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Predictors of Cirrhosis and Cholangiocarcinoma in Patients with Primary Sclerosing Cholangitis: An Academic Center Experience

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Predictors of Cirrhosis and Cholangiocarcinoma in Patients with Primary Sclerosing Cholangitis: An Academic Center Experience

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Abstract

Background and goals: Outcomes of patients with primary sclerosing cholangitis (PSC) in Central Missouri are unknown. The University of Missouri-Columbia services 600,000 individuals in Central Missouri. Our aims were to a) examine the outcomes of PSC patients receiving care at our academic institution, and b) identify predictors of PSC-related serious adverse events. **Methods:** A retrospective study of patients with PSC in a non-transplant center. Primary outcome was development of ≥ 1 of PSC-related serious adverse event: 1) progression to cirrhosis, or 2) development of cholangiocarcinoma. **Results**: From year 2000 to 2018, 42 patients fulfilled the criteria for the diagnosis of PSC. 55% were male, 79% had associated inflammatory bowel disease (IBD). The median follow-up from time of diagnosis of PSC until last follow up or death was 5.5 years. Fifty-seven percent of patients developed ≥1 PSC-related adverse event; 36% (8/22) of those who progressed to decompensation underwent liver transplantation. The median time from diagnosis of PSC until progression to decompensation was 6.3 years. The median time from decompensation to transplantation was 10.8 years. Twelve percent developed ≥1 cancer (cholangiocarcinoma=2; gallbladder cancer=2; colon cancer =1; and hepatocellular carcinoma =1). The overall mortality was 9.5%. The median time from PSC diagnosis until death was 10.2 years. Cox hazards regression analysis showed only age (HR=1.05; p=0.028; 95% CI, 1.01-1.11) and serum bilirubin (HR= 1.55; p=0.033; 95% CI, 1.03-2.28) at the time of PSC diagnosis. **Conclusion:** Age and bilirubin are important predictors of PSC-related outcomes.

Keywords: Primary sclerosing cholangitis; Cirrhosis; Cholangiocarcinoma; Colorectal Cancer; Gallbladder Cancer; Liver transplantation

1. Introduction

Primary Sclerosing Cholangitis (PSC) is a chronic biliary disease characterized by cholestasis and ongoing destruction of the intra- and/or extrahepatic biliary ducts, often leading to cirrhosis and its consequent complications.(*1*) PSC is often associated with inflammatory bowel disease (IBD), namely Ulcerative Colitis (UC).(*2*) PSC is one of the most important risk factors for the development of cholangiocarcinoma, a lethal bile duct cancer, with a lifetime risk up to 30%.(*3*) Moreover, PSC is the fifth leading indication for liver transplantation in Western population, and the leading indication for liver transplantation in some Nordic countries.(*4*) Furthermore, patients with PSC-IBD are at significantly higher risk for colorectal cancer, compared with patients with IBD alone. Studies have

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shown that colorectal cancer occurs at a much younger age in patients with PSC-IBD compared with patients with IBD alone.(*5*)

Epidemiological studies have found the highest prevalence rates of PSC in Northern

European countries and only very few parts of North America, ranging between 3.85 to 16.2 per 100,000 persons.(*5*) In contrast, the reported prevalence of PSC in Southern Europe(*6*) and South East Asia(*7*) is nearly 70 times lower.

Very little is known about the epidemiology of PSC in North America. The reported incidence and prevalence of PSC show quite variation, depending on the criteria used for ascertainment of PSC cases, the population under assessment, and the geographical area(s) studied. The highest reported prevalence rate for PSC of 13.6 per 100,000 age and sex-adjusted persons was in the year 2000 in Olmsted County, Minnesota, United States.(*8*) Toy et al. reported a lower age-adjusted PSC prevalence of 4.15 per 100,000 in Northern California in the year 2005.(*9*) In Alaska, no PSC patients were identified between the 1984 and 2000.(*10*) Only two Canadian studies reported the incidence and prevalence of PSC in Canada.(*11, 12*) These studies support the notion that PSC is a rare disease. Based on the studies reported, we estimate a PSC prevalence of 50,000 in the United States.

The University of Missouri-Columbia Healthcare System services 18 counties in Central Missouri, with an estimated population of more than 600,000 as of the 2017 census. In this paper, we describe the clinical features, natural history, morbidity, mortality, and outcomes of patients with PSC diagnosed and seen at the University of Missouri in Columbia.

2. Materials and Methods

This is a retrospective chart review of all patients suspected as having PSC between years 2000 and 2018 was performed at our non- liver transplant academic medical center. This study was approved by the University of Missouri-Columbia Institutional Review Board (IRB #2012024). All methods related to this study were performed in accordance with the relevant guidelines and regulations. The informed consent was waived by the University of Missouri IRB because this is a retrospective chart review study. The University of Missouri i2b2 searching database was queried for a search word "sclerosing cholangitis" between the years 2000 and 2018. The diagnosis of PSC was made based on the established criteria: a) presence of cholestasis as evidenced by elevated serum alkaline phosphatase (ALP) of ≥ 6 months in the absence of obstruction of the biliary tree, *and* b) cholangiographic findings consistent with PSC, *or* c) histological findings on liver biopsy compatible with PSC.(*13*) For each subject, the following data were collected: age at time of diagnosis of PSC; gender; presence or absence of IBD (UC, Crohn's disease (CD), or indeterminate colitis); PSC overlap with autoimmune hepatitis (AIH); magnetic resonance cholangiopancreatography (MRCP) findings; endoscopic retrograde cholangiopancreatography (ERCP) findings; laboratory parameters at the time of diagnosis of PSC (ALP; Aspartate aminotransferase (AST); Alanine aminotransferase (ALT); total bilirubin; albumin; hemoglobin; platelet count; prothrombin time (PT); carbohydrate antigen 19-9 (CA 19-9); carcinoembryonic antigen (CEA); perinuclear antineutrophil cytoplasmic (pANCA); total immunoglobulin G (IgG); and immunoglobulin G4 (IgG4)); endoscopic treatment (if applicable); treatment with ursodeoxycholic acid (UDCA); treatment with immunosuppressive agents (if applicable for PSC-AIH overlap); progression to cirrhosis; development of varices and ascites; liver transplantation; development of cholangiocarcinoma, hepatocellular carcinoma, colorectal cancer, and/or gallbladder cancer; and vital status at the time of chart review.

Liver biopsies were reviewed by an expert gastrointestinal pathologist (D.S.R). MRCPs and cholangiograms obtained during ERCPs were reviewed by experienced radiologists (N.D.T and A.H.G) and an interventional endoscopist (G.M.H).

Outcomes

The primary outcome of this study was development of ≥1 of the PSC-related serious events: progression to cirrhosis and consequent portal hypertension, and the development of cholangiocarcinoma. Secondary outcomes were development of gallbladder cancer, colorectal cancer,

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hepatocellular carcinoma, and whether patients experienced either normalization or stabilization of serum ALP within the first year after diagnosis of PSC.

Statistical Analysis

Continuous data were expressed as median with range. Categorical data were expressed as frequency and percentage. Chi-squared and Fisher's exact tests were used to compare patients with PSC who did and did not develop ≥1 PSC related serious event (i.e. progression to cirrhosis or development of cholangiocarcinoma). The Wilcoxon rank-sum test was used to compare means between PSC patients who did and did not experience ≥1 PSC-related serious events. Kaplan-Meier survival method was used to compare PSC patients who did and did not experience normalization of serum ALP within the first year of diagnosis of PSC using the logrank test. The primary endpoint was time from diagnosis of PSC to first occurrence of any of the defined PSC-related serious events (i.e. progression to cirrhosis and liver decompensation, or development of cholangiocarcinoma), and those were treated as a failures, whereas patients with PSC who were alive at the last known clinic follow-up were censored. Cox proportional hazards regression was used to determine independent predictors of PSC-related serious adverse events (i.e. progression to cirrhosis and liver decompensation, development of cholangiocarcinoma, or both). Statistical analyses were conducted using STATA v12.1 (Stata-Corp LP, College Station, TX), and graphs were created using GraphPad Prism. A p-value of <0.05 was considered statistically significant.

3. Results

The case-finding strategy using the University of Missouri-Columbia i2b2 yielded 288 patients (Figure 1). Between the years 2000 and 2018, 42 patients (39 Caucasians and 3 African-Americans) fulfilled the diagnostic criteria for PSC and followed up at the University of Missouri-Columbia. The median age at the time of PSC diagnosis was 36 years (range: 7-84 years), and 55% of patients (23/42) were male. Moreover, 79% (33/42) had concomitant IBD; UC was the most commonly associated IBD in this cohort (21 had UC, 8 had CD, and 4 had indeterminate colitis). The diagnosis of IBD preceded the diagnosis of PSC in the majority of patients; 85% (28/33) of patients were diagnosed with IBD before PSC, and IBD was detected by screening in five patients. Only one patient presented with abdominal pain and bloody diarrhea in conjunction with mixed pattern of elevated liver chemistries, and diagnosis of PSC and IBD had been made simultaneously. The median follow-up of this cohort from the time of diagnosis of PSC until the last known clinic follow-up or death was 5.5 years (range: 0.4-24.3 years).

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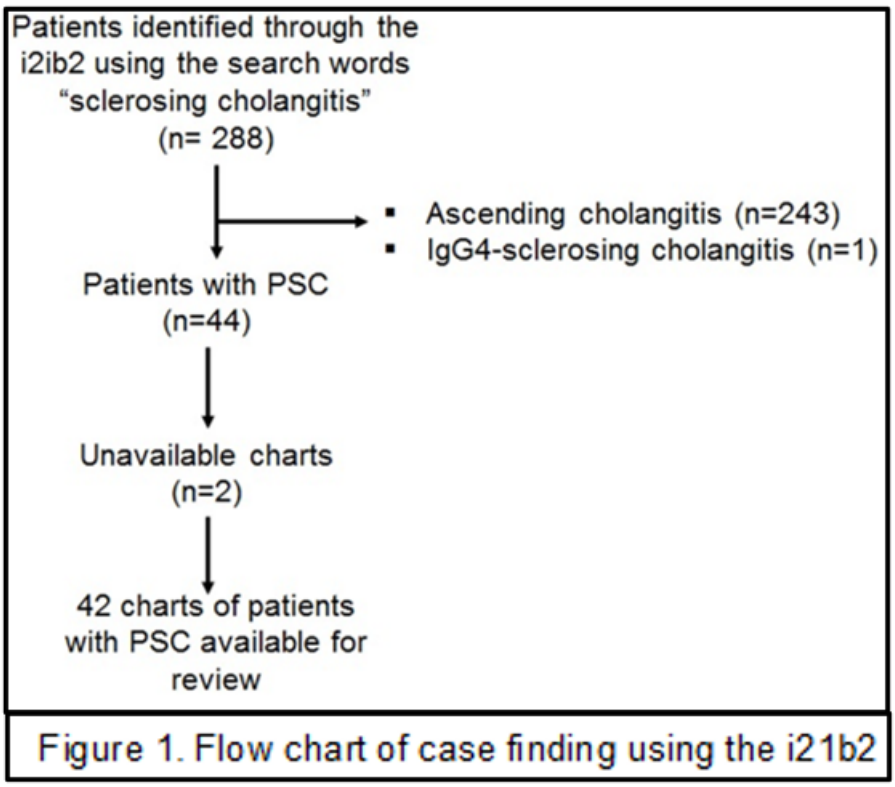

Figure 1. Please add figure caption here.

With respect to the diagnosis of PSC, 88% (37/42) of the subjects had MRCPs, of whom 95% (35/37) had MR findings consistent with PSC; the other 5 patients were diagnosed with PSC on ERCP. Sixty-two percent (26/42) of patients underwent ERCPs and evidence of PSC was found in all ERCPs, except in one patient. Indications for ERCP were cholestasis of unclear etiology (n=31), clinical features suspicious for acute cholangitis (n=3), and/or biliary stricture and/or dilatation or dominant stricture on MRCP (n=8). Intrahepatic PSC was more frequent than extrahepatic PSC (93% (39/42) vs. 50% (21/42), respectively). No case of small-duct PSC in this cohort was found. Forty-three percent (18/42) of the subjects had liver biopsy; 89% (16/18) had histological findings compatible with PSC; no patient had cirrhotic-stage PSC on histopathology. On microscopic examination of liver biopsies from patients with PSC, the classic lesion is well-established periductal fibrosis, which was seen in a subset of cases, while others demonstrated rather subtle features of bile duct injury and/or loss of bile ducts (i.e. ductopenia), given that PSC can be a focal liver disease. These histological findings, in conjunction with radiological features noted on cholangiographic studies, were supportive of the diagnosis of PSC.

PSC-AIH overlap syndrome was not uncommon. Of those who undergone evaluation by liver biopsy, 33% (6/18) had histological findings compatible with PSC-AIH overlap syndrome; thus, the prevalence of PSC-AIH overlap in this cohort was 14% (6/42). As for examination of liver biopsies from patients with PSC-AIH overlap syndrome, portal inflammation with numerous plasma cells and expanded fibrous tissue, portal edema, prominent interface hepatitis and foci of lobular necroinflammatory activity along with varying degrees of bile duct injury were noted. These histological findings are typical of liver biopsies from patients with PSC-AIH overlap syndrome. All patients presented with non-cirrhotic stage PSC, except for 3 patients. Table 1 shows the laboratory parameters for all patients at baseline.

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Table 1. Table caption.

Table 1. Laboratory parameters of the study population at the time of diagnosis of PSC (2000 and 2018).

Laboratory parameters	Median (range)
Alkaline phosphatase (40-129 U/L)	264 (51-2574)
Aspartate aminotransferase (0-30 U/L)	54 (15-276)
Alanine aminotransferase (10-32 U/L)	55 (14-691)
Total bilirubin (0.1-1 mg/dL)	0.9 (0.1-5.9)
Albumin (3.5-5 g/dL)	3.7 (2.4-5.2)
Total immunoglobulin (760-1590 mg/dL)	1388 (709-2998)
Prothrombin time (13.0-15.3 seconds)	14.1 (11.9-17.4)
Hemoglobin (12-15.5 g/dL)	11.9 (7.2-16.1)
Platelet count (150,000-450,000 cells/ml)	225,000 (50,000-691,000)
Carcinoembryonic antigen (<5 ng/ml)	2.7 (0.9-4.9)

Treatment

Thirty-one percent (13/42) of patients have had exposure to ursodeoxycholic acid (UDCA; median duration of treatment 2 years) at a median dose of 20mg/kg/body weight. Subjects with PSC-AIH overlap syndrome were treated with tapering courses of prednisone during acute flares, usually 40-60mg per day for 1 week, followed by reduction by 10mg every week until 10mg daily as maintenance, and with azathioprine at a dose of 50mg-100mg per day as maintenance therapy. Thirty-six percent (15/42) of patients developed biliary strictures with worsening of serum hepatic biochemistries requiring endoscopic intervention and biliary stenting.

Biochemical Course

Of the entire cohort, 17% (7/42) experienced either normalization (n=5) or stabilization (n=2) of serum ALP within the first 1 year of diagnosis of PSC. Of those who experienced normalization of serum ALP, only 2 patients were on UDCA for a median of 8 months at dose of 20mg/kg/day.

Outcomes

Fifty-seven percent (24/42) of patients developed ≥1 serious PSC-related event; 52% (22/42) progressed to cirrhotic-stage PSC and 12% (5/42) developed hepatobiliary and/or colorectal cancer. The median time from diagnosis of PSC until development of a PSC-related serious adverse event was 5 years (range: 1-21 years). Moreover, 86% (19/22) of those who progressed to cirrhosis developed clinically significant portal hypertension manifested as esophageal, gastric varices and ascites in 59% (13/22). No patient developed spontaneous bacterial peritonitis. The time from PSC diagnosis until progression to cirrhosis and liver decompensation was 6.3 years (range: 0.9-21.2 years). Of those who progressed to cirrhosis, 36% (8/22) underwent liver transplantation due to end-stage liver disease (time from progression to cirrhosis and liver decompensation until undergoing liver transplantation was 10.8 years (range: 1.8 -15.4 years); and time from undergoing liver transplantation until last known clinic follow-up was 1.7 years (range: 0.5-13 years). Of those who underwent liver transplantation, 12% (1/8) developed recurrent PSC in the liver allograft 3.2 years after liver transplantation. No patient had cholangiocarcinoma or hepatocellular carcinoma in their liver explant. With respect to IBD-related events, 9% (3/33) of patients with IBD underwent colectomy; 2 for IBD refractory to medical treatment, and one due to detection of low-grade dysplasia on

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surveillance colonoscopy. None of the patients who underwent colectomy had colorectal cancer on surgical specimen.

Twelve percent (5/42) of patients developed hepatobiliary and/or colorectal cancers during the follow-up (median time from PSC diagnosis until development of malignancy was 6 years; range: 1-21 years; Table 2). Two patients developed intrahepatic cholangiocarcinoma (4 and 8 years after diagnosis of PSC, respectively). Both underwent partial hepatectomy and had no locoregional metastasis. Both patients had no evidence of cholangiocarcinoma recurrence until their last clinic visit (8 and 11 years after diagnosis of cholangiocarcinoma, respectively). One patient developed perihilar cholangiocarcinoma 2.6 years after PSC diagnosis and underwent neoadjuvant chemotherapy and radiation, followed by orthotopic liver transplantation. This patient developed recurrent cholangiocarcinoma in the transplanted liver 7 months after liver transplantation. This patient was alive until last clinic visit (4 months after diagnosis of recurrent cholangiocarcinoma).

Table 2. Please add caption here.

Table 2. Patients with PSC who developed hepatobiliary and colorectal cancer during follow-up

Case	Cancers developed during follow-up
1	Cholangiocarcinoma
2	Cholangiocarcinoma, gallbladder cancer, and colon cancer
3	Cholangiocarcinoma and gallbladder cancers
4	Colon cancer
5	Hepatocellular carcinoma

Two patients developed gallbladder adenocarcinoma; both patients were undergoing routine cancer surveillance, and had gallbladder polyps that increased in size over a 1-year period. Both patients underwent open cholecystectomy and histology confirmed gallbladder adenocarcinoma. No patient had gallbladder cancer metastases to regional organs/lymph nodes, and none received chemotherapy. Both patients had no evidence of gallbladder cancer recurrence until their last clinic follow-up (8 and 10 years, respectively). One patient progressed to cirrhosis and developed hepatocellular carcinoma, and underwent liver transplantation for cirrhosis complicated by hepatocellular carcinoma; he had no metastases intraoperatively, and had no evidence of recurrent at his clinic visit (4.6 years after diagnosis of hepatocellular carcinoma, and 3.7 years after liver transplantation).

Two patients developed colorectal cancer in the setting of long-standing UC (time from diagnosis of PSC until diagnosis of colorectal cancer was 10 and 14 years, respectively). Of these 2 patients, one underwent routine surveillance for colorectal cancer; he had high-grade dysplasia on colonoscopy-obtained colonic mucosa biopsy. He underwent subtotal colectomy and had stage I colorectal cancer; there was no evidence of tumor in the 20 lymph nodes resected during colectomy. This patient had no evidence of recurrent colorectal cancer 21 years after diagnosis of colorectal cancer. The other patient had not undergone surveillance for colorectal cancer in the setting of PSC-UC. He was diagnosed with metastatic colon cancer 8 years after diagnosis of PSC, and died 6 months after diagnosis of colon cancer.

We examined whether patients who experienced normalization or stabilization of serum ALP had better PSC-related event-free survival (i.e. progression to cirrhosis or development of cholangiocarcinoma). Using Kaplan-Meier survival modeling (Figure 2), patients with PSC who experienced normalization or stabilization of serum ALP within one year after diagnosis of PSC tended to have better 5- and 10-year PSC-related event-free survival compared with those who did not experience normalization or stabilization of serum ALP within one year after the diagnosis of PSC; this difference was not statistically significant (100% and 50% vs. 73% and 44%, respectively; p=0.36). Using Cox hazards regression analysis (age at the time of diagnosis of PSC; gender;

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presence/absence of IBD; serum ALP, AST, ALT, total bilirubin, and total IgG at the time of diagnosis of PSC; treatment with UDCA), only age at the time of diagnosis of PSC (Hazards Ratio (HR) = 1.05; *p*=0.028; 95% CI, 1.01-1.11) and serum bilirubin at baseline (HR= 1.55; *p*=0.033; 95% CI, 1.03-2.28) were independently associated with high risk for development of PSC-related serious event (i.e. progression to cirrhosis and development of cholangiocarcinoma).

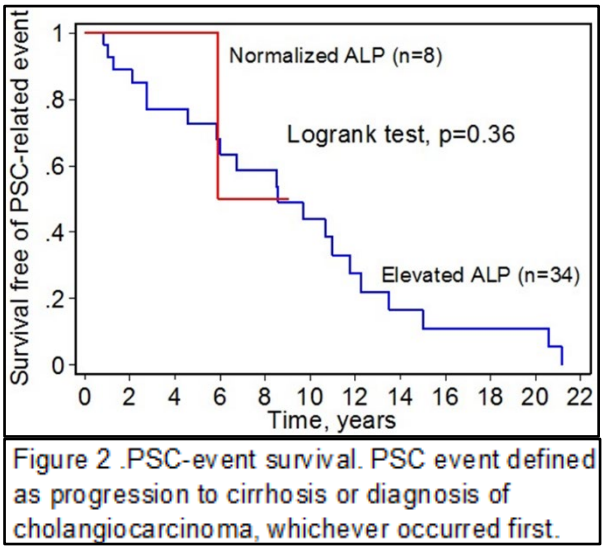

Figure 2 .PSC-event survival. PSC event defined as progression to cirrhosis or diagnosis of cholangiocarcinoma, whichever occurred first.

Figure 2. Please add Figure caption here.

4. Discussion

In this retrospective study, we report on the clinical features and outcomes of patients with PSC seen at the University of Missouri-Columbia between the years 2000 and 2018. The University of Missouri health system services many residents living in Central Missouri, with an estimated population of more than 600,000 as of the 2017 census. This study highlights the devastating outcomes of patients with PSC.(*14*) In addition, our study adds to the growing evidence that advanced age at the time of diagnosis of PSC and serum bilirubin at the time of diagnosis of PSC are important predictors of PSC-related serious adverse outcomes.(*15-18*) Furthermore, 12% experienced normalization of serum ALP within the first year of diagnosis of PSC. Moreover, although the difference was not statistically significant, patients with PSC who experienced normalization or stabilization of serum ALP within the first year of diagnosis of PSC tended to have a better 5- and 10-year survival, compared to those who had persistently elevated ALP; this finding is in agreement with previous studies, (*19-23*) and has important implications with regards to prognosis, patient counseling, and more importantly, in designing therapeutics clinical trials in PSC.(*24*)

PSC continues to be a medical threat. More than one-half of our PSC cohort developed a serious, life-altering PSC-related event. The majority of patients progressed to end stage liver disease and developed significant portal hypertension manifested as varices and/or ascites. Moreover, one-third of those who progressed to end-stage liver disease underwent liver transplantation. The recurrence rate of PSC in the liver allograft was 12% in our cohort, which is comparable to prior reports.(*25*)

In addition to the burden of progression to end-stage liver disease, PSC is an important risk factor for hepatobiliary and colorectal cancer.(*26*) Twelve percent of this cohort developed hepatobiliary and/or colorectal cancers. These findings highlight the impact of PSC on patients' quality of lives and outcomes. Surveillance for colorectal cancer and hepatobiliary cancers in patients with PSC has been shown to be associated with better survival.(*27, 28*) Currently, the leading societies recommend screening for colorectal cancer in patients with PSC-IBD and screening for gallbladder cancer in all PSC patients on an annual basis.(*13, 29, 30*) Moreover, the leading societies recommend

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surveillance for hepatocellular carcinoma at the time once diagnosis of cirrhosis is established. However, surveillance for cholangiocarcinoma remains a subject of debate.(*31, 32*)

Determining the incidence and prevalence of PSC in the geographical area served by our academic institution is challenging. Although our university health system services residents of 18 counties in Central Missouri, we see a small fraction of all patients at our institution, and many patients have access to other tertiary and academic centers in other surrounding states. To provide incidence and prevalence rates for a disease, the sample size should be large enough to include many (if not all) cases to be representative of the population under study. With rare diseases, such as PSC, this is even more challenging, because cases are more difficult to find. For the current study, we used only one research database for case finding; thus, it is possible that we could have missed many other cases of PSC, which would preclude examining the epidemiology of PSC in the geographical area served by our institution.

5. Conclusions

In conclusion, we report the clinical outcomes of patients with PSC between the years 2000 and 2018 at our institution that serves a large population of mid central Missouri. The natural history of PSC in central Missouri is similar to the natural history studies reported in other regions. More than one-half of the PSC cohort suffered from serious PSC-related events (progression to cirrhosis or development of cholangiocarcinoma). Age and serum bilirubin at the time of diagnosis of PSC are important predictors of PSC-related adverse events. Larger studies are needed to better define the epidemiology and outcomes of patients with PSC. Liver transplantation, even though extends the survival of patients with PSC, is fraught by its costs, invasive nature, shortage of organs and more importantly, recurrence of PSC in the liver allograft. Effective therapies are urgently needed for this cumbersome disease.

Author Contributions: AHA presented and conceptualized the research paper and performed the statistical analysis; AA assisted in drafting the manuscript; DSR interpreted liver biopsies and contributed in drafting the manuscript; JAI reviewed the manuscript and provided critical points; NDT and AHG interpreted cross-sectional imaging and contributed in drafting the final draft; and GMH conceptualized the research paper, provided critical points in the statistical analysis; re-interpreted all available endoscopic retrograde cholangiopancreatography (when applicable); and contributed to drafting the initial and final manuscript All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the University of Missouri School of Medicine (IRB protocol # 2012024; date of approval: 07/25/2018).

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study.

Data Availability Statement: Data sharing isn't applicable due to the retrospective nature of the study.

Conflicts of Interest: The authors declare no conflicts of interest.

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