment guidelines have been updated many times over the past 25 years, therapy has remained interferon (IFN)-based until very recently (see timeline in **Figure 2.1**). The earliest of these therapies, IFN-α, required three injections per week for up to twelve months and resulted in SVR in less than 30% of patients.[75] Ribavirin (RBV), an oral nucleoside analogue, became a standard addition to HCV therapy by the late 1990s and improved the proportion achieving SVR

2-3 fold.[76, 77] While IFN/RBV dual therapy had higher efficacy, it also had additional side-effects and contraindications which led to more frequent discontinuation of treatment.[65] Shortly after the shift to IFN/ribavirin dual therapy, pegylated (PEG) forms of IFN replaced standard preparations following trials showing improved efficacy and tolerability. [78, 79] Peg-IFN has slower clearance from the body and can be injected less frequently (once per week) making it more tolerable. Dual therapy with Peg-IFN/RBV for 48 or 24 weeks (depending on genotype) remained the standard-of-care treatment until very recently. Peg-IFN/RBV produces SVR rates of 38-49% for genotype 1 and up to 80% for others.[65, 80]

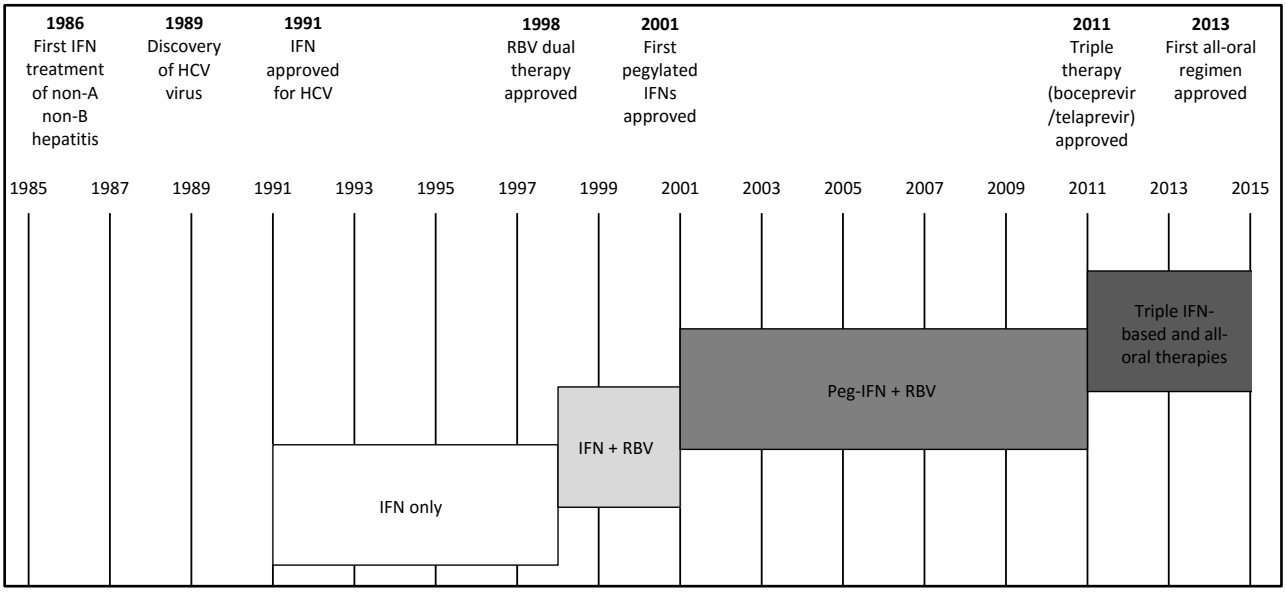

Figure 2.1 – Timeline of available therapies for chronic hepatitis C (HCV) from the discovery of the virus (1986) and the interferon (IFN)-based era until 2013 when the first all-oral regimens were approved. IFN – interferon, RBV – ribavirin.

Despite having available treatments for decades, the majority of patients diagnosed with HCV remain untreated due to factors including intolerability of the medications, lifestyle issues making long-term compliance difficult in HCV-infected populations (e.g., substance abuse, unstable living conditions), and lack of physician awareness.[81] Successful therapy can have enormous lifelong benefits. Unfortunately under previous regimens SVR was not attainable for many patients because of low efficacy or side-effects resulting in discontinuation. In vulnerable populations there are also many barriers and competing priorities to therapy.[81] Complex management, lack of resources, and poor physician awareness have been associated with under-treatment of patients who may have benefitted.[81]

In 2011, the first direct-acting antivirals (DAAs) were approved by the FDA to treat HCV genotype 1 in combination with Peg-IFN/RBV.[82, 83] Triple therapy with PEG-IFN/RBV and boceprevir or telaprevir improved SVR rates to approximately 61–75% in treatment-naïve patients, including those with compensated liver disease.[65, 80, 82, 83] These early DAAs had several drawbacks including toxicity and the potential for antiviral resistance. Today, there are several approved all-oral regimens with dramatically improved SVR rates of 90-100% after only 12-24 weeks of therapy.[63] Unfortunately access to these revolutionary new drugs is not universal, in part due to prohibitive prices which can reach up to $170,000 USD per course.[6, 84] As policymakers weigh the costs and benefits of expanding access to these drugs, there is a pressing need to better understand the disease and healthcare burden in HCV-infected populations particularly in subgroups with a higher risk of health services use.

2.1.6. Epidemiology

a) Global burden

The latest estimates place global HCV seroprevalence at approximately 1.6%, with 115 million people infected worldwide.[85] Central/East Asia and North Africa/Middle East are regions with the highest seroprevalence where an estimated 3.5% of the population is infected.[86] Results from the Global Burden of Disease Study indicate that as many as 499,000 deaths were attributable to HCV in 2010, primarily due to cirrhosis and liver cancer. HCV is ranked as the 25th leading cause of death, accounting for almost 1% of global mortality.[87]

b) Canada and Québec

Although Canada is a low-prevalence country, it is still home to a large number of people infected with HCV. Recent estimates suggest that between 220,000 and 240,000 Canadians are living with HCV infection (as of 2011) with a national prevalence of 0.64-0.71%.[1] Nearly half of these infections (44%) are likely undiagnosed and over a third (35%) are thought to occur in foreign-born populations.[1] The annual rate of reported cases climbed for the first eight years that data was collected (1991-1998), but has steadily fallen since 1998.[58] In 2012, 10,180 cases of HCV were reported (29.3 per 100,000 population), which corresponds to approximately a 50% reduction in the case notification rate relative to 1998.[58] The rate of HCV in men has consistently been about 2-fold higher than in women.[58] As of 2012, the highest rates of HCV for men and women are reported in ages 40-59 and 25-29 respectively.[58] Most new infections in Canada are

associated with injection drug use.[88] Other high prevalence/high-risk groups include MSM, aboriginal populations, and prison inmates.[88, 89] In the recent Ontario Burden of Infectious Disease Study, HCV was named the leading cause of health-adjusted life years lost (HALYs) and the 3rd highest cause of mortality.[90]

Québec has the third highest number of annual case reports, following British Columbia and Ontario respectively.[88] Generally, the epidemiology of HCV in Québec is similar to the rest of Canada. The HCV case notification rate in Québec is below the national average and has decreased annually since its peak in 2000 when 3,698 cases were reported.[88, 91] Over the last five years, an average of 1,400 HCV cases were reported each year in the province.[92] Males account for over 60% of cases and injection drug use is the most common risk factor for infection.[92]

c) Surveillance in Canada

The Canadian Notifiable Disease Surveillance System (CNDSS) is the national reportable disease surveillance system which receives data from reporting health ministries.[88] Reporting from ministries to CNDSS is voluntary for HCV, and while CNDSS has a standardized case definition, individual jurisdictions may use their own. National statistics for diagnosed HCV have been available since 1991 when it became a reportable disease. HCV cases were not reported from all provinces and territories until 1999.[88] The CNDSS definition requires a positive test for HCV antibodies or RNA but does not distinguish between acute and chronic infections.[88] In 1998, the enhanced hepatitis strain surveillance system (EHSSS) was created to collect additional data about cases at specific sites.[93] The EHSSS includes an acute case definition which relies on specific clinical and laboratory criteria.[93]

In Québec, HCV cases are reported provincially through the provincial public health department (*Institut national du santé publique du Québec*). Case reports for reportable diseases are recorded in a provincial database known as the *Maladies à déclaration obligatoire* (MADO). An HCV case definition was first added to MADO in 1997 but reporting did not become mandatory until April 2002.[94] The number of cases was relatively stable in the period immediately before and after mandatory reporting was introduced, suggesting that reporting was already widespread. A definition for acute HCV was added to MADO in 2002.[95]

Canadian HCV surveillance data rely on robust laboratory-based case definitions which minimize misclassification. However, these data sources are subject to the limitations inherent in passive surveillance. As HCV screening in Canada is risk factor-based, a select group of infected

people are being detected. The probability of detection may be influenced by disease progression, the presence of risk factors, medical comorbidities for which HCV testing might be indicated, and access to care. Therefore, HCV cases identified by surveillance are not likely representative of all prevalent cases, a large proportion of which remain undiagnosed. It is plausible that difficult-to-reach populations, those without risk factors, and those with poor access to care might be underrepresented while those with late-stage disease might be overrepresented. While an estimated 35% of cases occur in immigrants, CNDSS and MADO surveillance data do not include accurate information about immigrant status, leaving the true burden in this population unknown.[1]

2.1.7. Healthcare utilization and costs

Despite declining HCV incidence, the rate of complications among the aging cohort of persons already infected is expected to continue to rise for at least another 20 years.[5] HCV has already surpassed other diseases as the leading cause of liver transplantation in the U.S.[96] In an article published last year, Myers and coauthors predicted that annual costs due to HCV in Canada will increase by 60% between 2013 and 2032 to $258 million per year.[5] More than 80% of the annual cost in 2032 is expected to be related to healthcare utilization by patients with cirrhosis or other late-stage liver disease. These projections do not account for treatment costs which may be substantial given the high cost of new drugs and the expanding eligible population.

Hospital discharge data from large U.S. studies have suggested that crude rates of HCV-related healthcare utilization may be relatively stable, but disease severity and associated costs are increasing.[97, 98] Data from the nationwide inpatient sample (NIS) indicate that in-hospital mortality and resource utilization related to HCV increased from 2005-2009.[98] Another study examined over 2.3 million outpatient visits and 548,000 inpatient visits and found that the number of complications in the "baby-boomer" cohort was increasing.[97] Both studies observed that numbers of emergency visits increased more substantially than other types of utilization, suggesting worsening disease severity. Neither of these discharge-based studies had access to patient-level follow-up, preventing them from investigating re-admission or patient-level predictors of healthcare utilization.

For adequate resource allocation and planning, it is important that we understand the true burden of healthcare utilization in HCV patients in the Canadian context. Despite this need, there

are very few Canadian publications that address this. In 2008, Myers et al. examined HCV-related hospitalizations in a Calgary health region between 1994-2005 and found an increasing healthcare burden due to HCV over the study period.[4] The main outcomes were annual admittance frequency, total number of hospital days, and in-hospital mortality. This study used discharge-level data and identified events using diagnostic coding. The annual rate of all major outcomes increased approximately 4-fold (15-18% annually) from 1994-2005, suggesting a gradual increase in utilization surpassing previous estimates. Another study by Schanzer et al. performed a birth cohort analysis of inpatient admissions from 2004-2011 where an HCV diagnosis was present in the Canadian Discharge Abstract Database.[99] This study found that rates of admission with HCV and liver disease were highest among patients born 1950-1954 and 1955-1959, and suggested that the disease burden due to HCV in Canada will continue to rise.

The largest study examining HCV-related healthcare utilization was performed in British Columbia by Krajden and coauthors.[16] They performed a longitudinal follow-up of HCV seropositive subjects identified from the provincial public health department from 1997-2004. This study has several strengths, including its large size (over 20,000 subjects), use of patient-level follow-up, and use of a number of services including physician visits, hospitalizations, and drugs. Their unique study design controlled for baseline costs in the underlying population by comparing people who tested positive for HCV with people who got tested but were negative, assuming that risk factors would be similar among those were tested for HCV regardless of diagnosis. Krajden et al. found that healthcare costs increased with time since diagnosis. HCV-related healthcare spending in British Columbia was estimated to be approximately $136 million per year. This study was limited by its inability to compare utilization with the general population, as controls were likely to have very different characteristics. Costs were not attributed to HCV based on coding at the time of the procedure/service directly. Staging of disease was determined using ICD diagnostic codes, but all costs during a particular "stage" were considered. Temporal trends of HCV-attributable healthcare utilization over the study period were not analyzed in detail. Lastly, despite having patient-level data, no stratifications were performed using immigration status or country of origin.

The two population-based studies that describe HCV-related healthcare utilization in Canada have important limitations and their generalization to other HCV-infected populations may be limited. There are no such studies specific to the Québec population and none which

address healthcare utilization in HCV-infected immigrants compared with non-immigrants. Given studies conducted in British Columbia, Ontario, and Alberta, Québec likely has a similarly high burden of HCV-related disease.[4, 16, 90] However, specific healthcare utilization patterns might differ substantially as they are specific to the healthcare setting and population.

2.2. Canada's immigrant population

2.2.1. Size and composition

Canada's population has the second highest proportion of immigrants among the G8 countries, and continues to receive a large number of immigrants every year. According to the 2011 National Household Survey, more than 6.7 million foreign-born individuals live in Canada, comprising 20.6% of the population.[7] Each year approximately 240,000 international migrants are granted permanent residency in Canada. Almost a quarter of Canadian immigrants are recent arrivals (2006-2011), the majority of whom settled into one of three large urban centers (Montréal, Toronto, or Vancouver). While most immigrants who arrived before the 1970s were from Europe, new immigrants to the country have increasingly originated from Asia, Africa, and the Middle East, regions with intermediate or high HCV prevalence.[86] In Canada, Asian immigrants are the most frequent new arrivals, accounting for 60% and 56.9% of those arriving from 2001-2005 and 2006-2011 respectively.[7] The three categories under which most new permanent residents are granted entry are: economic (e.g., skilled workers), family (e.g., sponsored by a family member in Canada), and refugee. Approximately 60% of new entrants are admitted as economic immigrants, while family sponsored and refugee class entrants constitute about 30% and 10% respectively.[8]

Québec is home to approximately 14.4% of Canada's immigrant population. Currently, about 50,000 immigrants enter the province each year.[7] As of 2011, over 974,000 immigrants were living in Québec, comprising 12.6% of the provincial population. An overwhelming majority of immigrants (86%), reside in the metropolitan area of Montreal. Most new immigrants to Québec have knowledge of French (57%). In contrast to Canada, the most common region of origin is Africa (35%), particularly the "Maghreb" region of North Africa (17%).[100] The proportions of new immigrants (2001-2010) admitted as economic, family, and refugee class migrants in Québec are 63%, 22% and 14% respectively.[101, 102]

2.2.2. Health status and service use

Immigrants are on average healthier on arrival than their Canadian counterparts. The "healthy immigrant effect" has been demonstrated using self-assessed health and specific health outcomes (including mortality) but the effect is strongest for chronic diseases.[13, 103] The health advantage that is observed typically disappears with increasing length of stay. Superior health in immigrants may be due to the selected nature of this group, which is both self-selected and subject to selection by the immigration process which includes screening for some serious medical issues. Context-specific perceptions of health may also explain this trend. One 2005 study suggested that the early decline in self-assessed health is likely due to a re-assessment of health after adjusting to life in Canada, rather than an actual decline in health.[104] Immigrants also tend to have more healthful behaviours (e.g., diet, activity) which begin to more closely resemble those of the non-immigrant population over time. This is consistent with the lower prevalence of many chronic conditions that is observed on arrival.[13, 103]

Despite the initial advantage, immigrants experience an increase in the rate of many chronic diseases within 10-20 years of arrival. Immigrant rates of heart disease, type 2 diabetes, and some cancers have even been shown to surpass those in the Canadian-born population. In a study of cancer incidence, standardized incidence rates (SIRs) were lower in immigrants than in the Canadian-born population for all but three types: liver, nasopharyngeal and cervical cancer.[105] These exceptions are likely due to early exposures in the country of origin, including hepatitis B and C which can cause liver cancer. In an earlier study, DesMeules et al. also found elevated standardized mortality ratios for certain cancers, notably liver cancer in immigrants from Northeast Asia.[17]

Importantly, the immigrant population in Canada is heterogeneous, and this is reflected accordingly in findings related to the healthy immigrant effect. The same effect is not necessarily observed across all subgroups and can vary substantially according to factors including ethnicity, sex, year of arrival, socioeconomic status, and refugee status. For example, women and low-income immigrants are more likely to report a decline in self-reported health after arrival.[104]

The trend in the use of healthcare services in immigrants after arrival is similar to what would be expected given the healthy immigrant effect. Generally immigrants have been characterized as "under users" of health services. One study using data for immigrants from Québec, British Columbia, and Ontario found overall that immigrants had 5-24% fewer

physician visits and 36-54% fewer hospitalizations compared to the reference group after age and sex standardization.[106] This study also found variations between provinces and by region of origin. Refugees consistently had higher health services utilization compared to other immigration categories and in some cases, compared with Canadian-born reference subjects. Utilization can also vary by region of origin, ethnicity, and province.[106, 107] In Québec, immigrants from the Region of the Americas (WHO categorization) used more outpatient services than other groups. However, region-specific variations in utilization differed between provinces. Trends in utilization with time since arrival also varied between provinces. While in British Columbia outpatient utilization increased with time spent in Canada, Ontario and Québec saw decreases in utilization among immigrants during the first five years after arrival followed by an increase in later years. Authors suggest that differences in utilization by province and by immigrant sub-group may reflect different complex barriers to care including linguistic and cultural challenges.[106]

2.2.3. HCV in immigrants

Immigrants to Canada increasingly originate from intermediate and high HCV prevalence regions including Asia and Africa.[7, 8] In some areas around the world, HCV transmission occurs routinely through unsafe medical procedures such as injections.[9, 10] Immigrants originating from these areas may have been infected early in life in their countries of origin, despite no identifiable risk factor for infection such as a history of injection drug use. It follows that immigrants living with HCV in Canada may go undetected in the absence of systematic screening that identifies immigrant status as a risk factor. Unfortunately there is only limited information about the true burden of HCV in this population and currently, no such screening guidelines have been issued. The best current estimates suggest that approximately 35% of people with HCV in Canada are foreign-born.[1]

Several studies have demonstrated that immigrants have an increased rate of liver cancer and associated mortality compared with Canadian-born controls, which is likely related to viral hepatitis infection prior to arrival.[17, 105] One clinic-based study in Ontario showed that immigrants with HCV were typically older (55 vs. 48 years), more likely to be female (44 vs. 28%) and had about a 50% lower prevalence of lifestyle-related risk factors such as heavy drinking, injection drug use and smoking.[12] Among immigrant patients, only 12% had injection drug use as a presumed mode of HCV transmission (compared to 55% of non-immigrants).

Survival analysis revealed that immigrants with advanced fibrosis had a 2-fold higher risk of developing HCC compared to Canadian-born patients, an association that disappeared once adjusting for older age and a higher prevalence of diabetes.[12] These results suggest that longer duration of infection and certain comorbidities such as diabetes, may explain elevated disease severity in immigrants.

CHAPTER 3: STUDY OBJECTIVES

3.1. Rationale

The predicted healthcare utilization due to HCV is expected to increase as the infected population ages, but few population-based studies have examined HCV-related healthcare utilization in Canada.[4, 15, 16] We will address this gap by examining healthcare utilization in all diagnosed and reported HCV cases in Québec from 1991-2007 using population-based administrative data. Québec is a large province with a high burden of HCV cases, so characterizing HCV-related healthcare utilization in this population will be important for establishing the current burden of HCV and for future health system planning and resource allocation to address the growing number of HCV patients with complications.

Immigrants are estimated to account for up to 35% of prevalent HCV cases in Canada and may have different risk factors, health status and care-seeking behaviour compared to Canadian-born cases.[17-19] In addition, immigrants may be a high-risk group for disease progression and hepatocellular carcinoma, a deadly form of liver cancer related to HCV.[12] However, most HCV studies and particularly those related to healthcare utilization do not consider immigrant status specifically in their analyses. In order to better understand the burden of HCV in immigrants and to characterize this population which is expected to differ from the non-immigrant population infected with HCV, we will examine immigrant healthcare utilization for the first time in a large, population-based Canadian study of HCV cases. Differences between immigrant and non-immigrant cohorts, including patterns of healthcare utilization and demographic differences, may be important for targeting future interventions including screening and treatment.

3.2. Overall objective

To describe healthcare utilization in all diagnosed and reported cases of chronic HCV in Québec (1991-2007) (**objective 1**) and to use cases 1998-2007 (when routine reporting was taking place) to compare healthcare utilization between Canadian-born and immigrant cases **(objective 2**).

3.3. Specific objectives

1. Describe the annual all-cause and liver-related healthcare utilization from 1991-2007 in persons with diagnosed HCV in Québec and calculate the proportion of utilization occurring in immigrants each year.
2. Estimate and compare all-cause and liver-related healthcare utilization for immigrants and non-immigrants with HCV diagnosed from 1998-2007, identifying individual predictors of healthcare utilization.

3.4. Hypothesis

The annual healthcare utilization in cases with diagnosed and reported HCV in Québec is expected to increase over the study period for two main reasons (**objective 1**). First, other studies in Canada and the U.S. have reported increasing liver-related utilization, attributable to the aging cohort of prevalent cases and disease progression. Second, the number of HCV diagnoses reported annually rose between 1991-2000, increasing the cohort size and expected healthcare utilization each calendar year.

To our knowledge, no published studies have examined healthcare utilization in Canadian immigrants with HCV (**objective 2**). The "healthy immigrant effect" suggests that immigrants may have less all-cause utilization than non-immigrants. HCV-infected populations are highly burdened with comorbidities (i.e., substance abuse and mental illness), while immigrants may be relatively healthy. With respect to healthcare utilization related to HCV, there is some evidence that immigrant status predicts a higher risk of developing liver-related complications. Based on the limited evidence available, we would expect differences in all-cause and liver-related healthcare utilization between immigrants and non-immigrants. However, the expected direction and magnitude of these differences is unclear.

CHAPTER 4: METHODS

4.1. Study design

We used a retrospective longitudinal cohort design. Our data sources permitted individual-level follow-up as opposed to unlinked (aggregate) hospitalization data, a limitation of previous studies which used unlinked discharges.[4, 16, 97, 98] Cases of hepatitis C virus infection (HCV) were ascertained from laboratory-confirmed diagnoses in the Québec reportable disease database (MADO) and linked to administrative databases containing health services and demographic data. The use of administrative data was advantageous given the universal healthcare coverage in Québec and allowed healthcare utilization to be observed in a real-world setting.

4.2. Data sources and overview of linkages

4.2.1. Overview

Database linkage and cleaning, including removal of duplicates, were performed previously by the Greenaway research group as part of a larger investigation of viral hepatitis in immigrants. We collected all HCV cases that were diagnosed and reported to the Québec reportable disease database (MADO) from January 1^{st,} 1991 until December 31st, 2007 when the latest available data was collected. **Figure 4.1** gives an overview of the database linkages used in this study. HCV cases were deterministically linked to the following 4 provincial databases: (1) MIDI (landed immigrant database), (2) RAMQ FIPA (demographic information), (3) RAMQ Medical Services (physician billing), and (4) Med-Echo (hospitalizations). RAMQ and Med-Echo databases were linked to MADO cases using a unique health services ID number (RAMQ ID). Immigrants have a unique VISA number recorded in RAMQ FIPA which was linked to the landed immigrant database (MIDI) containing immigration-related variables.

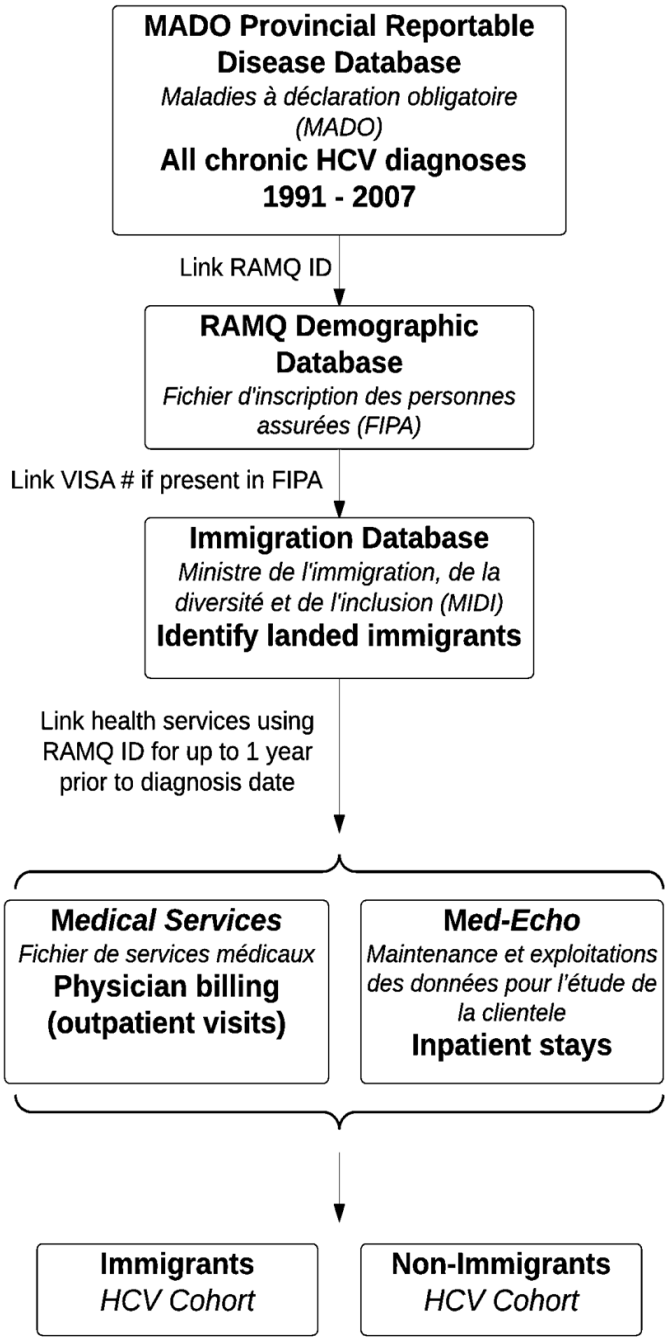

Figure 4.1 – Overview of study database linkages. Chronic hepatitis C (HCV) cases were ascertained from the Québec provincial mandatory disease reporting database (MADO) and linked to demographic information (RAMQ FIPA), immigration variables (MIDI) and health services (Med-Echo – inpatient data, Medical Services – physician billing).

4.2.2. M*aladies à déclaration obligatoire* (MADO)

M*aladies à déclaration obligatoire* (MADO) contains case reports made to the provincial public health department's passive surveillance system for reportable diseases. A standard HCV case definition based on highly sensitive and specific tests was introduced in 1997 and most laboratories were routinely reporting by 1998.[95] Reporting of HCV cases became mandatory in 2002, however most public health regions were reporting cases by this time and crude numbers of cases were relatively stable prior to and after the introduction of mandatory reporting.[94] From 1991-2001, all HCV cases were classified as "unspecified" (referring to chronic or acute infection). Beginning in 2002, a second definition was added for acute cases. We excluded all cases classified as "acute", as chronic HCV infection was the focus of this study. MADO HCV case definitions are given in **Table 4.1**.

Table 4.1 – Hepatitis C (HCV) case definitions for the Québec mandatory disease reporting database (MADO).[95]

Classification	Confirmed case definition
HCV not specified as chronic or acute	An individual > 1 year of age without sufficient criteria to classify as an acute case plus **either** of the following**:** 1) Serologic detection of anti-HCV IgG (EIA) confirmed either by a 2nd EIA or by a RIBA 2) Detection of HCV RNA by PCR*
Acute HCV *(added 2001)*	An individual > 1 year of age who **either:** 1) Satisfies clinical and laboratory criteria† 2) Seroconverts from anti-HCV IgG negative to positive within 6 months of a known exposure **OR** Detection of HCV RNA (PCR) in a person <1 year of age*

EIA: Enzyme immunoassay; RIBA: Recombinant immunoblot assay;

* HCV RNA testing was added to case definitions in 2001. † **Clinical criteria**: 1) symptoms consistent with acute hepatitis (e.g., jaundice, dark urine) or an increase in AST or ALT enzymes, 2) exposure in the previous 6 months to a transmission source (IV drug use, receipt of blood products, sexual contact with a known hepatitis C positive individual) and 3) no other apparent cause for hepatitis. **Laboratory criteria:** 1) elevated serum ALT or AST (>2.5x upper normal limit), 2) IgM anti-HAV negative, 3) HBsAg negative and IgM anti-HBc negative and 4) anti-HCV positive (confirmed by another test) or HCV RNA positive.

4.2.3. *Regie de l'assurance maladie du Québec* (RAMQ) databases

Health coverage in the province of Québec is universal and administered by the *Regie de l'assurance maladie du Québec* (RAMQ). Québec residents including landed immigrants are eligible for coverage. All residents who are registered with RAMQ have a unique RAMQ ID which is associated to any covered health services received. Immigrants with coverage also have a VISA number recorded in FIPA. Two RAMQ data sources were used in this study: (1) *Fichier d'inscription des personnes assurées* (FIPA) which contains demographic data for those with coverage and (2) *Fichier de services médicaux* (Medical Services) which contains physician billing claims submitted to RAMQ for inpatient and outpatient visits. Each Medical Services claim can contain one diagnostic code using the International Classification of Diseases, Ninth Revision, clinical modification (ICD-9-CM). Coding is performed by care providers and is not validated. We also obtained records of RAMQ eligibility for cohort subjects in order to appropriately censor follow-up based on loss of coverage for ≥ 6 months.

4.2.4. Landed immigrant database (MIDI)

The *Ministère d'immigration, diversité et inclusion* (MIDI) keeps a record of each immigrant given permission to live in Québec in the landed immigrant database. This database includes important information about each immigrant including the date of arrival in Québec, category of immigration, and country of origin. When an immigrant is registered by MIDI and settles in the province, they become eligible for health coverage and a RAMQ ID is recorded in the database.[108] We were able to obtain MIDI records for all immigrants admitted to Québec from 1985 until 2007. Arrivals prior to 1985 have a VISA number in RAMQ FIPA but do not link to MIDI and are therefore considered unlinked immigrant cases.

4.2.5. Québec hospital discharge database (Med-Echo)

Maintenance et exploitations des données pour l'étude de la clientele (Med-Echo) is a record of all acute care stays and day surgeries in Québec hospital centers since 1987.[109] Med-Echo is administered by the *Ministère de la Santé et des Services sociaux* (MSSS) and uses data compiled by each hospital. Med-Echo contains descriptive information (i.e., date, length of stay), medical diagnoses, procedures, stay-related physician reimbursements, and information about ICU visits. Diagnoses and procedures are extracted from medical records and coded by trained archivists. Each stay has at least one primary and up to 15 secondary diagnostic codes and can have a maximum of 20 procedure codes. Medical diagnoses were coded using the International Classification of Diseases, Ninth Revision, clinical modification (ICD-9-CM) until April 1st,

2006 when ICD-10-CM was adopted in Québec. Procedures were coded using the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP or CCA-DTC)[110] until 2006, followed by the Canadian Classification of Health Interventions (CCI)[111].

4.3. Cohort definition

For objective 1, the cohort consisted of newly diagnosed chronic hepatitis C cases reported in MADO from January 1st, 1991 to December 31st, 2007 who were registered in the RAMQ FIPA database. This was intended to be as inclusive as possible to quantify the magnitude of healthcare utilization in all diagnosed and reported cases in Québec. For objective 2, the cohort was restricted to cases diagnosed from January 1st, 1998 to December 31st, 2007 because prior to this date there was significant underreporting which may have been differential between comparison groups. Cohort entry (index date) was defined by the date of HCV diagnosis. Date of death (month and year) and dates for non-admissibility to RAMQ were specific variables in FIPA and a non-admissibility dataset respectively. Subjects were followed retrospectively from cohort entry to censoring at the first of (1) 6 months after the start date of a permanent RAMQ non-admissibility period (≥ 6 months), (2) death, or (3) December 31st, 2007 (end of study period). Follow-up time was defined as the time between diagnosis and censoring. For analysis of rates, cumulative length of stay was subtracted from follow-up time to appropriately reflect person-time at risk. Health services data for all HCV cases (immigrants and non-immigrants) were obtained up to 1 year prior to the date of cohort entry to assess baseline medical comorbidities. However, for cases diagnosed less than 1 year after becoming eligible for RAMQ, less than 1 year of data prior to diagnosis was used. One limitation presented by this is that immigrants may be less likely than non-immigrants to have a full year of data prior to diagnosis, meaning that we may be underestimating the prevalence of comorbidities in immigrants relative to non-immigrants. The following exclusion criteria were applied to ensure data validity: (1) non-linkage to RAMQ FIPA, (2) date of diagnosis > 14 days before admission to Canada (immigrants), (3) date of diagnosis > 30 days after death, (4) date of diagnosis > 1 month after permanent RAMQ non-admissibility, or (5) date of diagnosis > 15 days after any non-admissibility period. Diagnosis dates ≤ 14 days before admission (immigrants) were changed to match the date of admission, meaning that if immigrants were diagnosed up to two weeks prior to RAMQ eligibility, they would still be included. However, immigrants who were diagnosed more than two weeks prior to eligibility were excluded. Diagnosis dates within 30

days after death or permanent RAMQ non-admissibility were changed to match the dates of death or RAMQ non-admissibility, respectively.

4.4. Exposure and covariate definitions

4.4.1. Chronic HCV cases

Chronic HCV cases were ascertained from MADO and are laboratory-confirmed, with the majority of cases having been identified using highly sensitive and specific 2nd and 3rd generation assays (1st generation EIAs 1991-1992, 2nd generation 1992 – 1996, and 3rd generation 1996).[55, 57, 112] An overview of diagnostic tests for HCV is given in **Table 2.1** and MADO case definitions in **Table 4.1**. For most of the study period there was one case definition which did not distinguish between acute and chronic infection. Most acute cases of HCV infection are asymptomatic and thus HCV is usually detected in the chronic stage.[3] Prior to 2002, all cases of HCV were used (acute and chronic) and after 2002 all acute cases were excluded. This should have very little impact on the results as there were was a very small numbers of reported acute HCV cases over the study period (N =87). If there were duplicate HCV diagnoses in the same subject, only the first diagnosis was kept.

4.4.2. Immigrant status and immigration variables

Individuals were defined as immigrants when a VISA number was present in RAMQ FIPA. The majority of cases linked to the MIDI database and variables in this database including immigration class, date of arrival to Canada, and country of origin were available. For cases with a VISA number that did not link to the MIDI database, these variables were missing. These cases were assumed to have arrived prior to 1985. Countries of origin were grouped according to World Bank regions with minor modifications (**Appendix 1**, page IX).[113] Immigrants arriving to another province prior to arrival in Québec would not have been captured by this database, but typically represent a small proportion of the immigrant population. One study by Citizenship and Immigration Canada found that only 6% of tax-filing immigrants who arrived between 1980-1995 had originally settled in another province prior to moving to Québec; therefore, there are likely very few immigrant cases in our cohort that are misclassified as non-immigrants due to this limitation.[114]

4.4.3. Other covariates

Age and sex were obtained from specific RAMQ FIPA variables recorded at the time of diagnosis. Medical comorbidities were assessed during the 1 year period up to and including the date of diagnosis using Med-Echo hospitalization data and physician billing (Medical Services) codes. We examined outcomes of liver disease, including cirrhosis, hepatic decompensation, hepatocellular carcinoma and liver transplant. We also examined diabetes mellitus, drug abuse, alcohol abuse, psychoses, depression, and HIV infection to illustrate differences in the risk factors and health status between immigrants and non-immigrants.

Coding algorithms for comorbidities and relevant validation data are summarized in **Table 4.2**. Drug abuse, alcohol abuse, psychoses, depression, and HIV infection were coded based on an enhanced Elixhauser comorbidity coding scheme (ICD 9-CM) and reported ICD-10 conversions.[115] These algorithms had similar sensitivity/specificity for ICD-9 and 10 versions, and performed adequately in chart-based validation.[116] We used a modified version of an algorithm validated for detecting cases of diabetes in administrative data.[117] This definition had high sensitivity, specificity and positive predictive value (PPV) when it required at least 2 physician claims in 2 years or 1 hospitalization.[117] Given only 1 year of data prior to diagnosis was available in our dataset, only 1 physician claim was required. Liver-related conditions were coded according to previous validation studies, with the exception of liver transplant which was coded using specific procedure codes.

Table 4.2 – Diagnostic and procedure codes were identified to classify prevalent comorbidities in the 1 year prior to hepatitis C (HCV) diagnosis.

Condition	ICD-9 Codes	ICD-10 Codes	Sensitivity (Specificity), %	PPV, %
Cirrhosis[118]	571.2, 571.5, 456, 567.23, 572.2, 572.3, 572.4	K70.3, K74.0, K74.1, K74.2, K74.6, I85, K65.2, K72.9, K76.6, K76.7	98% (43%)[†]	78%[†]
Decompensated cirrhosis[119]	789.5, 567.0, 567.2, 567.23, 567.8, 567.9, 572.3, 456	R18, K76.6, K65.2, K67, I85	33% (99%)[*†]	91%[*]
Hepatocellular carcinoma[120]	155.0	C22.0	N/A	86%[†]
Liver transplant	*CCA-DTC:* 62.41, 62.49, 62.39, *CCI:* 1.OA.85		N/A	N/A
Diabetes mellitus[117]	250	E10-E14	92.3% (96.9%)[**]	77%[*]
Alcohol abuse[115, 116]	265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980, V11.3	E52, F10, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51, Z50.2, Z71.4, Z72.1	52-54% (>99%)	74-81%
Alcoholic liver disease[121]	571.0, 571.1, 571.2, 571.3	K70	N/A	71-83%[†]
Drug abuse (excluding alcohol)[115, 116]	292, 304, 305.2-305.9, V65.42	F11-F16, F18, F19, R78.1-R78.5, Z71.5, Z72.2	47-55% (≥99%)	74-81%
HIV/AIDS[115, 116]	042-044	B20-B22, B24	25-42% (~100%)	~100%
Psychoses[115, 116]	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297, 298	F20, F22-F25, F28, F29, F30.2, F31.2, F31.5	57-58% (>99%)	80-90%
Depression[115, 116]	296.2, 296.3, 296.5, 300.4, 309, 311	F20.4, F31.3-F31.5, F32, F33, F34.1, F41.2, F43.2	45-57% (>99%)	92-93%

ICD - International classification of diseases; PPV - Positive predictive value. [*]Denotes studies that used an algorithm requiring 1 inpatient or 2 outpatient codes. All other studies used 1 inpatient or 1 outpatient code. [†] Validation data is for ICD-9only.

4.5. Outcome definitions

4.5.1. Healthcare utilization

Healthcare utilization was examined using acute care hospitalizations and day surgeries which are recorded in Med-Echo and distinguishable using a specific variable. Examining other types of utilization (e.g., outpatient visits) would also be informative but was not feasible given the scope of this study. Primary outcomes were the number of acute care hospitalizations and cumulative length of stay ("hospital days"). Hospitalizations are an intuitive measure that is comparable to the literature. Hospital days were included to account for differences in the length of stay. Secondary analyses also examined day surgeries. Hospitalizations were identified using unique ID numbers. Length of stay was calculated by subtracting the date of admission from the date of discharge. If discharge and admission occurred on the same day, 1 day was recorded. Cumulative length of stay was calculated by summing the length of stay for all acute care hospitalizations for each subject. For simplicity, transfers were not accounted for. For example, if a patient was admitted at one facility, transferred, and readmitted at another, two hospitalizations were counted. The proportion of transfers was calculated overall and stratified by immigrant status for descriptive purposes.

4.5.2. Liver-related utilization

Liver-related hospitalizations were identified using discharge and procedure codes in Med-Echo. First, we compiled a list of all liver-related codes used in administrative database studies of HCV and HCV sequelae (e.g., cirrhosis, HCC).[115, 118-122] Many of these studies only reported ICD-9 codes. Codes were converted when necessary by reviewing ICD-9 and ICD-10 manuals for equivalent conditions, however these codes may not be entirely exchangeable. Fortunately we only expect a small proportion of events to be affected as the coding system was not changed until 2006. Most coding algorithms identified were used to assess the prevalence of a specific medical condition by combining information from multiple visits over follow-up.[118-122] We were instead interested in generally categorizing visits as "liver-related" or "non-liver related". Therefore, we adopted a more inclusive algorithm which would maximize sensitivity at the risk of including false-positives. Hospitalizations were classified as liver-related if *any code appeared at least once in any position* (i.e., primary or secondary diagnosis). **Table 4.3** gives the complete list of liver-related codes. The definition for "liver-related" events used for all primary

analyses only includes codes for diseases and conditions directly related to HCV and which were identified using relevant literature.

In a sensitivity analysis, we tested two additional definitions for liver-related events: (1) a restricted definition requiring that the code appears as a primary diagnosis and (2) an expanded definition including additional liver-related codes (marked with *). Additional codes were added by reviewing liver disease chapters in the ICD-9 and ICD-10 manuals and by reviewing non-specific "liver disease" coding algorithms.[115] We were concerned that our restrictive definition might misclassify events that were coded using non-specific liver disease codes and could create biases where ICD-9/ICD-10 conversions were inexact.

Table 4.3 – Diagnostic codes for identifying liver-related hospitalizations during follow-up. Note that codes marked with (*) belong to an expanded definition that was only used in a sensitivity analysis.

ICD-9 Codes	ICD-10 Code
070.0 Viral hepatitis A with hepatic coma*	B15.0 Hepatitis A with hepatic coma*
070.2 Viral hepatitis b with hepatic coma*	B16.0 Acute hepatitis B … with hepatic coma*
070.4 Other specified viral hepatitis with hepatic coma*	B16.2 Acute hepatitis B … with hepatic coma*
070.6 Unspecified viral hepatitis with hepatic coma*	B17.11 Acute hepatitis C with hepatic coma*
070.71 Unspecified viral hepatitis C with hepatic coma*	B19.0 Unspecified viral hepatitis with hepatic coma*
155.0 Malignant neoplasm of liver, primary	B19.11 Unspecified viral hepatitis B with … coma*
155.1 Malignant neoplasm of intrahepatic bile ducts	B19.21 Unspecified viral hepatitis C with … coma*
155.2 Malignant neoplasm of liver, not specified*	**C22.0 Liver cell carcinoma**
456 Esophageal varices	**C22.1 Intrahepatic bile duct carcinoma**
567.0 Peritonitis in infectious diseases...	C22.8 Malignant neoplasm of liver, unspecified*
567.2 Other suppurative peritonitis	**I85 Esophageal varices**
567.8 Other peritonitis	**K65.2 Spontaneous bacterial peritonitis**
567.9 Unspecified peritonitis	**K67 Disorders of peritoneum in infectious ….**
570 Acute and subacute necrosis of liver*	**K70.0 Alcoholic fatty liver**
571.0 Alcoholic fatty liver	**K70.2 Alcoholic fibrosis and sclerosis of liver**
571.1 Acute alcoholic hepatitis	**K70.3 Alcoholic cirrhosis of liver**
571.2 Alcoholic cirrhosis of liver	**K70.4 Alcoholic hepatic failure**
571.3 Alcoholic liver damage, unspecified	**K70.9 Alcoholic liver disease, unspecified**
571.4 Chronic hepatitis*	K71 Toxic liver disease*
571.5 Cirrhosis of liver without mention of alcohol	K72.0 Acute and subacute hepatic failure*
571.6 Biliary cirrhosis*	K72.1 Chronic hepatic failure*
571.8 Other chronic non-alcoholic liver disease*	**K72.9 Hepatic failure, unspecified**
571.9 Unspecified chronic liver disease without alcohol*	K73 Chronic hepatitis, not elsewhere classified*
572.0 Abscess of liver*	**K74.0 Hepatic fibrosis**
572.1 Portal pyemia*	**K74.1 Hepatic sclerosis**
572.2 Hepatic encephalopathy	**K74.2 Hepatic fibrosis with hepatic sclerosis**
572.3 Portal hypertension	K74.3 Primary biliary cirrhosis*
572.4 Hepatorenal syndrome	K74.4 Secondary biliary cirrhosis*
572.8 Other sequelae of chronic liver disease*	K74.5 Biliary cirrhosis, unspecified*
573.0 Chronic passive congestion of liver*	**K74.6 Other and unspecified cirrhosis of liver**
573.1 Hepatitis in viral diseases classified elsewhere*	K75 Other inflammatory liver diseases*
573.2 Hepatitis in other infectious diseases…*	K76.0 Fatty (change of) liver, not elsewhere …*
573.3 Hepatitis, unspecified*	K76.1 Chronic passive congestion of liver*
573.4 Hepatic infarction*	K76.2 Central hemorrhagic necrosis of liver*
573.5 Hepatopulmonary syndrome	K76.3 Infarction of liver*
573.8 Other specified disorders of liver*	K76.4 Peliosis hepatis*
573.9 Unspecified disorder of liver*	K76.5 Hepatic veno-occlusive disease*
789.5 Ascites	K76.7 Hepatorenal syndrome
	K76.8 Other specified diseases of liver*
CCA-DTC (procedures)	K76.9 Liver disease, unspecified*
62.41 Auxiliary liver transplant	K77 Liver disorders in diseases … elsewhere*
62.49 Other liver transplant	**R18 Ascites**
62.39 Total hepatectomy	
CCI (procedures)	
1.OA.85 Liver transplant	

4.6. Data analysis

4.6.1. Descriptive analysis and summary statistics

Descriptive statistics were calculated for the HCV cases diagnosed between 1991-2007 (objective 1) and for the subset of cases diagnosed 1998-2007 (objective 2). Both were stratified by immigrant status. The following variables were included: age, sex, follow-up time, reason for censoring, year of diagnosis, location (by Québec health region), year of arrival, visa type, country of origin, and medical comorbidities. Continuous variables were reported with mean, median, range, and standard deviation and means for immigrants and non-immigrants were compared using Student's T-tests. Categorical variables were reported as frequencies and percents and groups were compared using χ^2 tests.

4.6.2. Annual all-cause and liver-related healthcare utilization 1991 – 2007

We computed the number of all-cause and liver-related acute care hospitalizations, hospital days, and day surgeries occurring each year from 1991 – 2007. Events were grouped by the year of admission. Annual data were reported overall and stratified by immigrant status and the proportion that occurred among immigrants was reported. To examine the effect of changing cohort size, annual rates for all measures were calculated using the person-time contribution during each calendar year as the denominator.

4.6.3. Summary of all-cause and liver-related healthcare utilization by subject

All measures were reported for subjects diagnosed 1998-2007, stratified by immigrant status by all-cause versus liver-related. First, we reported the number and proportion of subjects who had any event (i.e., acute care hospitalization or day surgery) during follow-up. The frequency and mean number (per subject) of hospitalizations, hospital days, and day surgeries were reported. Additional mean values were computed using only subjects who had at least one event during follow-up as the denominator. Means were compared using the Wilcoxon rank-sum non-parametric test due to the expected non-normality of the outcome distributions.[123]

4.6.4. Characteristics of all-cause and liver-related hospitalizations

Acute care hospitalizations were described using information available from Med-Echo variables with statistics reported overall and stratified by whether the hospitalization occurred in an immigrant or non-immigrant. For all-cause, non-liver (all-cause excluding liver-related), and liver-related hospitalizations we reported the mean length of stay (per hospitalization), the

number and proportion admitted via the emergency room (ER), the number and proportion resulting in at least 1 intensive care unit stay (ICU), and number and proportion that resulted in death. The broad category of diagnosis was determined for each all-cause and non-liver hospitalization by matching the first primary diagnosis to the appropriate ICD chapter. Diagnoses matching our list of liver-related codes were separated from other digestive system diseases. Liver-related hospitalizations were further categorized based on the first liver-related code that appeared in the sequential list of diagnoses. Groups of codes corresponding to alcohol-related liver disease, hepatocellular carcinoma, and all other liver-related codes were used to categorize liver-related hospitalizations. Characteristics of hospitalizations (i.e., length of stay, primary diagnosis) were compared for immigrants and non-immigrants using p-values obtained from generalized estimating equations (GEE).[124] Length of stay was modelled as a continuous variable with a log-normal distribution. Categorical variables (e.g., ICU stay (yes/no)) were modelled using a binomial distribution with a logit link function.

4.6.5. Rates analysis of healthcare utilization

To account for differential follow-up, we modelled rates of utilization using regression analysis of count data. Immigrant status was included as a covariate to estimate rates of utilization in immigrants relative to non-immigrants. Age and sex distributions in immigrants and non-immigrants were expected to differ and are associated with healthcare utilization and liver disease progression. Therefore, we also used age and sex as covariates to help explain healthcare utilization patterns in these populations.

Analysis of healthcare utilization measures presents a number of challenges.[125-127] First, outcomes are typically recurrent and correlated. For example, within a subject the occurrence of one event may influence the probability of experiencing subsequent events. Typically the distribution of events is positively skewed with a high proportion of subjects who have no events. One solution would be to only consider the first event. However, this study is primarily interested in comparing overall burden between groups making consideration of all events necessary.

Poisson regression is a standard technique for analyzing count and rate data. However, the Poisson distribution assumes a variance that is equal to the mean. Healthcare data often violate this assumption by having a variance that exceeds the mean (also known as overdispersion). Poisson regression of overdispersed outcomes will seriously underestimate the standard error for effect estimates and could result in misleading conclusions. Quasi-poisson models account for

overdispersion by estimating a scale parameter for the variance whereby the variance is linearly related to the mean. Quasi-poisson has the advantage of providing the same estimates for regression coefficients as standard poisson. Notably, quasi-poisson parameter estimates are evaluated using moment-based scoring rather than maximum likelihood, which prevents reliance on likelihood-based tests for model fit. Negative binomial models are a likelihood-based alternative that address overdispersion by estimating a scale parameter quadratic to the mean.[128]

We compared poisson, quasi-poisson, and negative binomial regression for all-cause and liver-related hospitalizations and hospital days (primary outcomes). Specifically we examined goodness of fit and scale parameter estimates. All models were specified using a logarithmic link function and person-time as an offset term. Person-time was adjusted as previously specified by subtracting each subject's cumulative length of stay from follow-up time to better approximate person-time at risk. In cases where adjusted person-time was equal to zero (<0.5% of cases), one day was added in order to apply the log function. Empty models (intercept and offset only) were fitted, followed by univariate and full multivariate models for age (continuous), sex (male as reference group) and immigrant status (non-immigrants as reference group) using the GENMOD procedure in SAS/STAT. The scale parameter in quasi-poisson was estimated using Pearson-scaled deviance. Pseudo-R^2 values (Cox & Snell[129] and Nagelkerke[130]) and log-likelihood tests (nested models) were used to compare model types.

4.6.6. Software

All data manipulation and statistical analyses were performed using SAS software, Version 9.4 of the SAS system for Windows. Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks of SAS Institute Inc., Cary, NC, USA.

4.7. Ethical considerations

This study received ethics approval from the Jewish General Hospital and *la Commission d'accès à l'information du Québec* (CAI) and was approved by all data sources and participating public health regions. All data linkages were performed previously by RAMQ and unique identifiers were scrambled prior to receipt by investigators to protect subject privacy. Databases were stored in a locked unit on password protected computers at the Lady Davis Research Institute Center for Clinical Epidemiology and access was only granted to investigators.

CHAPTER 5: RESULTS

5.1. Cohort construction

A total of N=28,753 unique cases of chronic HCV were identified in MADO from 1991 to December 31st, 2007. (**Figure 5.1**). There were 5,781 cases (20.1%) that did not successfully link to RAMQ and were excluded. A further 394 cases were excluded due to not meeting pre-defined inclusion criteria leaving 22,589 subjects included in the final cohort diagnosed 1991 to 2007 (cohort 1). After restricting the study period to 1998 to 2007, cohort 2 contained 20,139 subjects (**Figure 5.2**).

5.2. Demographic characteristics

Baseline characteristics of cases diagnosed 1998 - 2007 are given in **Table 5.1**. Baseline characteristics were described using cohort 2 (1998 – 2007) due to possible selection bias introduced because of incomplete reporting prior to 1998. For reference, additional tables containing baseline characteristics and immigration variables for subjects diagnosed 1991 – 2007 are located in **Appendices 2 and 3** (page I-I).

Immigrants accounted for 9.0% of cases identified from 1998 - 2007. Immigrants were older at diagnosis (47.6 vs. 43.2 years) and more likely to be female (46.7 vs. 31.9%) compared to non-immigrants. The mean length of follow-up was 4.4 and 4.9 years for immigrants and non-immigrants respectively (cohort 2). Most subjects were censored because of the end of the study period (90% and 86% in immigrants and non-immigrants, respectively). A higher proportion of non-immigrants were censored due to death (13% vs. 8%) while immigrants were more likely to be censored due to permanent RAMQ non-admissibility (i.e., migrating out of the province)(2.9% vs. 1.2%). Montréal was the most common source of cases in the province, accounting for approximately 40% of diagnoses. Immigrant cases were very concentrated in Montréal (78%) while non-immigrant cases were more dispersed across the other provincial public health regions.

Immigration-specific characteristics are summarized in **Table 5.2**. Approximately 90% of subjects who had a VISA number present in RAMQ FIPA were successfully linked to the MIDI immigration database. The remaining 10% with missing data likely include immigrants who arrived prior to 1985 from whom immigration data is unavailable. The mean time from admission to Canada until HCV diagnosis was approximately 9.8 years. Immigrants most

commonly originated from the East Asia/Pacific region (25.9%), followed by Latin America/Caribbean (14.8%) and Sub-Saharan Africa (13.5%). In the general immigrant population in Québec, the most common region of origin is Africa (35%), specifically North Africa (17%).[100] Immigrants were grouped by VISA type into classes based on the category of entry. Economic and family class migrants accounted for 31% and 38% of immigrant cases, respectively. Refugee migrants (including those recognized after entry into Canada and family members of refugee claimants) accounted for 30% of cases. This is in contrast to the general population of newly admitted immigrants (2001-2010) in Québec, which are comprised of 63% economic, 22% family, and 14% refugee class entrants.[101, 102]

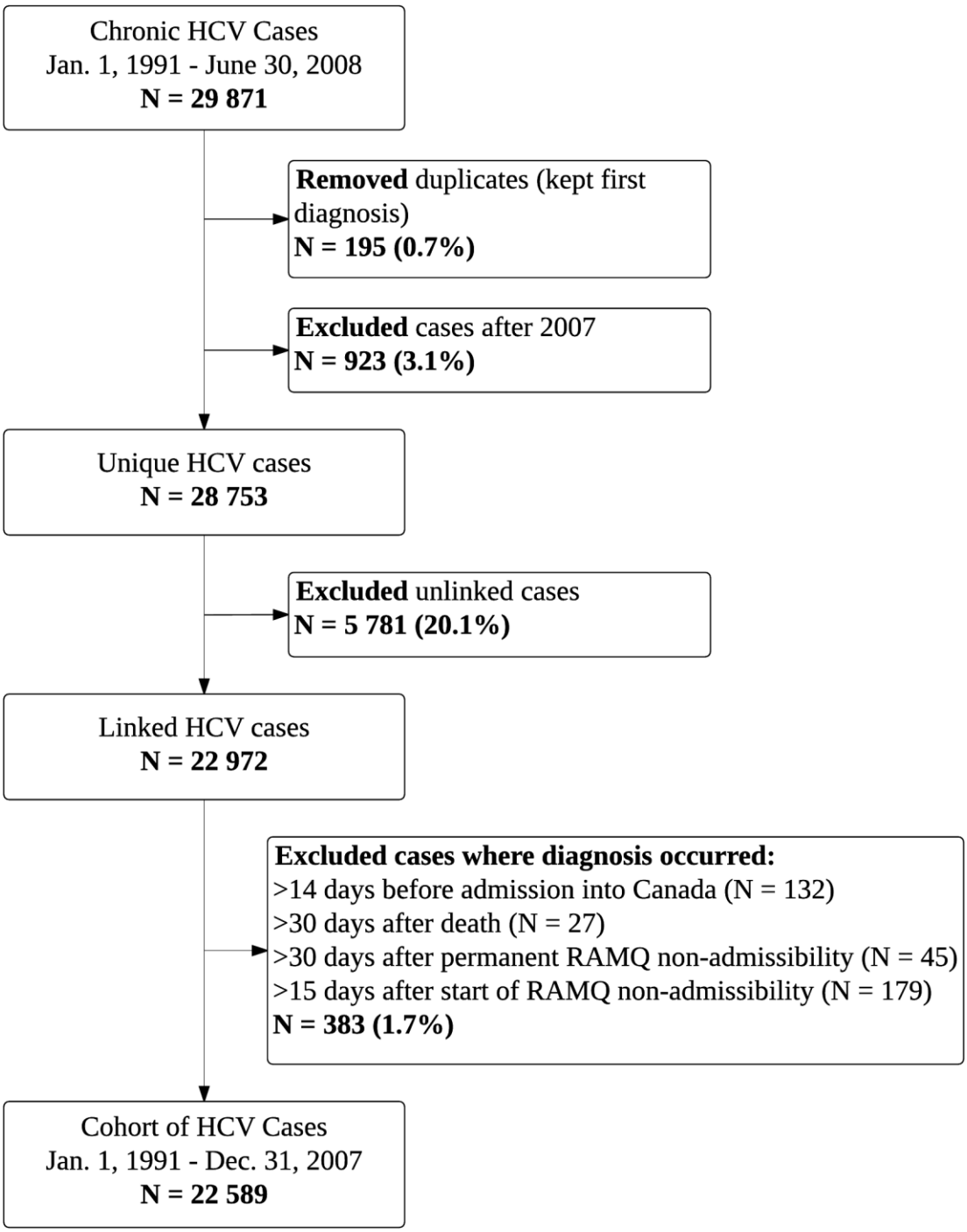

Figure 5.1 – Cohort selection diagram for subjects diagnosed with chronic hepatitis C (HCV) in Québec from 1991 – 2007 (cohort 1).

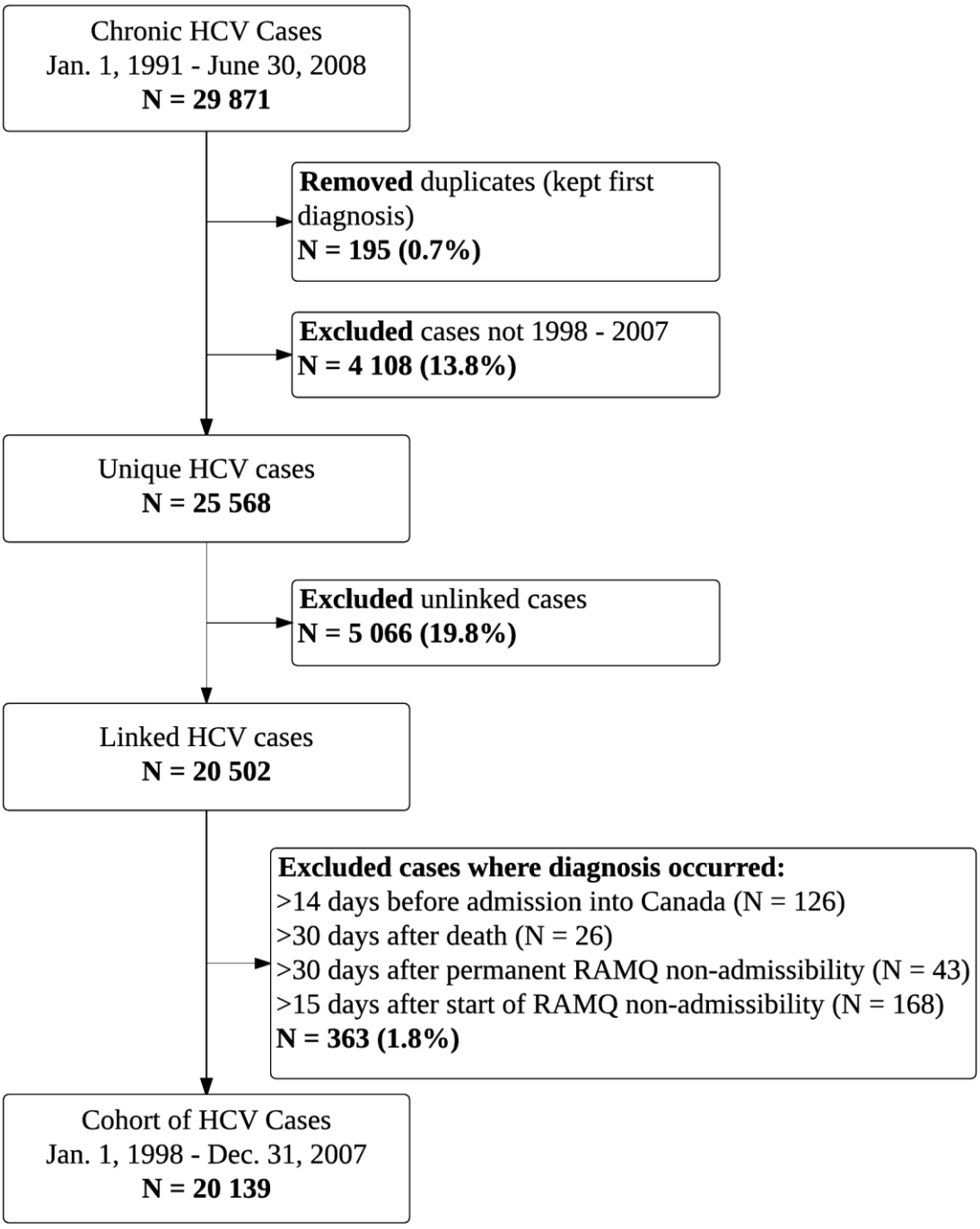

Figure 5.2 – Cohort selection diagram for subjects diagnosed with chronic hepatitis C (HCV) in Québec from 1998 – 2007 (cohort 2).

Table 5.1 – Baseline characteristics of chronic hepatitis C (HCV) cases diagnosed and reported in Québec from 1998 – 2007 (cohort 2), stratified by immigrant status.

Characteristic	Chronic HCV Cases		p
	Immigrant N = 1 821	Non-immigrant N = 18 318	
Mean age, *y* ± *SD*	47.6 ± 15.0	43.2 ± 13.4	*
Sex (female), *n (%)*	850 (46.7)	5836 (31.9)	*
Mean follow-up, *y* ± *SD*	4.4 ± 2.8	4.9 ± 2.9	*
Censoring, *n (%)*			*
End of study*	1630 (89.5)	15777 (86.1)	
Death	138 (7.6)	2318 (12.7)	
RAMQ non-admissibility	53 (2.9)	223 (1.2)	
Public health region, *n (%)*			*
Abitibi-Témiscamingue	3 (0.2)	384 (2.1)	
Bas-Saint-Laurent	1 (0.1)	172 (0.9)	
Capitale-Nationale	45 (2.5)	1654 (9.0)	
Chaudière-Appalaches	5 (0.3)	447 (2.4)	
Côte-Nord	1 (0.1)	129 (0.7)	
Estrie	24 (1.3)	661 (3.6)	
Gaspésie-Îles-de-la-Madeleine	0 (0.0)	83 (0.5)	
Lanaudière	11 (0.6)	774 (4.2)	
Laurentides	23 (1.3)	1532 (8.4)	
Laval	100 (5.5)	722 (3.9)	
Mauricie et du Centre-du-Québec	7 (0.4)	1100 (6.0)	
Montréal	1419 (77.9)	6886 (37.6)	
Montérégie	148 (8.1)	2588 (14.1)	
Nord-du-Québec	0 (0.0)	27 (0.1)	
Nunavik	0 (0.0)	12 (0.1)	
Outaouais	30 (1.6)	873 (4.8)	
Saguenay - Lac-Saint-Jean	4 (0.2)	253 (1.4)	
Terres-Cries-de-la-Baie-James	0 (0.0)	15 (0.1)	
Missing	0 (0.0)	6 (0.0)	
Medical comorbidities, *n (%)*			
Cirrhosis	95 (5.2)	950 (5.2)	
Decompensated cirrhosis	52 (2.9)	408 (2.2)	
Hepatocellular carcinoma	4 (0.22)	10 (0.11)	*
Liver transplant	1 (0.06)	12 (0.07)	
Diabetes mellitus	200 (11.0)	1100 (6.0)	*
Alcohol abuse	49 (2.7)	2566 (14.0)	*
Alcohol-related liver disease	29 (1.6)	568 (3.1)	*
Drug abuse	42 (2.3)	4359 (23.8)	*
HIV	16 (0.88)	583 (3.2)	*
Psychosis	31 (1.7)	1011 (5.5)	*
Depression	91 (5.0)	3060 (16.7)	*
Chronic hepatitis B	28 (1.5)	114 (0.62)	*

* $p < 0.05$ comparing immigrants vs. non-immigrants using Student's T test (continuous) or χ^2 test (categorical)

Table 5.2 – Immigration-related characteristics among foreign-born cases of hepatitis C (HCV) diagnosed and reported in Québec from 1998 – 2007 (cohort 2).

Characteristic	***n (%)***
Linked cases	1649 (90.6)
Unlinked cases (missing data)*	172 (9.5)
Mean time from admission to episode, $y \pm SD$	9.8 ± 6.9
Region of origin	
East Asia/Pacific	426 (25.9)
South Asia	160 (9.7)
Middle East/North Africa	139 (8.5)
Sub-Saharan Africa	222 (13.5)
Western Europe	190 (11.6)
Eastern Europe/Central Asia	44 (2.7)
Latin America/Caribbean	243 (14.8)
US/Australia/New Zealand	23 (1.4)
Other	197 (12.0)
Immigration class	
Economic	516 (31.3)
Family	634 (38.4)
Refugee	493 (29.9)
Other immigrant	6 (0.4)

*Analysis of immigration variables excludes unlinked cases from denominator.

5.3. Medical comorbidities

The prevalence of medical comorbidities was assessed using Med-Echo and Medical Services data up to 1 year prior to HCV diagnosis. Cirrhosis was prevalent in 5.2% of immigrants and non-immigrants at baseline. A smaller proportion of subjects (2.9% and 2.2% of immigrants and non-immigrants , respectively) had progressed to decompensated cirrhosis. Only 13 subjects (1 immigrant and 12 non-immigrants) had received a liver transplant before diagnosis. Hepatocellular carcinoma was found to be significantly more common in immigrants compared to non-immigrants at baseline (0.22% vs. 0.11%), although the number of events was small for this rare event (N = 14).

Diabetes mellitus was significantly more common in immigrants (11%) compared to non-immigrants (6%). Alcohol and drug-related comorbidities were 2-10 times more common in non-immigrants. Notably, drug abuse was prevalent in nearly a quarter (23.8%) of non-immigrants at baseline. Psychosis and depression were more than 3 times more common in non-immigrants compared to immigrants. While HIV co-infection was significantly more prevalent in non-

immigrants (3.2 vs. 0.9%), immigrants were more commonly co-infected with chronic hepatitis B at baseline (1.5 vs. 0.6%).

5.4. Specific objective 1 – Annual healthcare utilization (1991 – 2007)

The annual number of inpatient stays, in-hospital days, and day surgeries in all subjects diagnosed with HCV from 1991-2007 increased over the study period (**Figure 5.5**). Note that displayed data were truncated prior to 1998 due to insufficient numbers of events. Complete data for the 1991-2007 study period are tabulated in **Appendices 5 and 6** (page I-I).

We identified 33,282 inpatient stays due to any cause and a total of 375,853 days spent in-hospital. Liver-related stays accounted for 18% (N=5,879) of all inpatient visits and 21% (N=78,788) of in-hospital days. Only 2.5% (N=159/6,339) of all day surgeries were liver related. During the final and most recent year of follow-up in 2007, this cohort experienced 902 liver-related inpatient stays and 12,623 in-hospital days. The proportion of all-cause inpatient stays and in-hospital days which were liver-related exhibited an increasing trend from 1996 until 2007 in non-immigrants but not in immigrants (**Figure 5.3**).

Each year immigrants contributed an average of 5.5% of all-cause inpatient stays and 6.2% of liver-related stays (**Figure 5.4**). The proportion of all-cause and liver-related in-hospital days occurring in immigrants was similar to what was observed for inpatient stays. Overall, immigrants accounted for a higher proportion of the liver-related events than all-cause. Until approximately 2002, there was significant fluctuation in the proportion of events attributable to immigrants annually. However during the last five years of the study period (2002 to 2007), there appeared to be an increasing trend in the proportion of events occurring in immigrants (out of all subjects) for all outcomes (**Figure 5.4**).

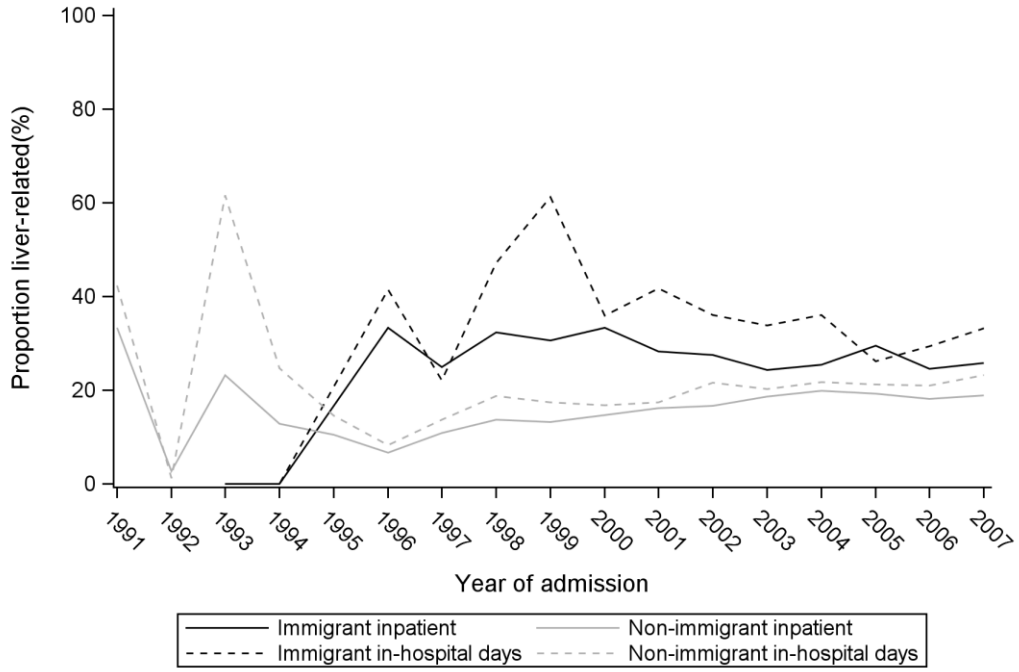

Figure 5.3 – The proportion of annual inpatient stays (solid) and in-hospital days (dashed) that were liver-related, stratified for immigrants (black) and non-immigrants (grey) with hepatitis C (HCV) diagnosed and reported from 1991 – 2007.

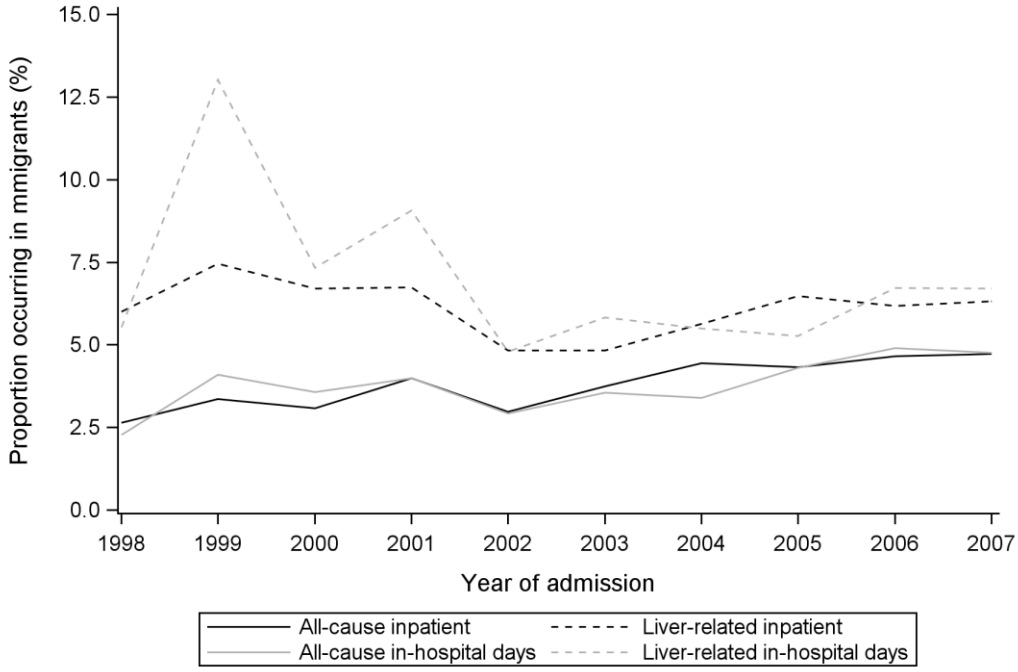

Figure 5.4 – The proportion of annual all-cause (solid) and liver-related (dashed) inpatient stays (black) and in-hospital days (grey) occurring in immigrants as a percentage of the total number of events in hepatitis C (HCV) cases diagnosed and reported from 1991 – 2007. Note that data prior to 1998 were truncated for clarity due to insufficient events.

While the annual number of events appeared to increase for all outcomes over the study period, this was hypothesized to be largely due to the increasing size of the cohort as more HCV cases (largely prevalent), were diagnosed, reported, and included during follow-up (a figure showing HCV diagnoses in Québec by calendar year is shown in **Appendix 4**, page I). To examine the effect of changing cohort size on annual healthcare utilization, we calculated annual event rates using the person-time contribution during each calendar year as the denominator. For all outcomes, the annual rates did not appear to exhibit a clear trend. Furthermore, substantial instability was observed in the rates during the early portion of the study period likely due to the relatively few subjects in the cohort at that time.

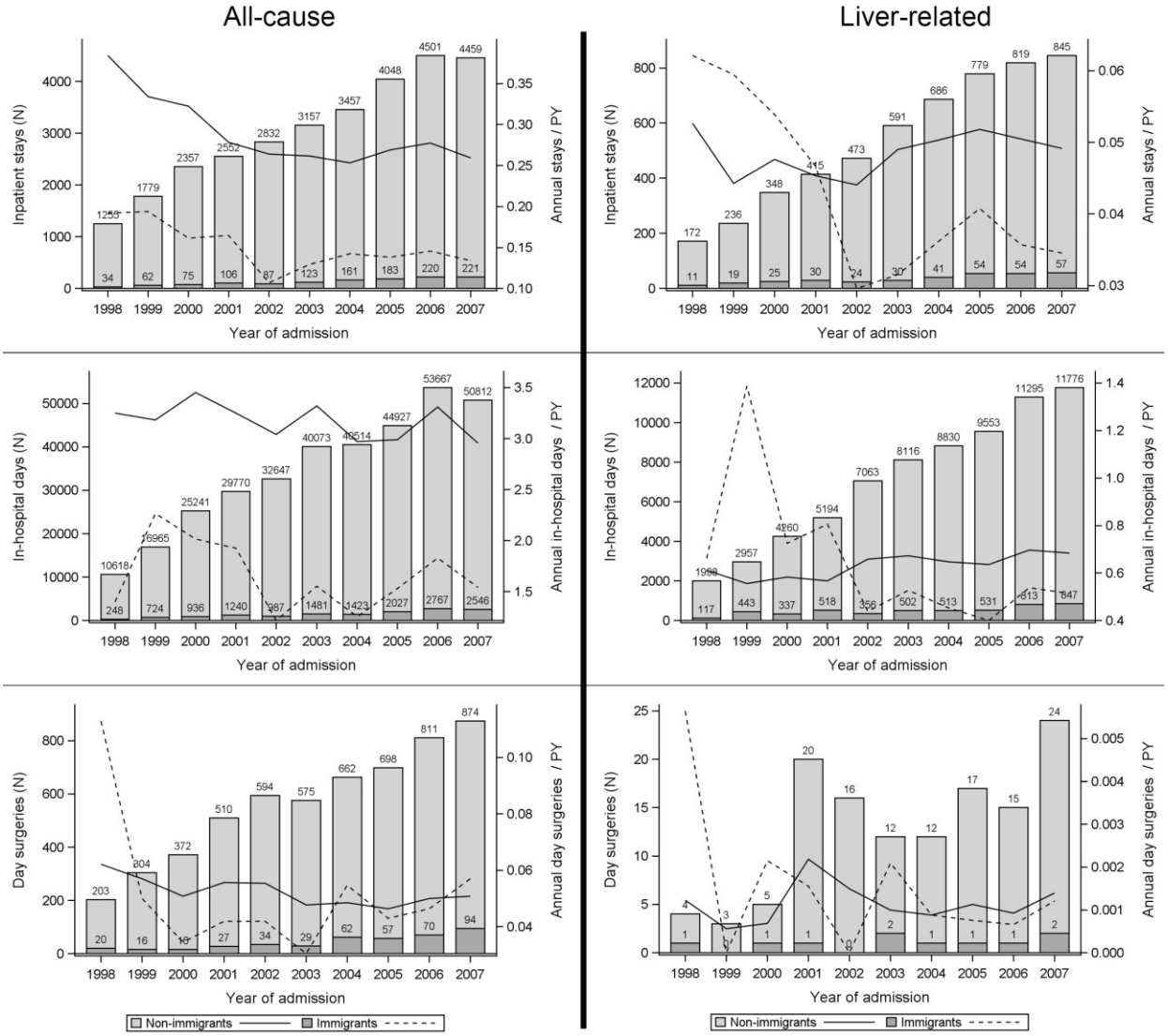

Figure 5.5 – Annual all-cause (left panel) and liver-related (right panel) inpatient visits (top), in-hospital days (center) and day surgeries (bottom) in immigrants and non-immigrants. Numbers of events are shown on the left y-axes while event rates per person-years (PY) of follow-up (during each calendar year) are displayed on the right y-axes. Note that data prior to 1998 were truncated for clarity due to insufficient events.

5.5. Specific objective 2 – Comparing healthcare utilization in immigrants and non-immigrants (1998 – 2007)

5.5.1. Summary of healthcare utilization in immigrants and non-immigrants

We compared all-cause and liver-related healthcare utilization between immigrants and non-immigrants diagnosed and followed from 1998 – 2007. We restricted the study period because there was incomplete reporting of cases prior to this time which may have been differential by immigrant status and other risk factors. We examined inpatient hospitalizations, in-hospital days, and day surgeries due to any cause ("all-cause") and those with any diagnoses of liver disease related to HCV ("liver-related") (**Table 5.3**).

Median follow-up for immigrants and non-immigrants was 3.9 and 4.8 years, respectively. Most subjects were never hospitalized during follow-up for any reason. Approximately 43% of non-immigrants had at least 1 inpatient stay during follow-up, compared to only 28% of immigrants. Mean numbers of all-cause inpatient stays, in-hospital days, and day surgeries per subject were consistently higher in non-immigrants compared to immigrants. There were an average of 0.62 and 1.35 stays per subject in immigrants and non-immigrants, equating to 7.1 and 15.5 in-hospital days per subject, respectively. Immigrants and non-immigrants who had been hospitalized at least once experienced an average of 2.2 and 3.2 hospitalizations during follow-up with a cumulative total of in-hospital time averaging 25.1 and 36.4 days, respectively.

Subjects with liver-related healthcare utilization comprised a small proportion of the cohort. Only 8.3% of immigrants and 8.7% of non-immigrants had any liver-related inpatient stay during follow-up. While all-cause utilization appeared to be elevated in non-immigrants compared to immigrants, results for liver-related utilization were similar between groups. Mean numbers of liver-related events per subject did not significantly differ between immigrants and non-immigrants.

Table 5.3 – Summary of all-cause and liver-related healthcare utilization during follow-up for immigrants and non-immigrants diagnosed with hepatitis C (HCV) from 1998 – 2007.

Measure	Immigrants N = 1 821	Non-immigrants N = 18 318	p*
Total person-time, *years*	8027	89519	.
Median person-time, *years (range)*	3.94 (0,10)	4.80 (0,10)	<.001
Median adjusted** person-time, *years (range)*	3.94 (0,10)	4.77 (0,10)	<.001
Mean age, *y* ± *SD*	47.6 ± 15.0	43.2 ± 13.4	<.001
Sex (female), *n (%)*	850 (46.7)	5836 (31.9)	
ALL-CAUSE UTILIZATION			
Inpatient hospitalizations			
Ever hospitalized, *n (%)*	514 (28.2)	7799 (42.6)	<.001
Total stays, *n*	1138	24664	.
Mean stays per person, *n* ± *SD*	0.62 ± 1.42	1.35 ± 2.84	<.001
Mean stays per person hospitalized†, *n* ± *SD*	2.21 ± 1.91	3.16 ± 3.64	<.001
Mean age (ever hospitalized), *y* ± *SD*	51.3 ± 17.4	44.1 ± 14.7	<.001
Sex (female) (ever hospitalized), *n (%)*	275 (53.5)	2849 (36.5)	<.001
In-hospital days			
Total days, *n*	12924	283811	.
Mean days per person, *n* ± *SD*	7.10 ± 22.42	15.49 ± 52.39	<.001
Mean days per person hospitalized, *n* ± *SD*	25.14 ± 36.46	36.39 ± 75.42	0.003
Day surgeries			
Ever had day surgery, *n (%)*	261 (14.3)	3093 (16.9)	0.005
Total day surgeries, *n*	382	4524	.
Mean day surgeries per person, *n* ± *SD*	0.21 ± 0.59	0.25 ± 0.68	0.007
Mean per person with day surgery†, *n* ± *SD*	1.46 ± 0.75	1.46 ± 0.96	0.209
LIVER-RELATED UTILIZATION			
Inpatient hospitalizations			
Ever hospitalized (liver-related only), *n (%)*	151 (8.3)	1585 (8.7)	0.601
Total stays, *n*	306	4370	.
Mean stays per person, *n* ± *SD*	0.17 ± 0.68	0.24 ± 1.09	0.520
Mean stays per person hospitalized†, *n* ± *SD*	2.03 ± 1.35	2.76 ± 2.63	0.012
Mean age (ever hospitalized for liver), *y* ± *SD*	61.2 ± 13.8	52.3 ± 13.6	<.001
Sex (female) (ever hospitalized for liver), *n (%)*	69 (45.7)	462 (29.2)	<.001
In-hospital days			
Total days, *n*	4401	58765	.
Mean days per person, *n* ± *SD*	2.42 ± 13.08	3.21 ± 17.78	0.561
Mean days per person hospitalized, *n* ± *SD*	29.15 ± 35.95	37.08 ± 48.96	0.251
Day surgeries			
Ever had day surgery, *n (%)*	9 (0.5)	95 (0.5)	0.890
Total day surgeries, *n*	10	110	.
Mean day surgeries per person, *n* ± *SD*	0.01 ± 0.08	0.01 ± 0.09	0.890
Mean per person with day surgery†, *n* ± *SD*	1.11 ± 0.33	1.16 ± 0.49	0.950

*Comparing immigrants vs. non-immigrants using Student's T test (person-time, age), χ^2 test (sex, ever/never hospitalized) or Wilcoxon rank-sum test (healthcare utilization measures). ** Excluding in-hospital days from person-time at risk. †Mean number of events using only subjects with ≥ 1 event in the denominator.

5.5.2. Characteristics of hospitalizations

Table 5.4 compares characteristics of immigrant and non-immigrant inpatient stays, including average length of stay, whether time was spent in an intensive care unit (ICU), and the category of the first primary diagnosis recorded (based on International Classification of Diseases revision 9 and 10 chapters). Stays are stratified according to whether they were liver-related or not liver-related.

Overall there were 25,802 inpatient stays experienced by our cohort during follow-up from 1998 to 2007, 18% of which were liver-related. Liver-related stays were longer on average compared to non-liver related stays, averaging 13.5 days in length compared to 11.1 days (non-liver). There was no significant difference in the mean length of stay between immigrants and non-immigrants. For both non-liver and liver-related hospitalizations, non-immigrants were more likely to be admitted via the ER compared to immigrants. We did not explicitly account for transfers in our analyses (i.e., if a patient was admitted on a transfer, it was counted as a separate admission). Approximately 6-9% of all admissions were transfers, but this did not appear to differ by immigrant status for either liver-related or non-liver related stays. Reasons for hospitalization (based on first primary diagnosis) differed between immigrants and non-immigrants. Mental disorders accounted for 27.8% of non-liver stays in non-immigrants. The other most common diagnoses in non-immigrant non-liver stays were injury and poisoning (11.9%) and circulatory system disorders (8.2%). Top diagnoses in immigrant non-liver stays were conditions related to pregnancy and childbirth (13.2%), followed by mental disorders (10.7%) and circulatory system disorders (9.5%).

Top primary diagnoses were also compared for liver-related stays. Liver-related stays were defined by the presence of *any primary or secondary diagnosis* related to liver disease (see methods). Therefore, some liver-related stays would not necessarily have liver disease listed as the primary diagnosis. However, we found that a liver-related code was the primary diagnosis in 39.9% and 37.2% of liver-related stays in immigrants and non-immigrants, respectively. Of the liver-related stays, the proportion related to HCC was higher in immigrants (39.3% vs. 14.2%), while a larger proportion were alcohol-related in non-immigrants (30.9% vs. 3.3%). The second most common primary diagnosis in immigrant liver-related stays was infectious/parasitic disease and in non-immigrants was digestive system disorders (excluding liver-related codes).

A larger proportion of immigrant hospital stays resulted in death compared to non-immigrant stays, for both liver-related and non-liver stays. There were 75 in-hospital deaths in immigrants (6.6% of immigrant hospital stays) and 899 in non-immigrants (3.6% of non-immigrant hospital stays). There were apparent differences in the cause of death diagnoses, including a higher proportion due to HCC in immigrants (45% vs 27.7%) and a higher proportion related to alcohol in non-immigrants (25.5% vs. 5%); however these were not statistically significant differences (p =0.08). **Appendix 7** (page I) lists the category of cause of death diagnoses for all in-hospital deaths stratified by immigrant status.

Table 5.4 – Characteristics of liver and non-liver related inpatient stays for immigrants and non-immigrants with chronic hepatitis C (HCV) diagnosed in Québec from 1998 – 2007.

Characteristic	Non-liver related stays N = 21 126			Liver-related stays N = 4 676		
	Immigrant N = 832	Non-immigrant N = 20 294	p*	Immigrant N = 306	Non-immigrant N = 4 370	p*
Mean length of stay, *days ± SD*	10.2 ± 15.5	11.1 ± 26.0		14.4 ± 19.1	13.5 ± 21.4	
Admitted as transfer, *N (%)*	60 (7.2)	1276 (6.3)		27 (8.8)	266 (6.1)	
Admitted via ER, *N (%)*	469 (56.4)	13846 (68.2)	*	220 (71.9)	3467 (79.3)	*
ICU stay (≥1), *N (%)*	75 (9.0)	2268 (11.2)	**	63 (20.6)	746 (17.1)	
Stay resulted in death, *N (%)*	29 (3.5)	450 (2.2)		46 (15.0)	449 (10.3)	
Category of main diagnosis†						
Liver-related‡	0 (0.0)	0 (0.0)		122 (39.9)	1627 (37.2)	
Alcohol-related	-	-		4 (3.3)	503 (30.9)	
Hepatocellular carcinoma	-	-		48 (39.3)	231 (14.2)	
Decompensated cirrhosis				31 (25.4)	292 (18.0)	
Other	-	-		39 (32.0)	601 (36.9)	
Infectious and parasitic diseases	37 (4.5)	714 (3.5)		34 (11.1)	235 (5.4)	
Neoplasms	65 (7.8)	797 (3.9)		12 (4.0)	110 (2.5)	
Endocrine/metabolic/immunity	33 (4.0)	407 (2.0)		19 (6.2)	110 (2.5)	
Blood and blood-forming organs	29 (3.5)	279 (1.4)		7 (2.3)	70 (1.6)	
Mental disorders	89 (10.7)	5646 (27.8)		4 (1.3)	366 (8.4)	
Nervous system	20 (2.4)	370 (1.8)		1 (0.3)	66 (1.5)	
Circulatory system	79 (9.5)	1654 (8.2)		13 (4.3)	239 (5.5)	
Respiratory system	29 (3.5)	1434 (7.1)		7 (2.3)	199 (4.6)	
Digestive system‡	69 (8.3)	1453 (7.2)		29 (9.5)	545 (12.5)	
Genitourinary system	48 (5.8)	730 (3.6)		10 (3.3)	87 (2.0)	
Pregnancy/childbirth	110 (13.2)	833 (4.1)		0 (0.0)	1 (0.02)	
Skin/subcutaneous tissue	11 (1.3)	1067 (5.3)		4 (1.3)	93 (2.1)	
Musculoskeletal/connective tissue	52 (6.3)	1035 (5.1)		6 (2.0)	90 (2.1)	
Congenital anomalies	2 (0.2)	27 (0.1)		0 (0.0)	2 (0.1)	
Symptoms and ill-defined	54 (6.5)	830 (4.1)		13 (4.3)	205 (4.7)	
Injury and poisoning	67 (8.1)	2407 (11.9)		17 (5.6)	232 (5.3)	
Supplementary classifications	38 (4.6)	610 (3.0)		8 (2.6)	93 (2.1)	
Missing/other	0 (0.0)	1 (0.01)		0 (0.0)	0 (0.0)	

ER – emergency room/department.

* $p<0.05$ comparing immigrant hospitalizations vs. non-immigrant hospitalizations using generalized estimating equations (GEE). G.E.E. parameter estimates and full p-values are shown in **Appendix 8** (page I).

** $p = 0.05$

†First primary diagnostic code (ICD 9 or ICD 10) was grouped according to chapter-level categorizations. Full chapter names have been shortened for clarity.

‡Liver-related codes (Table 4.3) were categorized separately from other digestive system disorders.

5.5.3. Age, sex, and immigrant status as predictors of healthcare utilization

In order to examine the effect of age and sex on healthcare utilization in immigrants and non-immigrants, we modelled all-cause and liver-related inpatient stays and in-hospital days using regression analysis. In preliminary analyses we compared estimates and goodness-of-fit criteria between three models: poisson, quasi-poisson and negative binomial. Negative binomial regression was selected as the most appropriate model based on better model fit as determined by a number of goodness-of-fit statistics (AIC, BIC, likelihood ratio test, pseudo-R^2 values)(**Appendix 9**, page I). Estimates for all models are shown in **Appendix 10-Appendix 13** (page I-I)

Immigrant status was associated with lower rates of all-cause inpatient stays and in-hospital days compared to non-immigrants, without adjusting for other variables (**Table 5.5** and **Table 5.6**). In univariate analyses, increasing age and female sex were also associated with significantly higher rates of stays and in-hospital days. After adjusting for age and sex in a multivariate analysis, immigrant status was still associated with significantly lower rates of all-cause inpatient stays (RR: 0.45, 95% CI: 0.40-0.51) and in-hospital days (RR: 0.57, 95% CI: 0.49-0.67) compared to non-immigrants.

Unlike all-cause utilization, rates of liver-related stays and in-hospital days were not significantly different for immigrants and non-immigrants prior to adjusting for other covariates. However, after adjusting for age and sex, immigrants had lower rates of inpatient stays and in-hospital days compared to non-immigrants. While female sex was associated with higher rates of all-cause healthcare utilization, rates of liver-related inpatient stays were lower in females compared to males. The rate ratio point estimate for female sex decreased for both inpatient stays and in-hospital days after adjustment for immigrant status and age; however the confidence interval for in-hospital days was not significant.

Table 5.5 – Univariate and multivariate negative binomial regression models for the rate of inpatient hospitalization (per person-year) during follow-up in subjects diagnosed with chronic hepatitis C (HCV) from 1998 – 2007.

Variable	All-cause hospitalizations				Liver-related hospitalizations			
	Univariate RR (95% CI)	p	Multivariate RR (95% CI)	p	Univariate RR (95% CI)	p	Multivariate RR (95% CI)	p
Immigrant status								
Immigrant	0.52 (0.47 - 0.58)	*	0.45 (0.40 - 0.51)	*	0.85 (0.63 - 1.15)		0.53 (0.40 - 0.70)	*
Non-imm.	Reference		Reference		Reference		Reference	
Sex								
Female	1.20 (1.13 - 1.28)	*	1.26 (1.19 - 1.34)	*	0.80 (0.68 - 0.96)	*	0.69 (0.59 - 0.81)	*
Male	Reference		Reference		Reference		Reference	
Age	1.02 (1.02 - 1.02)	*	1.02 (1.02 - 1.02)	*	1.08 (1.07 - 1.09)	*	1.08 (1.08 - 1.09)	*

* $p < 0.05$

Table 5.6 – Univariate and multivariate negative binomial regression models for the rate of in-hospital days (per person-year) during follow-up in subjects diagnosed with chronic hepatitis C (HCV) from 1998 – 2007.

Variable	All-cause hospitalizations				Liver-related hospitalizations			
	Univariate RR (95% CI)	p	Multivariate RR (95% CI)	p	Univariate RR (95% CI)	p	Multivariate RR (95% CI)	p
Immigrant status								
Immigrant	0.73 (0.62 - 0.86)	*	0.57 (0.49 - 0.67)	*	1.45 (0.95 - 2.20)		0.63 (0.42 - 0.93)	*
Non-imm.	Reference		Reference		Reference		Reference	
Sex								
Female	1.33 (1.21 - 1.47)	*	1.25 (1.14 - 1.37)	*	1.15 (0.90 - 1.47)		0.82 (0.65 - 1.04)	
Male	Reference		Reference		Reference		Reference	
Age	1.03 (1.03 - 1.04)	*	1.03 (1.03 - 1.04)	*	1.10 (1.09 - 1.11)	*	1.10 (1.09 - 1.11)	*

* $p < 0.05$.

5.6. Sensitivity analysis using alternative definitions for liver-related events

We repeated analyses using two variations of our definition for liver-related events: (1) a restricted version which required a primary diagnosis (as opposed to any primary or secondary diagnosis) matching one of our pre-specified codes and (2) an expanded definition including additional codes for liver disease. Sensitivity analysis results for annual healthcare utilization (objective 1) are located in **Appendix 5 and 6** (page I-I).

The restricted definition found approximately 2-3 fold fewer events than the primary definition, indicating that a significant proportion of events identified using our primary definition were not related to a primary diagnosis of liver disease (**Table 5.8**). This is supported by an analysis of characteristics of hospitalizations (**Table 5.4**) which found that 37-40% of liver-related hospitalizations had liver disease as the primary diagnosis. Rate ratios for immigrant status, age, and sex were not significantly different when comparing rates of liver-related inpatient stays using the primary or restricted definitions (**Table 5.9**). However, when comparing in-hospital days, immigrant status had a significantly positive association in the univariate analysis when the restricted definition was used, while no association was found with the primary and expanded definitions (**Table 5.10**).

In contrast to the restricted definition, the expanded definition detected approximately twice as many events as the primary definition (**Table 5.8**). When the expanded definition was used, immigrant status became significantly associated with a lower rate of liver-related inpatient stays compared to non-immigrants (in contrast to the null association that was observed with the restrictive definition) (**Table 5.9**). However, adjusting for age and sex in the sensitivity analysis decreased the point estimate which is similar to what was observed using the primary liver-related definition). Additionally, female sex was no longer a significant predictor in univariate and multivariate analysis of liver-related inpatient visits. Using an expanded definition seemed to have less of an effect on analyses of in-hospital days compared with analyses of inpatient visits (**Table 5.10**). Using the expanded definition, immigrant status was a non-significant predictor in the univariate analysis, but became significant and negatively associated with the rate of in-hospital days after adjusting for age and sex in the multivariate model. This is the same pattern of association that was observed for immigrant status using the restricted definition. Similar to what was observed for inpatient stays, female sex became non-significant as a predictor using the expanded definition, in both univariate and multivariate analyses of in-hospital days.

Table 5.7 – Sensitivity analysis of liver-related hospitalizations and day surgeries using two alternative definitions for liver-related events: (1) a restricted definition (code must be a primary diagnosis) and (2) an expanded definition (expanded list of possible codes).

Liver-related utilization	Immigrants N = 1 821	Non-immigrants N = 18 318	p*
(1) RESTRICTED DEFINITION (sensitivity analysis using only primary diagnoses)			
Inpatient hospitalizations			
Ever hospitalized (liver-related only), *n (%)*	77 (4.2)	762 (4.2)	0.889
Total hospitalizations, *n*	122	1627	.
Mean hospitalizations per person, *n ± SD*	0.07 ± 0.36	0.09 ± 0.56	0.462
Mean hospitalizations per person hospitalized†, *n ± SD*	1.58 ± 0.80	2.14 ± 1.78	0.028
In-hospital days			
Total days, *n*	1713	20918	.
Mean days per person, *n ± SD*	0.94 ± 7.47	1.14 ± 8.84	0.456
Mean days per person hospitalized, *n ± SD*	22.25 ± 29.26	27.45 ± 34.04	0.126
Day surgeries			
Ever had day surgery, *n (%)*	4 (0.22)	22 (0.12)	0.259
Total day surgeries, *n*	4	23	.
Mean day surgeries per person, *n ± SD*	0.00 ± 0.05	0.00 ± 0.04	0.130
Mean day surgeries per person with day surgery†, *n ± SD*	1 ± n/a	1.05 ± 0.21	0.375
(2) EXPANDED DEFINITION (sensitivity analysis using expanded list of codes)			
Inpatient hospitalizations			
Ever hospitalized (liver-related only), *n (%)*	251 (13.78)	3944 (21.53)	<.001
Total hospitalizations, *n*	504	9735	.
Mean hospitalizations per person, *n ± SD*	0.28 ± 0.87	0.53 ± 1.54	<.001
Mean hospitalizations per person hospitalized†, *n ± SD*	2.01 ± 1.43	2.47 ± 2.48	0.093
In-hospital days			
Total days, *n*	7054	121691	.
Mean days per person, *n ± SD*	3.87 ± 16.74	6.64 ± 28.23	<.001
Mean days per person hospitalized, *n ± SD*	28.10 ± 36.84	30.86 ± 54.37	0.338
Day surgeries			
Ever had day surgery, *n (%)*	46 (2.53)	463 (2.53)	0.997
Total day surgeries, *n*	53	524	.
Mean day surgeries per person, *n ± SD*	0.03 ± 0.20	0.03 ± 0.19	0.996
Mean day surgeries per person with day surgery†, *n ± SD*	1.15 ± 0.47	1.13 ± 0.39	0.931

*Comparing immigrants vs. non-immigrants using Student's T test (person-time, age), χ^2 test (sex, ever/never hospitalized) or Wilcoxon rank-sum test (healthcare utilization measures). ** Excluding in-hospital days from person-time at risk. †Mean number of events using only subjects with ≥ 1 event in the denominator.

Table 5.8 – Characteristics of liver-related stays for immigrants and non-immigrants with chronic hepatitis C (HCV) diagnosed in Québec from 1998 – 2007, comparing the primary definition for liver-related events with restricted and expanded definitions.

Characteristic	Primary Definition			Restricted Definition			Expanded Definition		
	Immigrant N= 306	Non-immigrant N= 4370	p*	Immigrant N = 122	Non-immigrant N = 1627	p*	Immigrant N = 504	Non-immigrant N = 9 735	p*
Mean length of stay, *days ± SD*	14.4 ± 19.1	13.5 ± 21.4		14.0 ± 22.4	12.9 ± 19.5		14.0 ± 19.7	12.5 ± 23.8	
Admitted as transfer, *N (%)*	27 (8.8)	266 (6.1)		12 (9.8)	76 (4.7)		44 (8.7)	618 (6.4)	
Admitted via ER, *N (%)*	220 (71.9)	3467 (79.3)		91 (74.6)	1297 (79.7)	*	324 (64.3)	7257 (74.6)	
ICU stay (≥1), *N (%)*	63 (20.6)	746 (17.1)		29 (23.8)	299 (18.4)		79 (15.7)	1314 (13.5)	
Stay resulted in death, *N (%)*	46 (15.0)	449 (10.3)					53 (10.5)	576 (5.9)	
Category of main diagnosis†									
Liver-related‡	122 (39.9)	1627 (37.2)		122 (100)	1627 (100)		135 (26.79)	1787 (18.4)	
Alcohol-related	4 (3.9)	503 (30.9)		4 (3.9)	503 (30.9)		4 (3.0)	503 (28.1)	
HCC	48 (39.3)	231 (14.2)		48 (39.3)	231 (14.2)		48 (35.6)	237 (13.3)	
Other	70 (57.4)	893 (54.9)		70 (57.4)	893 (54.9)		83 (61.5)	1048 (58.6)	
Infectious and parasitic diseases	34 (11.1)	235 (5.4)		-	-		50 (9.9)	569 (5.8)	
Neoplasms	12 (4.0)	110 (2.5)		-	-		25 (5.0)	308 (3.2)	
Endocrine/metabolic/immunity	19 (6.2)	110 (2.5)		-	-		34 (6.8)	237 (2.4)	
Blood and blood-forming organs	7 (2.3)	70 (1.6)		-	-		17 (3.4)	152 (1.6)	
Mental disorders	4 (1.3)	366 (8.4)		-	-		24 (4.8)	1751 (18.0)	
Nervous system	1 (0.3)	66 (1.5)		-	-		3 (0.6)	154 (1.6)	
Circulatory system	13 (4.3)	239 (5.5)		-	-		24 (4.8)	666 (6.8)	
Respiratory system	7 (2.3)	199 (4.6)		-	-		13 (2.6)	567 (5.8)	
Digestive system‡	29 (9.5)	545 (12.5)		-	-		33 (6.6)	912 (9.4)	
Genitourinary system	10 (3.3)	87 (2.0)		-	-		24 (4.8)	246 (2.5)	
Pregnancy/childbirth	0 (0.0)	1 (0.02)		-	-		11 (2.2)	143 (1.5)	
Skin/subcutaneous tissue	4 (1.3)	93 (2.1)		-	-		6 (1.2)	434 (4.5)	
Musculoskeletal/connective tissue	6 (2.0)	90 (2.1)		-	-		17 (3.4)	392 (4.0)	
Congenital anomalies	0 (0.0)	2 (0.1)		-	-		1 (0.2)	7 (0.1)	
Symptoms and ill-defined	13 (4.3)	205 (4.7)		-	-		34 (6.75)	475 (4.88)	
Injury and poisoning	17 (5.6)	232 (5.3)		-	-		33 (6.55)	743 (7.63)	
Supplementary classifications	8 (2.6)	93 (2.1)		-	-		20 (3.97)	192 (1.97)	

* $p<0.05$

Table 5.9 – Comparison of regression coefficient estimates (immigrant status, age, sex) using a *primary definition* for liver-related events a *restricted definition* (primary diagnosis only), and an *expanded definition* (additional codes) used in a sensitivity analysis. Results are shown for models of liver-related inpatient stays.

Variable	Univariate RR (95% CI)						Multivariate RR (95% CI)					
	Primary	p	Restricted	p	Expanded	p	Primary	p	Restricted	p	Expanded	p
Immigrant	0.85 (0.63 - 1.15)		0.91 (0.59 - 1.40		0.57 (0.49 - 0.68)*		0.53 (0.40 - 0.70)*		0.55 (0.36 - 0.83)*		0.45 (0.38 - 0.53)*	
Non-imm.	Reference		Reference		Reference		Reference		Reference		Reference	
Sex												
Female	0.80 (0.68 - 0.96) *		0.68 (0.52 - 0.87)*		0.98 (0.89 - 1.07)		0.69 (0.59 - 0.81)*		0.52 (0.41 - 0.66)*		1.01 (0.92 - 1.11)	
Male	Reference		Reference		Reference		Reference		Reference		Reference	
Age	1.08 (1.07 - 1.09) *		1.09 (1.08 - 1.10)*		1.03 (1.03 - 1.04)*		1.08 (1.08 - 1.09)*		1.09 (1.08 - 1.10)*		1.04 (1.03 - 1.04)*	

* $p < 0.05$.

Table 5.10 – Comparison of regression coefficient estimates (immigrant status, age, sex) using a *primary definition* for liver-related events, a *restricted definition* (primary diagnosis only), and an *expanded definition* (additional codes) used in a sensitivity analysis. Results are shown for models of liver-related in-hospital days.

Variable	Univariate RR (95% CI)						Multivariate RR (95% CI)					
	Primary	p	Restricted	p	Expanded	p	Primary	p	Restricted	p	Expanded	p
Immigrant	1.45 (0.95 - 2.20)		2.24 (1.22 - 4.13)*		0.96 (0.74 - 1.23)		0.63 (0.42 - 0.93)*		0.75 (0.42 - 1.33)		0.55 (0.43 - 0.70)*	
Non-imm.	Reference		Reference		Reference		Reference		Reference		Reference	
Sex												
Female	1.15 (0.90 - 1.47)		0.99 (0.69 - 1.43)		1.38 (1.19 - 1.60)*		0.82 (0.65 - 1.04)		0.64 (0.45 - 0.90)		1.31 (1.14 - 1.51)*	
Male	Reference		Reference		Reference		Reference		Reference		Reference	
Age	1.10 (1.09 - 1.11) *		1.12 (1.10 - 1.14)*		1.05 (1.04 - 1.05)*		1.10 (1.09 - 1.11)*		1.12 (1.10 - 1.14)*		1.05 (1.05 - 1.06)*	

* $p < 0.05$.

CHAPTER 6: DISCUSSION

6.1. Summary of main findings

There were 22,589 cases of HCV diagnosed and reported in Québec between 1991 – 2007 after exclusions and data linkage. Annual all-cause and liver-related hospital stays, in-hospital days, and day surgeries increased from 1991 to 2007. Annual rates of these outcomes although unstable did not appear to increase over time, suggesting that rising numbers of events were due to cohort growth as prevalent cases were detected (**Figure 5.5**). Approximately 20% of inpatient healthcare utilization in the cohort was liver-related (primary or secondary diagnosis), accounting for 5,879 inpatient stays and 78,788 days spent in hospital over the study period. Eighteen percent of inpatient stays and 21% of in-hospital days were liver-related overall. Immigrants accounted for an average of 5.5% of all-cause and 6.2% of liver-related inpatient stays annually.

When comparing immigrants to non-immigrants diagnosed with HCV from 1998 – 2007, we found that immigrants were a distinct group with respect to demographic characteristics, risk factors, and medical comorbidities. Immigrants accounted for 9% (N=1,821) of cases, were older at diagnosis (47.6 vs. 43.2 years) and more likely to be female (46.7 vs. 31.9%). The average delay between admission to Canada and HCV diagnosis was 9.8 years (± 6.9 SD). Immigrants most frequently originated from regions with moderate to high HCV prevalence including East Asia/Pacific (25.9%), Latin America/Caribbean (14.8%) and Sub-Saharan Africa (13.5%). Compared to non-immigrants, immigrants were 5 and 10 times less likely to have alcohol and drug abuse (respectively) at baseline and almost 3 times less likely to have been diagnosed with psychosis or depression. These differences support the hypothesis that immigrants have distinct risk factors for HCV infection and are likely to have been exposed to HCV through unsafe medical procedures or unscreened blood products in their countries of origin. This is in contrast to non-immigrants who are primarily exposed through injection drug use and have a high burden of disease related to substance abuse and mental illness. Diabetes mellitus was more common in immigrants at baseline (11% vs. 6%), consistent with findings from a study with HCV-infected immigrants[12] and with observations of other immigrant populations in Canada (e.g., non-recent immigrants, South Asian immigrants).[104, 131, 132] It is unclear whether the higher prevalence of diabetes in HCV-infected immigrants is due to the high prevalence of diabetes that exists in certain ethnic groups or due to metabolic complications of HCV. Approximately 5% and 2-3%

of subjects had already progressed to cirrhosis and decompensated cirrhosis respectively by the time of diagnosis. Generally, the prevalence of HCV-related liver disease was not significantly different in immigrants compared to non-immigrants despite risk factors for disease progression (e.g., alcohol use, HIV infection) being more common in non-immigrants. Notably, hepatocellular carcinoma was more common in immigrants than non-immigrants at diagnosis (0.2% vs. 0.1%).

This study found that non-immigrants had a higher burden of all-cause healthcare utilization (inpatient visits, days in-hospital, and day surgeries) compared to immigrants. Non-immigrants were 1.5 times more likely to have ever been hospitalized during follow-up and mean numbers and rates of visits and hospital days per subject were consistently higher in non-immigrants. Based on the top reasons for hospitalization, increased all-cause utilization in non-immigrants appears largely driven by a high burden of mental illness and substance abuse.

Crude measures of liver-related healthcare utilization were largely similar for immigrants and non-immigrants, again despite the high prevalence of risk factors for disease progression in non-immigrants. Only 8.3% and 8.7% of immigrants and non-immigrants had any liver-related inpatient stay during follow-up. Liver-related stays appeared to be more serious, as they had a longer average length of stay (13.5 and 14.4 days vs. 10.2 and 11.1 days) and a higher proportion resulted in an ICU stay or death.

Regression analysis of inpatient stays and in-hospital days suggested that after adjustment for age and sex differences, immigrants have lower rates of liver-related utilization than non-immigrants, consistent with what might be expected given that this population has fewer relevant comorbidities and less all-cause utilization. These results suggest that there is excess burden in immigrants due to older age at diagnosis which is supported by the long delay observed between arrival and diagnosis of almost 10 years. Given that current HCV screening in Canada is risk factor-based, immigrants may be detected later in disease progression if they are not injection drug users and have no specific risk factors for infection other than country of origin.

6.2. Interpretation of findings

6.2.1. Demographic characteristics and baseline comorbidities

Demographic characteristics and the prevalence of medical comorbidities were compared for immigrants and non-immigrants diagnosed from 1998 – 2007. Immigrants accounted for 9% of cases in our cohort, in contrast to estimates suggesting that up to 35% of prevalent HCV cases

in Canada occur in immigrants.[1] Our results suggest that at the population level, there may be significant underdetection of HCV in the immigrant population which is supported by our observation that immigrants accounted for an increasing proportion of annual new cases over the study period.

The demographic characteristics and prevalence of medical comorbidities for non-immigrants are consistent with Canadian and U.S. studies of HCV-infected populations. We found that non-immigrant cases were mostly male (68%) with an average age of 43.2 years at diagnosis, figures which are in good agreement with the literature.[12, 15, 133] In contrast, immigrants were older at diagnosis (47.6 years) with a more equal gender distribution (53.3% male). In British Columbia, Yu et al. found that 64% of chronic HCV cases (N = 29,689) were male, and the average age at diagnosis was 43.4 years.[15] An Ontario study by Chen and coauthors examined HCV-infected patients with advanced fibrosis stratified by immigrant status, and found that non-immigrants (N = 190) were 72% male with an average age of 48 years.[12] While there is little data available on HCV-infected immigrants in Canada, our results are in agreement the Chen et al. study which also demonstrated older age (55.0 years) and a smaller proportion of males (56.3%) in HCV-infected immigrants compared to non-immigrants.[12] The older age in the Chen et al. study is likely because they restricted their cohort to patients with advanced liver disease. Our study provides strong evidence supporting the pattern in their findings, which were limited by having a small sample (N=318 total) taken from a specific Ontario clinic. The majority of the HCV-infected population in Canada and the United States is male, which is likely in part due to sex differences in engaging in high risk behaviours such as injection drug use. Male sex has also been identified as an independent risk factor for progression of liver disease in HCV infection, whereas females may have an increased rate of spontaneous clearance of acute infection.[134] Increasingly, HIV co-infected men who have sex with men are also at high risk for HCV infection.[28] As there is often a long delay between infection and diagnosis, cases diagnosed during the study period largely reflect past patterns of exposure. Transmission patterns in Canada continue to evolve and the current gender gap has narrowed with respect to incident HCV.[1] In groups such as immigrants where medical procedures[11] are the primary risk factor for infection, it follows that the gender distribution should be less skewed, which is what was observed in our study.

Death due to any cause occurred in 12.7% of non-immigrants during follow-up which is in agreement with cumulative mortality rates of 10-17% reported in studies with 4-6 years of mean follow-up.[12, 15, 135] A control cohort was not available in our study but we would expect that non-immigrant mortality in our cohort would be elevated compared to uninfected controls given the elevated mortality demonstrated in other HCV-infected populations and our agreement with reported mortality figures in the literature.[15, 135] We found that fewer immigrants died during follow-up (7.6% vs. 12.7%) compared to non-immigrants, which is inconsistent with findings from the Chen et al. study which found that death was twice as common in immigrant patients (29.7%). This discrepancy is explained by the fact that immigrants in our study were younger and likely had less advanced liver disease compared with the Chen et al. study which only examined patients who had advanced liver disease. While both groups might be expected to have high liver-related mortality on account of their HCV infection, typically HCV-infected populations have high all-cause mortality that is also driven by drug use and other high risk circumstances or behaviours.[15] Immigrants appear to be less affected by these types of risk factors (see medical comorbidities) and therefore, it is reasonable that they would have less all-cause mortality. However, we did observe that a higher proportion of immigrant in-hospital deaths were due to HCC compared to non-immigrants (45% vs. 27.7%), while a high proportion of non-immigrant liver-related deaths were due to alcohol-related liver disease (25.5% vs. 5%).

The geographic distribution of reported cases in Québec has been previously documented by the Institut national de santé publique du Québec and is consistent with our findings.[92] The highest numbers of cases were located in urban areas: Montreal and Québec City. Montreal accounted for 37.6% of non-immigrant cases and 77.9% of immigrant cases. Immigrant cases would be expected to be concentrated in Montreal because it is home to approximately 86% of the province's immigrant population.[100] The high proportion of immigrant cases in urban areas has implications for targeting interventions and resources which could be focused on these high burden areas.

Immigration-related variables were available for the 90% of subjects with a VISA number in RAMQ FIPA who linked to the MIDI database. Subjects with a VISA number who did not link were likely immigrants who arrived prior to 1985 and therefore would not have had a record present in MIDI. While these unlinked immigrants only represented 10% of all immigrant cases, it is likely that they would have different characteristics particularly given that

there were waves of immigration pre-1985 that included a high proportion of refugees and immigrants from high burden countries including Vietnam and Cambodia. The mean time between admission to Canada and HCV diagnosis was 9.8 years which may be an underestimate of the true delay because 10% of immigrants were unlinked likely because they arrived prior to 1985 (when data became available), and thus had a longer delay before diagnosis. East Asia/Pacific was the most common region of origin (25.9%) followed by Latin America/Caribbean (14.8%) and Sub-Saharan Africa (13.5%). The high proportion of immigrant cases from East Asia Pacific was expected given that most new arrivals to Canada originate from Asia (60% from 2001 – 2005).[7] Additionally, all three of the most common regions correspond to areas containing intermediate to high HCV prevalence countries (e.g., Vietnam, Cambodia, and China).[86] Our cohort contained more refugees (N=493 or 30% of immigrants) than would be expected given that only 18% of new arrivals to Québec between 1985 and 2005 were refugees.[102] In contrast, economic migrants account for approximately 52% of new arrivals (1985 – 2005) but only 31% of immigrants in our cohort.[102] Refugees may be more likely to originate from moderate to high HCV prevalence countries and could also be at high risk for transmission due to past exposure to harmful living conditions or trauma as the result of being displaced. There may also be increased detection of HCV in refugees because of specialized services and screening available for this vulnerable population.

A minority of cases had developed cirrhosis (5.2%) or decompensated cirrhosis (2.3%) by the time they were diagnosed with HCV, with similar proportions of immigrants and non-immigrants affected. Literature reports for the prevalence of cirrhosis in patients with HCV vary widely (7% - > 30%)[32, 136, 137] due to differences in the patient population (i.e., selection criteria, risk factors) and how disease was assessed (i.e., systematic screening vs. medical chart review). Modelled projections estimated that 9% of HCV cases in Canada were affected by cirrhosis in 2007.[19] We are likely underestimating the true number of cases with cirrhosis at diagnosis because patients are not necessarily screened for cirrhosis on diagnosis and administrative coding algorithms for cirrhosis are more specific than they are sensitive. Hepatocellular carcinoma (HCC) was twice as common in immigrants compared to non-immigrants. High HCC incidence and mortality have been previously demonstrated[17, 105] in Canadian immigrants and may be related to longer duration of infection and other exposures more common in certain regions of origin (e.g., viral hepatitis B and C, aflatoxin)[138]. Indeed we found that a higher proportion of

immigrants were co-infected with chronic hepatitis B (1.5% vs. 0.6%) which could increase the risk of cirrhosis, HCC and death in this group.[139] Chen et al. found that immigrant status was significantly associated with developing HCC (HR: 2.22) but was not an independent risk factor after adjustment for age and diabetes.[12]

All other non-liver related comorbidities were more common in non-immigrants compared to immigrants except for diabetes and hepatitis B which were more common in immigrants. The high burden of substance abuse disorders, mental illness, and HIV in HCV-infected populations has been well documented[16, 140, 141] and reflects the vulnerable populations most affected by HCV including people who inject drugs, street-youth, and people who have been incarcerated. As alcohol abuse and HIV infection increase rates of liver disease progression, we would expect a higher burden of liver-related healthcare utilization in non-immigrants.[40, 41]

There is limited data describing the characteristics of immigrants with HCV but immigrants in general tend to have fewer behavioural risk factors (e.g., smoking, alcohol use) compared to the general population.[18, 104] HCV-infected immigrants have been shown to be less likely to report poor mental or physical health[142], heavy drinking, heavy smoking[12], and IDU or tattooing as risk factors for transmission[12]. Our finding that immigrants were far less likely to have HCV-associated comorbidities (e.g., drug abuse, alcohol abuse, mental illness, HIV) is consistent with these reports from the literature and supports the assertion that immigrants are predominantly exposed in their countries of origin. Immigrants had a higher prevalence of diabetes at baseline which is consistent with a higher risk of diabetes that has been demonstrated both in the general immigrant population and HCV-infected immigrants.[12, 131] An association between diabetes and HCV has been posited by the literature but remains controversial. Many studies have demonstrated increased incidence or prevalence of diabetes in HCV-infected patients, although a large recent analysis of population-based data did not reproduce this association citing limitations in previous investigations.[52] Diabetes has also been identified as a predictor of serious outcomes in patients with liver disease.[48, 49]

6.2.2. Specific objective 1 – Describe the annual all-cause and liver-related healthcare utilization from 1991-2007 in persons with diagnosed HCV in Québec and calculate the proportion of utilization occurring in immigrants each year

We attribute the increasing annual numbers of all-cause and liver-related events observed over the study period to the increasing size of the cohort. Until approximately the year 2000, annual rates of HCV diagnosis increased in Québec and the rest of Canada as HCV testing became available and widespread and prevalent cases were identified.[1, 92] We examined the effect of increasing cohort size on annual healthcare utilization by calculating event rates per annual person-time contribution. Event rates did not exhibit any consistent increasing trend over the study period, supporting the idea that the increasing annual utilization that was observed is a reflection of a growing cohort as prevalent cases are identified and followed. For the first portion of the study period, event numbers and rates fluctuated significantly, particularly in analyses stratified by immigrant status. We attribute this mainly to the small numbers of events and people followed up during this period (e.g., zero or < 5 events per year). One possible cause for higher than average event rates during the first half of the study period (e.g., "spikes" observed for several outcomes) could be that cases diagnosed during this time had poorer prognosis because HCV treatments were poor and effective treatments for HIV were not yet available.[143] The sparse and varying data prior to 1998 support our decision to restrict the comparative analyses for **objective 2** to only cases 1998 – 2007.

Liver-related hospitalizations accounted for 18% of all inpatient stays and 21% of in-hospital days from 1991 – 2007, suggesting that HCV-related disease contributes substantially to healthcare utilization and costs in this population. In studies of HCV-infected populations, up to 48-56% of total healthcare costs and up to 89% of inpatient-related costs were found to be related to HCV.[16, 137] While we did not measure costs with our study, we found that liver-related stays were longer on average with a higher proportion requiring an ICU stay or resulting in death, suggesting that liver-related stays likely incur high costs compared to other visits. The proportion of all-cause utilization that was liver-related appeared to increase between 1996 and 2007, however this trend was only observed in non-immigrants. There are many possible explanations for why this would occur, including disease progression in an aging cohort or increasing sensitivity of diagnostic tools or coding algorithms.

6.2.3. Specific objective 2 – Estimate and compare all-cause and liver-related healthcare utilization for immigrants and non-immigrants with HCV diagnosed 1998 – 2007, identifying predictors of healthcare utilization

Non-immigrants appeared to have a higher burden of all-cause inpatient and day surgery utilization. This was first supported by examining mean numbers of events and in-hospital days (inpatient stays) for immigrants and non-immigrants. The agreement between trends observed for numbers of inpatient stays and days-in hospital confirms a higher overall burden both with respect to frequency of admission and the amount of time spent in hospital. Even only among patients with >1 stay, we observed a higher mean number of visits and hospital days in non-immigrants. The magnitude of the association appeared large, with non-immigrants being almost 50% more likely to have ever been hospitalized relative to immigrants with more than twice the number of visits per person on average. When rates of inpatient utilization were modelled to account for differential follow-up between groups, non-immigrants were associated with higher rates of all-cause inpatient stays and in-hospital days both before and after adjustment for age and sex.

Other studies have demonstrated that significant all-cause utilization in HCV-infected populations is attributable to services for mental health issues and drug abuse rather than to HCV sequelae.[16, 144] Our analyses of primary diagnoses for inpatient stays substantiates this argument, as non-immigrants were more likely to be hospitalized for mental illness and injury/poisoning. The observed lower burden of all-cause utilization in immigrants again reflects the differences in risk factors and health status in immigrants with HCV compared to non-immigrants. However, higher incremental all-cause and liver-related costs and utilization due to HCV infection have been demonstrated, suggesting that on comparison with an uninfected reference population, utilization for immigrant and non-immigrant cases in our cohort may surpass observations for their respective control groups.[145, 146] In a study of 8,861 HCV cases in the U.S., McCombs et al. found that 34.2% had been hospitalized ever during the 1 year post diagnosis, compared to only 18.2% of matched controls.[147] Similar results were observed in another study where 24% of cases were ever hospitalized (1 year follow-up) compared to 7% of controls.[145] Our proportion of non-immigrants and immigrants ever hospitalized (42.6% and 28.2% respectively) surpass previous findings, likely due to our longer follow-up (approximately 5 years compared to 1 year used in these previous studies). These comparisons suggest that there may be a disproportionately high burden of hospitalization during the first year post-diagnosis compared to subsequent years. Our adjusted analyses also revealed that female sex was associated with increased all-cause utilization but with decreased liver-related utilization. We did not exclude

pregnancy-related admissions and found that these comprised a large proportion of all-cause admissions in immigrants, who were more likely to be female compared to non-immigrants. This in combination with differences in health seeking behaviour may account for this effect. The association between male sex and development of liver-related events has been previously documented. Male sex has been previously associated with developing complications of liver disease. It is possible that patterns of utilization for other types healthcare encounters would differ from what we observed for inpatient stays and day surgeries.

Liver-related visits accounted for less than 10% of all inpatient stays and day surgeries, affecting 9% of subjects in the cohort. In contrast to findings for all-cause healthcare utilization, measures of liver-related use were generally not statistically different between immigrants and non-immigrants. Liver-related hospitalizations appeared to be more serious than those related to other causes based on the significantly longer average length of stay and increased likelihood of resulting in time spent in an ICU. A liver-related code was the primary diagnosis for 37% of all liver-related inpatient stays indicating that the actual costs or burden that was specifically related to liver disease may have been variable. Our rates analysis for inpatient stays and in-hospital days further supported our finding that immigrants and non-immigrants had a similar burden of liver-related utilization. Both outcomes yielded non-significant rate ratio confidence intervals for immigrant status in univariate analysis. We had hypothesized that one reason that we were observing similar liver-related utilization by immigrant status, despite non-immigrants having high prevalence of risk factors for disease progression, was because immigrants were older (and likely had a longer duration of infection). This was confirmed by our multivariate analysis including age and sex as covariates where we found that after adjustment for age and sex differences, immigrants had significantly lower rates of liver-related inpatient stays (RR: 0.53, 95% CI: 0.40 – 0.70) and in-hospital days (RR: 0.63, 95% CI: 0.42 – 0.93).

6.3. Study strengths

The main strength of this study is the large, population-based sample of cases from MADO which were diagnosed with HCV using highly specific serologic tests. This is in contrast to other large studies of HCV-related healthcare utilization which have relied on disease coding in administrative databases to ascertain HCV status. Using the MADO database ensured that we used all diagnosed and reported cases across the province in which HCV reporting has been routine since 1998 and mandatory since 2002. This method of ascertaining cases gives us a

broader and more representative picture of HCV cases in the province compared to what would be obtained through sampling at specific clinics or in high risk populations. Québec is a province with a universal healthcare coverage system which allowed us to deterministically link cases to detailed records of health services (inpatient stays, physician billing), demographic information, and most uniquely, immigration data. To our knowledge we are the first population-based study to examine characteristics and healthcare utilization in immigrants with HCV. In addition to immigrant status (immigrant vs. non-immigrant) we also have information about the country of origin, time of admission into Canada, and immigration class for 90% of the immigrants in our study. All health services data were also available for up to a year before cohort entry, enabling us to ascertain prevalent comorbidities in the population.

6.4. Study limitations

Given most recent national HCV seroprevalence estimates (0.64-0.71% for 2011)[1] and Québec's population size (7.9 million in 2011)[148], the true number of prevalent cases in the province at a given time was plausibly close to 50,000-56,000. This rough approximation suggests that our cohort accounts for a large but incomplete proportion of all people who were infected with HCV during the study period. A large proportion of unaccounted for cases are likely undiagnosed (up to 44%)[1], with the remainder being unreported (prior to 1998), having insufficient data for linkage (N=5,781 or 20.1% of reported cases), or excluded due to data validity concerns (N=383). The large proportion of unlinked cases occurred due to missing identifiers, likely because of anonymous or non-nominal reporting. The proportion of cases that were unlinked was similar for each year of the study period, and a separate analysis of our data using inverse probability weighing suggests that the missing data is not differential by immigrant status (Greenaway et al., *manuscript in preparation*).

Cases prior to 1998 were not being consistently reported, meaning that we are underestimating the true burden of diagnosed HCV in the province. Widespread testing was not occurring by this time so this is unlikely to be a large proportion of cases relative to our study size however earlier diagnoses may be systematically different from later cases. Furthermore, case ascertainment relied on passive surveillance and was therefore limited to the population of diagnosed and reported cases. Because infection is typically asymptomatic and sequelae can take decades to develop, a large proportion of cases remain undiagnosed. There is no systematic screening for HCV and so cases may be more likely to be diagnosed if they present with

symptoms of liver disease or if they have specific risk factors for screening (i.e., a history of injection drug use). As a result, our cohort likely over represents people with more advanced disease, people with known risk factors for exposure, and individuals who come into contact with the healthcare system frequently. Factors affecting access to care and care seeking behaviour in immigrants and non-immigrants are complex, and likely are associated with the probability of being included in our cohort.

Our study lacked a control group without HCV which would enable us to compare characteristics and healthcare utilization with what would be expected in the general population. Our results for non-immigrants match closely with literature reports from other HCV-infected populations as discussed. However, healthcare utilization can be highly context specific and a control group would help us to better understand the proportion of excess healthcare utilization that is related to HCV infection. Unfortunately there is limited data available on Canadian immigrants with HCV, so a control group matched on immigrant status would be particularly important for understanding this population. We know little about which groups of immigrants are at highest risk for HCV infection, sequelae, and HCV-associated healthcare utilization, so more information is critical for tailoring interventions to the HCV-infected immigrant population.

There is limited accuracy of the administrative coding that was used to identify prevalent comorbidities and liver-related health services. We used inpatient codes to categorize hospitalizations during follow up. These records (Med-Echo) are coded by trained medical archivists and contains up to 15 diagnostic codes per admission, but errors and inconsistencies in coding are still possible. Physician billing codes were used in addition to inpatient records for identifying prevalent comorbidities. Physician billing encounters only contain 1 code added by the care provider which is not validated, meaning that there may be further limited accuracy and precision for prevalent conditions (e.g., drug abuse and cirrhosis). Also, not all subjects had a full year prior to diagnosis available meaning that we may be less sensitive for medical comorbidities in some groups, such as very recent immigrants. While we based all coding algorithms on literature-reported schemes, some were modified as necessary and none had been validated in the context of the Québec health system. For example, to assess baseline comorbidities we only had data available for up to 1 year prior to follow-up in contrast to some validation studies which had a longer time window in which to assess medical conditions. We

decided, therefore, to make our definitions less stringent (i.e., by requiring only 1 outpatient code compared to 2 codes) compared to those validated, due to our shorter period for capturing comorbidities.

Additionally, our study period occurred during a transition from ICD-9 to the ICD-10 coding scheme which differ substantially for how diseases are classified. Not all of the coding algorithms used had been validated in both schemes, and even those with validation could have slightly different test characteristics in ICD-9 vs. ICD-10. With respect to comparisons on immigrant status, this could affect our results because a higher proportion of immigrants were diagnosed later in the study period and therefore would have had follow-up events coded with ICD-10 compared to non-immigrants. Liver-related comorbidities were identified if any code from a list of codes related to HCV-associated liver disease was present. Therefore, complaints relevant to HCV and liver disease may not have been equally important in all events identified (e.g., a primary diagnosis of cirrhosis versus a secondary diagnosis) although we did find that a large proportion (37%) of all liver-related inpatient stays had a liver-related code as the primary diagnosis.

We used a sensitivity analysis to examine the importance of our coding scheme in identifying liver-related events. We tested both a restricted definition (requiring a primary diagnosis of liver disease instead of primary or secondary) and an expanded definition, which used an expanded list of codes for liver. Our restricted definition appeared to be more specific, identifying fewer events but without significant differences by immigrant status. In the context of liver disease, these codes are likely more specific than they are sensitive, particularly given that conditions such as liver fibrosis or HCC may not be diagnosed without specific clinical screening (e.g., via liver biopsy). To quantify true burden, we decided to prioritize improved sensitivity, which was the rationale for allowing primary or secondary diagnoses in our primary definition. Our sensitivity analysis suggests that this is reasonable. Alternatively, we also wanted to examine an expanded definition where we included additional non-specific codes for liver disease in addition to those related to HCV sequelae of interest. We did this because we were aware that there can sometimes be ambiguity in how conditions are assigned codes by archivists, and many codes do not interconvert exactly between ICD-9 and 10, meaning that a conservative definition could introduce imbalances in how many events are detected by each ICD version. We found that with an expanded list of liver-related codes, more events were detected overall,

suggesting that we may be underestimating the true burden of liver-related healthcare utilization in our cohort. While with the primary definition and the restricted definition, all-cause and liver-related utilization measures were similar by immigrant status, the expanded definition found more liver-related events in non-immigrants which likely reflects the reduced specificity of this scheme and the higher all-cause utilization in non-immigrants. There were some differences for our rates analysis wherein sex was no longer a significant predictor in some models. Overall, we still found a similar pattern of association for rates of all-cause and liver-related healthcare utilization by immigrant status.

6.5. Significance of findings

To our knowledge this is the first Canadian study to describe healthcare utilization in immigrants with HCV and one of the only population-based studies of HCV-related healthcare utilization in Canada. We identified immigrants as a unique subgroup of HCV cases that has fewer behavioural comorbidities and less all-cause healthcare utilization compared to non-immigrants. The average time between arrival to Canada and diagnosis of HCV in immigrants was 9.8 years, and immigrants commonly originated from regions with moderate to high HCV prevalence. Immigrants more frequently had hepatocellular carcinoma at baseline and had rates of liver-related healthcare utilization that were similar to non-immigrants during follow-up despite indications that immigrants were healthier with fewer medical risk factors for disease progression (i.e., HIV infection, alcohol use). Immigrant status was associated with having less liver-related utilization only after adjusting for age and sex differences, emphasizing the importance of older age on liver disease progression in this group.

As the burden of HCV is expected to continue rising in Canada, it is critical that the characteristics of the HCV population are well understood particularly as revolutionary but costly therapies for HCV become available. We have demonstrated in a large cohort that immigrants, a so-far underappreciated group with HCV, have fewer HCV-associated risk factors (e.g., IDU, HIV), but have similar rates of liver-related healthcare utilization compared to non-immigrants. The higher proportion with HCC at diagnosis, the long delay before diagnosis after arrival and the significance of age in predicting liver-related utilization all signal possible missed opportunities for diagnosis and treatment in this population. Furthermore, as demonstrated by our comparison of baseline characteristics, immigrants may have fewer competing health priorities (e.g., ongoing drug or alcohol abuse) that might influence treatment success and overall health,

meaning that there might be a disproportionately high benefit to intervening in the immigrant population. Interventions in Canada that are aimed at improving diagnosis and treatment and reducing transmission in high-risk groups such as injection drug users may not be useful in this unique population. While there is currently no systematic screening for HCV in Canada, new guidelines are forthcoming and our results provide important evidence about the importance of immigrants as an at risk group for HCV. Our findings suggest that immigrants, particularly those originating from regions with high HCV prevalence, may be appropriate candidates for more systematic as opposed to risk factor-based HCV screening. Unfortunately, because high quality seroprevalence data for HCV in Canada are not available, it is difficult to make conclusions about the cost-effectiveness of specific screening recommendations. As new highly effective HCV treatments become available, it is certainly possible that the high costs of successful treatment will decrease and become less influential in the decision making related to testing for HCV and preventing HCV-related complications.

6.6. Next steps

A cohort without HCV, matched on immigrant status and demographic characteristics (age, sex, location), will be used to compare characteristics and healthcare utilization between HCV-infected and uninfected groups. We will also examine other types of healthcare utilization including ER and outpatient visits in order to obtain a more comprehensive representation of healthcare utilization in our cohort. As the burden of costs due to HCV is expected to increase over the next two decades, extending the cohort follow-up time past 2007 could provide valuable insight into the temporal trends of healthcare utilization in the province. We may also examine additional variables in our models of healthcare utilization, including immigrant class (i.e., economic, family and refugee) and interaction terms for immigrant status, age, and sex.

CHAPTER 7: CONCLUSIONS

Rising annual utilization in diagnosed and reported HCV in Québec is attributable to an increase in the number of identified cases, and may underestimate true burden as cases prior to 1998 were not consistently reported. We identified immigrants as a unique subgroup of HCV cases that has fewer behavioural comorbidities and less all-cause healthcare utilization compared to non-immigrants. The average time between arrival to Canada and diagnosis of HCV in immigrants was 9.8 years, and immigrants commonly originated from regions with moderate to high HCV prevalence. Higher numbers and rates of all-cause hospitalizations in non-immigrants likely reflects more prevalent lifestyle comorbidities. Immigrants had similar numbers and rates of liver-related hospitalization despite having fewer risk factors for disease progression (lower proportion male, less HIV co-infection and alcohol use). We found that the older age of HCV-infected immigrants was a key driver of this, which is also supported by the long delay observed between arrival and HCV diagnosis and higher prevalence of HCC at diagnosis. These results highlight that immigrants are an important and demographically distinct part of the Québec HCV-infected population who may benefit from targeted early HCV screening and treatment. Ongoing analyses will compare utilization by immigrant status and with an uninfected reference cohort to understand drivers of hospitalization in this population including the association between healthcare utilization and HCV status.

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APPENDICES

Appendix 1 – List of countries of origin grouped according to World Bank Classifications with minor modifications.

Australia/New Zealand
Australia
New Zealand

East Asia/Pacific
American Samoa
Brunei Darussalam
Cambodia
China
Cook Islands
East Timor
Fiji
French Polynesia
Guam
Hong Kong
Indonesia
Japan
Kiribati
Korea, North
Korea, South
Laos
Macau
Malaysia
Marshall Islands
Micronesia
Mongolia
Myanmar
Nauru
New Caledonia
Palau
Papua New Guinea
Philippines
Pitcairn
Samoa
Singapore
Solomon Islands
Taiwan
Thailand
Tonga
Tuvalu
Vanuatu
Viet Nam
Wallis and Fatuna

Eastern Europe/Central Asia
Albania
Armenia
Azerbaijan
Belarus
Bosnia and Herzegovina
Bulgaria
Croatia
Estonia
Georgia
Hungary
Kazakhstan
Kyrgyzstan
Latvia
Lithuania
Macedonia
Moldova
Romania
Russian Federation
Serbia and Montenegro
Slovenia
Tajikistan
Turkey
Turkmenistan
Ukraine
Uzbekistan
Yugoslavia

High Income Europe
Andorra
Austria
Belgium
Cyprus
Czech Republic
Denmark
Finland
France
Germany
Gibraltar
Greece
Iceland
Ireland
Italy
Liechtenstein
Luxembourg
Malta
Monaco
Netherlands
Norway
Poland
Portugal
San Marino
Slovakia
Spain
Sweden
Switzerland
United Kingdom

Latin America/Caribbean
Anguilla
Antigua and Barbuda
Argentina
Aruba
Bahamas
Barbados
Belize
Bermuda
Bolivia
Brazil
Cayman Islands
Chile
Colombia
Costa Rica
Cuba
Dominica
Dominican Republic
Ecuador
El Salvador
Falkland Islands
French Guiana
Grenada
Guadeloupe
Guatemala
Guyana
Haiti
Honduras
Jamaica
Martinique
Mexico
Montserrat
Netherlands Antilles

Latin America/Caribbean
Nicaragua
Panama
Paraguay
Peru
Puerto Rico
Saint Kitts and Nevis
Saint Lucia
Saint Vincent and the Grenadines
Suriname
Trinidad and Tobago
Turks and Caicos Islands
Uruguay
Venezuela
Virgin Islands (British)
Virgin Islands (US)

Middle East/North Africa
Algeria
Bahrain
Djibouti
Egypt
Iran
Iraq
Israel
Jordan
Kuwait
Lebanon
Libya
Morocco
Oman
Palestine/West Bank/Gaza Strip
Qatar
Saudi Arabia
Syria
Tunisia
United Arab Emirates
Western Sahara
Yemen

South Asia
Afghanistan
Bangladesh
Bhutan
India
Maldives
Nepal
Pakistan
Sri Lanka

Sub-Saharan Africa
Angola
Benin
Botswana
Burkina Faso
Burundi
Cameroon
Cape Verde
Central African Republic
Chad
Comoros
Congo, Republic of the
Congo, Democratic Republic of
Cote D'Ivoire
Equatorial Guinea
Eritrea
Ethiopia
Gabon
Gambia
Ghana
Guinea
Guinea-Bissau
Kenya
Lesotho
Liberia
Madagascar
Malawi
Mali
Mauritania
Mauritius
Mayotte
Mozambique
Namibia
Niger
Nigeria
Réunion
Rwanda
Saint Helena
Sao Tomé and Principe
Senegal
Seychelles
Sierra Leone
Somalia
South Africa
Sudan
Swaziland
Tanzania
Togo
Uganda
Zambia
Zimbabwe

United States

Other
Greenland
Saint Pierre and Miquelon

Appendix 2 – Baseline characteristics of chronic hepatitis C (HCV) cases diagnosed and reported in Québec from 1991 – 2007 (cohort 1), stratified by immigrant status.

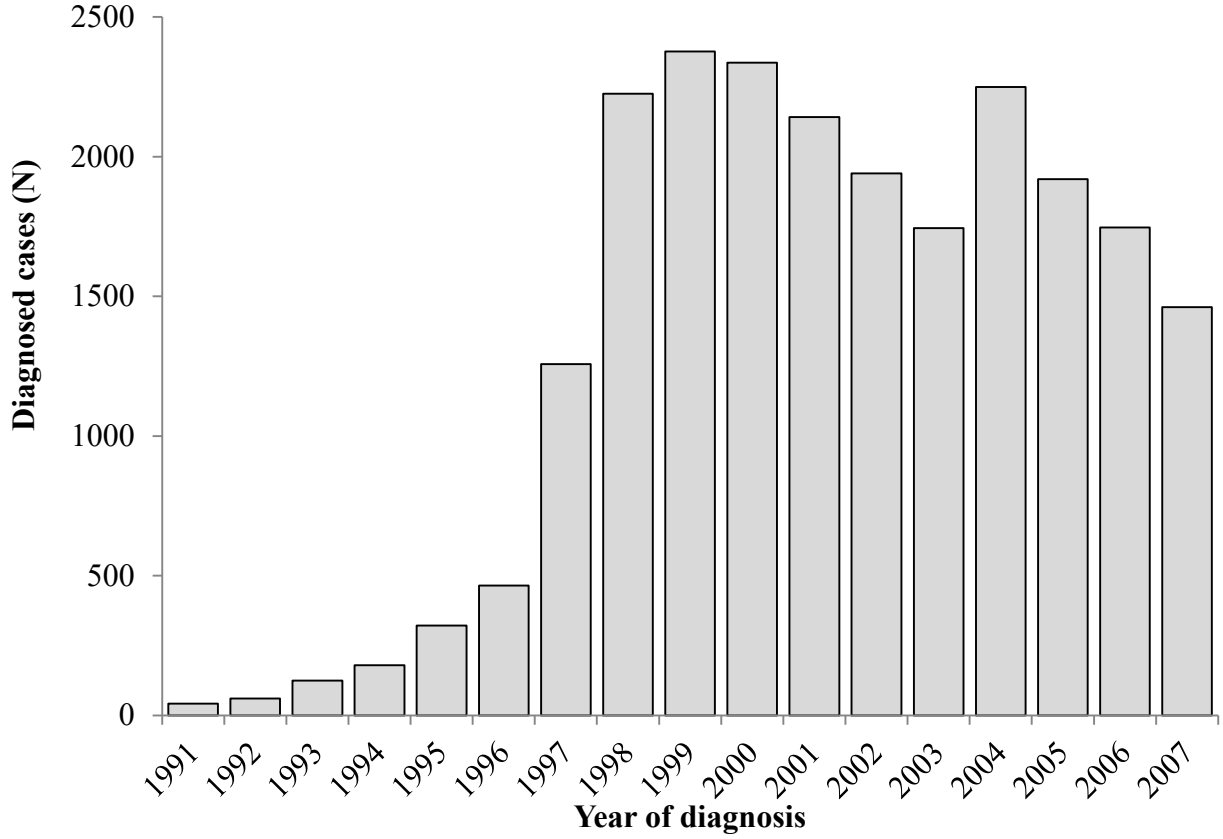
Characteristic	Chronic HCV Cases		p
	Immigrant N = 1 929	Non-immigrant N = 20 660	
Mean age, *y* ± *SD*	47.6 ± 15.0	42.6 ± 13.4	*
Sex (female), *n (%)*	909 (47.1)	6641 (32.1)	*
Mean follow-up, *y* ± *SD*	5.2 ± 3.2	5.9 ± 3.4	*
Censoring, *n (%)*			*
End of study*	1692 (87.7)	17384 (84.1)	
Death	173 (9.0)	2975 (14.4)	
RAMQ non-admissibility	64 (3.3)	301 (1.5)	
Public health region, *n (%)*			*
Abitibi-Témiscamingue	3 (0.2)	395 (1.9)	
Bas-Saint-Laurent	2 (0.1)	197 (1.0)	
Capitale-Nationale	50 (2.6)	2100 (10.2)	
Chaudière-Appalaches	5 (0.3)	505 (2.4)	
Côte-Nord	1 (0.1)	162 (0.8)	
Estrie	27 (1.4)	736 (3.6)	
Gaspésie-Îles-de-la-Madeleine	0 (0.0)	87 (0.4)	
Lanaudière	11 (0.6)	922 (4.5)	
Laurentides	24 (1.2)	1719 (8.3)	
Laval	115 (6.0)	926 (4.5)	
Mauricie et du Centre-du-Québec	7 (0.4)	1125 (5.4)	
Montréal	1492 (77.3)	7624 (36.9)	
Montérégie	157 (8.1)	2785 (13.5)	
Nord-du-Québec	0 (0.0)	29 (0.1)	
Nunavik	0 (0.0)	12 (0.1)	
Outaouais	30 (1.6)	1030 (5.0)	
Saguenay - Lac-Saint-Jean	5 (0.3)	283 (1.4)	
Terres-Cries-de-la-Baie-James	0 (0.0)	16 (0.1)	
Missing	0 (0.0)	7 (0.03)	
Medical comorbidities, *n (%)*			
Cirrhosis	103 (5.3)	1051 (5.1)	
Decompensated cirrhosis	55 (2.9)	440 (2.1)	
Hepatocellular carcinoma	4 (0.2)	10 (0.05)	*
Liver transplant	1 (0.1)	14 (0.1)	
Diabetes mellitus	209 (10.8)	1197 (5.8)	*
Alcohol abuse	57 (3.0)	2947 (14.3)	*
Alcohol-related liver disease	32 (1.7)	640 (3.1)	*
Drug abuse	47 (2.4)	5134 (24.8)	*
HIV	17 (0.9)	657 (3.2)	*
Psychosis	34 (1.8)	1134 (5.5)	*
Depression	102 (5.3)	3444 (16.7)	*
Chronic hepatitis B	32 (1.7)	147 (0.7)	*

* $p < 0.05$ comparing immigrants vs. non-immigrants using Student's T test (continuous) or χ^2 test (categorical)

Appendix 3 – Immigration-related characteristics among foreign-born cases of hepatitis C (HCV) diagnosed and reported in Québec from 1991 – 2007 (cohort 1).

Characteristic	***n (%)***
Linked cases	1744 (90.4)
Unlinked cases (missing data)*	185 (9.6)
Mean time from admission to episode, $y \pm SD$	9.7 ± 6.8
Region of origin	
East Asia/Pacific	448 (25.6)
South Asia	172 (9.8)
Middle East/North Africa	147 (8.4)
Sub-Saharan Africa	229 (13.1)
Western Europe	206 (11.8)
Eastern Europe/Central Asia	49 (2.8)
Latin America/Caribbean	256 (14.6)
US/Australia/New Zealand	24 (1.4)
Other	217 (12.4)
Immigration class	
Economic	540 (31.0)
Family	673 (38.6)
Refugee	525 (30.1)
Other immigrant	6 (0.3)

Appendix 4 – Number of chronic hepatitis C cases (after exclusions and non-linkage) diagnosed and reported annually in Québec from 1991 – 2007.



Appendix 5 – Annual all-cause healthcare utilization in immigrants and non-immigrants between 1991 and 2007 in Québec.

Year of admission	Inpatient Stays		In-hospital Days		Day surgeries	
	Total, n	Immigrant, n (%)	Total, n	Immigrant, n (%)	Total, n	Immigrant, n (%)
1991	7	1 (14.3)	94	2 (2.1)	0	n/a
1992	40	4 (10)	343	26 (7.6)	12	0 (0)
1993	62	6 (9.7)	1323	77 (5.8)	18	1 (5.6)
1994	130	13 (10)	1110	49 (4.4)	43	2 (4.7)
1995	239	12 (5)	1936	66 (3.4)	53	4 (7.5)
1996	388	18 (4.6)	4813	299 (6.2)	55	2 (3.6)
1997	747	20 (2.7)	6621	226 (3.4)	130	3 (2.3)
1998	1289	34 (2.6)	10866	248 (2.3)	223	20 (9)
1999	1841	62 (3.4)	17689	724 (4.1)	320	16 (5)
2000	2432	75 (3.1)	26177	936 (3.6)	388	16 (4.1)
2001	2658	106 (4)	31010	1240 (4)	537	27 (5)
2002	2919	87 (3)	33634	987 (2.9)	628	34 (5.4)
2003	3280	123 (3.8)	41554	1481 (3.6)	604	29 (4.8)
2004	3618	161 (4.4)	41937	1423 (3.4)	724	62 (8.6)
2005	4231	183 (4.3)	46954	2027 (4.3)	755	57 (7.5)
2006	4721	220 (4.7)	56434	2767 (4.9)	881	70 (7.9)
2007	4680	221 (4.7)	53358	2546 (4.8)	968	94 (9.7)
Total	**33282**	**1346 (4.0)**	**375853**	**15124 (4.0)**	**6339**	**437 (6.9)**

Appendix 6 – Annual liver-related healthcare utilization in immigrants and non-immigrants between 1991 and 2007 in Québec.

Year of admission	Inpatient Stays		In-hospital Days		Day surgeries	
	Total, n	Immigrant, n (%)	Total, n	Immigrant, n (%)	Total, n	Immigrant, n (%)
1991	2	0 (0)	39	0 (0)	0	n/a
1992	1	0 (0)	4	0 (0)	3	0 (0)
1993	13	0 (0)	767	0 (0)	2	1 (50)
1994	15	0 (0)	262	0 (0)	5	1 (20)
1995	24	0 (0)	272	0 (0)	2	0 (0)
1996	31	6 (19.4)	500	124 (24.8)	0	n/a
1997	84	5 (6)	925	50 (5.4)	9	0 (0)
1998	183	11 (6)	2115	117 (5.5)	5	1 (20)
1999	255	19 (7.5)	3400	443 (13)	3	0 (0)
2000	373	25 (6.7)	4597	337 (7.3)	6	1 (16.7)
2001	445	30 (6.7)	5712	518 (9.1)	21	1 (4.8)
2002	497	24 (4.8)	7419	356 (4.8)	16	0 (0)
2003	621	30 (4.8)	8618	502 (5.8)	14	2 (14.3)
2004	727	41 (5.6)	9343	513 (5.5)	13	1 (7.7)
2005	833	54 (6.5)	10084	531 (5.3)	18	1 (5.6)
2006	873	54 (6.2)	12108	813 (6.7)	16	1 (6.3)
2007	902	57 (6.3)	12623	847 (6.7)	26	2 (7.7)
Total	**5879**	**356 (6.1)**	**78788**	**5151 (6.5)**	**159**	**12 (7.5)**

Appendix 7 – Category of diagnostic code for cause of death in inpatient hospitalizations that resulted in death.

Category of cause of death	Immigrants N = 75	Non-immigrants N = 899
Liver-related	20 (26.7)	188 (20.9)
Alcohol-related	1 (5.0)	48 (25.5)
HCC	9 (45.0)	52 (27.7)
Other	10 (50.0)	88 (46.8)
Infectious and parasitic diseases	5 (6.7)	79 (8.8)
Neoplasms	12 (16.0)	136 (15.1)
Endocrine/metabolic/immunity	1 (1.3)	10 (1.1)
Blood and blood-forming organs	2 (2.7)	7 (0.8)
Mental disorders	-	2 (0.2)
Nervous system	2 (2.7)	30 (3.3)
Circulatory system	9 (12.0)	115 (12.8)
Respiratory system	9 (12.0)	98 (10.9)
Digestive system‡	9 (12.0)	84 (9.3)
Genitourinary system	2 (2.7)	29 (3.2)
Skin/subcutaneous tissue	-	1 (0.1)
Musculoskeletal/connective tissue	-	2 (0.2)
Injury and poisoning	3 (4.0)	68 (7.6)
Supplementary classifications	1 (1.3)	49 (5.5)
Missing/other	-	1 (0.1)

p not-significant (>0.05) for χ^2 comparing immigrants and non-immigrants (p=0.822 for all N = 16 categories; p = 0.077 for N=3 categories of liver-related deaths).

Appendix 8 – Parameter estimates and p-values for G.E.E. modelling of comparisons of immigrant versus non-immigrant hospital stays.

	Non-liver		Liver-related	
	β estimate	P value	β estimate	P value
Length of stay (days)	-0.0549	0.4029	0.0446	0.5943
Admitted through ER (y/n)	-0.4587	<.0001	-0.3616	0.0241
Had an ICU stay (y/n)	-0.2559	0.0507	0.2182	0.1639
Transfer (y/n)	0.0828	0.5790	0.3551	0.1426
Death	0.4648	0.0156	0.4768	0.0027

Appendix 9 – Goodness of fit parameters for full models (containing age, sex, and immigrant status) (all-cause hospitalizations).

	All-cause inpatient stays				Liver-related inpatient stays			
	Poisson	QP1	QP2	NB	Poisson	QP1	QP2	NB
Likelihood ratio*	1666.90	40.80	217.35	509.98	2667.33	-75.16	216.72	699.06
McFadden R^2	0.043	0.007	0.018	0.054	0.104	-0.027	0.012	0.063
Cox & Snell R^2	0.079	0.002	0.011	0.025	0.124	-0.004	0.011	0.034
Nagelkerke R^2	0.093	0.009	0.024	0.067	0.172	-0.029	0.018	0.080

*Compared to null model (no covariates).

Appendix 10 – Comparison of regression estimates for 3 models: poisson, quasi-poisson, and negative binomial for all-cause inpatient stays.

Parameter	**Poisson**		**Quasi-poisson**		**Negative binomial**	
	RR, 95% CI	**p**	**RR, 95% CI**	**p**	**RR, 95% CI**	**p**
Univariate analysis						
Immigrant	0.51 (0.48 - 0.54)	<.001	0.51 (0.44 - 0.60)	<.001	0.52 (0.47 - 0.58)	<.001
Age (cont.)	1.01 (1.01 - 1.01)	<.001	1.01 (1.01 - 1.01)	<.001	1.02 (1.02 - 1.02)	<.001
Sex, F	1.21 (1.18 - 1.24)	<.001	1.21 (1.13 - 1.30)	<.001	1.20 (1.13 - 1.28)	<.001
Multivariate analysis						
Immigrant	0.46 (0.43 - 0.49)	<.001	0.46 (0.39 - 0.54)	<.001	0.45 (0.40 - 0.51)	<.001
Age (cont.)	1.01 (1.01 - 1.01)	<.001	1.01 (1.01 - 1.02)	<.001	1.02 (1.02 - 1.02)	<.001
Sex, F	1.23 (1.19 - 1.26)	<.001	1.23 (1.15 - 1.31)	<.001	1.26 (1.19 - 1.34)	<.001

Appendix 11 – Comparison of regression estimates for 3 models: poisson, quasi-poisson, and negative binomial for all-cause in-hospital days.

Parameter	**Poisson**		**Quasi-poisson**		**Negative binomial**	
	RR, 95% CI	**p**	**RR, 95% CI**	**p**	**RR, 95% CI**	**p**
Univariate analysis						
Immigrant	0.51 (0.50 - 0.51)	<.001	0.51 (0.37 - 0.68)	<.001	0.73 (0.62 - 0.86)	<.001
Age (cont.)	1.02 (1.02 - 1.02)	<.001	1.02 (1.02 - 1.03)	<.001	1.03 (1.03 - 1.04)	<.001
Sex, F	1.16 (1.15 - 1.17)	<.001	1.16 (1.02 - 1.32)	0.023	1.33 (1.21 - 1.47)	<.001
Multivariate analysis						
Immigrant	0.43 (0.43 - 0.44)	<.001	0.43 (0.32 - 0.59)	<.001	0.57 (0.49 - 0.67)	<.001
Age (cont.)	1.02 (1.02 - 1.02)	<.001	1.02 (1.02 - 1.03)	<.001	1.03 (1.03 - 1.04)	<.001
Sex, F	1.14 (1.14 - 1.15)	<.001	1.14 (1.01 - 1.30)	0.041	1.25 (1.14 - 1.37)	<.001

Appendix 12 – Comparison of regression estimates for 3 models: poisson, quasi-poisson, and negative binomial for liver-related inpatient stays.

Parameter	Poisson		Quasi-poisson		Negative binomial	
	RR, 95% CI	**p**	**RR, 95% CI**	**p**	**RR, 95% CI**	**p**
Univariate analysis						
Immigrant	0.78 (0.69 - 0.87)	<.001	0.78 (0.55 - 1.10)	0.160	0.85 (0.63 - 1.15)	0.293
Age (cont.)	1.05 (1.05 - 1.05)	<.001	1.05 (1.04 - 1.06)	<.001	1.08 (1.07 - 1.09)	<.001
Sex, F	0.81 (0.77 - 0.87)	<.001	0.81 (0.67 - 0.99)	0.036	0.80 (0.68 - 0.96)	0.013
Multivariate analysis						
Immigrant	0.59 (0.52 - 0.66)	<.001	0.59 (0.42 - 0.82)	0.002	0.53 (0.40 - 0.70)	<.001
Age (cont.)	1.05 (1.05 - 1.06)	<.001	1.05 (1.05 - 1.06)	<.001	1.08 (1.08 - 1.09)	<.001
Sex, F	0.68 (0.64 - 0.72)	<.001	0.68 (0.57 - 0.82)	<.001	0.69 (0.59 - 0.81)	<.001

Appendix 13 – Comparison of regression estimates for 3 models: poisson, quasi-poisson, and negative binomial for liver-related in-hospital days.

Parameter	Poisson		Quasi-poisson		Negative binomial	
	RR, 95% CI	**p**	**RR, 95% CI**	**p**	**RR, 95% CI**	**p**
Univariate analysis						
Immigrant	0.83 (0.81 - 0.86)	<.001	0.83 (0.51 - 1.36)	0.461	1.45 (0.95 - 2.20)	0.081
Age (cont.)	1.06 (1.05 - 1.06)	<.001	1.06 (1.05 - 1.06)	<.001	1.10 (1.09 - 1.11)	<.001
Sex, F	0.86 (0.85 - 0.88)	<.001	0.86 (0.66 - 1.13)	0.294	1.15 (0.90 - 1.47)	0.271
Multivariate analysis						
Immigrant	0.60 (0.59 - 0.62)	<.001	0.60 (0.39 - 0.93)	0.021	0.63 (0.42 - 0.93)	0.021
Age (cont.)	1.06 (1.06 - 1.06)	<.001	1.06 (1.05 - 1.07)	<.001	1.10 (1.09 - 1.11)	<.001
Sex, F	0.69 (0.68 - 0.70)	<.001	0.69 (0.54 - 0.88)	0.003	0.82 (0.65 - 1.04)	0.103

Appendix 14 – Annual liver-related healthcare utilization in immigrants and non-immigrants between 1991 and 2007 in Québec *using a restricted definition for liver-related events* (sensitivity analysis).

Year of admission	Inpatient Stays		In-hospital Days		Day surgeries	
	Total, n	Immigrant, n (%)	Total, n	Immigrant, n (%)	Total, n	Immigrant, n (%)
1991	0	N/A	0	N/A	0	N/A
1992	0	N/A	0	N/A	3	0 (0)
1993	4	0 (0)	11	0 (0)	1	0 (0)
1994	8	0 (0)	128	0 (0)	4	0 (0)
1995	12	0 (0)	48	0 (0)	1	0 (0)
1996	14	5 (35.7)	211	111 (52.6)	0	N/A
1997	34	3 (8.8)	376	40 (10.6)	7	0 (0)
1998	84	3 (3.6)	1061	13 (1.2)	3	1 (33.3)
1999	106	9 (8.5)	1692	259 (15.3)	0	N/A
2000	140	10 (7.1)	1772	139 (7.8)	2	0 (0)
2001	168	20 (11.9)	1875	309 (16.5)	7	0 (0)
2002	182	11 (6)	2499	270 (10.8)	3	0 (0)
2003	225	11 (4.9)	3513	248 (7.1)	2	0 (0)
2004	231	15 (6.5)	3003	220 (7.3)	3	0 (0)
2005	279	23 (8.2)	3412	167 (4.9)	3	1 (33.3)
2006	322	21 (6.5)	4475	185 (4.1)	3	1 (33.3)
2007	355	19 (5.4)	4728	276 (5.8)	4	1 (25)
Total	**2164**	**150 (6.9)**	**28804**	**2237 (7.8)**	**46**	**4 (8.7)**

Appendix 15 – Annual liver-related healthcare utilization in immigrants and non-immigrants between 1991 and 2007 in Québec *using an expanded definition for liver-related events* (sensitivity analysis).

Year of admission	Inpatient Stays		In-hospital Days		Day surgeries	
	Total, n	Immigrant, n (%)	Total, n	Immigrant, n (%)	Total, n	Immigrant, n (%)
1991	2	0 (0)	39	0 (0)	0	N/A
1992	7	0 (0)	26	0 (0)	5	0 (0)
1993	27	0 (0)	842	0 (0)	6	1 (16.7)
1994	40	1 (2.5)	536	1 (0.2)	20	2 (10)
1995	77	2 (2.6)	675	2 (0.3)	10	2 (20)
1996	102	9 (8.8)	1440	253 (17.6)	6	0 (0)
1997	253	6 (2.4)	2341	73 (3.1)	29	1 (3.4)
1998	521	16 (3.1)	5253	141 (2.7)	59	12 (20.3)
1999	799	31 (3.9)	9293	505 (5.4)	63	3 (4.8)
2000	1129	46 (4.1)	13460	649 (4.8)	57	3 (5.3)
2001	1324	59 (4.5)	16875	961 (5.7)	99	8 (8.1)
2002	1320	43 (3.3)	17516	700 (4)	89	5 (5.6)
2003	1602	67 (4.2)	22510	977 (4.3)	72	8 (11.1)
2004	1741	79 (4.5)	20760	819 (3.9)	102	10 (9.8)
2005	2108	98 (4.6)	24453	1049 (4.3)	88	7 (8)
2006	1278	66 (5.2)	16166	1044 (6.5)	34	2 (5.9)
2007	994	61 (6.1)	13719	940 (6.9)	29	2 (6.9)
Total	**13324**	**584 (4.4)**	**165904**	**8114 (4.9)**	**768**	**66 (8.6)**