Epidemiology and Liver Transplantation Burden of Primary Biliary Cholangitis: A Retrospective Cohort Study Using National Administrative Data

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List of Abbreviations:

PBC	Primary Biliary Cholangitis
ICD Diagnosis	International Classification of Diseases Diagnosis
MELD Score	Model of End-Stage Liver Disease

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Figures	1
Tables	3

ABSTRACT

Background & Aims:

There is a wealth of data documenting the epidemiology of primary biliary cholangitis (PBC) globally; however, no recent assessment of PBC epidemiology in Canada. Global data suggests the prevalence of PBC is a growing healthcare concern. To investigate these trends, our study characterized the Canadian prevalence of PBC and the number of liver transplantations due to PBC.

Methods:

Hospital administrative records with national coverage from the Canadian Institute for Health Information (in-patient, ambulatory, outpatient), with the exception of Quebec,

and British Columbia transplant data, were used for the study. Patients were identified by ICD-10 PBC diagnosis.

Results:

In 2015, 8,680 PBC patients were identified in Canada, translating to a prevalence of 318 cases per million. Annual prevalence by province varied, ranging from 283 to 465 (95% CI 275-309, 426-504) cases per million, and the 6-year PBC liver transplant rate ranged from 3.17 to 5.92 (95% CI 1.27-6.54, 3.71-9.08) per million. The Atlantic Provinces exhibited the highest PBC prevalence, and close to the highest 6-year liver transplant rate per million [465 and 5.70 cases per million (95% CI 426-504, 3.19-9.56) respectively]. We observed the lowest PBC prevalence and the second lowest 6-year liver transplant rate in Ontario [283 and 3.37 cases per million (95% CI 269-297, 2.47-4.50) respectively].

Interpretation:

Our study demonstrates the prevalence of PBC in Canada is similar to other PBC prevalence studies. Due to geographic clustering of PBC across the Canadian Provinces, we hypothesize that PBC pathogenesis is linked to environmental and genetic factors.

Key Words: Primary Biliary Cholangitis, Prevalence, Liver Transplant

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic rare autoimmune cholestatic liver disease characterized by destruction of the small intrahepatic bile ducts. It predominantly affects middle-aged and elderly women.(1, 2) Despite its rarity, PBC is an important cause of liver related morbidity.(2-5) In the US the annual economic burden of PBC has been estimated to be $69-115 million.(3) There is concern that the economic impact of PBC could increase significantly in the future because of its

increasing incidence and prevalence;(6-12) however, with improved treatment options, these costs may be attenuated.(13-15) The epidemiology of PBC was first described as early as 40 years ago,(16) although decades later no study has investigated the national prevalence of PBC in Canada. It predominantly affects middle-aged and elderly women.(1, 2) A number of studies have examined the epidemiology of PBC globally, illustrating considerable variability in the prevalence ranging from 6.7 to 402 cases per million, while incidence rates range from 0.7 to 58 cases per million.(1) A growing number of studies suggest the incidence and prevalence of PBC is increasing.(6-12) The driver of this growth remains unclear, but may be the result of an increase in incidence, longer survival, as well as advances in diagnosis and treatment. In addition, there is increasing evidence to suggest PBC etiology is related to complex interactions between genetic predisposition and environmental triggers,(3, 17-21) such as infectious disease agents.(3, 22-24)(25)

Recent advances in the understanding of PBCprovide the opportunity to improve patient outcomes and to lower the economic and epidemiologic burden of PBC. In this study our primary objective was to provide a national prevalence estimate of PBC in Canada, as well as to investigate the regional PBC prevalence by geographic areas across Canada. Our secondary objective was to characterize liver transplantation trends and geographic distribution in PBC patients, since this is a costly procedure, and a proportion of PBC patients require liver transplants.

METHODS

Data sources and study population:

The study used patient-level records over a 9-year period from April 1, 2007 to March 31, 2015 for the prevalent population, and over a 6-year period from April 1, 2010 to March 31, 2015 for the liver transplant population. This study sourced data

across three databases from the Canadian Institute for Health Information (CIHI). The National Ambulatory Care Reporting System (NACRS) database contains data on hospital and community-based emergency and ambulatory care visits, including visits to day surgery, and outpatient clinics in Canada.[36] The Discharge Abstract Database (DAD) contains data on hospitalizations from acute inpatient care, select day surgery, chronic, rehabilitation and psychiatric institutions in Canada.[37] The Canadian Organ Replacement Register (CORR) records information on all transplanted organs across Canada.(38) Data from 9 of 10 provinces in Canada, with the exception of Quebec, was made available for the prevalence estimate, and 8 of 10 provinces in Canada, with the exception of British Columbia and Quebec, for the transplant analysis. For the provinces with incomplete data coverage or unreleased data we extrapolated results from the other provinces by applying age adjusted prevalence or transplant rates to the known populations within those provinces as reported by Statistics Canada.(39) To capture diagnoses made in clinics the authors used the available data from Alberta to estimate diagnoses in other provinces. Data of individual provinces were then grouped into geographic regions: Atlantic (Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland), Ontario, Prairies (Manitoba and Saskatchewan), Alberta, and British Columbia. Ethics approval for this study was obtained from Institutional Review Board Services (Pro00017376).

Administrative data case definition:

PBC case identification for the prevalent population required one hospital visit with a diagnosis code for PBC (International Classification of Diseases Version 10-Canadian Edition K74.3) recorded as the most responsible reason for a visit, or as a comorbidity diagnosis during the study period. In all study databases unique patient identifiers were used to prevent double counting patients. Similar to previous

studies,(2, 4, 5) PBC case identification for the liver transplant population required the primary reason for the transplant to be PBC.

Liver disease severity indexes:

Alberta patients were further identified as late-stage PBC if their medical records included at least one late-stage PBC associated diagnosis. The list of diagnosis codes associated with late-stage PBC were generated using published literature, (18, 34, 40) and expert clinical opinion(41). This additional analysis was limited to Alberta as it was the only province with full coverage of outpatient clinics and hospital visits required for a robust determination of late-stage disease.

For the liver transplant population, the Model for End Stage Liver Disease (MELD) and Child Pugh score were used as a measure of prognostic survival, liver disease severity, and are traditionally used to determine liver transplant priority.(42) MELD score uses the patient's values for serum bilirubin, serum creatinine and the International normalized ratio for prothrombin time.(43) The Child Pugh score employs five clinical measures of liver disease namely: total bilirubin, serum albumin, prothrombin time, ascites and hepatic encephalopathy. Each measure is scored between 1 and 3, with 3 indicating most severe condition.(42)

Statistical analysis:

The prevalence estimate was evaluated between April 1, 2013 and March 31, 2015 for the prevalent population, and April 1, 2010 to March 31, 2015 for the liver transplant population. The annual prevalence was determined by dividing the number of PBC cases alive at March 31 for each year by the populations for each geographic area from Statistics Canada. Due to the disease's chronic nature, patients were considered prevalent with PBC until a hospital death occurred. Our study used all available history in the look-back period to establish prevalence. For geographic

distribution in the PBC liver transplant population, a 6-year liver transplant rate per million estimate was used to account for low annual transplant rates. Regional estimates were age and sex adjusted to the 2015 and 2013 Canadian population for the prevalent and liver transplant population, respectively.(44) Wait-time for liver transplantation was defined as the number of days from the date that the patient was placed on the transplant list to the date of liver transplant. Patients who died while on the transplant list were not included in CORR and therefore unavailable for analysis. Descriptive statistics were used to summarize the characteristics of the study cohorts. P-values between prevalence estimates were calculated using the two-sided Wilson method with a continuity correction. The Kaplan-Meier method was used to assess transplant wait-time and survival.

RESULTS

National Prevalence of PBC:

In 2015, 8,680 cases of PBC patients were identified in Canada, excluding Quebec, which translates into a prevalence of 318 (95% CI 309-327) cases per million, Table 1). Geographic analysis revealed variance in the prevalence of PBC across the Canadian provinces. In 2015, Atlantic Provinces had the highest PBC prevalence (465 [95% CI: 426-504] cases per million) in Canada, followed by the Prairie Provinces (399 [95% CI: 360-438] cases per million), British Columbia (327 [95% CI: 302-352] cases per million), then Alberta (292 [95% CI 275-309] cases per million). The lowest prevalence PBC rate was observed in Ontario, (283 [95% CI: 269-297] cases per million) (Table1). Relative to Ontario, the Atlantic Provinces ($p<0.01$), Prairie Provinces ($p<0.01$), and British Columbia ($p<0.05$) had a significantly higher PBC prevalence. However, Alberta was not statistically different from Ontario ($p=0.4$).

The demographic characteristics of the PBC population are shown in Table 2. PBC was approximately five times as common among females in our study population . The majority of PBC cases were diagnosed among individuals 40-64 years of age for women, and among 0-17 years of age for men. Disease severity varied by province. Of the Alberta PBC patients, 29% (95% CI: 26%-32%) were identified as having late-stage PBC due to a late-stage associated diagnosis. Further segmenting the population by treatment location, 8% (95% CI 6%-10%) of PBC treated only in a clinic were identified as late-stage, while 48% (95% CI 44%-53%) of patients who received a PBC diagnosis in the hospital were considered late-stage.

National liver transplantation for PBC:

A total of 92 patients received a liver transplant due to PBC between April 1, 2010 and March 31, 2015 in Canada (excluding Quebec, British Columbia), accounting for 5% of all liver transplants in this time frame. The annual rate of liver transplants due to PBC varied and ranged from 0.49 to 1.03 cases per million in the general population (Table 1). The geographic analysis showed that the 6-year liver transplant rate per million due to PBC was highest in Alberta (5.92 [95% CI: 3.71-9.08] cases per million) followed by the Atlantic Provinces (5.70 [95% CI: 3.19-9.56] cases per million), then Ontario (3.37 [95% CI: 2.47-4.50] cases per million). The lowest 6-year liver transplant rate per million due to PBC was observed in the Prairie Provinces (3.17 [95% CI: 1.27-6.54] cases per million). Relative to Ontario, Alberta ($p<0.05$) had a significantly higher 6-year PBC liver transplant rate per million. However, the Atlantic ($p=0.1$) and Prairie ($p=1$) provinces were not statistically different from Ontario.

Liver transplants were approximately 5 times more common among females than among males, which aligns with findings with the PBC prevalence analysis.

Further, PBC was the leading cause of liver transplantation among women. Among males and females in this study, the highest number of liver transplants was observed in patients between the ages of 40-64 (Table 3). Close to half of PBC liver transplant patients have the most severe liver dysfunction measured by a Child Pugh score of 10-15 (58%) and MELD score of >22 (39%) (Table 3).

When analyzing wait times to receive a transplant, the median wait time for PBC patients was 2 months (95% CI: 1-3) (Figure 1). Post-transplant, the 2-year survival for PBC patients was estimated to be 89% (95% CI: 83%-96%) (Figure 1).

INTERPRETATION

This study improves upon previous studies estimating the regional or local prevalence of PBC by describing the first national epidemiological trends of PBC and associated liver transplants in and across Canada. This study found that the annual prevalence varied by province from 283 to 465 (95% CI 275-309, 426-504) cases per million, and the 6-year PBC liver transplant count ranged from 3.17 to 5.92 (95% CI 1.27-6.54, 3.71-9.08) per million. The last time prevalence of PBC in the United States was published was for the period of 1975-1995.(9) Previous prevalence studies of PBC show a wide range of estimates ranging from 6.7 to 402 per million.(1, 7, 9-12, 16, 45) The PBC prevalence figures reported in this study (2015 prevalence of 318 per million) are among the highest reported, and when projected nationally to extrapolate for the Quebec population, correspond to 11,290 prevalent PBC cases in Canada in 2015. Earlier, Canadian studies(11, 12) have reported prevalence estimates of between 3 and 25 per million, an order of magnitude lower than the current study. The most recent Canadian estimate by Myers and colleagues reported a 2002 prevalence of 227 per million(10) which is consistent with our estimate for the PBC prevalence in the province of Alberta (292 per million).

There are several potential contributing factors to the increase in PBC prevalence. It is possible greater disease awareness and testing, earlier diagnosis, or prolonged survival could each contribute. Several studies on the temporal trends of liver transplants and outcomes of PBC patients suggest prolonged survival may be a key factor.(9, 33, 46, 47) Lee and colleagues described a reduction in the number of transplantations for PBC patients thought to be attributed to the introduction of ursodeoxycholic acid (UDCA), indicating possible improved outcomes and therefore prolonged survival.(9, 33, 48)

The current study provides the first analysis of clustering effects of PBC across Canada. Our geographic analysis showed large disparities in the PBC prevalence across Canadian provinces ranging from 283 to 465 per million for the prevalence analysis, and 3.17 to 5.92 liver transplants per million in the general population for the liver transplant analysis. Notably, the Atlantic Provinces had high PBC prevalence (465 per million) and 6-year PBC liver transplant rate per million (5.7 per million). This geographic clustering of PBC may suggest genetic and environmental influences on the aetiology and pathogenesis of PBC. In particular, these patterns could potentially be explained by the founder effect. A large percentage of the Atlantic populations are descendent of immigrants from the British Isles and Northern France. Approximately 29% of Newfoundland and Labrador's, 19% of PEI's, 16% of Nova Scotia's, and 12% of New Brunswick's population are descended solely from the United Kingdom, with even higher proportions having some United Kingdom descent.(49) In comparison, only 9% of the Ontario population, the Canadian province with the lowest estimated PBC prevalence, is solely from the United Kingdom.(49) A systematic review by Boonstra *et al.* found that the United Kingdom population has one of the highest PBC prevalence.(1)

Literature suggests that PBC is typically considered a disease of middle age,(11, 12) and our results echoed the same findings. Out of the total study population, approximately 55% of patients were found to be PBC prevalent within the age group of 40-59 years.(49) Liver transplantation survival rates for PBC patients in the present analysis (2-year survival: 89%) is comparable to the CORR annual report (5-year survival: 81.8%). Fosby and colleagues observed a similar PBC liver transplant survival rate in Nordic countries between 2004 and 2013, with the 1-year and 5-year survival for patients transplanted for PBC reported to be 94% and 87%, respectively.(4)

As our study has several limitations due to the challenges inherent in using administrative datasets, we recommend careful interpretation of results. Our study is potentially limited by the risk of misclassification of individuals with PBC due to reliance on administrative data. The definition used by Myers and colleagues required two distinct diagnoses of PBC and was shown to have a positive predictive value (PPV) of 73% for definite or probable PBC cases(51); therefore, we can expect our PPV value would be lower based on a single PBC diagnosis in this study. Second, the data coverage for the DAD and NACRS (emergency department) database was not complete across the provinces. However, the number of PBC patients identified through the ER was small (5%), hence we consider this adjustment was minor. For clinic visits, we used Alberta, which had 100% clinic coverage, to project for lack of visibility in other provinces. We observed 58% the PBC population is identified through the clinic, and therefore this part of the projection had a greater impact on the prevalence estimate.

In conclusion, using population-based administrative data we have provided insight into the geographic distribution and temporal trends of PBC in Canada for

both the PBC prevalent and liver transplant population. Notwithstanding the limitations outlined above, the observed prevalence demonstrate that PBC is a growing healthcare concern in Canada, and warrants further investigations of the interplay between genetic and environmental influences on PBC disease.

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Table 1. Annual Prevalence Among Primary Biliary Cholangitis (PBC) and PBC Liver Transplant Population

	Prevalence (95% CI)	
Year	**PBC Prevalent Population**	**PBC Liver Transplant Population**
2010	-	1.03 (0.93-1.06)
2011	-	0.55 (0.37-0.73)
2012	-	1.02 (0.92-1.11)
2013	255 (248-264)	0.59 (0.47-0.71)
2014	288 (279-297)	0.58 (0.52-0.65)
2015	318 (309-327)	0.49 (0.41-1.06)

Note: CI = confidence interval. Data shows national annual prevalence trend with the age/sex adjusted prevalence as PBC or Liver Transplant cases per million population.

Table 2. Demographics the Primary Biliary Cholangitis Prevalent Population

Age Group	**Male (%)**	**Female (%)**
0-17	62%	38%
18-39	35%	65%
40-64	20%	80%
65-79	22%	78%
>80+	17%	83%

Note: CI = confidence interval. The data show the proportion of the 2015 PBC prevalent population.

Table 3. Demographics and Disease Severity of the Primary Biliary Cholangitis Liver Transplant Population

Age	**Male (%)**	**Female (%)**
0-17	4%	0%
18-39	0%	11%
40-64	60%	83%
65+	36%	6%
Child Pugh Category	**Proportion Patients (%)**	
5-6	0%	
7-9	41%	
10-15	58%	
MELD Category	**Proportion Patients (%)**	
<12	7%	
12-15	24%	
15-22	29%	
>22	39%	

Note: MELD = model of end-stage liver disease. The data are show the crude unadjusted counts for the liver transplant population by age. The data show the 2010-2015 PBC liver transplant study cohort with the distribution of patients' liver disease severity as measured by Child Pugh and MELD Score.

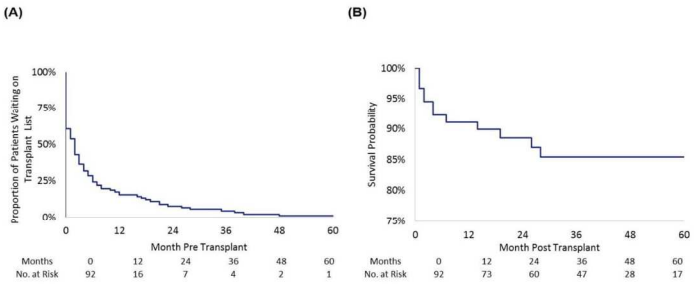

Figure 1: Primary Biliary Cholangitis Liver Transplant Wait-time and Survival Analysis

A) Transplant Wait-Time Analysis. The data shown is the proportion of patients waiting to receive a liver transplant by month since being listed on the transplant list. B) Survival Post Liver Transplant. The data shown demonstrates the probability of survival post-liver transplant by month.

Primary Biliary Cholangitis Liver Transplant Wait-time and Survival Analysis

599x776mm (72 x 72 DPI)