UNIVERSITY OF CALGARY

Epidemiology and outcomes of primary biliary cirrhosis in the Calgary Health Region: A population-based study

by

Robert Paul Myers

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

SEPTEMBER, 2008

UNIVERSITY OF
CALGARY

ABSTRACT

Primary biliary cirrhosis (PBC) is a chronic hepatic disorder that affects predominantly females and may necessitate transplantation. The epidemiology and outcomes of PBC in Canada are poorly defined partly due to the difficulty of case ascertainment. In this study, we validated an administrative data coding algorithm for PBC that requires at least two health care contacts with this diagnosis. Using this algorithm, we described the epidemiology of PBC in the Calgary Health Region and the natural history in newly-diagnosed cases. Between 1996 and 2002, the annual incidence was stable (30 cases per million), however, the prevalence increased from 100 to 227 per million population. The estimated 10-year survival and requirement for liver transplantation were 73% and 5.7%, respectively. In summary, this study demonstrates the feasibility of identifying PBC patients using administrative data, and for the first time, describes the epidemiology and outcomes of this condition from a Canadian, population-based perspective.

ACKNOWLEDGEMENTS

This thesis would not have been possible without the help of numerous individuals. I would like to acknowledge my supervisor, Dr. Hude Quan, and the other members of my thesis committee, Drs. Bob Hilsden, Mark Swain, and Lloyd Sutherland, who helped me plan and conduct this research. I would also like to thank my friend and research fellow, Dr. Abdel Aziz Shaheen, whose assistance was pivotal in me completing this thesis.

I must also acknowledge Andrew Fong for his tireless work in extracting Calgary Health Region administrative data. In addition, I would like to thank Dr. Vince Bain and Glenda Meeberg for providing data from the University of Alberta Liver Transplant Research Database.

Finally, I would like to thank my family for their unconditional support and encouragement throughout this process and my many preceding years of education. A special thank you to my wife Gabriela for her patience and understanding that allowed me to complete this thesis during a very busy period of our lives. I love you.

DEDICATION

This thesis is dedicated to the two greatest joys of my life, my sons, Carlos and Santiago.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACCS	Ambulatory Care Classification System
AHCIP	Alberta Health Care Insurance Plan
AIH	autoimmune hepatitis
AMA	antimitochondrial antibody
CHR	Calgary Health Region
CI	confidence interval
DAD	Discharge Abstract Database
ELTR	European Liver Transplant Registry
GP	general practitioner
HR	hazard ratio
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
IQR	interquartile range
IRR	incidence rate ratio
OPTN	Organ Procurement and Transplant Network
PBC	primary biliary cirrhosis
PDC	pyruvate dehydrogenase complex
PHN	personal health number
PPV	positive predictive value
PSC	primary sclerosing cholangitis
RSR	relative survival ratio
UDCA	ursodeoxycholic acid
UK-GPRD	United Kingdom General Practice Research Database
UNOS	United Network for Organ Sharing

CHAPTER ONE

INTRODUCTION

BACKGROUND

Primary Biliary Cirrhosis (PBC)

PBC is a chronic cholestatic liver disorder characterized by nonsuppurative destruction of the interlobular and septal bile ducts. The consequent cholestasis leads to progressive liver fibrosis, cirrhosis, and liver failure in many affected patients. The etiology of PBC is unknown although autoimmune, genetic, and environmental factors likely play a role.[1-4] A hallmark of this condition is the presence of antimitochondrial antibodies (AMA) in the serum of 90-95% of affected patients.[5, 6] These antibodies, in addition to hypergammaglobulinemia, other antibodies (e.g. antinuclear antibodies), and concomitant autoimmune conditions (e.g. sicca syndrome and thyroid disease) suggest that autoimmune mechanisms play a major role in the pathogenesis of PBC.[1-4]

PBC is primarily a disease of middle-aged females. Although most patients (60%) are asymptomatic at diagnosis, common symptoms include fatigue and pruritus. Complications include osteoporosis and fat-soluble vitamin deficiency.[7-9] Due to progressive fibrosis, end-stage liver disease (manifested by ascites, jaundice, encephalopathy, and/or portal hypertensive bleeding) requiring liver transplantation is a potential complication.[10, 11] Because of our limited understanding of the pathogenesis of PBC, curative therapy is not available. The

only approved treatment is ursodeoxycholic acid (UDCA).[12] UDCA has been shown to improve liver biochemistry and histology, reduce the formation of esophageal varices, and prolong transplant-free survival.[13-16] Unfortunately, only one-third of patients have biochemical normalization on UDCA, and despite therapy, 25% of patients may die or require transplantation within four years of initiating treatment.[13]

Epidemiology of PBC

Numerous population-based studies have examined the epidemiology of PBC (see Table 1.1).[3, 17, 18] PBC is considered to be most prevalent in England and Scandinavia; it is rarely reported in Africa and Asia. However, comparisons in incidence and prevalence rates across studies are hampered by the identification of small numbers of patients and methodological flaws in some studies, poorly defined patient populations, non-uniform case definitions, and uncertainty in defining the date of diagnosis, thus making a distinction between incidence and prevalence unclear. Moreover, studies that attempt to identify a change in PBC incidence over time cannot exclude the potential bias of growing disease awareness and testing among health care providers. Similarly, studies identifying an increase in prevalence rates may be confounded by differing methods of case ascertainment, increased disease awareness leading to earlier diagnosis, and better survival due to improved medical treatment (e.g. UDCA and liver transplantation).[3, 17, 18]

Table 1.1: Summary of Population-Based Epidemiologic Studies of PBC

Location	Author (Year)	Case Finding (n)	Diagnostic Criteria	Incidence (Per 10^6)	Prevalence (Per 10^6)	Gender Ratio (F:M)
England						
Sheffield, UK	Triger (1980)[19]	PS, lab reports (34)	AMA+ and LFTs or histology	5.8	54	16:1
Dundee, UK	Hislop (1981)[20]	Liver histology (21)	AMA+ and histology	10.6	40.2	10:1
Newcastle, UK	Hamlyn (1983)[21]	Registers, lab reports, death certificates (117)	AMA+, LFTs and histology	10	37-144	14:1
Newcastle, UK	Metcalf (1997)[17]	PS, registers, lab reports, death certificates (160)	AMA+, LFTs and histology	43	392	9.5:1
Northern UK	Myszor (1990)[22]	PS, registers, lab reports (347)	AMA+ and LFTs or histology	19	129-154	9:1
Scandinavia						
Malmoe, Sweden	Erikksson (1984)[23]	PS, lab reports, death certificates (33)	AMA+, LFTs and histology	4-24	28-92	3:1
Orobro, Sweden	Lofgren (1985)[24]	Lab reports (18)	AMA+, LFTs and histology	14	128	3.5:1
Umea, Sweden	Danielsson (1990)[25]	PS, registers, lab reports, death certificates (111)	Histology	13	151	6:1
Oslo, Norway	Boberg (1998)[26]	Registers (21)	AMA+, LFTs and histology	16	146	3.2:1
Other Europe						
Western Europe	Triger (1984)[27]	PS (569)	Non-uniform	4	23 (5-75)	10:1
Glasgow, Scotland	Goudie (1987)[28]	Lab reports (373)	AMA+ and histology	11-15	70-93	N/A
Estonia	Remmel (1995)[29]	PS, registers, lab reports (69)	AMA+, LFTs and histology	2.3	26.9	22:1
Australia						
Victoria, Australia	Watson (1995)[30]	PS, registers (84)	AMA+, LFTs and histology	N/A	19.1	11:1
Victoria, Australia	Sood (2004)[31]	PS, registers, lab reports (249)	AMA+, LFTs and histology	N/A	51	11:1
North America						
Ontario, Canada	Witt-Sullivan (1990)[32]	PS (225)	AMA+ and histology	3.3	22.4	13:1
Quebec, Canada	Villeneuve (1991)[33]	Register (228)	AMA+, LFTs and/or histology	3.9	25.4	10:1
Olmsted Cty., US	Kim (2000)[34]	Registers, lab reports, liver histology (46)	LFTs and AMA+ or histology	27	402	8:1
Alaska, USA	Hurlburt (2002)[35]	Registers (18)	AMA+, LFTs and histology	N/A	160	18:0

Adapted from Selmi *et al.*[3] AMA+, anti-mitochondrial antibody positive; LFTs, abnormal liver biochemistry; NA, not available; PS, physician survey

Many of the published epidemiologic studies of PBC have emerged from England.[19-22, 36, 37] A 1980 study from Sheffield was important because it was the first well-designed study to suggest a link between PBC and an environmental factor.[19] In this study, Triger *et al.* identified cases of PBC over a 3-year interval (1976-1979) via physician surveys and a search of laboratory results. Diagnostic criteria included AMA-positivity and either compatible liver histology or abnormal liver biochemistry. The authors identified 34 cases, corresponding to an annual incidence and prevalence of 5.8 and 54 per million, respectively. Interestingly, a cluster of cases sharing the same water supply was identified; the prevalence of cases receiving water from this reservoir was approximately 10-times higher than observed elsewhere. Although these findings suggest a potential waterborne source of PBC, the reservoir was analyzed and no significant toxins were found. In a subsequent study employing formal geographical analysis,[37] Prince *et al.* identified an uneven distribution of PBC in Northeast England, again suggesting an environmental risk factor for PBC pathogenesis.

Studies conducted in the Newcastle-upon-Tyne area of England have reported some of the highest prevalence rates of PBC.[21, 36] In the first study conducted in 1983,[21] Hamlyn *et al.* reported an annual incidence of 10 per million and prevalence varying from 37 to 144 per million in rural and industrial urban areas, respectively. In an update from 1997,[36] despite using a stricter case definition, Metcalf *et al.* reported an annual incidence and prevalence of 22 and 240 per

million, respectively, suggesting an increase in disease burden. However, as previously stated, confounding factors such as increasing awareness and improved prognosis cannot be excluded.

Rates of PBC reported in Scandinavian epidemiologic studies are comparable to those reported from England.[23-26] For example, in a population-based study from Norway between 1986 and 1995,[26] the mean annual incidence of PBC was 16.2 per million; the prevalence was 146 per million. Similar rates have been reported in studies from Sweden.[23-25] In a study from Australia,[31] the prevalence of PBC in 2002 was 51 cases per million, more than 2.5-times higher than that reported in 1991 by the same investigators.[30] The more recent study employed more rigorous case-finding methods including physician surveys; and review of a liver transplant database, medical records at major teaching hospitals, and a laboratory database for AMA results. This may explain the increase in prevalence observed in the recent study.

The epidemiology of PBC in North America is less well described at least partly due to difficulties in case ascertainment. Thus far, only four population-based studies have been published.[32-35] In a study from Olmsted County, Minnesota,[34] Kim *et al.* identified 46 cases of PBC over a 20-year interval (1975-1995). Cases were identified using the Rochester Epidemiology Project administrative database for a diagnosis of PBC, and histopathology and laboratory databases for compatible liver biopsies and AMA results. In this study, the overall age- and

sex-adjusted incidence was 27 per million and prevalence was 402 cases per million, among the highest rates ever reported. The incidence was stable over time. This study is limited by the small number of cases and potential selection bias due to the well known expertise in cholestatic liver diseases at the Mayo Clinic, the main providers of gastroenterology care in this region. In the second American study,[35] Hurlbut *et al.* described the epidemiology of PBC in Alaskan natives, an admittedly selected population. Between 1984 and 2000, 18 patients were diagnosed with PBC, corresponding to a prevalence of 160 per million.

Only two studies have described the epidemiology of PBC in Canada. In the first,[32] Witt-Sullivan *et al.* reported an incidence of AMA-positive, biopsy-proven PBC in 1987 of 3.26 per million; the prevalence was 22.39 per million. These figures are much lower than typically reported likely due to: 1) incomplete physician response to the survey (87%); 2) poor sensitivity of physician reporting for case finding (i.e. reliance on memory of names); and 3) the strict case definition employed by the authors (i.e. requirement for histological confirmation of PBC diagnosis). Other limitations include the reliance on patient reports for defining the date of diagnosis and the failure to explicitly identify the population at risk. Findings in this study that warrant confirmation include an apparent increase in incidence during the study interval (1980-1987), and a lack of geographical clustering or racial predisposition to PBC. In the second Canadian study from Quebec,[33] Villeneuve and colleagues reported an incidence (between 1980 and 1986) and point prevalence (in 1986) of 3.9 and 25.4 cases per million,

respectively. Because this study was limited to PBC patients that had been hospitalized, it undoubtedly underestimated the true burden of this disease, which is predominantly one of outpatients. Both of these studies warrant updating using contemporary Canadian data.

Risk Factors for PBC

As observed in most autoimmune conditions, PBC is more common in females. In population-based studies, females outnumber males on average 9:1 (see Table 1.1).[3, 17, 18] Although the reason for this gender discrepancy is unclear, female sex hormones may augment the risk of PBC by modulation of the immune system.[38] In addition to female gender, a genetic predisposition to PBC has been shown; PBC appears to be more common in people who have a family history of the disease. In studies from many countries, between 1-6% of PBC patients had a family member with the disease.[39-43] Family members of PBC patients have up to a 100-fold higher risk of developing PBC. The concordance rate in monozygotic twins is 63%.[44, 45] Although all of these findings support a genetic predisposition to PBC, definitive evidence for a specific genetic allele has not been reported.[46]

Other factors that have been proposed to increase the risk of PBC include the presence of other autoimmune conditions,[47] gravidity,[48] and lifestyle factors such as smoking[49] and dietary fat intake.[50] A significant association between PBC and

previous tonsillectomy, chronic bronchitis, and vaginal or urinary tract infection has been reported in some,[51] but not all,[49] studies. The common link between these risks is the potential role of infectious agents (e.g. *Escherichia coli, Chlamydia pneumoniae,* human betaretrovirus) in PBC pathogenesis due to "molecular mimicry".[52-54] Finally, exposure to chemical compounds such as hydrocarbons from toxic waste sites[55] and air pollution[18] may increase the risk of PBC.

Liver-Related Outcomes in PBC

PBC has a highly variable natural history, with some patients requiring liver transplantation within months of diagnosis and others remaining asymptomatic for decades.[10, 11] Although early reports from tertiary referral centers suggested a poor prognosis, more recent studies are more optimistic, likely due to the diagnosis of patients at an earlier stage with the widespread availability of AMA testing. For example, in a recent study by Prince *et al.*,[56] the natural history of a population-based cohort of 770 patients with PBC from Northern England was described. Median survival was 9.3 years after the diagnosis and mortality was nearly 3-times higher than expected based on the general population. Forty-two percent of deaths were liver-related. Within 10 years of diagnosis, 26% of patients developed liver failure and 5% underwent liver transplantation within the study period. In three large European studies including over 750 patients, 10-year survival rates of 71% to 92% were reported.[57-59] Improved survival in the

latter studies likely reflects their restriction to patients treated with UDCA and their more recent recruitment periods.

Multiple studies have examined predictors of survival in patients with PBC. A widely used model was developed by the Mayo Clinic investigators[60] and validated in multiple settings including population-based cohorts.[34, 56, 61-63] In this model, independent predictors of mortality without transplantation include advanced age, presence of edema, lower albumin levels, and higher prothrombin times and bilirubin levels.[60] In the Prince *et al.* study,[56] independent predictors were age and levels of bilirubin, alkaline phosphatase and albumin. Other studies have shown improved survival in asymptomatic patients,[64-66] those with minimal fibrosis,[57-59, 66-69] and patients treated with UDCA.[13, 70]

Administrative Databases in Health Services Research

Administrative databases are increasingly used in studies of outcomes, effectiveness, and health care utilization in a variety of fields including liver disease research.[71-79] Their availability and readiness to be analyzed, broad geographic coverage, and relatively complete capture of health care encounters, are important advantages over other data sources.[71] With the widespread use of administrative data, their accuracy and completeness is paramount such that valid conclusions can be drawn.[80] Administrative data have been validated using different methodologies in multiple fields.[81-84] However, information is limited

regarding the accuracy of administrative data in liver-related research. In one study,[85] Karam *et al.* assessed the quality of the European Liver Transplant Registry (ELTR) via a chart audit of 734 files from 21 participating centers. The authors reported rates of ELTR incompleteness and inconsistency ≤ 5% and kappa values ≥ 0.81 for all variables, including the underlying diagnosis necessitating liver transplantation. However, some items, including cause of death or graft failure and patient outcome, were targeted for improvement. In another study employing administrative data from the Calgary Health Region (CHR),[86] Myers and colleagues derived coding algorithms for acetaminophen-related hepatotoxicity and acute liver failure that were highly accurate (c-statistics 0.87 and 0.88, respectively), and subsequently used in a natural history study of this condition.[77] Finally, Steinke *et al.* derived diagnostic algorithms based on data from multiple sources (e.g. hospital discharge, laboratory, and medication databases) to classify subjects with liver disease in Tayside, Scotland.[87] In this study, agreement between the electronic and clinical diagnoses was 98%, thus validating the information contained within the electronic databases. For PBC specifically, 17 of 24 suspected cases (71%) according to the algorithm truly had PBC. While several other studies have used administrative databases to identify patients with PBC, to our knowledge, only one has specifically reported on the validity of this case-finding approach.[33] In this study by Villeneuve and colleagues, the charts of 648 patients who had a diagnosis code for PBC in a hospitalization database were reviewed. Of these patients, only 257 (40%) had definite or probable PBC according to standard definitions.[7] Clearly, refinement

of this approach to PBC case ascertainment using administrative data is necessary.

RESEARCH OBJECTIVES

The primary objective of this research was to determine the validity of a diagnosis of PBC based on administrative data. As secondary objectives, we aimed to describe the epidemiology and outcomes of PBC in a well-defined Canadian population (the CHR) using administrative data. To achieve these goals, we employed a framework consisting of the following series of questions that form the basis of this thesis:

1) Is administrative data valid for the identification of patients with PBC?
2) What are the incidence and prevalence of PBC in the CHR? Has the epidemiology of PBC changed between 1996 and 2002?
3) What is the natural history of PBC in the CHR?

CHAPTER TWO

IS ADMINISTRATIVE DATA VALID FOR THE IDENTIFICATION OF PATIENTS WITH PBC?

INTRODUCTION

Administrative databases are ubiquitous and used in all areas of health care financing and delivery. Health care providers, policy-makers, and payers use administrative data for reimbursement, budgetary planning, monitoring clinical activities, measuring the quality of care, and health services research.[71, 88] The critical variable in all of these applications is the patient diagnosis, typically recorded using the International Classification of Diseases (ICD) Ninth Revision, Clinical Modification (ICD-9-CM)[89] or Tenth Revision (ICD-10)[90] coding systems. This data can be used to identify specific patient cohorts and assess disease epidemiology, risk factors, and clinical outcomes. Clearly, the accuracy and completeness of diagnoses within administrative databases is vital to reaching valid conclusions.[80] As such, the validation of administrative data has been the focus of numerous investigations, typically via audits of medical records.[86, 91-102] The results of validation studies have varied depending on the type of administrative data (eg. inpatient versus outpatient and diagnostic versus procedural), the specific disease area and codes used for case identification, and underlying disease severity.[80]

Administrative databases have been used in numerous studies to help identify patients with PBC,[21, 22, 25, 26, 29-31, 33-36] but their accuracy has not been rigorously evaluated. In the majority of these reports, multiple additional case-finding approaches have been utilized including physician surveys, transplant registries, death certificates, liver histology databases, and laboratory reports for positive AMA serology. Although such multifaceted approaches to case ascertainment may have improved sensitivity compared with administrative data alone, the added complexity, time, and cost may not be justified. Moreover, administrative databases have several advantages over these alternative data sources including their broad geographic coverage, relatively complete capture of health care encounters, and limited expense.[71] In addition, because administrative databases are ubiquitous, they may facilitate comparisons of PBC between regions in which the availability of these other data sources may vary. In order to embark on such studies, the accuracy of a PBC diagnosis based on administrative data must be confirmed.

Therefore, the objectives of our study were: 1) to determine the validity of ICD-9-CM and ICD-10 diagnosis codes for PBC using three population-based administrative databases; and 2) to derive accurate coding definitions for the identification of PBC patients for use in future studies that describe the epidemiology and natural history of this condition.

METHODS

Data Sources

This study utilized administrative data to identify potential cases of PBC in the CHR between fiscal years 1994 to 2002 (April 1, 1994 to March 31, 2003). The CHR is one of the largest fully integrated, publicly funded health care systems in Canada. The CHR provides all medical and surgical care to residents of Calgary and surrounding communities in southern Alberta (population ~1.1 million in 2002). Included within the region are 12 academic and community hospitals, including four large hospitals within the city of Calgary. Three databases were utilized to identify potential PBC cases:[103]

1. *Physician Claims Database.* This database records claims submitted for payment by Alberta physicians for services provided to registrants of the Alberta Health Care Insurance Plan (AHCIP). Approximately 4,500 providers submit over 36 million claims annually.[103] Each record in the database includes up to three diagnosis fields, the date of service, and the specialty of the care provider.
2. *Inpatient Discharge Abstract Database (DAD).* The Inpatient DAD contains patient demographic, diagnosis, procedure, and mortality information on all discharges from hospitals within the CHR. This data is routinely transmitted to the Canadian Institute for Health Information for aggregation with nationwide hospitalization data.[103] Chart validation studies have shown rates of agreement exceeding 95% for demographic data and 75-96% for most responsible diagnosis codes.[104]

3. *Ambulatory Care Classification System (ACCS) Database.* This database contains information on facility-based ambulatory care including clinic and emergency department visits, same-day surgery, day procedures, and rehabilitation services. Data is available from fiscal year 1996 onwards.[103]

These databases have been used to examine the epidemiology,[79, 105, 106] outcomes,[77, 107-109] and coding accuracy[86, 93-96] of a variety of medical conditions. The data was provided by the Health System Analysis Unit of the Quality, Safety and Health Information portfolio of the CHR. Studies such as those described in this thesis are important because they facilitate our understanding of disease burden and natural history and may help improve outcomes among CHR patients. To protect patient privacy, personal identifiers were removed from the datasets after linkage of the administrative and medical record data (see below), and only aggregate statistics are reported. Moreover, we did not have access to physician identifiers in the administrative data. Finally, only Dr. Myers and his data analyst had access to individual patient data.

Study Population

The administrative database population included adult patients (≥ 20 years old) with at least one health care encounter in which an ICD-9-CM (571.6) or ICD-10 diagnosis code for PBC (K74.3) was recorded during the study interval.[89, 90] Whereas the ICD-10 code is specific to PBC, the ICD-9-CM code also codes for "biliary cirrhosis". Therefore, this code may misclassify cases of secondary biliary

cirrhosis (e.g. that due to biliary strictures) as PBC. Date of birth and gender were extracted from the AHCIP Registry, which contains demographic details on the over 99% of Alberta residents who participate in this government-administered universal health care plan.[103]

To facilitate calculations of the sensitivity of the administrative data (see Statistical Analyses), we also included a cohort of 17 well-characterized PBC patients who participated in two clinical trials restricted to patients with PBC at the University of Calgary.[110, 111] All of these patients were female and diagnosed with PBC before or during the current study interval. Sixteen of the 17 patients (94%) had definite or probable PBC (see Case Definitions for PBC in Medical Records). The remaining patient, who relocated to the CHR after being diagnosed with PBC by a hepatologist, was classified as having suspected PBC because the diagnostic details could not be obtained.

Validation Study

The validation component of the study was designed to develop coding algorithms for the diagnosis of PBC using administrative data. The personal health number (PHN), a unique patient identifier captured in the administrative databases, was used to identify medical records for this part of the study. These records included the outpatient charts of all hepatologists and gastroenterologists practicing at the University of Calgary Medical Clinic. Due to the rarity of PBC and the potential requirement for liver transplantation, most patients are referred

to a hepatologist at some point during their disease. All hepatologists within the CHR practice at this clinic. We also reviewed the inpatient medical records of cases from each of the three adult, acute care hospitals in Calgary (Foothills Medical Centre, Rockyview General Hospital, and the Peter Lougheed Hospital). Medical records were reviewed by a trained physician.

Case Definitions for PBC in Medical Records

Using data obtained from the review of medical records, the strength of each PBC diagnosis from the administrative data was graded as definite, probable, suspected, not PBC, or unconfirmed. A diagnosis of PBC was considered definite when all three of the following criteria were met: 1) cholestatic liver biochemistry (i.e. raised serum alkaline phosphatase and/or gamma-glutamyl-transpeptidase concentration); 2) AMA positivity with a titer ≥ 1:40, and/or positivity for antibodies against the pyruvate dehydrogenase complex (anti-PDC);[6, 112, 113] and 3) compatible liver histology.[114] Probable PBC was defined when any two of these criteria were met. Since it is widely accepted that fulfillment of at least two of these criteria is pathognomonic of PBC,[7, 31] our primary outcome measure was definite or probable PBC. As previously described,[115] the date of diagnosis was defined as the earliest date at which the patient was found to have fulfilled any two of these three diagnostic criteria.

A PBC diagnosis was considered suspected if any physician note (eg. admission history, progress note, discharge summary) stated that a patient had PBC.

Although not a rigorous definition, we hypothesized that misclassification would be minimal due to the rarity and specialized nature of this disease. We assumed that patients would be unlikely to state that they had PBC unless truly afflicted with this condition due to a lack of general awareness about its existence. Similarly, a physician would be unlikely to record this condition if he/she were uncertain of the diagnosis. Therefore, as a secondary outcome measure, we considered the presence of definite, probable, or suspected PBC. A diagnosis was considered not PBC if there was clear evidence according to conventional criteria of an alternative hepatic condition. Finally, a diagnosis was considered unconfirmed if we lacked sufficient data to assign a particular liver-related diagnosis.

Administrative Data Coding Definitions

A variety of administrative data coding definitions were examined as predictors of a diagnosis of PBC. We utilized data from all three of the databases combined and individually over the entire study interval. For the Inpatient DAD and ACCS databases, we considered the presence of at least one and at least two encounters with a code for PBC. Since professional health records coders input these data, we assumed that misclassification would be minimal. For the Physician Claims database, the following case definitions were examined:

1) At least one claim by any physician;
2) At least one claim by a general practitioner (GP);
3) At least one claim by a specialist;

4) At least two claims (≥ 2, ≥ 3, ≥ 4, and ≥ 5) by any physician;
5) At least one claim by a GP and at least one claim by a specialist; and
6) At least two claims by a GP and at least two claims by a specialist.

Since PBC is an uncommon disorder and these patients are typically diagnosed and cared for by specialists, we hypothesized that specialists would be more accurate than GPs in coding for this condition. Moreover, since PBC is a chronic disease, we hypothesized that multiple uses of the code(s) over a prolonged period of time would be associated with greater validity of the administrative data. Therefore, sensitivity analyses were conducted to determine the effect of the interval between the first and second health care contact (within 1, 2, and 3 years). Finally, since PBC affects predominantly females, sensitivity analyses were conducted according to gender.

Statistical Analyses

Using data obtained from medical records as the gold standard, the positive predictive values (PPVs) (with exact binomial confidence intervals [CI]) of these administrative data coding definitions for the diagnosis of PBC were calculated. Due to the absence of an unselected control group, specificities and negative predictive values could not be determined. However, the sensitivities of these definitions were calculated using the aforementioned cohort of 17 PBC patients who participated in clinical trials at the University of Calgary (see Study Population).[110, 111]

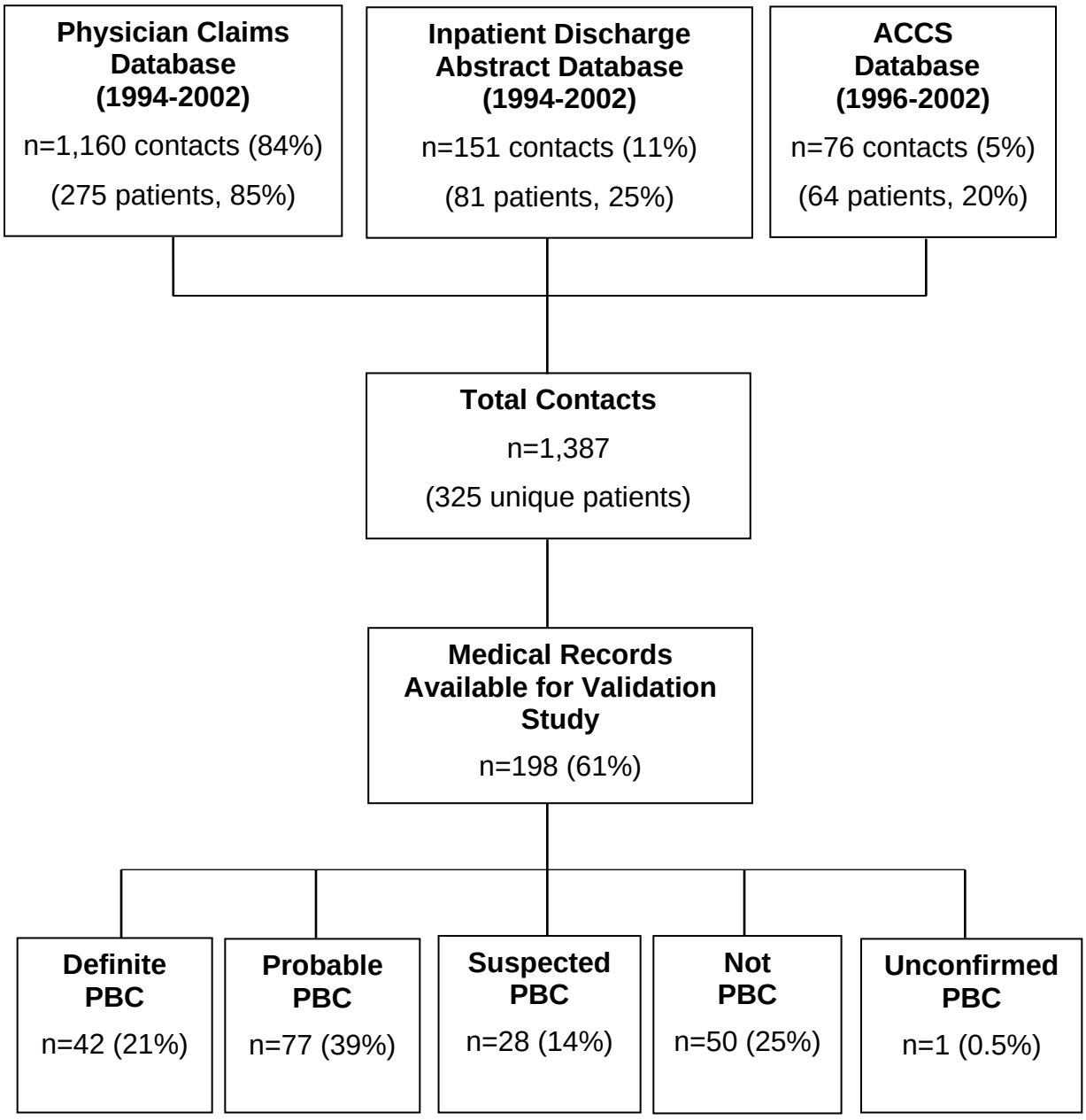
Descriptive statistical methods were used to describe the characteristics of the study cohort. Comparisons between groups were made using Fisher's exact and chi-square tests for categorical variables, and Mann-Whitney and Kruskal-Wallis rank tests for continuous variables. Statistical analyses were performed using Stata/IC 10.0 (StataCorp, College Station, TX) and SAS 9.1.3 (SAS Institute, Carey, NC) software. The study protocol was approved by the Conjoint Health Research Ethics Board of the University of Calgary (see Appendix A).

RESULTS

Study Population

Between April 1, 1994 and March 31, 2003, there were 1,387 "hits" in the administrative data (herein referred to as "contacts") including a diagnosis code for PBC among 325 unique individuals. A flow chart demonstrating the derivation of the study population is available in Figure 2.1. The majority of these contacts (84%) were identified from the Physician Claims database. Of the 325 unique patients, the medical records of 198 (61%) were available for review. According to our PBC case definitions, 21% of these patients had definite PBC, 39% had probable PBC, 14% had suspected PBC, and in one case (0.5%), a hepatic diagnosis could not be established ("unconfirmed PBC"). Fifty patients (25%) had a liver condition other than PBC.

Figure 2.1: Flow Diagram Illustrating Derivation of the Study Population



The etiologies of liver disease in patients with hepatic conditions other than PBC are listed in Table 2.1. The most frequently misclassified diseases were (PSC) (28%) and autoimmune hepatitis (AIH) (20%). One patient (2%) had a PSC/AIH overlap syndrome. Most PSC cases were male (87%) versus only 9% of those with definite or probable PBC ($P<0.00005$). The proportion of patients under the age of 40 years was also higher among patients with PSC (33% vs. 14%; $P=0.07$). The sex ($P=0.38$) and age distributions ($P=0.10$) of AIH and definite or probable PBC cases did not differ significantly. Secondary biliary cirrhosis, which is identified using the same ICD-9-CM code as PBC, accounted for 10% of false positive cases.

Table 2.1: Etiology of Liver Disease in Patients Misclassified with PBC According to the Administrative Data (n=50)

Etiology of Liver Disease	Number of Cases	%
Primary sclerosing cholangitis (PSC)	14	28
Autoimmune hepatitis (AIH)	10	20
PSC-AIH overlap syndrome	1	2
Secondary biliary cirrhosis	5	10
Hepatitis C (with cirrhosis)	5 (4)	10 (8)
Alcoholic cirrhosis	4	8
Cryptogenic cirrhosis	4	8
Idiopathic adulthood ductopenia	1	2
Chronic pancreatitis	1	2
Nonalcoholic fatty liver disease	1	2
Wilson disease	1	2
Other	3	6

Characteristics of the Study Population

Demographic characteristics and details of the administrative data according to disease classification are outlined in Table 2.2. The single patient with "unconfirmed PBC" has been excluded from this table for ease of presentation.

Table 2.2: Characteristics of the Study Population

Characteristics	Definite or Probable PBC (n=119)	Suspected PBC (n=28)	Not PBC (n=50)	*P*-value
Demographic characteristics				
Female gender	91% (108)	82% (23)	50% (25)	<0.0005
Age, *years*				
At first contact	52 (44-63)	57 (49-72)	50 (42-63)	0.04
20-39 years	14% (17)	4% (1)	20% (10)	<0.0005
40-59 years	50% (60)	50% (14)	52% (26)	
60-79 years	34% (40)	36% (10)	24% (12)	
≥ 80 years	2% (2)	11% (3)	4% (2)	
Administrative data coding details				
Total PBC contacts	4 (2-8)	4 (2-8)	2 (1-4)	0.0001
≥ 2 contacts	82% (98)	79% (22)	30% (15)	0.0001
Total PBC claims	3 (2-6)	3 (1-5)	1 (1-1)	0.0001
Total inpatient PBC contacts	0 (0-0)	1 (0-2)	0 (0-0)	0.0001
Total ACCS PBC contacts	0 (0-1)	0 (0-0)	0 (0-0)	0.07

All data are median (IQR) or proportions (%, n).

Compared with patients with definite or probable PBC (n=119), those with alternative liver conditions (n=50) were more likely to be male and slightly

younger at the first use of a PBC code. Importantly, among 7 male patients under the age of 40 years – in whom PBC is uncommon - six (86%) had conditions other than PBC (PSC [n=4]; PSC/AIH [n=1], AIH [n=1]). On the contrary, among 21 females in this age group, 17 patients (81%) had definite, probable, or suspected PBC. Compared with patients with definite or probable PBC, those with other hepatic diagnoses had fewer total PBC contacts, physician claims, and inpatient contacts for PBC.

In patients with definite or probable PBC, the median age at diagnosis was 51 years (interquartile range [IQR] 43-61) and 91% were female. The majority (79%) of these patients were AMA-positive with a median titer of 1:640 (IQR 1:160-1:640). An additional 9 patients (8% of those with definite or probable PBC) were anti-PDC positive (E2-positive, n=9; X-positive, n=4). The median (IQR) serum alkaline phosphatase, alanine aminotransferase, and total bilirubin concentrations at diagnosis were 268 U/L (176-373), 67 U/L (45-100), and 11 umol/L (7-15), respectively. In 60 patients (50%), the diagnosis of PBC was confirmed with liver biopsy.

Validity of Administrative Data for the Diagnosis of Definite or Probable PBC

Of the 198 patients identified in the validation study with at least one contact for PBC, 119 were confirmed to have definite or probable PBC (PPV 60%; 95% CI 53-67%). This definition was 94% sensitive (95% CI 71-100%) in identifying the 17 PBC clinical trial patients. The median delay between the diagnosis of PBC in definite or probable cases and the first contact in the administrative data was 54 days (IQR, 0 to 309 days). The PPV of the administrative data increased and the sensitivity decreased as the number of contacts necessary to confirm a diagnosis of PBC increased (Table 2.3). The optimal definition when all three databases were combined required at least two health care contacts for PBC (PPV 73% [95% CI 61-75%]; sensitivity 94% [95% CI 71-100%]). The PPV of this definition (and the remainder) was much higher in females than males (78% vs. 40%; *P*=0.0009). If male patients under the age of 40 years with at least two contacts (n=3) – all of whom had PSC - were removed from the analysis due to the rarity of PBC in this subgroup, the PPV was 74% (98/132; 95% CI 66-81%). The sensitivity was unchanged. The PPV of this definition was higher during the later years of the study period (1994-1996: 61% vs. 1997-1999: 66% vs. 2000-2002: 90%; *P*=0.004).

Since the majority of health care contacts were identified using the Physician Claims database, the PPV of the optimal definition in this database was similar to that of all three databases combined (75%; 95% CI 66-82%). However, the

sensitivity was slightly lower (88%; 95% CI 64-99%). As illustrated in Table 2.3, coding by GPs was much less sensitive than that of specialists (18% vs. 82%; *P*=0.0004), but the PPVs were similar (73% vs. 66%; *P*=0.51). Although the PPVs in the ACCS database were similar (74%-78%) to those of the optimal definition from all three databases, the sensitivities were much poorer (6-24%). Similarly, the Inpatient database was insensitive and had a maximum PPV of 51%.

Table 2.3: Operating Characteristics of Coding Algorithms for Definite or Probable PBC

Data Source and Diagnostic Criterion	PPV Overall % (95% CI), (n)	PPV Females % (95% CI), (n)	PPV Males % (95% CI), (n)	Sensitivity for PBC Trial Patients % (95% CI), (n)
All databases				
≥ 1 contact	60 (53-67), (119/198)	69 (61-76), (108/157)	27 (14-43), (11/41)	94 (71-100), (16/17)
≥ 2 contacts	73 (61-75), (98/135)	78 (70-85), (90/115)	40 (19-64), (8/20)	94 (71-100), (16/17)
≥ 3 contacts	73 (64-81) (79/108)	79 (70-87), (73/92)	38 (15-65), (6/16)	71 (44-90), (12/17)
≥ 4 contacts	72 (61-81), (61/85)	79 (68-88), (57/72)	31 (9.1-61), (4/13)	65 (33-82), (10/17)
≥ 5 contacts	75 (63-85), (48/64)	82 (69-91), (44/54)	40 (12-74), (4/10)	47 (23-72), (8/17)
Physician Claims database				
≥ 1 claim	64 (56-71), (109/171)	74 (65-81), (100/136)	26 (13-43), (9/35)	88 (64-99), (15/17)
≥ 1 GP claim	73 (52-88), (19/26)	90 (68-99), (18/20)	17 (0.4-64), (1/6)	18 (3.8-43), (3/17)
≥ 1 specialist claim	66 (58-73), (107/163)	74 (65-81), (98/133)	30 (15-49), (9/30)	82 (57-96), (14/17)
≥ 2 claims	75 (66-82), (91/122)	79 (71-87), (85/107)	40 (16-68), (6/15)	88 (64-99), (15/17)
≥ 3 claims	75 (65-84), (70/93)	82 (72-90), (65/79)	36 (13-65), (5/14)	71 (44-90), (12/17)
≥ 4 claims	73 (61-83), (51/70)	81 (69-90), (47/58)	33 (10-65), (4/12)	53 (28-77), (9/17)
≥ 5 claims	78 (64-88), (42/54)	85 (71-94), (39/46)	38 (8.5-76), (3/8)	41 (18-67), (7/17)
≥ 1 GP & ≥ 1 specialist claims	94 (73-100), (17/18)	94 (71-100), (16/17)	100 (2.5-100), (1/1)	12 (1.5-36), (2/17)
≥ 2 GP & ≥ 2 specialist claims	89 (52-100), (8/9)	88 (47-100), (7/8)	100 (2.5-100), (1/1)	0 (0.1-9.5), (0/17)
Inpatient database				
≥ 1 inpatient contact	51 (37-64), (29/57)	55 (39-70), (24/44)	39 (14-68), (5/13)	5.9 (0.1-29), (1/17)
≥ 2 inpatient contacts	48 (26-70), (10/21)	60 (32-84), (9/15)	17 (0.4-64), (1/6)	5.9 (0.1-29), (1/17)
ACCS database				
≥ 1 ACCS contact	74 (58-86), (31/42)	77 (60-90), (27/35)	57 (18-90), (4/7)	24 (6.8-50), (4/17)
≥ 2 ACCS contacts	78 (40-97), (7/9)	83 (36-100), (5/6)	67 (9.4-99), (2/3)	5.9 (0.1-29), (1/17)

ACCS, Ambulatory Care Classification System; CI, confidence interval; GP, general practitioner; PPV, positive predictive value.

Validity of Administrative Data for the Diagnosis of Definite, Probable, or Suspected PBC

Table 2.4 includes the operating characteristics of the same coding definitions for the identification of patients with definite, probable, or suspected PBC (n=147). As described above, the definition requiring at least two contacts from any of the three databases was optimal with respect to the balance between PPV (89%; 95% CI 82-94%) and sensitivity (94%; 95% CI 71-100%). For this case definition, the PPVs among females and males were 94% (95% CI 88-98%) and 60% (36-81%), respectively (*P*=0.0002). Exclusion of males under 40 years of age yielded a PPV of 91% (120/132; 95% CI 85-95%). The remainder of the analyses paralleled those described for the diagnosis of definite or probable PBC although all PPVs were higher for this less stringent case definition.

Table 2.4: Operating Characteristics of Coding Algorithms for Definite, Probable, or Suspected PBC

Data Source and Diagnostic Criterion	PPV Overall % (95% CI), (n)	PPV Females % (95% CI), (n)	PPV Males % (95% CI), (n)	Sensitivity for PBC Trial Patients % (95% CI), (n)
All databases				
≥ 1 contact	74 (68-80), (147/198)	83 (77-89), (131/157)	39 (24-56), (16/41)	94 (71-100), (16/17)
≥ 2 contacts	89 (82-94), (120/135)	94 (88-98), (108/115)	60 (36-81), (12/20)	94 (71-100), (16/17)
≥ 3 contacts	90 (83-95), (97/108)	95 (88-98), (87/92)	63 (35-85), (10/16)	71 (44-90), (12/17)
≥ 4 contacts	91 (82-96), (77/85)	96 (88-99), (69/72)	62 (32-86), (8/13)	65 (33-82), (10/17)
≥ 5 contacts	95 (87-99), (61/64)	100 (93-100), (54/54)	70 (35-93), (7/10)	47 (23-72), (8/17)
Physician Claims database				
≥ 1 claim	77 (70-83), (132/171)	88 (81-93), (119/136)	37 (22-55), (13/35)	88 (64-99), (15/17)
≥ 1 GP claim	77 (56-91), (20/26)	95 (75-100), (19/20)	17 (0.4-64), (1/6)	18 (3.8-43), (3/17)
≥ 1 specialist claim	80 (73-86), (130/163)	88 (81-93), (117/133)	43 (26-63), (13/30)	82 (57-96), (14/17)
≥ 2 claims	90 (83-95), (110/122)	94 (88-98), (101/107)	60 (32-84), (9/15)	88 (64-99), (15/17)
≥ 3 claims	90 (82-96), (84/93)	96 (89-99), (76/79)	57 (29-82), (8/14)	71 (44-90), (12/17)
≥ 4 claims	90 (81-96), (63/70)	97 (71-91), (56/68)	58 (28-85), (7/12)	53 (28-77), (9/17)
≥ 5 claims	94 (85-99), (51/54)	100 (92-100), (46/46)	63 (24.5-92), (5/8)	41 (18-67), (7/17)
≥ 1 GP & ≥ 1 specialist claims	100 (82-100), (18/18)	100 (81-100), (17/17)	100 (2.5-100), (1/1)	12 (1.5-36), (2/17)
≥ 2 GP & ≥ 2 specialist claims	100 (66-100), (9/9)	100 (63-100), (8/8)	100 (2.5-100), (1/1)	0 (0.1-9.5), (0/17)
Inpatient database				
≥ 1 inpatient contact	81 (68-90), (46/57)	84 (70-93), (37/44)	69 (39-91), (9/13)	5.9 (0.1-29), (1/17)
≥ 2 inpatient contacts	86 (64-97), (18/21)	93 (68-100), (14/15)	67 (22-96), (4/6)	5.9 (0.1-29), (1/17)
ACCS database				
≥ 1 ACCS contact	88 (74-96), (37/42)	91 (77-98), (32/35)	71 (29-96), (5/7)	24 (6.8-50), (4/17)
≥ 2 ACCS contacts	89 (52-100), (8/9)	100 (54-100), (6/6)	67 (9.4-99), (2/3)	5.9 (0.1-29), (1/17)

ACCS, Ambulatory Care Classification System; CI, confidence interval; GP, general practitioner; PPV, positive predictive value.

Sensitivity Analysis of the Diagnostic Definitions for PBC According to the Time Interval between Contacts

As illustrated in Table 2.5, the PPVs of the diagnostic definitions requiring at least two heath care contacts for PBC did not change significantly (72-74%) according to the interval between the first and second contact. However, restricting the analyses to patients with the first and second contact within the same year led to a substantial reduction in sensitivity (from 94% to 71% with all three databases combined, and from 88% to 71% with the Physician Claims database). These data suggest that more than one year of administrative data is necessary to maximize the identification of PBC patients.

Table 2.5: Sensitivity Analysis of Diagnostic Definitions for PBC According to the Time Interval between First and Second Contacts in the Administrative Data

Data Source and Interval between Contacts	n	Definite or Probable PBC PPV % (95% CI), (n)	Definite, Probable, or Suspected PBC PPV % (95% CI), (n)	Sensitivity for PBC Trial Patients % (95% CI), (n)
All databases				
Within 1 year	112	72 (63-80), (81/112)	91 (84-96), (102/112)	71 (44-90), (12/17)
Within 2 years	129	73 (64-80), (94/129)	90 (83-95), (116/129)	94 (71-100), (16/17)
Within 3 years	133	72 (64-80), (96/133)	89 (82-94), (118/133)	94 (71-100), (16/17)
Physician Claims database				
Within 1 year	103	74 (64-82), (76/103)	90 (83-95), (93/103)	71 (44-90), (12/17)
Within 2 years	117	74 (66-82), (87/117)	91 (84-95), (106/117)	88 (64-99), (15/17)
Within 3 years	121	74 (66-81), (90/121)	90 (83-95), (109/121)	88 (64-99), (15/17)

CI, confidence interval; PPV, positive predictive value.

DISCUSSION

Our study demonstrates the feasibility of using administrative data to identify patients with PBC. Using three outpatient and inpatient administrative databases with 9 years of data, the optimal case definition required at least two health care contacts for PBC. This definition had a PPV of 73% for definite or probable PBC, and 89% for definite, probable, or suspected PBC. Its sensitivity in a well-characterized cohort of PBC patients who participated in clinical trials restricted to this disease was 94%. In our opinion, this degree of accuracy is sufficient to justify use of administrative data in future studies of this condition. To our knowledge, only one other study has examined the utility of administrative data for this purpose. In this study,[33] Villeneuve and colleagues used province-wide hospitalization data to describe the epidemiology and outcomes of PBC in Quebec. In total, the charts of 648 patients who had an ICD-9 code for PBC were reviewed, and of these, only 257 had definite or probable PBC according to our case definitions. The corresponding PPV (40%) is similar to the 51% that we observed in the Inpatient database. However, the poor sensitivity of this approach (6% in our study) reinforces the importance of using multiple data sources, particularly outpatient databases (see below).

We identified a broad spectrum of diseases that were misclassified as PBC when a single contact in the administrative data suggested this diagnosis (Table 2.1). As these false positive cases had a fewer number of contacts for PBC,

increasing the number required to establish a diagnosis reduced the frequency of misclassification, but at the expense of a significant loss in sensitivity. In terms of specific conditions, misclassification of secondary biliary cirrhosis was inevitable because it shares the same ICD-9-CM code as PBC. Since this disease is uncommon, we expect this cause of error to have a minimal impact on future studies of PBC that utilize this methodology. On the other hand, patients with PSC represented a sizable proportion of false positive cases (28% vs. 20% in Villeneuve *et al.*'s study).[33] This finding likely reflects a transcription error in some circumstances since the ICD-9-CM codes for these conditions are very similar (571.6 for PBC versus 576.1 for PSC). In addition, both are chronic disorders characterized by cholestatic liver biochemistry, symptoms including fatigue and pruritus, the frequent existence of autoantibodies, and in many cases, overlapping histological features.[9, 116] Finally, patients with coexisting PBC and PSC ("PBC/PSC overlap syndrome"),[117] including one from the CHR,[118] have been described. However, as confirmed by our results, the usual patient demographics in these diseases differ; whereas PBC affects predominantly middle-aged females, PSC is more common in young males. In fact, if male patients under 40 years with at least two health care contacts for PBC were excluded from our analyses due to the rarity of PBC in this subgroup, the PPVs of the optimal definition increased slightly (from 73% to 74% for definite or probable PBC, and from 89% to 91% for definite, probable, or suspected PBC). Exclusion of these patients did not affect an analysis of the epidemiology of PBC (see Chapter Three) due to the small number of affected patients. Twenty

percent of false positive cases were due to AIH. Both AIH and PBC are more common in females and often associated with autoantibodies (e.g. antinuclear and smooth muscle antibodies).[119] However, the typically “hepatitic” biochemical profile and liver histology of AIH assists in differentiating these disorders. Finally, we identified a single patient with a PSC-AIH overlap syndrome who had two contacts for PBC.[120] Since the appreciation of syndromes with overlapping features between autoimmune liver diseases (e.g. PBC, PSC, and AIH) is increasing,[121] the optimal means of identifying these patients using administrative data should be explored.

We conducted a variety of sensitivity and subgroup analyses in order to refine our use of administrative data for identifying PBC patients. Our results demonstrate the benefits of using multiple rather than single data sources. The majority of our patients (85%) was identified using the Physician Claims database, an anticipated finding considering the predominantly outpatient nature of this disease. Although the PPVs of the Claims database were similar to that of all three databases combined, its sensitivity for the 17 clinical trial patients was slightly lower (88% vs. 94%). Nevertheless, based on this diagnostic performance, it would be reasonable to use this type of database to identify PBC patients in situations where the other databases are unavailable. Although reasonable for studies of incidence and prevalence, this approach would not be appropriate for outcome studies in PBC (e.g. analyses of rates of hepatic failure)

because these events would require hospitalization data for identification. On the other hand, the operating characteristics of the Inpatient and ACCS databases, particularly their poor sensitivities (from 6-24% for definite or probable PBC), preclude their use in isolation for identifying PBC cases. This finding is not unexpected since the Inpatient database is most useful for detecting patients with complications of PBC (e.g. the minority who develop hepatic decompensation), or those hospitalized for non-liver related conditions in which PBC may fail to be recorded. Similarly, the major role of the ACCS database is identifying emergency department visits, expected to be uncommon in PBC, or day procedures such as liver biopsy and endoscopy, which play only a secondary role in the management of patients with PBC.

Since PBC is more common in females than males, we examined the performance of the coding algorithms according to gender. In these analyses, the PPVs were much higher in females. For example, for definite or probable PBC, the definition requiring at least two PBC contacts had a PPV of 78% in females versus only 40% in males (comparisons of sensitivity could not be calculated because all clinical trial patients were female). This gender-specific variation in PPVs is likely mediated by differences in disease prevalence. Specifically, since PBC is more common in women, the PPVs, which are prevalence-dependent, would be expected to be higher in this subgroup. On the contrary, many of the conditions that may be confused with PBC (e.g. PSC, hepatitis C, and alcoholic

cirrhosis) are more common in men than women. Thus, the probability of a diagnosis code for PBC being erroneously recorded would be expected to be higher in men, an effect that would lead to lower PPVs in this subgroup. An alternative explanation is that clinicians have greater difficulty diagnosing PBC in male patients, although empiric evidence to support this suggestion is lacking.

We also confirmed our hypothesis that specialists are better than GPs at coding for PBC. Although the PPVs of at least one claim by a specialist or GP were similar (~80%), the sensitivity of this criterion among specialists was much higher (82% vs. 18%). This finding likely reflects a greater awareness of PBC among specialists, the methods of making its diagnosis, and its specific diagnosis codes. In an inflammatory bowel disease (IBD)-related study that addressed the latter issue among Canadian physicians,[122] gastroenterologists were more likely than GPs to be aware of the diagnosis codes for IBD, and more frequently used these codes for both IBD and non-IBD-related services. Since PBC is typically managed by specialists, the latter finding likely explains, at least in part, the increased sensitivity of specialist claims for this condition.

In our final sensitivity analysis, we assessed the impact of the duration over which the diagnosis codes were recorded on the performance of the administrative data. In this analysis, the PPV of the definition requiring at least two health care contacts was similar when the first and second contact occurred

within 1, 2, or 3 years of each other. However, the sensitivity of the algorithm was significantly lower when restricted to patients in whom these contacts occurred within the same year (71% vs. 94% for < 2 and < 3 years). This finding is likely due to the typically infrequent follow-up of PBC patients who may be seen on an annual basis (or less often) if stable.[7] It suggests that future analyses of PBC using administrative databases should include more than a single year of data so as to avoid missing close to 30% of cases who would otherwise have an insufficient observation period to accrue two or more health care contacts.

Our findings support the use of administrative data in future studies of the epidemiology and natural history of PBC. First, our data suggests that accurately timing the date of diagnosis is feasible using administrative data. Specifically, we demonstrated a short interval between diagnosis dates established using clinical data and the first contact in the administrative data (median less than 2 months). Interestingly, the PPVs of the coding algorithms were higher in recent years, suggesting improved accuracy over time. This finding likely relates to greater difficulty in confirming a diagnosis of PBC during the earlier years of the validation study (e.g. due to missing laboratory reports and clinical data [see below]), or perhaps increased awareness of the diagnosis codes for PBC among treating physicians in more recent years. This finding must be considered when interpreting temporal changes in PBC incidence and prevalence (i.e. that they truly reflect fluctuations in disease burden rather than the accuracy of case

ascertainment). The major advantage of the administrative databases that we used in the current study is their population-based nature, which limits the selection bias inherent in many studies that originate in tertiary referral centers. If future studies validate our findings in different health care settings, comparisons of PBC epidemiology and outcomes between regions will be facilitated.

Our study has several limitations. Most importantly, we were unable to locate the medical records of approximately 40% of patients who had at least one health care contact for PBC. In many cases, charts could not be retrieved due to the prolonged nature of our study period, which dated back to 1994. In addition, we could not access the records of GPs or specialists practicing outside of the University of Calgary Medical Clinic. Since coding accuracy was associated with physician specialty, this limitation may have introduced selection bias with a resultant overestimation of the performance of the coding algorithms. On a related note, a significant proportion of patients (n=28, 14%) were labeled as having “suspected PBC” and excluded from our primary outcome (definite or probable PBC) due to a lack of diagnostic information. In all likelihood, many if not all of these patients truly had PBC. For example, three patients were AMA-positive with cholestasis, but could not be given a diagnosis of “probable PBC” because their AMA titer was unavailable. Many additional patients – including one of the 17 clinical trial patients - were diagnosed in other health regions by experienced physicians who prescribed UDCA, the only approved treatment for

PBC.[12] Thus, we would argue that the correct PPV of the optimal coding algorithm is closer to the 89% that we observed in our analysis of definite, probable, or suspected PBC.

In conclusion, this study demonstrates the feasibility of identifying patients with PBC using administrative data. We recommend that future studies utilize a coding algorithm requiring at least two health care contacts and at least one year of administrative data for the ascertainment of PBC cases. In the following studies, we utilize this algorithm to describe the epidemiology and outcomes of PBC from a Canadian, population-based perspective.

CHAPTER THREE

WHAT ARE THE INCIDENCE AND PREVALENCE OF PBC IN THE CALGARY HEALTH REGION? HAS THE EPIDEMIOLOGY OF PBC CHANGED BETWEEN 1996 AND 2002?

INTRODUCTION

PBC is a chronic idiopathic liver disorder characterized by progressive, nonsuppurative destruction of the interlobular and septal bile ducts that may lead to cirrhosis.[7-9] The hallmark serologic feature is the presence of AMAs that are highly specific for PBC.[5, 6] Since the first descriptive epidemiologic study of PBC published by Hamlyn and Sherlock nearly 35 years ago,[123] a wealth of literature has examined the epidemiology of this condition (see Table 1.1).[3, 17, 18] In general, PBC is considered a rare disease that affects predominantly females (female to male ratio approximately 9:1). Although geographic variation exists, PBC occurs worldwide, and represents a substantial cause of morbidity, mortality, and health care expenditures. In one study, the Healthcare Cost and Utilization Project estimated the annual economic burden from PBC at between $69 and $115 million for hospital charges alone.[124]

The literature describing the epidemiology of PBC has reported variable rates of disease frequency depending on the specific population under investigation, the study period, the methods of case ascertainment, and the diagnostic criteria used to define PBC. Reported incidence and prevalence rates vary widely from 2 to 49

cases per million and 19 to 402 per million, respectively.[3, 17, 18] Thus far, two studies have described the epidemiology of PBC in Canada; both require updating.[32, 33] In the first study from Ontario,[32] Witt-Sullivan *et al.* reported a PBC incidence of 3.3 per million and prevalence of 22.4 per million in 1987. In the second study from Quebec,[33] Villeneuve and colleagues reported an incidence (between 1980 and 1986) and point prevalence (in 1986) of 3.9 and 25.4 cases per million, respectively. As reported by others,[22, 31, 36, 115, 125] the study by Witt-Sullivan and colleagues suggested that the burden of PBC has increased over time. For example, in sequential studies from the Northeast of England, the annual incidence increased from 11.3 cases per million in 1976 to 31.1 per million in the years 1991 to 1994.[22, 36, 115] During the same interval, the prevalence rose from 16 to 251 cases per million. However, a major limitation of many of these studies is the use of variable methodologies for case ascertainment over time that hinder the differentiation of true trends from artifactual changes.

The objective of the current study was to provide updated information regarding the incidence and prevalence of PBC in a well-defined, Canadian population. To conduct this study, we employed a novel methodology for case ascertainment using population-based administrative databases and a validated diagnostic coding algorithm (see Chapter Two). By using consistent methodology for the

identification of cases during the entire study interval, we aimed to determine whether the incidence and prevalence of PBC have changed over recent years.

METHODS

Data Sources and Study Population

The study population included adult patients (≥ 20 years old) with PBC residing in the CHR between fiscal years 1994 to 2003. PBC cases were identified from the Physician Claims, Inpatient DAD, and ACCS databases[103] using an administrative data case definition requiring at least two health care contacts with a diagnosis code for PBC (ICD-9-CM 571.6, and ICD-10 K74.3) during the study interval.[89, 90] This definition was 94% (95% CI 71-100%) sensitive and had PPVs of 73% (95% CI 61-75%) for definite or probable PBC and 89% (95% CI 82-94%) for definite, probable, or suspected PBC in a chart validation study (see Chapter Two). Gender and age at the first PBC contact, an acceptable proxy for the date of diagnosis, were determined using the AHCIP Registry.[103]

Statistical Analyses

The incidence of PBC within the CHR was evaluated between fiscal years 1996 and 2002 (April 1, 1996 to March 31, 2003). The point prevalence on March 31st of each year was also determined. Non-residents of the CHR and individuals not registered in the AHCIP, as determined from the AHCIP Registry, were excluded from these analyses. For our prevalence calculations, we also excluded patients

who died prior to March 31st of the fiscal year, as determined using the Vital Statistics database.[103] In calculating incidence and prevalence rates, the end-of-fiscal year population of the CHR was considered at risk.[126] Overall rates were directly age-, sex-, and/or age-sex-adjusted to the 2001 Canadian population.[127] Temporal changes in rates were evaluated using generalized linear models assuming a Poisson error structure.[128] For all analyses, a washout period of two fiscal years at the beginning of the study (1994 and 1995) was utilized. This interval was selected to avoid the inclusion of prevalent cases in our incidence analyses. Because the majority of PBC patients are evaluated approximately yearly for their condition,[7] we assumed this period would be sufficient to achieve this goal. This assumption is supported by our validation study which showed that the use of more than two years of data did not improve the sensitivity or PPV of the coding algorithm (see Chapter Two). Moreover, because our definition for PBC required the presence of at least two administrative data contacts for PBC, we sought to avoid underestimating incidence and prevalence at the beginning of the study interval. For the same reason, incidence and prevalence rates for fiscal year 2003 are not presented because patients with their first encounter during this year had an insufficient observation period for the accrual of at least two health care contacts for PBC (see Chapter Two).

Descriptive statistical methods were used to describe the characteristics of the study cohort. Comparisons between groups were made using Fisher's exact

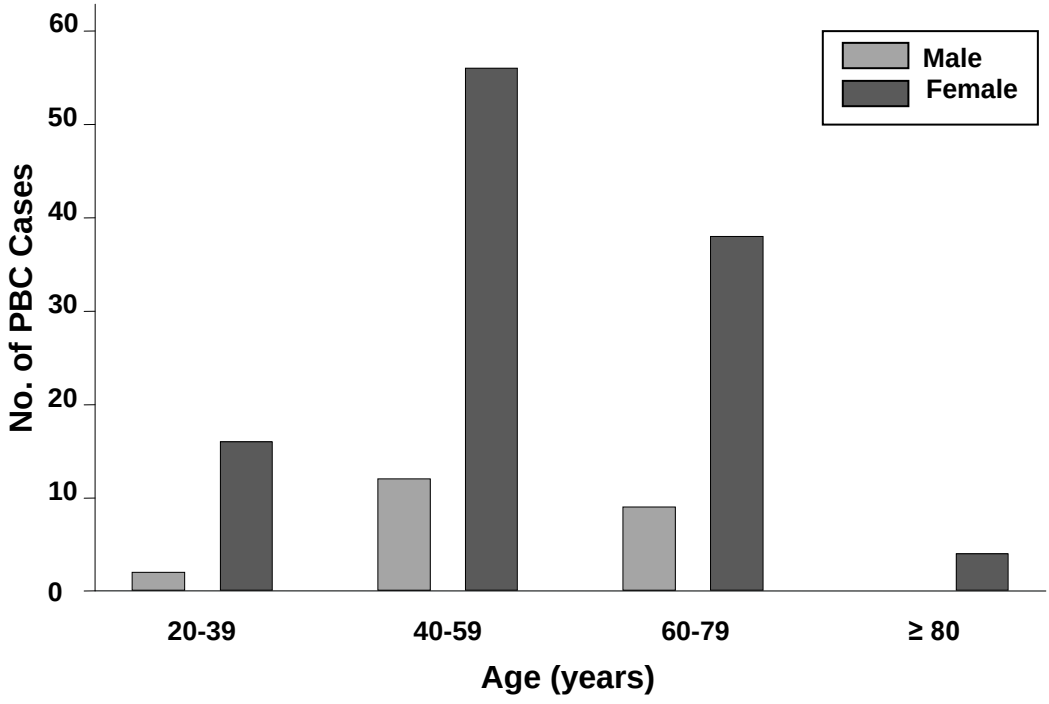
tests for categorical variables and Kruskal-Wallis rank tests for continuous variables. Statistical analyses were performed using Stata/IC 10.0 (StataCorp, College Station, TX) and SAS 9.1.3 (SAS Institute, Carey, NC) software.

RESULTS

Incidence of PBC

Between April 1, 1996 and March 31, 2003, 137 CHR residents were newly diagnosed with PBC, corresponding to an overall age-sex-adjusted, annual incidence of 30.3 per million population. The majority of these patients (83%) were female and the median age at diagnosis was 53 years (IQR 44-64 years). The age and sex distributions of incident cases were stable during the study period (*P*=0.25 and *P*=0.75, respectively). The numbers of incident PBC cases by age category and sex are illustrated in Figure 3.1.

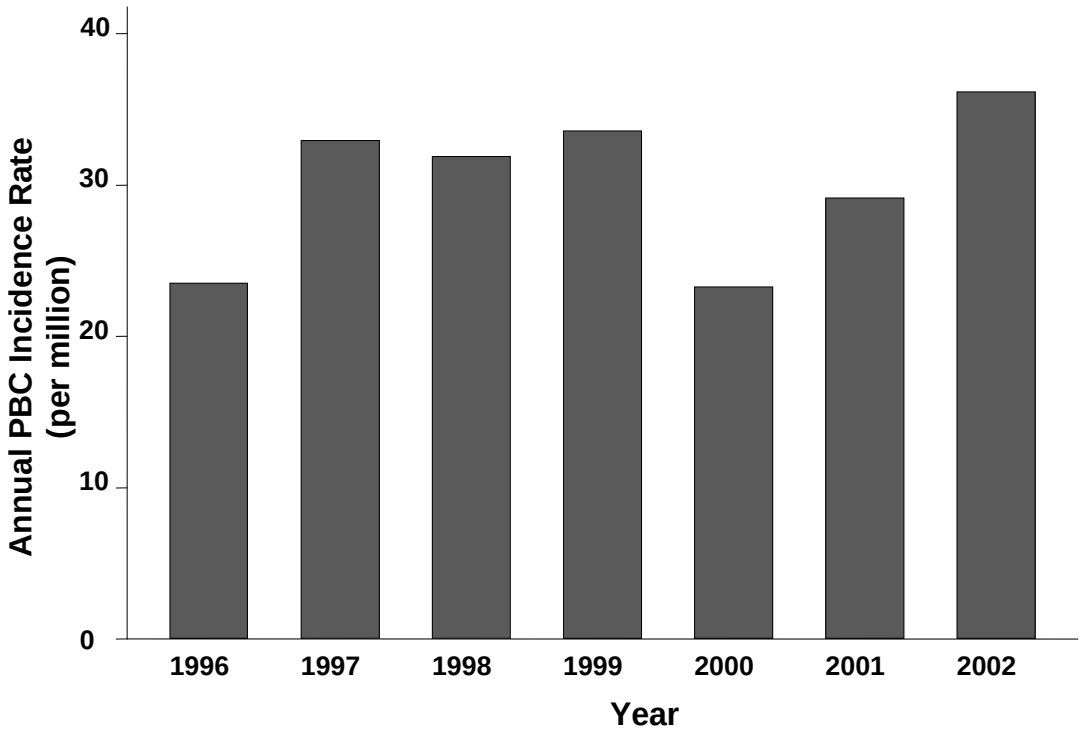
Figure 3.1: Incident Cases of PBC in the CHR between 1996 and 2002 Stratified by Age Category and Sex



Females were nearly five-times more likely to be diagnosed with PBC than males. Age-adjusted incidence rates were 48.4 per million in females versus 10.4 per million in males (incidence rate ratio [IRR] 4.83; 95% CI 4.76-4.90).

The age-sex-adjusted annual incidence of PBC did not change during the 7-year study interval (Figure 3.2). Although the incidence appeared lower in 1996 than 2002 (23.5 vs. 36.2 per million), the rate did not change significantly across years in formal Poisson regression analysis (*P*=0.89).

Figure 3.2: Annual Age-Sex-Adjusted Incidence of PBC in the CHR between 1996 and 2002



The incidence of PBC is highly dependent on patient age (Table 3.1). The highest adjusted incidence was observed among 60-79 year olds (63.0 per million population; IRR vs. 20-39 year age category, 8.27 [95% CI 8.13-8.42]).

Table 3.1: Incidence Rates of PBC (per Million Population) According to Age and Gender in the CHR between 1996 and 2002

Age Category	Female Rate *	Male Rate *	Total Rate †	IRR (95% CI)
20-39 years	13.7	1.7	7.9	1.00 (reference)
40-59 years	59.0	12.3	36.4	4.57 (4.50-4.65)
60-79 years	97.4	26.0	63.0	8.27 (8.13-8.42)
≥ 80 years	43.4	0	22.4	3.72 (3.59-3.85)
All ages	**48.4**	**10.4**	**30.3**	---

CI, confidence interval; IRR, incidence rate ratio.

* Age-specific incidence rates are unadjusted. Overall incidence rates are age-adjusted to the 2001 Canadian population.

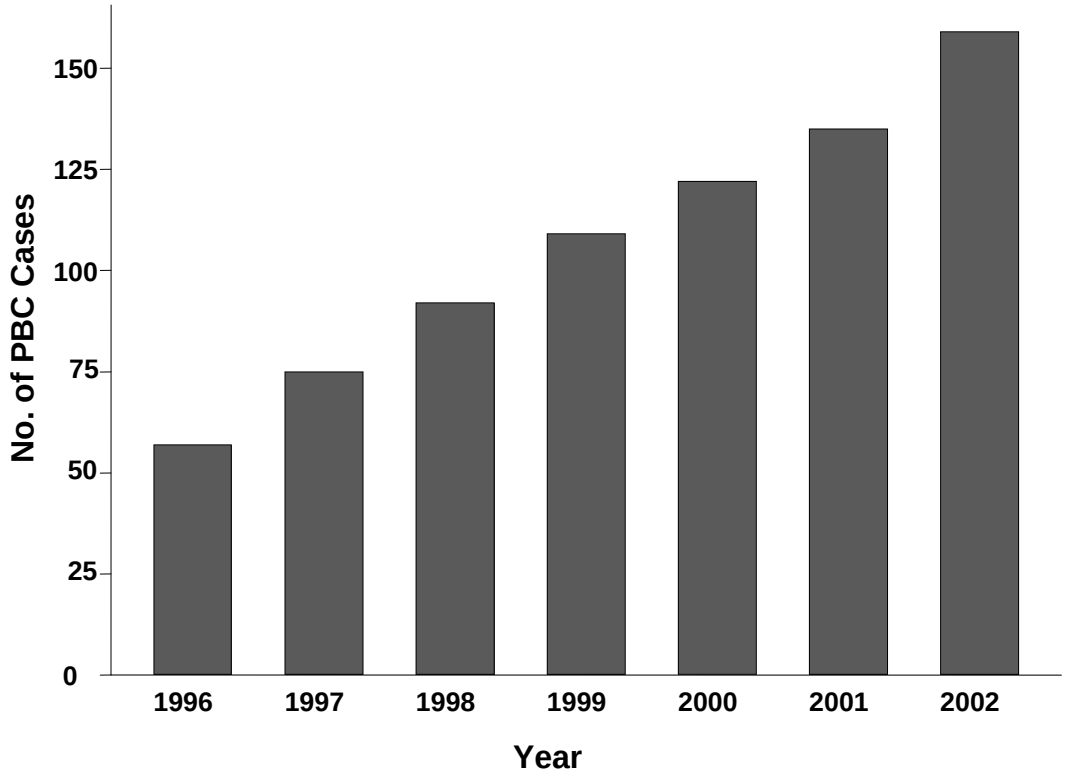
† Age-specific incidence rates sex-adjusted to the 2001 Canadian population. Overall incidence rate is age-sex-adjusted.

Prevalence of PBC

A total of 224 PBC patients resided in the CHR at some point during fiscal years 1996 through 2002. The majority of these patients were women (85%) and the median age at diagnosis was 53 years (IQR 45-64 years). The median age (IQR) of prevalent cases was greater in 2002 than 1996 (57 [48-67] vs. 53 [44-63]

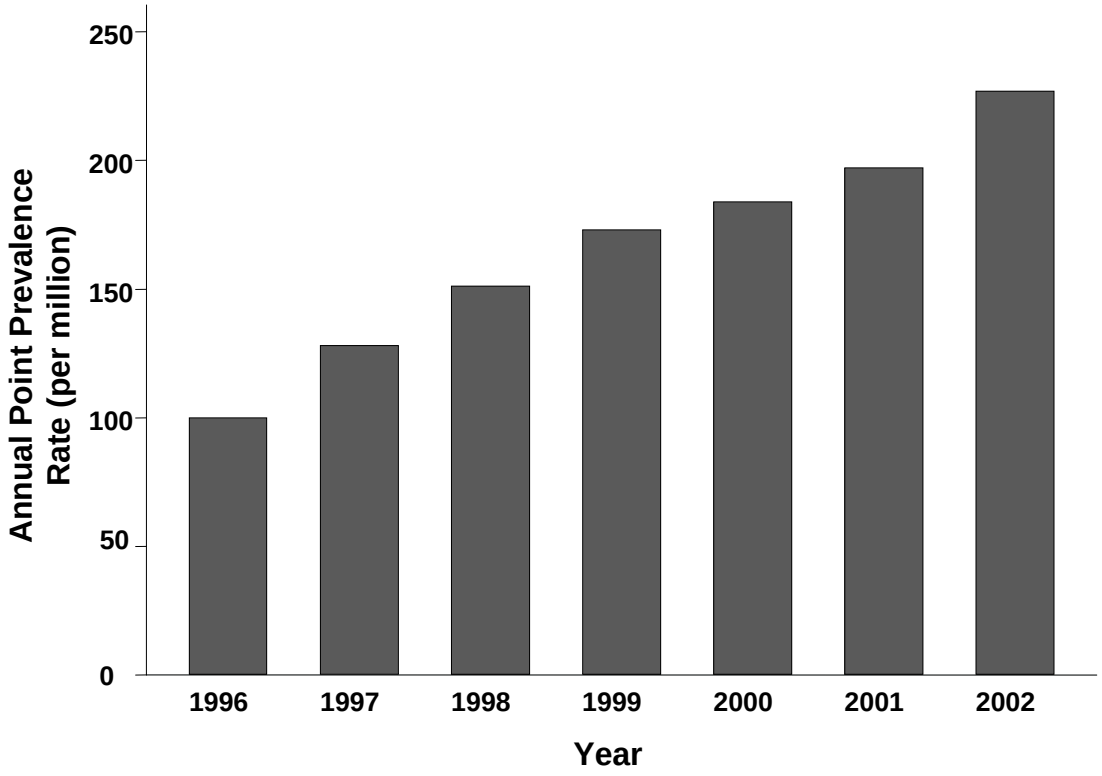
years). The number of prevalent cases increased during the study interval (Figure 3.3).

Figure 3.3: Prevalent Cases of PBC Residing in the CHR between 1996 and 2002



Corresponding age-sex-adjusted, point prevalence rates (as of March 31st for each fiscal year) increased from 100 per million in 1996 to 227 per million in 2002 (Poisson $P<0.0005$; Figure 3.4).

Figure 3.4: Annual Age-Sex-Adjusted Point Prevalence Rates of PBC in the CHR between 1996 and 2002



As expected, adjusted point prevalence rates (as of March 31, 2002) were much higher among women (383 per million) than men (55 per million). The prevalence of PBC was also highly dependent on age (Table 3.2). The highest prevalence was observed among individuals aged 60-79 years (573 per million; rate ratio 15.5 [95% CI 15.2-15.8] vs. the 20-39 year old age category). In females of this age group, the prevalence was 952 per million population.

Table 3.2: Point Prevalence Rates of PBC (per Million Population) Stratified According to Age and Gender in the CHR in 2002

Age Category	Female Rate *	Male Rate *	Total Rate †	Rate Ratio (95% CI)
20-39 years	58	17	38	1.00 (reference)
40-59 years	437	43	247	6.37 (6.25-6.49)
60-79 years	952	167	573	15.5 (15.2-15.8)
≥ 80 years	264	0	137	4.61 (4.45-4.77)
All ages	**383**	**55**	**227**	---

CI, confidence interval.

* Age-specific prevalence rates are unadjusted. Overall prevalence rates are age-adjusted to the 2001 Canadian population.

† Age-specific prevalence rates sex-adjusted to the 2001 Canadian population. Overall prevalence rate is age-sex-adjusted.

DISCUSSION

In this study, we describe recent trends in the epidemiology of PBC in Canada. The major strength of our study design is the ability to accurately define both the numerator and denominator populations. Specifically, we employed a validated diagnostic definition for the ascertainment of PBC cases and used an administrative database linkage system that ensures complete capture of health care encounters. Moreover, the background population was clearly defined based on geographic boundaries.

Previous epidemiologic studies of PBC, the majority of which originate in Europe, have reported incidence rates of 2 to 49 cases per million and prevalence rates of 19 to 402 per million population.[3, 17, 18] The estimates from our study (incidence and prevalence of 36 and 227 per million, respectively, in 2002) are among the highest ever reported. If projected nationally, this data suggests that there are at least 5,500 prevalent cases and 900 new cases diagnosed annually in Canada. The epidemiology of PBC in North America is thus far poorly described; only four population-based studies have been reported.[32-35] In the first Canadian study,[32] Witt-Sullivan and colleagues surveyed 502 gastroenterologists and internists practicing in acute care Ontario hospitals (with at least 150 beds) regarding their patients with PBC. Of those surveyed, 85 physicians reported a total of 225 PBC patients under their care. The incidence and prevalence of AMA-positive, biopsy-proven PBC in 1987 were 3.3 per million and 22.4 per million, respectively. In another Canadian study,[33] Villeneuve and colleagues reported incidence and

prevalence rates in Quebec of 3.9 and 25.4 per million, respectively during the early to mid-eighties. The figures from these studies are an order of magnitude lower than we observed likely due to a variety of factors. In the study by Witt-Sullivan *et al.*,[32] an incomplete survey response (87%), the poor sensitivity of physician reporting for case ascertainment (i.e. reliance on memory), and the requirement for histological confirmation likely led to underestimation of the true burden of PBC. In the Quebec study,[33] only hospitalized cases were identified. As described in our validation study (see Chapter Two), hospitalization databases are too insensitive (6% in our study) to accurately identify what is predominantly a disease of outpatients. These points aside, we likely overestimated the burden of PBC in our study since we employed a case definition that is not 100% accurate. Specifically, in our validation study, the PPV of this definition for definite, probable, or suspected PBC was 89% and the sensitivity was 94% (i.e. 11% false positives and 6% false negatives).

In a study from Olmsted County, Minnesota,[34] Kim *et al.* identified 46 incident cases of PBC over a 20-year interval (1975-1995). The corresponding annual incidence of 27 per million is similar to that of our study, while the prevalence of 402 cases per million is the highest ever reported. In a second American study of Alaskan natives,[35] Hurlbut *et al.* identified 18 patients with PBC between 1984 and 2000, corresponding to a prevalence of 160 per million. Both of these studies are limited by small sample sizes. Moreover, the Minnesota study is subject to referral bias in that the well known expertise in cholestatic liver diseases at the

Mayo Clinic may have prompted patients to relocate to this area. This could potentially account for the very high prevalence reported by these authors. In addition, Olmsted County has a very homogeneous ethnic composition (predominantly of Scandinavian descent),[34] whereas the CHR is more ethnically diverse.

Between 1996 and 2002, the incidence of PBC in our region was stable, but the point prevalence increased two-fold. These findings confirm data from some, but not all investigators. For example, in a study by Steinke and colleagues using data from Tayside, Scotland between 1986 and 1996,[125] the annual incidence of PBC was stable (48-55 cases per million), but the prevalence increased from 186 to 379 cases per million. In Northeast England, James and colleagues reported a rise in prevalence between 1984 and 1994 from 149 to 251 cases per million; the incidence did not change over this interval.[115] Finally, the incidence was unchanged in Olmsted County between 1975 and 1995 (trends in prevalence were not reported).[34] Based on the stable incidence of PBC in our region, we cannot attribute the local rise in prevalence to a true increase in disease frequency or recognition (i.e. greater awareness and diagnostic testing). This finding may reflect earlier diagnosis during recent years with prolonged survival due to lead time bias. However, the stable age distribution of incident cases over time would argue against this hypothesis. Alternatively, patients with PBC may be living longer due to an improved prognosis. Indeed, the median age of prevalent cases was greater in 2002 than 1996 (57 vs. 53 years). Recent

American data supports the latter hypothesis. In an analysis of 1995-2006 data from the Organ Procurement and Transplant Network (OPTN)/United Network for Organ Sharing (UNOS) database,[129] Lee and colleagues demonstrated a significant reduction in the number of transplants for PBC (~5 patients per year), while transplants for all indications increased (~249 cases per year). Similarly, the number of additions to the waiting list for all indications increased 265 patients per year, whereas additions for PBC decreased an average of 12 patients per year. These findings are supported by a study by Kim and colleagues that reported trends in PBC-related mortality using U.S. death certificate data.[130] Between 1980 and 1998, PBC-related mortality fell in males and females under 65 years, whereas older women had an increase in mortality. The authors hypothesized that these results may be attributable to the more widespread use of liver transplantation (at least in the eighties) and a beneficial effect of UDCA on delaying disease progression. The fact that PBC prevalence increased while the number of liver transplants for this condition in Alberta remained stable between 1996 and 2002 (G. Meeberg, personal communication, August 2008) would tend to support this hypothesis. In addition, prior to the increase in prevalence that we observed, UDCA was in widespread use since pivotal studies in the early nineties demonstrated its efficacy.[131-134]

The remainder of our findings is largely confirmatory of other data. As expected, the risk of PBC was markedly higher among females than males. However, the

female to male ratio that we observed (~5:1) is lower than in most other studies (see Table 1.1). This may relate to greater diagnostic misclassification in males, for whom the PPV of our case definition was lower. The burden of PBC is also highly age-dependent. Although typically considered a disease of middle-age, as supported by the high number of cases in patients aged 40-59 years, the highest incidence and prevalence rates were actually observed in the 60-79 year age category (63 and 573 cases per million, respectively). In females of this age group, the incidence approached 1 in 10,000 and prevalence was nearly 1 in 1,000. The proportionately smaller size of the population in this age stratum accounts for these high rates despite the relatively small number of absolute cases.

Our study has several limitations. Importantly, misclassification of individuals without PBC may have affected our estimates of disease burden. Although the PPV of our coding algorithm was higher during recent years (see Chapter Two), we are confident in the validity of our observations regarding PBC prevalence. Specifically, this bias would tend to nullify any increase in prevalence that we observed. On the other hand, due to a greater number of false positive cases during the earlier years of the study, the stable incidence that we observed may be erroneous (i.e. the incidence may actually have increased). Second, as a result of our reliance on administrative data without clinical confirmation, we may have labeled some prevalent cases that relocated to the CHR after 1995 as incident cases. Third, other than age and gender, we could not examine potential

risk factors for PBC because we lacked clinical data. For example, environmental exposures such as chemical toxins (e.g. hydrocarbons from toxic waste dumps,[55] air pollution,[18] and smoking)[49] and microorganisms (e.g. *Chlamydia pneumoniae*[52] and human betaretrovirus)[53] may play a role in disease pathogenesis. We plan to conduct future studies assessing local geographic variation in the burden of PBC that would strengthen the case for environmental influences on this disease. Finally, the applicability of our results to other regions of Canada and elsewhere warrants confirmation. Since we have demonstrated the feasibility of using administrative databases, which are ubiquitous, to describe PBC epidemiology, similar studies in other areas should be conducted. Investigations of this kind have the potential to further our understanding of the interplay between environmental and genetic influences on disease pathogenesis.

In summary, using population-based administrative data, we have described the recent epidemiology of PBC in Canada. The incidence and prevalence of PBC in southern Alberta are among the highest ever reported. Whereas the incidence was stable between 1996 and 2002, the prevalence increased, perhaps due to an improved prognosis or earlier diagnosis during recent years.

CHAPTER FOUR

WHAT IS THE NATURAL HISTORY OF PBC IN THE CALGARY HEALTH REGION?

INTRODUCTION

PBC is a chronic cholestatic liver disorder characterized by progressive destruction of the interlobular and septal bile ducts and the presence of AMA in the serum.[7-9] Although initially thought to be a rare disease associated with rapid progression to liver failure, recent studies suggest that PBC encompasses a more diverse clinical spectrum.[10, 11] In fact, contemporary series have demonstrated that only a small proportion of PBC patients will progress to end-stage liver disease and die of liver-related causes.[57-59] With the widespread use of automated screening liver biochemistry, the majority of newly-diagnosed patients are asymptomatic and at earlier stages of their disease. Accordingly, patient survival is now recognized to be much better than previously described.[10, 11]

For example, in two early studies that examined the natural history of PBC in the fifties and sixties, the average survival following symptom onset was approximately six years in 49 patients studied by Foulk *et al.*[135] and in 23 patients followed by Sherlock.[136] In a study from the early eighties, Roll and colleagues reported an average survival of 11.9 years among 238 patients followed at Yale University.[66] However, more recent natural history studies have yielded more

promising outcomes. For example, in three large European studies including over 750 patients in total, 10-year survival rates of 71% to 92% were reported.[57-59] Although these studies were restricted to patients receiving UDCA therapy, which may explain the improved survival versus earlier reports, the true impact of UDCA on the natural history of PBC remains controversial.[12, 137, 138] It is more likely that the differences in survival between studies relates to an earlier diagnosis of PBC in contemporary series and selection bias inherent in early studies that were restricted to only a few, often tertiary referral centers. In fact, the latter point represents a major limitation of most natural history studies in PBC. To our knowledge, only three population-based studies have described the outcomes of PBC in an unselected group of patients.[34, 56] In the first, Prince *et al.* described a median survival of 9.3 years among 770 patients from Northeast England.[56] In the second small study from Minnesota (n=46), a 10-year survival rate of 59% was reported.[34] Finally, Jackson and colleagues recently reported an 8-year survival rate of approximately 75% among 930 PBC patients who were treated with UDCA and identified using the United Kingdom General Practice Research Database (UK-GPRD). Both incident and prevalent cases were included in this study. To our knowledge, no data from an unselected Canadian population has been published.

Therefore, the objective of our study was to examine the natural history of PBC in a Canadian cohort of patients from a population-based perspective. Knowledge

of the prognosis of PBC is essential for patient counseling and decisions regarding treatment. In addition, since PBC may require liver transplantation and its prevalence is rising in an era of donor organ shortage, a thorough understanding of its natural history will be useful for resource planning.

METHODS

Data Sources and Study Population

The study population included 137 residents of the CHR (≥ 20 years old) newly diagnosed with PBC between April 1, 1996 and March 31, 2003. As described in Chapters Two and Three, these incident PBC cases were identified from the Physician Claims, Inpatient DAD, and ACCS databases[103] using a case definition requiring at least two health care contacts for PBC. The date of the first contact for PBC was used as a proxy for the date of diagnosis.

Study Outcome Measures

The primary outcome measure was all-cause mortality. Secondary outcome measures included liver transplantation and transplant-free survival. Mortality data was obtained from the AHCIP Registry and Vital Statistics databases.[103] The latter contains death certificate verified data regarding the underlying cause of death for CHR residents dying within Alberta. To identify patients who underwent liver transplantation and the date of transplantation, the University of Alberta Liver Transplant Database was queried.[139] Because the CHR does not

have a liver transplant program, residents of the CHR requiring a liver transplant undergo this surgery at the University of Alberta.

Statistical Analyses

Descriptive statistical methods were used to describe the characteristics of the study cohort. All-cause mortality, liver transplantation, and transplant-free survival were examined using Kaplan-Meier survival analyses with between group comparisons made using the log-rank test.[140] Censoring for these analyses occurred upon deregistration from the AHCIP or March 31, 2007, whichever came first. The cumulative survival of PBC patients was compared with the expected survival of the age- and sex-matched, Canadian population, and expressed as the relative survival ratio (RSR). The RSR, which is frequently reported in studies of cancer survival, reflects the net mortality of patients in the hypothetical situation in which PBC is the only cause of death.[141] The RSR was determined using the Ederer II method, which involves calculating survival estimates at discrete points in follow-up (in this case, annually) and taking the product of interval-specific estimates over sub-intervals of follow-up.[142, 143] Age- and sex-specific conditional probabilities of death in the subsequent year for the Canadian population were obtained from life tables published by Statistics Canada.[144]

The impact of age, sex, and year of diagnosis (categorized as 1996-1999 vs. 2000-2002) on outcomes were examined using Cox proportional hazards

regression.[145] Log-log plots of survival confirmed that these analyses satisfied the proportional hazards assumption.

Statistical analyses were performed using Stata/IC 10.0 (StataCorp, College Station, TX) and SAS 9.1.3 (SAS Institute, Carey, NC) software.

RESULTS

Patient Characteristics and Survival

The majority of the 137 incident cases of PBC were female (83%) and the median age at diagnosis was 53 years (IQR 44-64 years). Total follow-up was 801 person-years from diagnosis. After a mean and median follow-up period of 5.8 years (IQR 4.2-8.0 years; range 10 days to 10.9 years), 6 patients underwent liver transplantation (4.4%) and 27 patients died (20%). No patient died after being transplanted. The causes of death were available in 24 of these 27 patients (89%). Deaths were liver-related in 12 patients (50%), due to malignancy in 2 patients (8%; one each of pancreatic and laryngeal cancer), ischemic heart disease in 2 patients (8%), septicemia in 2 patients (8%), and miscellaneous causes in the remainder (n=6). The proportion of liver-related deaths was higher among patients less than 60 years of age (100% vs. 37%; P=0.04), but did not differ according to gender (53% in females vs. 44% in males; P=1.00).

The overall survival of PBC patients following their diagnosis (with 95% confidence bands) is illustrated in Figure 4.1. The annual mortality rate was 3.4% (95% CI 2.3-4.9%). Observed 1-, 5-, and 10-year survival were 93% (95% CI 87-96%), 83% (76-89%), and 73% (60-83%), respectively.

Figure 4.1: Overall Survival (95% CI) of Patients with PBC Following Diagnosis

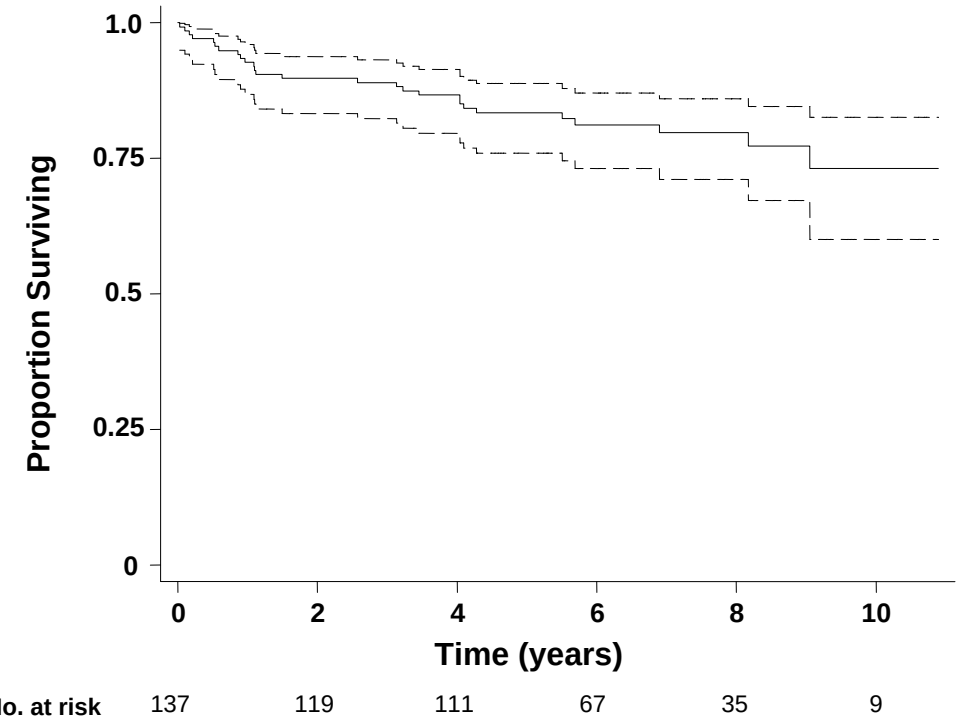
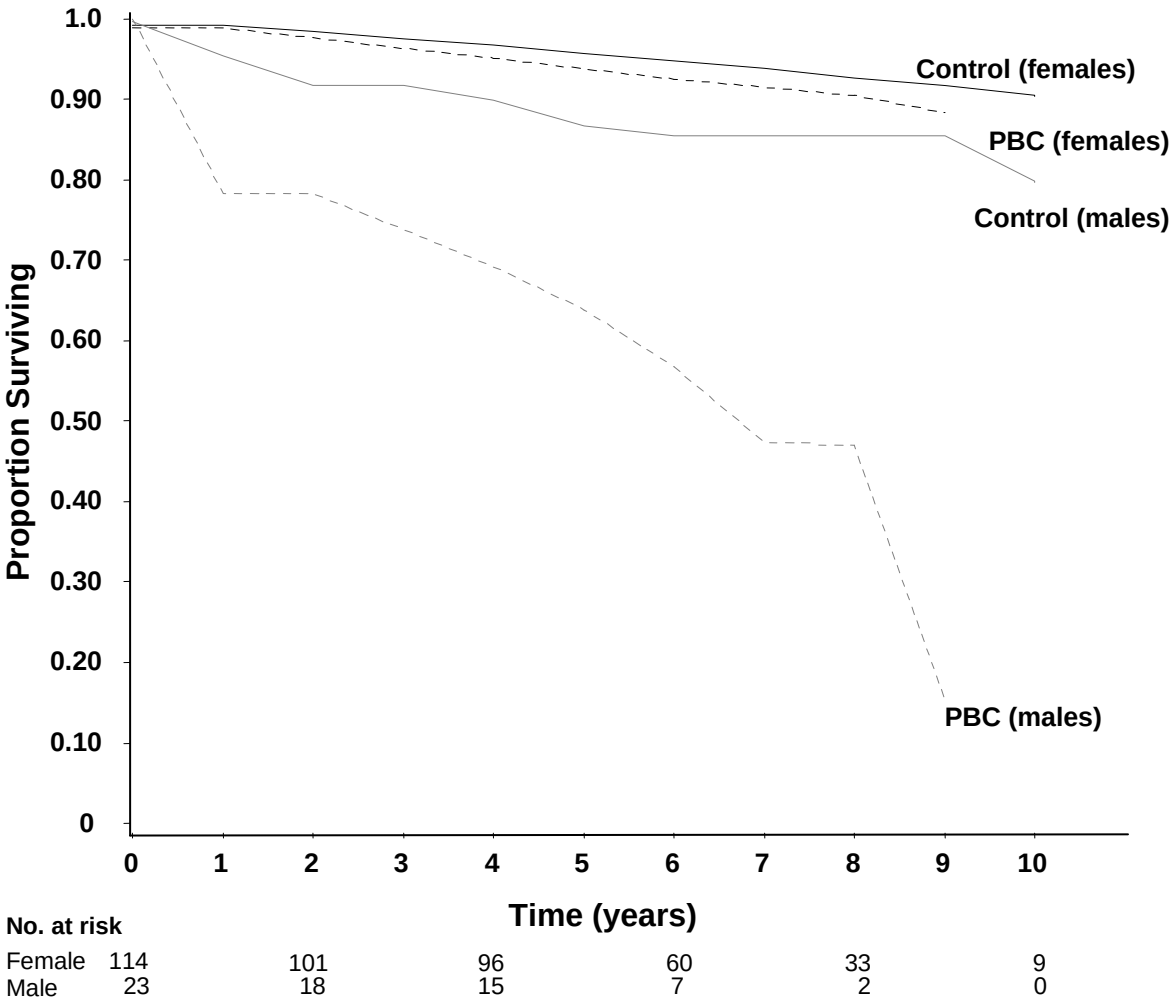


Figure 4.2 illustrates overall survival of PBC patients compared with the age- and sex-matched Canadian population with stratification according to gender. Survival was significantly lower in males than females (log-rank $P<0.00005$) and

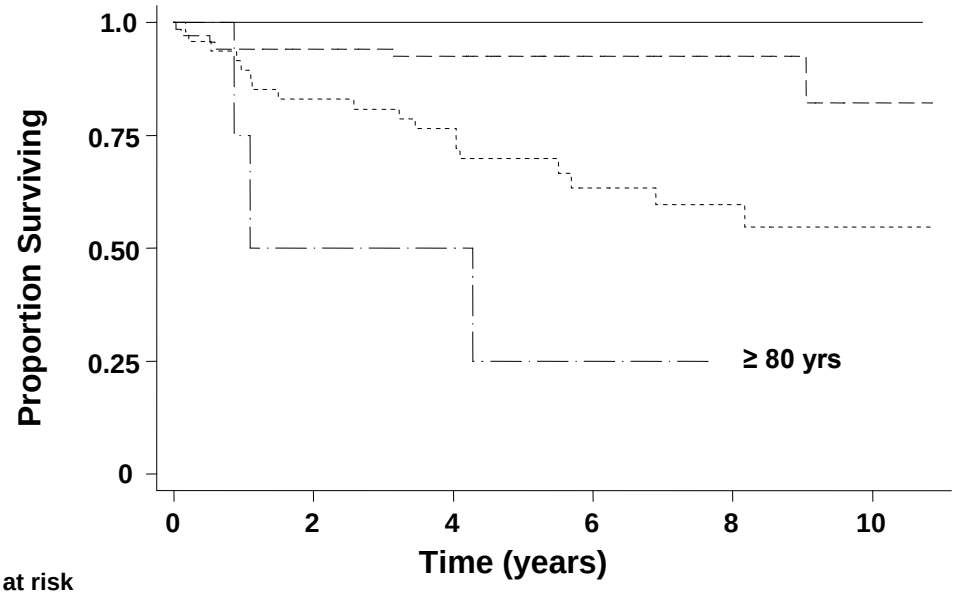
in both groups compared with that expected among the general population. In females specifically, observed 1- and 5-year survival were 96% (95% CI 90-98%) and 87% (79-92%), respectively. The 10-year survival of females with PBC was 80% (95% CI 64-90%) compared with 90% expected in the age-sex-matched population (RSR 0.88 [95% CI 0.71-0.99]). In males with PBC, observed 1- and 5-year survival were 78% (95% CI 55-90%) and 64% (40-80%), respectively (10-year survival could not be calculated). After 9 years of follow-up, observed survival of males with PBC was 16% (95% CI 0.2-59%) compared with 88% expected in the control population (RSR 0.18 [95% CI 0.002-0.67]).

Figure 4.2: Observed Survival of Patients with PBC According to Gender Compared with Expected Survival of the Age- and Sex-Matched Canadian Population



Patient survival was also significantly lower with an older age at diagnosis (log-rank *P*<0.00005; Figure 4.3). For ease of presentation, 95% confidence bands are not illustrated in this figure.

Figure 4.3: Survival of Patients with PBC Stratified According to the Age at Diagnosis



No. at risk						
20-39 yrs	18	17	16	16	8	2
40-59 yrs	68	61	57	32	15	4
60-79 yrs	47	39	36	18	12	3
≥ 80 yrs	4	2	2	1	0	0

The year of diagnosis (1996-1999 vs. 2000-2002) did not have a significant impact on patient survival (log-rank *P*=0.81). In multivariate Cox proportional hazards regression analysis, both male sex (hazard ratio [HR] 5.06; 95% CI 2.29-

11.17) and older age at diagnosis (HR per additional year, 1.10; 95% CI 1.06-1.14) were associated with an increased risk of death during follow-up.

Liver Transplantation and Transplant-Free Survival

Six patients (4.4% of total; 5.6% of patients 65 years and under) underwent liver transplantation and 33 patients (24%) died or were transplanted during follow-up. Survival curves for liver transplantation and transplant-free survival are illustrated in Figures 4.4 and 4.5, respectively. The 10-year probability of transplantation was 5.7% (95% CI 2.5-12.6%). In an analysis excluding patients over 65 years at diagnosis (n=29) in whom transplantation is generally contraindicated, the 10-year probability of transplantation was 6.9% (95% CI 3.1-15.0%). Observed 1, 5, and 10-year probabilities of transplant-free survival were 92% (95% CI 86-95%), 80% (72-86%), and 68% (55-78%), respectively. Neither age (*P*=0.28) nor gender (*P*=0.85) were significantly associated with liver transplantation in multivariate Cox proportional hazards analysis. However, males (HR 3.80; 95% CI 1.85-7.82) and older patients (HR per additional year, 1.06; 95% CI 1.03-1.10) had a greater risk of the combined endpoint of death and/or liver transplantation.

Figure 4.4: Liver Transplantation (95% CI) during Follow-Up in Patients with PBC

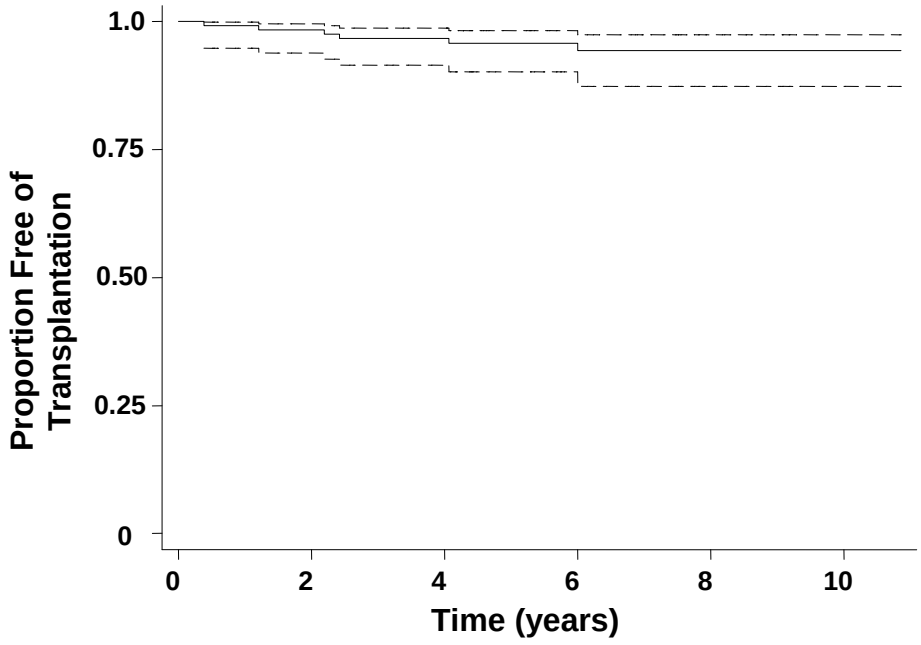
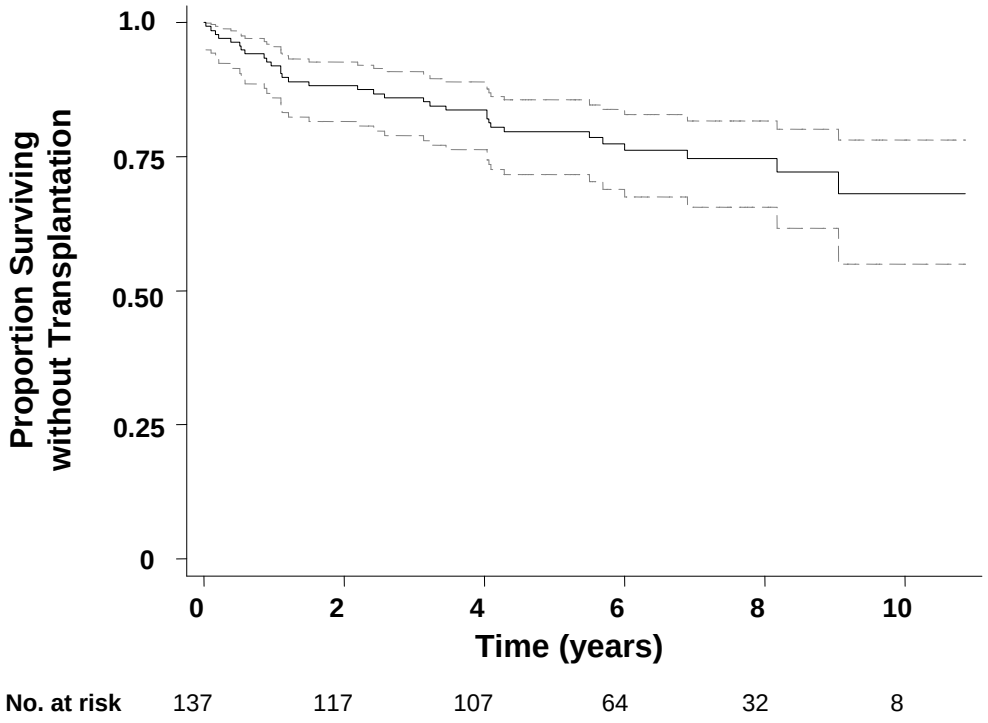


Figure 4.5: Transplant-Free Survival (95% CI) of Patients with PBC



DISCUSSION

In this study, we describe the natural history of PBC in a population-based cohort of Canadian patients. Unlike most outcome studies in this condition, ours was not restricted to a few health care providers or tertiary referral centers. As a result, our study is not subject to the selection bias inherent in most reports, and may therefore provide a more accurate description of the natural history of PBC in an unselected population. After a median follow-up of 5.8 years, the 10-year probabilities of survival, liver transplantation, and transplant-free survival were 73%, 6%, and 68%, respectively. For comparison purposes, in the only other natural history of PBC reported in Canada using population-based data, Villeneuve and colleagues reported a 10-year survival rate of 49% among 228 patients with PBC from Quebec.[33] Importantly, all of these patients were identified using hospital discharge data, which subjects this study to selection bias.

The figures that we report compare favorably to other contemporary natural history studies of PBC. For example, in a multicenter study of 297 patients from Holland, ter Borg and colleagues reported 10-year overall and transplant-free survival rates of 78% and 71%, respectively.[57] Five percent of patients were transplanted after a median follow-up of 68 months. Similarly, Poupon *et al.* reported a 10-year transplant-free survival rate of 78% among 225 patients followed at multiple centers in France.[69] Finally, in a Spanish study of 192 patients, 10-year survival was 77%; 4% of patients were transplanted during an

average follow-up of 6.8 years.[59] Importantly, these studies were restricted to patients on UDCA treatment, which has been shown to improve liver biochemistry and histology and reduce the formation of esophageal varices in patients with PBC.[12-16] Although two meta-analyses have questioned the clinical efficacy of UDCA,[137, 138] a combined analysis of three randomized trials,[13] an updated meta-analysis restricted to trials with sufficient treatment dosage and duration,[70] and multiple cohort studies[57-59, 69] have suggested a survival benefit in UDCA-treated patients. This point may partly explain the apparent increase in survival observed in these studies and our own compared with two other population-based natural history studies of PBC that have been reported. Specifically, among 770 patients from Northeast England, Prince *et al.* reported a median survival of 9.3 years (10-year survival approximately 45%).[56] Only 37% of patients in this cohort were treated with UDCA and the median dosage was 450 mg/day, much lower than that which is currently recommended (13-15 mg/kg/day).[7, 12] In the second study including 46 patients from Olmsted County, Minnesota, 10-year survival was 59%.[34] Only one-third of the follow-up in these patients was during UDCA treatment. Unfortunately, pharmacy data is not available in the administrative databases that we examined, thus the proportion of our cohort that received UDCA is unclear. However, among incident cases whose charts were reviewed for our validation study (see Chapter Two), 91% (67/74) were treated with UDCA. We expect that the majority of the remainder were also on UDCA because our recruitment period (1996-2002) began several years after the first pilot study (published in 1987)[146] and early randomized trials

(published in 1991-1994)[131-134] supported the benefits of this medication. Although the lack of complete data regarding UDCA treatment is a weakness of our study, our goal was to describe overall survival in PBC rather than examine the specific effects of this treatment, nor was this a randomized, controlled trial to truly document its benefit. Another potential explanation for the observed differences in survival between these population-based studies relates to the difference in recruitment periods (1975-1995 for the Kim study;[34] 1987-1994 for the Prince study;[56] and 1996-2002 for our study), since evidence suggests that the prognosis for patients with PBC has improved over time. Specifically, two recent studies described a reduction in the number of liver transplants and deaths due to PBC during recent years in the United States.[129, 130] We did not observe a significant difference in survival according to the year of diagnosis in our study, however, the time intervals that we studied (1996-1999 vs. 2000-2002) are likely too close to properly examine this issue.

The remainder of our findings is largely confirmatory of other reports. As previously described,[34, 56, 57, 59, 64, 69, 147] we observed reduced survival of Canadian patients with PBC compared with an age- and sex-matched, control population (Figure 4.2). The RSR in female and male patients with PBC were 0.88 (95% CI 0.71-0.99) and 0.18 (95% CI 0.002-0.67), respectively, after 9-10 years of follow-up. This outlook (at least in females) is more optimistic than reported by Prince and colleagues who described three-fold mortality among

PBC patients compared with the general population.[56] Unfortunately, limitations in our databases precluded examination of survival stratified according to other known prognostic factors including the histological stage at diagnosis and the biochemical response to UDCA.[10, 11] For example, Poupon *et al.* reported that 10-year survival among UDCA-treated patients was slightly lower than that of the French population, although this difference was mainly explained by increased mortality among cirrhotic patients.[69] More recently, using a Markov modeling approach with longer follow-up, the same investigators reported that overall survival in UDCA-treated patients was similar to that of a control population, although the subgroup of patients with advanced disease (stages 3 or 4) were at higher risk.[58] In another study by Pares and colleagues, responders to UDCA (defined as normalization or greater than 40% decline in alkaline phosphatase concentration at one year of therapy) had similar survival to the standardized Spanish population.[59] However, patients who did not respond to UDCA had increased mortality during follow-up.

After a median follow-up period of 5.8 years, 20% of our cohort died. In total, 50% of these deaths were recorded as liver-related on death certificates. This data is in keeping with other studies. For example, Prince, ter Borg, and Kim and colleagues reported that the proportion of liver-related deaths in their cohorts were 42%, 47%, and 56%, respectively.[34, 56, 57] As observed in Prince's study,[56] liver-related deaths were more common in our patients under 60 years, likely due

to fewer competing risks in these younger individuals. On the contrary, in the study by Poupon *et al.*, 77% of deaths were liver-related.[69] Nonetheless, all of these results must be interpreted cautiously because the accuracy of death certificate-based methods for ascertaining deaths due to chronic liver disease has been questioned. In a recent study, Manos and colleagues estimated that the use of diagnosis codes to estimate rates of chronic liver disease mortality underestimates the true burden by nearly 50%.[148] This discrepancy is largely due to the exclusion of hepatocellular carcinoma as a cause of liver-related death. In our study, no patients died of hepatocellular carcinoma.

We identified two significant predictors of survival, namely the age at diagnosis and gender. As expected, mortality was greater in patients diagnosed at an older age. While no patients under 40 years died, 10-year survival was 82% and 54% in those aged 40-59 years and 60-79 years, respectively. No patients over 80 years survived 10 years; only 25% were living 5 years after diagnosis. As mentioned above, we also observed substantially increased mortality in males versus females (HR 5.06, Figure 4.2). The proportion of deaths due to liver disease was similar between males and females. Increased mortality among male patients with PBC has been reported,[57] but not confirmed in most studies.[56, 58, 59, 66, 69] We suspect that much of this discrepancy in survival relates to greater diagnostic misclassification in males, in whom our validation study demonstrated a lower PPV of our administrative data case definition (60% vs. 94% in females).

For example, patients with PSC and alcoholic cirrhosis – two conditions with a worse prognosis than PBC[149, 150] - were more likely to be erroneously labeled as PBC in males.

Our data has several additional limitations. As mentioned, we lacked detailed clinical data to evaluate all known prognostic factors in PBC including treatment with UDCA (or other medications such as methotrexate), baseline liver histology, and autoantibody profiles (eg. anti-gp210 and anti-centromere antibodies).[10, 11, 151] In addition, laboratory data for calculation of the Mayo risk score, a validated prognostic measure in PBC, is not available in the administrative databases that we utilized.[60, 61] Second, due to the imperfect accuracy of our diagnostic coding algorithm for case ascertainment, we likely failed to identify some patients with PBC and included others with alternative hepatic conditions. However, we expect these numbers to be small considering the high sensitivity and PPV (94% and 89%, respectively) of our coding algorithm. Finally, in the absence of detailed clinical data, we based the diagnosis date (“time zero”) for our survival analyses on the date of the first health care encounter with a diagnosis code for PBC. Our validation study demonstrated that this is a median of two months after the date of diagnosis recorded in the medical record. Although this bias would tend to overestimate mortality rates, it likely had a minimal impact on our results due to the prolonged natural history of PBC.

In conclusion, our study supports contemporary series documenting the natural history of PBC in a population-based, Canadian cohort. Patient survival is lower than that of the age- and sex-matched Canadian population, emphasizing the importance of developing new therapies for this condition.

CHAPTER FIVE

FINAL DISCUSSION

SUMMARY OF THE FINDINGS

In the studies included within this thesis, we utilized CHR administrative data to further our understanding of the epidemiology and outcomes of PBC in Canada. To achieve these goals, we employed a framework consisting of three series of questions: 1) Is administrative data valid for the identification of patients with PBC? 2) What are the incidence and prevalence of PBC in the CHR? Has the epidemiology of PBC changed between 1996 and 2002? and 3) What is the natural history of PBC in the CHR?

Is Administrative Data Valid for the Identification of Patients with PBC?

We answered this question by conducting a chart validation study of patients in whom a diagnosis code for PBC was recorded in at least one of three CHR administrative databases (Physician Claims, Inpatient DAD, and ACCS databases) over a 9-year study interval. Upon review of the medical records of nearly 200 such individuals, we determined that only 60% of patients had definite or probable PBC (our primary outcome measure). Seventy-four percent had definite, probable, or suspected PBC, a less stringent, but acceptable secondary outcome measure. Frequently misclassified diseases included PSC, secondary biliary cirrhosis, and autoimmune hepatitis, which in total, accounted for 60% of false positive cases. However, by increasing the number of contacts required to

make a diagnosis of PBC, the optimal definition *vis-à-vis* the balance between sensitivity and PPV was determined. Specifically, the presence of at least two contacts for PBC was 94% sensitive in a cohort of 17 well-characterized clinical trial patients with PBC and had PPVs of 73% and 89% for definite or probable PBC and definite, probable, or suspected PBC, respectively. The PPVs of this algorithm were greater in females than males in large part due to the greater prevalence of PBC among women.

These and several ancillary findings support the use of administrative data in future studies of PBC. First, the interval between the first administrative data contact for PBC and the actual date of diagnosis based on chart review was short, a median of slightly less than 2 months in our study. Thus, disease onset for the definition of incidence and outcome studies can be accurately estimated using administrative data. Second, we demonstrated the importance of multiple data sources and a sufficient period of observation when using administrative databases in studies of PBC. For example, the most sensitive approach employed all three databases rather than single databases in isolation. The ACCS and Inpatient databases were too insensitive to be used on their own. On the contrary, the Physician Claims database could be used in isolation for case ascertainment (e.g. for incidence and prevalence studies). However, this database would be insufficient to identify adverse outcomes of PBC (e.g. hepatic failure) for natural history studies, in which case other data sources such as the ACCS and Inpatient databases would be useful. Moreover, we clearly

demonstrated that databases limited to one year of data underestimate the true burden of PBC due to an insufficient observation period for the accrual of at least two health care contacts for this condition.

What are the Incidence and Prevalence of PBC in the CHR? Has the Epidemiology of PBC Changed between 1996 and 2002?

Having demonstrated the utility of administrative data for identifying PBC patients, we proceeded to describe the epidemiology of this condition in the CHR. The major finding of this part of the study is the high burden of PBC in our region, an order of magnitude higher than previously reported in Canada. Specifically, between 1996 and 2002, the overall age-sex-adjusted annual incidence was 30 cases per million and the point prevalence in 2002 was 227 cases per million. These figures are among the highest ever reported. As expected, we demonstrated that rates of PBC are age and sex-dependent. Women and individuals in their sixties and seventies have the highest incidence of disease. A striking finding was the very high prevalence of PBC in females aged 60-79 years, which approached 1 in 1,000 individuals.

The second major finding of this part of the study relates to temporal trends in the incidence and prevalence of PBC in our health region. Specifically, we observed a stable incidence of PBC, but a two-fold increase in the number of prevalent cases between 1996 and 2002. These findings have been reported by some, but

not all, investigators. We hypothesize that the increased prevalence in the face of stable incidence relates to earlier diagnosis and/or improved prognosis during recent years due to the widespread use of UDCA and liver transplantation for this condition.[129, 130]

What is the Natural History of PBC in the CHR?

The third and final part of this study aimed to describe the outcomes of PBC in an unselected Canadian population. To our knowledge, there is no Canadian data of this kind in the literature. To achieve this goal, we examined survival and the requirement for liver transplantation among 137 incident cases of PBC identified in the second part of this study. The aforementioned administrative databases, as well as the University of Alberta Liver Transplant Database were used in these analyses. During a total follow-up of 801 person-years and median follow-up per patient of 5.8 years from diagnosis, the 10-year probabilities of survival, transplantation, and transplant-free survival were 73%, 6%, and 68%, respectively. Independent predictors of mortality included an older age at diagnosis and male gender, but not the year of diagnosis. The outcomes that we observed in this population-based cohort are consistent with several other large cohort studies reported from Europe.[57, 59, 69] Interestingly, survival rates in our patients and in these cohort studies were better than those reported in two other population-based studies in this condition.[34, 56] We assume that this relates to differences in UDCA usage and recruitment periods across studies.

The second major finding in this part of the study is the reduced survival of PBC patients compared to the age- and sex-matched Canadian population. Again, this finding is not completely novel, but has not been reported in Canada. Although a sobering finding that points to the necessity of developing more effective treatments for this condition, the survival disadvantage that we observed in our cohort was smaller than reported in many earlier studies of the natural history of PBC.

IMPLICATIONS OF THE FINDINGS

Our study has two major implications. First, we have added to the literature describing the epidemiology and natural history of PBC. Although many of our findings have been reported, a major gap has been filled in the Canadian literature on this important topic. Second, and perhaps most significantly, we have demonstrated the feasibility of using a novel methodology and information source – a coding definition based on administrative data - in future studies of PBC. Previous reports have employed complex, time-consuming, and often expensive case finding approaches to study this condition. In addition to the accuracy that we have demonstrated, other advantages of administrative data include its limited expense and complete capture of health care encounters that permit examination of PBC from a population-based perspective. Moreover, if the approaches that we have described are externally validated, this methodology

can be utilized in various geographic locations considering the widespread availability of this data source. Investigations of this kind will facilitate our understanding of the interplay between environmental and genetic influences on the pathogenesis and outcomes of PBC.

LIMITATIONS OF THE STUDY

This study has several limitations that have been acknowledged throughout this thesis. Most importantly, no source of administrative data is perfect. Therefore, we have undoubtedly included patients who do not have PBC and missed a few with PBC in our studies of the epidemiology and natural history of this condition. Unfortunately, this limitation cannot be avoided, but simply must be recognized when one is interpreting the findings and drawing conclusions. For example, we would argue that the small number of false positives and negatives attributable to our case definition cannot refute the very high incidence and prevalence of PBC that we observed, particularly when compared to previous Canadian studies in this field.

The second major limitation of our study is the lack of information sources other than administrative data. Ideally, clinical details (e.g. history and physical examination findings), laboratory data (e.g. for calculation of the Mayo risk score), histology reports (e.g. to define the stage of PBC), and pharmacologic data (e.g. UDCA therapy) would be used to enrich our study. Although several of

these data sources exist in the CHR, their accuracy has not been validated, nor is linkage with the databases that we employed feasible at this point in time.

FUTURE RESEARCH QUESTIONS

This study will facilitate several further lines of research in the study of PBC and other conditions. First, we plan to widen the scope of our study to include these databases in the remainder of Alberta and hopefully additional regions within and outside of Canada. As mentioned, the ubiquitous nature of administrative data will support the examination of PBC epidemiology over a broader geographic area and help improve our understanding of the pathogenesis of this condition. On a related note, we plan to describe the spatial distribution of PBC cases in Alberta in order to investigate potential environmental influences on the epidemiology and natural history of this condition. For example, other investigators have used geographical clustering analyses to document an increased prevalence of PBC near toxic waste sites in New York City[55] and in areas of high air pollution across the United States.[18] This data supports basic science investigations that have suggested a role of environmental agents (i.e. xenobiotics)[152] on PBC occurrence. As a first extension of the current data, I plan to use information available from an air pollution monitoring network maintained by Environment Canada to examine the role of environmental pollutants on the incidence of PBC in Alberta. Additional studies will investigate the natural history of PBC in the CHR in more detail. For example, I plan to use the Inpatient and

ACCS databases to identify complications of the disease (e.g. features of hepatic decompensation such as variceal bleeding, hepatic encephalopathy, and ascites). Similarly, linkage with the Alberta Cancer Registry[153] will facilitate an investigation of the risk of malignancy, particularly hepatocellular carcinoma, in this condition.

In terms of additional studies, the methodology that we have described can be applied to other hepatic and non-hepatic conditions. Administrative data is particularly useful for studying uncommon disorders such as PBC due to its large catchment population.

REFERENCES

1. Jones DE. Pathogenesis of primary biliary cirrhosis. Clin Liver Dis 2008;12:305-21; viii.
2. Kita H, Nalbandian G, Keeffe EB, Coppel RL, Gershwin ME. Pathogenesis of primary biliary cirrhosis. Clin Liver Dis 2003;7:821-39.
3. Selmi C, Invernizzi P, Keeffe EB, Coppel RL, Podda M, Rossaro L, Ansari AA, Gershwin ME. Epidemiology and pathogenesis of primary biliary cirrhosis. J Clin Gastroenterol 2004;38:264-71.
4. Kita H, He XS, Gershwin ME. Autoimmunity and environmental factors in the pathogenesis of primary biliary cirrhosis. Ann Med 2004;36:72-80.
5. Bogdanos DP, Baum H, Vergani D. Antimitochondrial and other autoantibodies. Clin Liver Dis 2003;7:759-77, vi.
6. Leung PS, Coppel RL, Ansari A, Munoz S, Gershwin ME. Antimitochondrial antibodies in primary biliary cirrhosis. Semin Liver Dis 1997;17:61-9.
7. Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. Hepatology 2000;31:1005-13.
8. Talwalkar JA, Lindor KD. Primary biliary cirrhosis. Lancet 2003;362:53-61.
9. Angulo P, Lindor KD. Primary biliary cirrhosis and primary sclerosing cholangitis. Clin Liver Dis 1999;3:529-70.

10. Pares A, Rodes J. Natural history of primary biliary cirrhosis. Clin Liver Dis 2003;7:779-94.

11. Mayo MJ. Natural history of primary biliary cirrhosis. Clin Liver Dis 2008;12:277-88; viii.

12. Lindor K. Ursodeoxycholic acid for the treatment of primary biliary cirrhosis. N Engl J Med 2007;357:1524-9.

13. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 1997;113:884-90.

14. Poupon RE, Lindor KD, Pares A, Chazouilleres O, Poupon R, Heathcote EJ. Combined analysis of the effect of treatment with ursodeoxycholic acid on histologic progression in primary biliary cirrhosis. J Hepatol 2003;39:12-6.

15. Lindor KD, Jorgensen RA, Therneau TM, Malinchoc M, Dickson ER. Ursodeoxycholic acid delays the onset of esophageal varices in primary biliary cirrhosis. Mayo Clin Proc 1997;72:1137-40.

16. Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology 2000;32:1196-9.

17. Metcalf J, James O. The geoepidemiology of primary biliary cirrhosis. Semin Liver Dis 1997;17:13-22.

18. Gross RG, Odin JA. Recent advances in the epidemiology of primary biliary cirrhosis. Clin Liver Dis 2008;12:289-303; viii.

19. Triger DR. Primary biliary cirrhosis: an epidemiological study. Br Med J 1980;281:772-5.

20. Hislop WS, Main G, Robertson AJ. Primary biliary cirrhosis: experience in a non-referral centre. Lancet 1981;2:144.

21. Hamlyn AN, Macklon AF, James O. Primary biliary cirrhosis: geographical clustering and symptomatic onset seasonality. Gut 1983;24:940-5.

22. Myszor M, James OF. The epidemiology of primary biliary cirrhosis in north-east England: an increasingly common disease? Q J Med 1990;75:377-85.

23. Eriksson S, Lindgren S. The prevalence and clinical spectrum of primary biliary cirrhosis in a defined population. Scand J Gastroenterol 1984;19:971-6.

24. Lofgren J, Jarnerot G, Danielsson D, Hemdal I. Incidence and prevalence of primary biliary cirrhosis in a defined population in Sweden. Scand J Gastroenterol 1985;20:647-50.

25. Danielsson A, Boqvist L, Uddenfeldt P. Epidemiology of primary biliary cirrhosis in a defined rural population in the northern part of Sweden. Hepatology 1990;11:458-64.

26. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing

cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol 1998;33:99-103.

27. Triger DR, Berg PA, Rodes J. Epidemiology of primary biliary cirrhosis. Liver 1984;4:195-200.

28. Goudie BM, MacFarlane G, Boyle P. Epidemiology of antimitochondrial antibody seropositivity and primary biliary biliary cirrhosis in west of Scotland. Gut 1987;28:A1346.

29. Remmel T, Remmel H, Uibo R, Salupere V. Primary biliary cirrhosis in Estonia. With special reference to incidence, prevalence, clinical features, and outcome. Scand J Gastroenterol 1995;30:367-71.

30. Watson RG, Angus PW, Dewar M, Goss B, Sewell RB, Smallwood RA. Low prevalence of primary biliary cirrhosis in Victoria, Australia. Melbourne Liver Group. Gut 1995;36:927-30.

31. Sood S, Gow PJ, Christie JM, Angus PW. Epidemiology of primary biliary cirrhosis in Victoria, Australia: high prevalence in migrant populations. Gastroenterology 2004;127:470-5.

32. Witt-Sullivan H, Heathcote J, Cauch K, Blendis L, Ghent C, Katz A, Milner R, Pappas SC, Rankin J, Wanless IR. The demography of primary biliary cirrhosis in Ontario, Canada. Hepatology 1990;12:98-105.

33. Villeneuve JP, Fenyves D, Infante-Rivard C. Descriptive epidemiology of primary biliary cirrhosis in the province of Quebec. Can J Gastroenterol 1991;5:174-8.

34. Kim WR, Lindor KD, Locke GR, 3rd, Therneau TM, Homburger HA, Batts KP, Yawn BP, Petz JL, Melton LJ, 3rd, Dickson ER. Epidemiology and natural history of primary biliary cirrhosis in a US community. Gastroenterology 2000;119:1631-6.

35. Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska Natives. Am J Gastroenterol 2002;97:2402-7.

36. Metcalf JV, Bhopal RS, Gray J, Howel D, James OF. Incidence and prevalence of primary biliary cirrhosis in the city of Newcastle upon Tyne, England. Int J Epidemiol 1997;26:830-6.

37. Prince MI, Chetwynd A, Diggle P, Jarner M, Metcalf JV, James OF. The geographical distribution of primary biliary cirrhosis in a well-defined cohort. Hepatology 2001;34:1083-8.

38. Rubel LR, Rabin L, Seeff LB, Licht H, Cuccherini BA. Does primary biliary cirrhosis in men differ from primary biliary cirrhosis in women? Hepatology 1984;4:671-7.

39. Bach N, Schaffner F. Familial primary biliary cirrhosis. J Hepatol 1994;20:698-701.

40. Brind AM, Bray GP, Portmann BC, Williams R. Prevalence and pattern of familial disease in primary biliary cirrhosis. Gut 1995;36:615-7.

41. Floreani A, Naccarato R, Chiaramonte M. Prevalence of familial disease in primary biliary cirrhosis in Italy. J Hepatol 1997;26:737-8.

42. Galbraith RM, Smith M, Mackenzie RM, Tee DE, Doniach D, Williams R. High prevalence of seroimmunologic abnormalities in relatives of patients with active chronic hepatitis or primary biliary cirrhosis. N Engl J Med 1974;290:63-9.

43. Tsuji K, Watanabe Y, Van De Water J, Nakanishi T, Kajiyama G, Parikh-Patel A, Coppel R, Gershwin ME. Familial primary biliary cirrhosis in Hiroshima. J Autoimmun 1999;13:171-8.

44. Selmi C, Mayo MJ, Bach N, Ishibashi H, Invernizzi P, Gish RG, Gordon SC, Wright HI, Zweiban B, Podda M, Gershwin ME. Primary biliary cirrhosis in monozygotic and dizygotic twins: genetics, epigenetics, and environment. Gastroenterology 2004;127:485-92.

45. Chohan MR. Primary biliary cirrhosis in twin sisters. Gut 1973;14:213-4.

46. Tanaka A, Borchers AT, Ishibashi H, Ansari AA, Keen CL, Gershwin ME. Genetic and familial considerations of primary biliary cirrhosis. Am J Gastroenterol 2001;96:8-15.

47. Culp KS, Fleming CR, Duffy J, Baldus WP, Dickson ER. Autoimmune associations in primary biliary cirrhosis. Mayo Clin Proc 1982;57:365-70.

48. Parikh-Patel A, Gold E, Utts J, Gershwin ME. The association between gravidity and primary biliary cirrhosis. Ann Epidemiol 2002;12:264-72.

49. Howel D, Fischbacher CM, Bhopal RS, Gray J, Metcalf JV, James OF. An exploratory population-based case-control study of primary biliary cirrhosis. Hepatology 2000;31:1055-60.

50. Fernandes G. Dietary lipids and risk of autoimmune disease. Clin Immunol Immunopathol 1994;72:193-7.

51. Parikh-Patel A, Gold EB, Worman H, Krivy KE, Gershwin ME. Risk factors for primary biliary cirrhosis in a cohort of patients from the United States. Hepatology 2001;33:16-21.

52. Abdulkarim AS, Petrovic LM, Kim WR, Angulo P, Lloyd RV, Lindor KD. Primary biliary cirrhosis: an infectious disease caused by Chlamydia pneumoniae? J Hepatol 2004;40:380-4.

53. Xu L, Shen Z, Guo L, Fodera B, Keogh A, Joplin R, O'Donnell B, Aitken J, Carman W, Neuberger J, Mason A. Does a betaretrovirus infection trigger primary biliary cirrhosis? Proc Natl Acad Sci U S A 2003;100:8454-9.

54. Selmi C, Gershwin ME. Bacteria and human autoimmunity: the case of primary biliary cirrhosis. Curr Opin Rheumatol 2004;16:406-10.

55. Ala A, Stanca CM, Bu-Ghanim M, Ahmado I, Branch AD, Schiano TD, Odin JA, Bach N. Increased prevalence of primary biliary cirrhosis near Superfund toxic waste sites. Hepatology 2006;43:525-31.

56. Prince M, Chetwynd A, Newman W, Metcalf JV, James OF. Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: follow-up for up to 28 years. Gastroenterology 2002;123:1044-51.

57. ter Borg PC, Schalm SW, Hansen BE, van Buuren HR. Prognosis of ursodeoxycholic Acid-treated patients with primary biliary cirrhosis.

Results of a 10-yr cohort study involving 297 patients. Am J Gastroenterol 2006;101:2044-50.

58. Corpechot C, Carrat F, Bahr A, Chretien Y, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology 2005;128:297-303.

59. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology 2006;130:715-20.

60. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: model for decision making. Hepatology 1989;10:1-7.

61. Grambsch PM, Dickson ER, Kaplan M, LeSage G, Fleming TR, Langworthy AL. Extramural cross-validation of the Mayo primary biliary cirrhosis survival model establishes its generalizability. Hepatology 1989;10:846-50.

62. Klion FM, Fabry TL, Palmer M, Schaffner F. Prediction of survival of patients with primary biliary cirrhosis. Examination of the Mayo Clinic model on a group of patients with known endpoint. Gastroenterology 1992;102:310-3.

63. Murtaugh PA, Dickson ER, Van Dam GM, Malinchoc M, Grambsch PM, Langworthy AL, Gips CH. Primary biliary cirrhosis: prediction of short-term survival based on repeated patient visits. Hepatology 1994;20:126-34.

64. Springer J, Cauch-Dudek K, O'Rourke K, Wanless IR, Heathcote EJ. Asymptomatic primary biliary cirrhosis: a study of its natural history and prognosis. Am J Gastroenterol 1999;94:47-53.

65. Beswick DR, Klatskin G, Boyer JL. Asymptomatic primary biliary cirrhosis. A progress report on long-term follow-up and natural history. Gastroenterology 1985;89:267-71.

66. Roll J, Boyer JL, Barry D, Klatskin G. The prognostic importance of clinical and histologic features in asymptomatic and symptomatic primary biliary cirrhosis. N Engl J Med 1983;308:1-7.

67. Christensen E, Altman DG, Neuberger J, De Stavola BL, Tygstrup N, Williams R. Updating prognosis in primary biliary cirrhosis using a time-dependent Cox regression model. PBC1 and PBC2 trial groups. Gastroenterology 1993;105:1865-76.

68. Christensen E, Neuberger J, Crowe J, Altman DG, Popper H, Portmann B, Doniach D, Ranek L, Tygstrup N, Williams R. Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis. Final results of an international trial. Gastroenterology 1985;89:1084-91.

69. Poupon RE, Bonnand AM, Chretien Y, Poupon R. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. The UDCA-PBC Study Group. Hepatology 1999;29:1668-71.

70. Shi J, Wu C, Lin Y, Chen YX, Zhu L, Xie WF. Long-term effects of mid-dose ursodeoxycholic acid in primary biliary cirrhosis: a meta-analysis of randomized controlled trials. Am J Gastroenterol 2006;101:1529-38.

71. Iezzoni LI. Coded data from administrative sources. In: Iezzoni LI, ed. Risk adjustment for measuring health care outcomes. 3rd ed. Chicago: Foundation of the American College of Healthcare Executives, 2003.

72. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. N Engl J Med 2001;345:663-8.

73. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745-50.

74. Edwards EB, Roberts JP, McBride MA, Schulak JA, Hunsicker LG. The effect of the volume of procedures at transplantation centers on mortality after liver transplantation. N Engl J Med 1999;341:2049-53.

75. Nguyen GC, Segev DL, Thuluvath PJ. Racial disparities in the management of hospitalized patients with cirrhosis and complications of portal hypertension: a national study. Hepatology 2007;45:1282-9.

76. Myers RP, Papay KD, Shaheen AA, Kaplan GG. Relationship between hospital volume and outcomes of esophageal variceal bleeding in the United States. Clin Gastroenterol Hepatol 2008;6:789-98.

77. Myers RP, Shaheen AA, Li B, Dean S, Quan H. Impact of liver disease, alcohol abuse, and unintentional ingestions on the outcomes of acetaminophen overdose. Clin Gastroenterol Hepatol 2008;6:918-25; quiz 837.

78. Schrag D, Cramer LD, Bach PB, Cohen AM, Warren JL, Begg CB. Influence of hospital procedure volume on outcomes following surgery for colon cancer. JAMA 2000;284:3028-35.

79. Myers RP, Liu M, Shaheen AA. The burden of hepatitis C virus infection is growing: a Canadian population-based study of hospitalizations from 1994 to 2004. Can J Gastroenterol 2008;22:381-7.

80. Iezzoni LI. Assessing quality using administrative data. Ann Intern Med 1997;127:666-74.

81. Edouard L, Rawson NS. Reliability of the recording of hysterectomy in the Saskatchewan health care system. Br J Obstet Gynaecol 1996;103:891-7.

82. Fisher ES, Whaley FS, Krushat WM, Malenka DJ, Fleming C, Baron JA, Hsia DC. The accuracy of Medicare's hospital claims data: progress has been made, but problems remain. Am J Public Health 1992;82:243-8.

83. Romano PS, Mark DH. Bias in the coding of hospital discharge data and its implications for quality assessment. Med Care 1994;32:81-90.

84. Whittle J, Steinberg EP, Anderson GF, Herbert R. Accuracy of Medicare claims data for estimation of cancer incidence and resection rates among elderly Americans. Med Care 1991;29:1226-36.

85. Karam V, Gunson B, Roggen F, Grande L, Wannoff W, Janssen M, Guckelberger O, Delvart V, Bismuth H, Hockerstedt K, Rogiers X, Adam R. Quality control of the European Liver Transplant Registry: results of audit visits to the contributing centers. Transplantation 2003;75:2167-73.

86. Myers RP, Leung Y, Shaheen AA, Li B. Validation of ICD-9-CM/ICD-10 coding algorithms for the identification of patients with acetaminophen overdose and hepatotoxicity using administrative data. BMC Health Serv Res 2007;7:159.

87. Steinke DT, Weston TL, Morris AD, MacDonald TM, Dillon JF. The epidemiology of liver disease in Tayside database: a population-based record-linkage study. J Biomed Inform 2002;35:186-93.

88. De Coster C, Quan H, Finlayson A, Gao M, Halfon P, Humphries KH, Johansen H, Lix LM, Luthi JC, Ma J, Romano PS, Roos L, Sundararajan V, Tu JV, Webster G, Ghali WA. Identifying priorities in methodological research using ICD-9-CM and ICD-10 administrative data: report from an international consortium. BMC Health Serv Res 2006;6:77.

89. International Classificiation of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Practice Management Information Corporation, 2001.

90. International Statistical Classifications of Diseases and Related Health Problems, 10th Revision (ICD-10). World Health Organization, 2005.

91. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. Am J Epidemiol 1999;149:916-24.

92. Abraham NS, Cohen DC, Rivers B, Richardson P. Validation of administrative data used for the diagnosis of upper gastrointestinal events following nonsteroidal anti-inflammatory drug prescription. Aliment Pharmacol Ther 2006;24:299-306.

93. Quan H, Parsons GA, Ghali WA. Assessing accuracy of diagnosis-type indicators for flagging complications in administrative data. J Clin Epidemiol 2004;57:366-72.

94. Quan H, Parsons GA, Ghali WA. Validity of information on comorbidity derived from ICD-9-CCM administrative data. Med Care 2002;40:675-85.

95. Quan H, Parsons GA, Ghali WA. Validity of procedure codes in International Classification of Diseases, 9th revision, clinical modification administrative data. Med Care 2004;42:801-9.

96. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130-9.

97. Zgibor JC, Orchard TJ, Saul M, Piatt G, Ruppert K, Stewart A, Siminerio LM. Developing and validating a diabetes database in a large health system. Diabetes Res Clin Pract 2007;75:313-9.

98. Tirschwell DL, Longstreth WT, Jr. Validating administrative data in stroke research. Stroke 2002;33:2465-70.

99. Kashner TM. Agreement between administrative files and written medical records: a case of the Department of Veterans Affairs. Med Care 1998;36:1324-36.

100. Movig KL, Leufkens HG, Lenderink AW, Egberts AC. Validity of hospital discharge International Classification of Diseases (ICD) codes for identifying patients with hyponatremia. J Clin Epidemiol 2003;56:530-5.

101. Benesch C, Witter DM, Jr., Wilder AL, Duncan PW, Samsa GP, Matchar DB. Inaccuracy of the International Classification of Diseases (ICD-9-CM)

in identifying the diagnosis of ischemic cerebrovascular disease. Neurology 1997;49:660-4.

102. Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. Stroke 1998;29:1602-4.

103. Data Disclosure Handbook: Alberta Health and Wellness, 2003:1-15.

104. Williams JI, Young W. A summary of studies on the quality of health care administrative databases in Canada. In: Goel V, Williams JI, Anderson GM, Blackstein-Hirsch P, Fooks C, Naylor CD, eds. Patterns of Health Care in Ontario: The ICES Practice Atlas. 2nd ed. Ottawa, ON: The Canadian Medical Association, 1996:339-345.

105. Quan H, Cujec B, Jin Y, Johnson D. Acute myocardial infarction in Alberta: temporal changes in outcomes, 1994 to 1999. Can J Cardiol 2004;20:213-9.

106. Kaplan GG, Gregson DB, Laupland KB. Population-based study of the epidemiology of and the risk factors for pyogenic liver abscess. Clin Gastroenterol Hepatol 2004;2:1032-8.

107. Johnson D, Jin Y, Quan H, Cujec B. Beta-blockers and angiotensin-converting enzyme inhibitors/receptor blockers prescriptions after hospital discharge for heart failure are associated with decreased mortality in Alberta, Canada. J Am Coll Cardiol 2003;42:1438-45.

108. Khan NA, Quan H, Bugar JM, Lemaire JB, Brant R, Ghali WA. Association of postoperative complications with hospital costs and length of stay in a tertiary care center. J Gen Intern Med 2006;21:177-80.

109. Cujec B, Quan H, Jin Y, Johnson D. Association between physician specialty and volumes of treated patients and mortality among patients hospitalized for newly diagnosed heart failure. Am J Med 2005;118:35-44.

110. Theal JJ, Toosi MN, Girlan L, Heslegrave RJ, Huet PM, Burak KW, Swain M, Tomlinson GA, Heathcote EJ. A randomized, controlled crossover trial of ondansetron in patients with primary biliary cirrhosis and fatigue. Hepatology 2005;41:1305-12.

111. Myers RP, Shaheen AA, Swain MG, Lee SS, Cole S, Coffey-Williamson S, Burak KW. Rituximab for primary biliary cirrhosis (PBC) refractory to ursodeoxycholic acid (UDCA). Hepatology 2007;46:550A.

112. Leung PS, Chuang DT, Wynn RM, Cha S, Danner DJ, Ansari A, Coppel RL, Gershwin ME. Autoantibodies to BCOADC-E2 in patients with primary biliary cirrhosis recognize a conformational epitope. Hepatology 1995;22:505-13.

113. Leung PS, Watanabe Y, Munoz S, Teuber SS, Patel MS, Korenberg JR, Hara P, Coppel R, Gershwin ME. Chromosome localization and RFLP analysis of PDC-E2: the major autoantigen of primary biliary cirrhosis. Autoimmunity 1993;14:335-40.

114. Ludwig J, Dickson ER, McDonald GS. Staging of chronic nonsuppurative destructive cholangitis (syndrome of primary biliary cirrhosis). Virchows Arch A Pathol Anat Histol 1978;379:103-12.

115. James OF, Bhopal R, Howel D, Gray J, Burt AD, Metcalf JV. Primary biliary cirrhosis once rare, now common in the United Kingdom? Hepatology 1999;30:390-4.

116. Wiesner RH, LaRusso NF, Ludwig J, Dickson ER. Comparison of the clinicopathologic features of primary sclerosing cholangitis and primary biliary cirrhosis. Gastroenterology 1985;88:108-14.

117. Kingham JG, Abbasi A. Co-existence of primary biliary cirrhosis and primary sclerosing cholangitis: a rare overlap syndrome put in perspective. Eur J Gastroenterol Hepatol 2005;17:1077-80.

118. Burak KW, Urbanski SJ, Swain MG. A case of coexisting primary biliary cirrhosis and primary sclerosing cholangitis: a new overlap of autoimmune liver diseases. Dig Dis Sci 2001;46:2043-7.

119. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. Hepatology 2002;36:479-97.

120. Kaya M, Angulo P, Lindor KD. Overlap of autoimmune hepatitis and primary sclerosing cholangitis: an evaluation of a modified scoring system. J Hepatol 2000;33:537-42.

121. Rust C, Beuers U. Overlap syndromes among autoimmune liver diseases. World J Gastroenterol 2008;14:3368-73.

122. Farrokhyar F, McHugh K, Irvine EJ. Self-reported awareness and use of the International Classification of Diseases coding of inflammatory bowel disease services by Ontario physicians. Can J Gastroenterol 2002;16:519-26.

123. Hamlyn AN, Sherlock S. The epidemiology of primary biliary cirrhosis: a survey of mortality in England and Wales. Gut 1974;15:473-9.

124. Gershwin ME, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, Lindor KD, Kaplan MM, Vierling JM. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. Hepatology 2005;42:1194-202.

125. Steinke D, Weston T, Morris A, MacDonald T, Dillon J. Incidence, prevalence and resource use of primary biliary cirrhosis in Tayside, Scotland. J Hepatol 2001;34:532A.

126. Quality, Safety, and Health Information. Calgary Health Region. Calgary Health Region Historical Population (http://www.crha-health.ab.ca/qshi/hsau/Demographic_Data/chr_calgary_rural_pop.xls). Accessed July 2008.

127. Profile of age and sex, for Canada, provinces, territories, census divisions and census subdivisions, 2001 census. Statistics Canada (http://www12.statcan.ca/english/census01/home/index.cfm). Accessed March 2006.

128. Cameron AC, Trivedi PK. Regression Analysis of Count Data. Cambridge University Press, 1998.

129. Lee J, Belanger A, Doucette JT, Stanca C, Friedman S, Bach N. Transplantation trends in primary biliary cirrhosis. Clin Gastroenterol Hepatol 2007;5:1313-5.

130. Mendes FD, Kim WR, Pedersen R, Therneau T, Lindor KD. Mortality attributable to cholestatic liver disease in the United States. Hepatology 2008;47:1241-7.

131. Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. N Engl J Med 1991;324:1548-54.

132. Lindor KD, Dickson ER, Baldus WP, Jorgensen RA, Ludwig J, Murtaugh PA, Harrison JM, Wiesner RH, Anderson ML, Lange SM, et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. Gastroenterology 1994;106:1284-90.

133. Heathcote EJ, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, Michieletti P, Minuk GY, Pappas SC, Scully LJ, et al. The Canadian Multicenter Double-blind Randomized Controlled Trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1994;19:1149-56.

134. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. N Engl J Med 1994;330:1342-7.

135. Foulk WT, Baggenstoss AH, Butt HR. Primary biliary cirrhosis: Reevaluation by clinical and histologic study of 49 cases. Gastroenterol 1964;47:354-74.

136. Sherlock S. Primary biliary cirrhosis (chronic intrahepatic obstructive jaundice). Gastroenterol 1959;37:574-86.

137. Gong Y, Huang Z, Christensen E, Gluud C. Ursodeoxycholic acid for patients with primary biliary cirrhosis: an updated systematic review and meta-analysis of randomized clinical trials using Bayesian approach as sensitivity analyses. Am J Gastroenterol 2007;102:1799-807.

138. Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. Lancet 1999;354:1053-60.

139. Kizilisik TA, Larsen IM, Bain VG, Kneteman NM. Liver transplantation at the University of Alberta Hospitals: a review of the first three years. Transplant Proc 1993;25:2203-5.

140. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. . J Am Stat Assoc 1958;53:457-481.

141. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med 2004;23:51-64.

142. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 1961;6:101-21.

143. Dickman, P.W. Estimating and modelling relative survival in SAS and Stata (http://www.pauldickman.com/rsmodel/index.php). Accessed August 2008.

144. Statistics Canada. Life tables, Canada, provinces and territories (http://www.statcan.ca/english/freepub/84-537-XIE/84-537-XIE2006001.htm). Accessed August 2008.

145. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. Springer, 2000.

146. Poupon R, Chretien Y, Poupon RE, Ballet F, Calmus Y, Darnis F. Is ursodeoxycholic acid an effective treatment for primary biliary cirrhosis? Lancet 1987;1:834-6.

147. Koulentaki M, Moscandrea J, Dimoulios P, Chatzicostas C, Kouroumalis EA. Survival of anti-mitochondrial antibody-positive and -negative primary biliary cirrhosis patients on ursodeoxycholic acid treatment. Dig Dis Sci 2004;49:1190-5.

148. Manos MM, Leyden WA, Murphy RC, Terrault NA, Bell BP. Limitations of conventionally derived chronic liver disease mortality rates: Results of a comprehensive assessment. Hepatology 2008;47:1150-7.

149. Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, Fleming TR, Fisher LD, Beaver SJ, LaRusso NF. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. Hepatology 1989;10:430-6.

150. Orrego H, Israel Y, Blake JE, Medline A. Assessment of prognostic factors in alcoholic liver disease: toward a global quantitative expression of severity. Hepatology 1983;3:896-905.

151. Nakamura M, Kondo H, Mori T, Komori A, Matsuyama M, Ito M, Takii Y, Koyabu M, Yokoyama T, Migita K, Daikoku M, Abiru S, Yatsuhashi H, Takezaki E, Masaki N, Sugi K, Honda K, Adachi H, Nishi H, Watanabe Y, Nakamura Y, Shimada M, Komatsu T, Saito A, Saoshiro T, Harada H, Sodeyama T, Hayashi S, Masumoto A, Sando T, Yamamoto T, Sakai H, Kobayashi M, Muro T, Koga M, Shums Z, Norman GL, Ishibashi H. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology 2007;45:118-27.

152. Amano K, Leung PS, Xu Q, Marik J, Quan C, Kurth MJ, Nantz MH, Ansari AA, Lam KS, Zeniya M, Coppel RL, Gershwin ME. Xenobiotic-induced loss of tolerance in rabbits to the mitochondrial autoantigen of primary biliary cirrhosis is reversible. J Immunol 2004;172:6444-52.

153. Alberta Cancer Board. What is the Alberta Cancer Registry? (http://www.cancerboard.ab.ca/CancerAlberta/AlbertaCancerRegistry/) Accessed September 2008.

APPENDIX A

ETHICAL APPROVALS

FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

2005-06-13

OFFICE OF MEDICAL BIOETHICS
Room 93, Heritage Medical Research Bldg
3330 Hospital Drive NW
Calgary, AB, Canada T2N 4N1
Telephone: (403) 220-7990
Fax: (403) 283-8524
Email: omb@ucalgary.ca

Dr. H. Quan
Community Health Sciences
HMRB
Calgary, Alberta

Dear Dr. Quan:

RE: Population-Based Study of the Epidemiology of Primary Billiary Cirrhosis in the Calgary Health Region

Grant ID: 18520
MSc Student: Robert Myers

The above-noted thesis proposal (Version: 4, dated April 27, 2005) have been submitted for Committee review and found to be ethically acceptable.

Please note that this approval is subject to the following conditions:
(1) consent for access to personal identified health information in retrospective chart review is not required on grounds considered under Section 50 of the Health Information Act,
(2) a copy of the informed consent form must have been given to each research subject, if required for this study;
(3) a Progress Report must be submitted by 2006-06-13, containing the following information:
   i) the number of subjects recruited;
   ii) a description of any protocol modification;
   iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
   iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
   v) a copy of the current informed consent form;
   vi) the expected date of termination of this project.
(4) a Final Report must be submitted at the termination of the project.

Please note that you have been named as a principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.

Yours sincerely,

Christopher J. Doig, MD, MSc, FRCPC

Chair, Conjoint Health Research Ethics Board

CJD/km
c.c. Adult Research Committee Dr. T. Noseworthy (information) Research Services R. Myers (MSc Student)
Office of Information & Privacy Commissioner

FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

August 11, 2008

OFFICE OF MEDICAL BIOETHICS
Room 93, Heritage Medical Research Bldg
3330 Hospital Drive NW
Calgary, AB, Canada T2N 4N1
Telephone: (403) 220-7990
Fax: (403) 283-8524
Email: omb@ucalgary.ca

Dr. Hude Quan
Department of Medicine
HSC
Calgary
Alberta

Dear Dr. Quan:

Re: Population-Based Study of the Epidemiology of Primary Biliary Cirrhosis in the Calgary Health Region

Ethics ID: 18520

Your request to modify the above named research protocol has been reviewed and approved.

I am pleased to advise you that it is permissible for you to use the revised protocol to enable you to link the present dataset with the records of 17 PBC patients who have participated in two clinical trials performed in the Heritage Medical Research Clinic under the supervision of yourself and colleagues in the Liver Unit, based on the information contained in your correspondence of August 8, 2008.

A progress report concerning this study is required annually, from the date of the original approval 2005-06-13. The report should contain information concerning:

(i) the number of subjects recruited;
(ii) a description of any protocol modification;
(iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
(iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
(v) a copy of the current informed consent form;
(vi) the expected date of termination of this project;

Thank you for the attention which I know you will bring to these matters.

Yours sincerely,

Glenys Godlovitch, BA(Hons) LLB, PhD.
Chair, Conjoint Health Research Ethics Board
GG/eb
c.c. Dr. R. Myers