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ORIGINAL ARTICLE

Epidemiology and clinical course of primary biliary cholangitis in Eastern Slovakia

Sylvia Drazilova[1] · Ingrid Babinska[2] · Jakub Gazda[3] · Monika Halanova[2] · Martin Janicko[3] · Branislav Kucinsky[3] · Dominik Safcak[3,4] · Dominika Martinkova[1] · Lucia Tarbajova[1] · Anna Cekanova[3] · Peter Jarcuska[3] · Eastern Slovakia PBC Group

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Abstract

Objective To determine both the incidence and the prevalence of primary biliary cholangitis (PBC) in Eastern Slovakia and to describe its clinical course and the response to ursodeoxycholic acid (UDCA).

Methods We recorded data of patients with PBC, who were followed up in gastroenterology and hepatology centers in Eastern Slovakia during the period from June 30, 1999, through June 30, 2019.

Results The annual incidence of PBC varied from 0.7 to 1.5 cases per 100,000 inhabitants between 2014 and 2018. PBC prevalence steadily increased from initial 10.2 cases per 100,000 inhabitants in 2014 to 14.9 cases per 100,000 inhabitants in June 2019. The mean age at the time of diagnosis was 56.3 ± 10.9 years. 95.7% of patients were females, and female/male gender ratio was 22.3:1. In June 2019, prevalence in the female population was 28 cases per 100,000 women. At the time of diagnosis, three-quarters of patients were symptomatic and 10% of patients had liver cirrhosis. The mean follow-up was 7.3 ± 5.2 years. Response to UDCA was observed in 72.1% of patients. Patients with higher baseline alkaline phosphatase (ALP) levels, liver cirrhosis at entry or at the end of follow-up and women younger than 45 years responded worse to UDCA. One-quarter of patients had liver cirrhosis at the end of follow-up. During follow-up, 1.6% of patients underwent liver transplantation and 5.5% of patients died. Five-year and 10-year liver-related mortalities were 2.7% and 4.3%, respectively.

Conclusion PBC prevalence in Eastern Slovakia is increasing, and most of the patients respond to therapy with UDCA.

Keywords Primary biliary cholangitis · Prevalence · Incidence · Clinical course · Ursodeoxycholic acid

Abbreviations

AIH	Autoimmune hepatitis
ALT	Alanine transaminase
ALP	Alkaline phosphatase
AMA	Antimitochondrial antibodies
AST	Aspartate transaminase
GGT	Gamma-glutamyl transferase
g/l	Grams per liter
HDL-C	High-density lipoprotein cholesterol
IgM	Immunoglobulin M
INR	International normalized ratio
LDL-C	Low-density lipoprotein cholesterol
mmol/l	Millimoles per liter
µmol/l	Micromoles per liter
N	Number
OCA	Obeticholic acid
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
RR	Risk ratio
SD	Standard deviation
TC	Total cholesterol
TG	Triglycerides
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
95% CI	95% Confidence interval

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Extended author information available on the last page of the article

Introduction

Primary biliary cholangitis (PBC) is a chronic inflammatory autoimmune liver disease that is characterized by chronic nonsuppurative inflammation and progressive cholestasis accompanied by fibrosis. In the course of the disease, liver fibrosis may progress to liver cirrhosis. Consecutively, in a cirrhotic liver hepatocellular carcinoma can develop. Both decompensated cirrhosis and hepatocellular carcinoma are the most common causes of liver-related mortality in patients with PBC (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2017).

At the time of diagnosis, patients are frequently asymptomatic. Dominating symptoms are fatigue and itching that often manifest years ahead of diagnosis. Clinical signs of liver cirrhosis may be observed at a late stage of the disease, and the appearance of jaundice is a poor prognostic factor. Cholestasis with elevated alkaline phosphatase (ALP) is a typical laboratory finding. Antimitochondrial antibodies (AMA), particularly the M2 subtype, are present in 95% of the patients' sera. Other autoantibodies are present to a lesser extent; however, antinuclear antibodies (anti-sp100 and anti-gp210) may play a role in PBC confirmation (Lindor et al. 2018). Increased concentrations of immunoglobulin M (IgM), explained by epigenetic modifications, are present in many patients with PBC (Lleo et al. 2012). Elevated levels of aspartate transaminase (AST) and alanine transaminase (ALT) may be present in the setting of chronic inflammation, liver fibrosis and liver necrosis as well (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2017). Histological assessment of the liver confirms the diagnosis. PBC has four histological stages: (1) portal inflammation with or without florid bile duct lesions; (2) increase in size of periportal lesions with interface hepatitis; (3) distortion of hepatic architecture with numerous fibrous septa; and (4) cirrhosis (Purohit and Cappell 2015). Patients with PBC may suffer from either autoimmune hepatitis or primary sclerosing cholangitis overlap. Furthermore, other autoimmune diseases such as Sjögren syndrome, autoimmune thyroiditis and celiac disease are more prevalent as well (Lindor et al. 2018).

Worldwide epidemiological data report wide difference in PBC incidence and prevalence. Global PBC incidence rates range from 0.3 to 5.8 cases per 100,000 inhabitants per year and global PBC prevalence rates range from 1.9 to 40.2 cases per 100,000 inhabitants (Boonstra et al. 2012). Prevalence of PBC increased steadily over the course of last years, although concurrent decrease in mortality has been observed (Lu et al. 2018). PBC has been regarded as female predominant; however, this phenomenon remains to be explained (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2017).

Ursodeoxycholic acid (UDCA) is the gold-standard therapy, and daily dosage ranges from 13 to 15 mg/kg. UDCA is a safe and mostly well tolerated. The treatment slows down or even completely stops the disease progression and liver fibrosis when treatment response is achieved (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2017). Second-line therapy in nonresponders is the addition of obeticholic acid (OCA) to the UDCA. The combination of UDCA and OCA has 50% effectivity in the group of non-responders to UDCA (Nevens et al. 2016). Alternative option is fibrates, particularly bezafibrate, although this treatment option is still off-label (Corpechot et al. 2008).

Incidence or prevalence of PBC in Eastern Slovakia, which forms approximately one-third of the Slovakia population, is unknown. The primary aim of this study was to determine both the incidence and prevalence of PBC in Eastern Slovakia. The secondary aim of this study was to describe the natural course of PBC, response to UDCA, treatment and natural course differences between male and female patients and younger and older female patients.

Methods

To include every patient with PBC (K74.3), we invited all gastroenterology (33) and hepatology (3) centers to participate on the data collection. Thirty-four (31 gastroenterology and 3 hepatology) centers responded to the survey (94% response rate for gastroenterology centers and 100% response rate for hepatology centers. Only 10 of them (7 gastroenterology—21% and 3 hepatology—100% centers) found records of patients with PBC in their respective database during period from June 30, 1999, through June 30, 2019. Detailed demographic and clinical information were collected as follows: sex, age at diagnosis, duration of follow-up, biochemical and hematological profile at entry and at the end of follow-up, immunological profile (AMA, AMA M2, anti-sp100, anti-gp210), histological assessment where available, concomitant autoimmune liver disease (autoimmune hepatitis, primary sclerosing cholangitis), liver cirrhosis presence at entry or during follow-up, UDCA therapy, compensation of liver cirrhosis, hepatocellular carcinoma, liver transplant and liver-related mortality. The case report form was completed by local investigators during period from July through September 2019 (with June 30, 2019, as cut-off date) with on-site assistance from the coordinators. All completed case report forms were centrally evaluated for the confirmation of PBC diagnosis. The diagnosis of PBC was based on established

diagnostic criteria: (1) elevated ALP, (2a) presence of AMA at a titer > 1:40 or (2b) presence of anti-sp100/antigp210 and (3) in the absence of PBC-specific antibodies, liver biopsy was required for the confirmation of PBC diagnosis. The study protocol was approved on May 5, 2019, by the Ethical committee of Poprad Hospital, a.s.

Statistical analysis

Continuous variables were expressed as means ± standard deviations, and categorical variables were expressed as absolute and relative frequencies. Differences in means of demographic and clinical characteristics were determined using *t* test and Mann–Whitney U test where appropriate according to data distribution. Differences in proportions were determined by the Chi-square test and Fisher's exact test where appropriate, and in case of statistical significance, risk ratio with its 95% confidence interval was calculated. Pearson's correlation coefficient was used to address any possible relation between clinical characteristics and age at diagnosis. All tests were two-sided and performed at a 95% significance level. Data were analyzed using the R language (version 3.6.1). Choropleth maps with color progression were created using ArcView software (version 9.3.1).

Table 1 Baseline biochemical and hematological characteristics of patients with primary biliary cholangitis (Slovakia, 2019)

		Mean	SD
IgM	g/l	4.3	3.1
Total bilirubin	μmol/l	17.1	19.5
Indirect bilirubin	μmol/l	9.2	17.7
Albumin	g/l	41.8	4.8
Platelets	10^9/l	232.8	84.7
PT	INR	1.0	0.2
Glycemia	mmol/l	5.7	1.9
ALT	% Of upper limit of normal	189.1	202.6
AST	% Of upper limit of normal	164.6	136.8
ALP	% Of upper limit of normal	233.8	209.9
GGT	% Of upper limit of normal	438.5	418.4
TC	mmol/l	5.9	1.7
LDL-C	mmol/l	3.7	1.2
HDL-C	mmol/l	1.7	0.5
TG	mmol/l	1.5	0.7

ALT alanine transaminase; *ALP* alkaline phosphatase; *AST* aspartate transaminase, *GGT* gamma-glutamyl transferase; *g/l* grams per liter; *HDL-C* high-density lipoprotein cholesterol; *IgM* immunoglobulin M; *INR* international normalized ratio; *LDL-C* low-density lipoprotein cholesterol; *mmol/l* millimoles per liter; *μmol/l* micromoles per liter; *PT* prothrombin time; *SD* standard deviation; *TC* total cholesterol; *TG* triglycerides

Results

Three hundred and six patients were centrally evaluated for the confirmation of PBC diagnosis. Out of 306 patients, 32 patients did not meet diagnostic criteria and 18 patients lacked enough data; therefore, 50 patients were excluded from the study, and 256 patients were included in the final analysis (Supplementary Fig. 1).

Out of 256 patients, 245 were female (95.7%). The mean age at diagnosis was 56.3 ± 10.9 years, and 41 patients (16%) were younger than 45 years at the time of diagnosis. All patients had elevated levels of ALP at least for 6 months, 245 patients (95.7%) were AMA M2 positive, 8 patients (3.1%) were AMA M2 negative, but were either anti-sp100 or anti-gp210 positive, and 3 patients (1.2%) were all AMA M2, anti-sp210 and anti-gp210 negative, but liver biopsy confirmed PBC diagnosis (Supplementary Table 1).

Baseline biochemical and hematological characteristics of patients are presented in Table 1.

The annual incidence of PBC varied from 0.7 to 1.5 cases per 100,000 inhabitants between 2014 and 2018. PBC prevalence steadily increased from initial 10.2 cases per 100,000 inhabitants in 2014 to 14.9 cases per 100,000 inhabitants in June 2019 (Fig. 1). In female population, annual PBC incidence varied from 1.2 to 2.7 cases per 100,000 women between 2014 and 2018 and prevalence increased from 19 cases in 2014 to 28 cases per 100,000 women in June 2019 (Fig. 2).

PBC prevalence varied among districts of Eastern Slovakia. The lowest prevalence was recorded in Michalovce district (3.61 cases per 100,000 inhabitants), and the highest one was recorded in Svidnik district (55.61 cases per 100,000 inhabitants). In two districts, overall prevalence and prevalence in the female population exceeded 50 and 100 cases per 100,000 inhabitants/women, respectively (Supplementary Fig. 2).

One-quarter of patients (24.6%) was asymptomatic, and three-quarters (75.4%) suffered from either or both fatigue and itching, and 26 patients (10.2%) had liver cirrhosis at the time of diagnosis (Supplementary Table 2).

UDCA therapy (13–15 mg/kg/day) was initiated after PBC diagnosis. Treatment response was evaluated in 226 patients with the mean follow-up 7.3 ± 5.2 years, and 30 patients have not attended follow-up visits yet. UDCA daily dosage range was 500–1500 mg at the last follow-up visit, and only 4 patients did not tolerate UDCA due to side effects. Treatment response was defined as ALP ≤ 167% and total bilirubin ≤ 200% of the upper limit of normal (ULN), and complete treatment response was defined as normal levels of both ALP and total bilirubin. Treatment response was achieved by 163 patients (72.1%), and 63

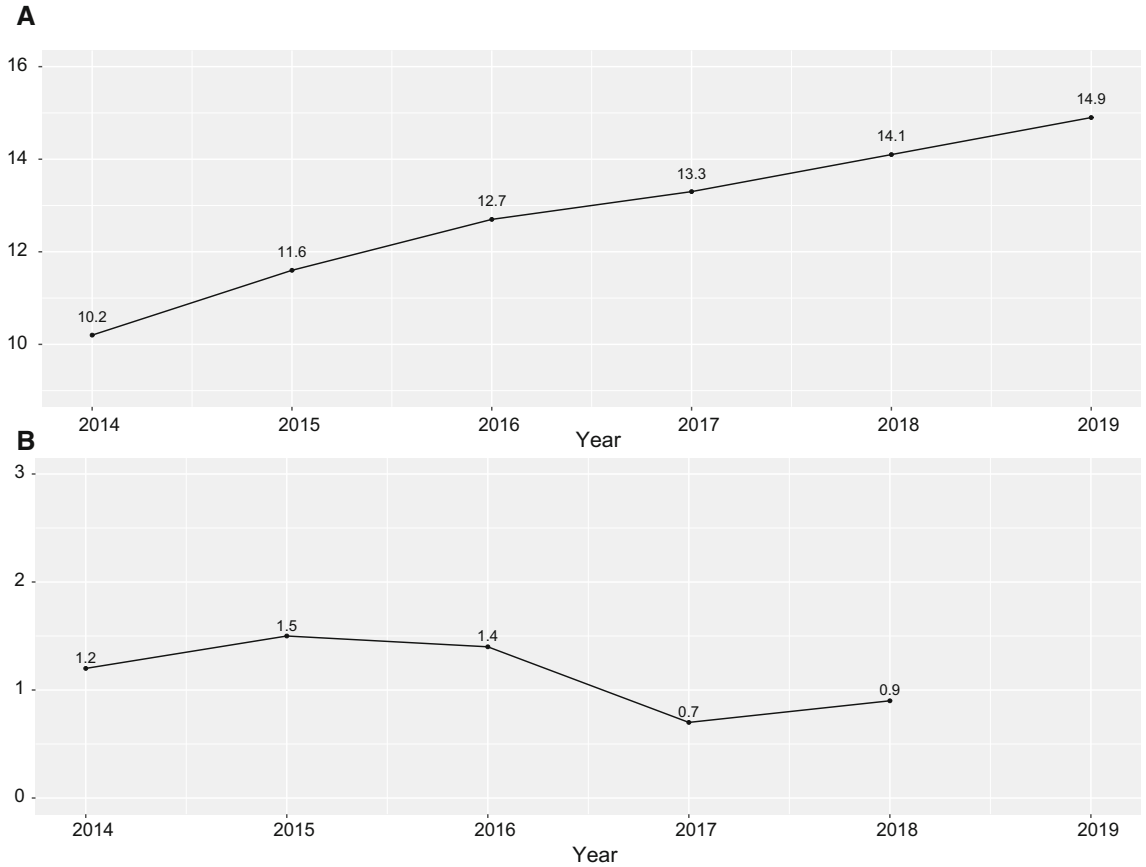

Fig. 1 **a** Prevalence of primary biliary cholangitis in Eastern Slovakia (as of June 2019, cases per 100,000 inhabitants). **b** Incidence of primary biliary cholangitis in Eastern Slovakia (cases per 100,000 inhabitants per year) (Slovakia, 2019)

patients (27.9%) did not respond to UDCA. A complete treatment response was achieved by 87 patients (38.5%) (Supplementary Table 3).

Clinical and demographic differences between male and female patients with PBC are summarized in Supplementary Table 4. Male patients had significantly higher baseline ALP levels ($p = 0.05$) and were insignificantly older than female patients at the time of diagnosis ($p = 0.12$). The response to the treatment was numerically higher in female patients, but the difference was not statistically significant due to low number of male patients ($p = 0.79$).

We also present clinical and demographic differences between women younger and older than 45 years in Supplementary Table 5. Female patients younger than 45 years responded worse to UDCA (55.0%) than female patients older than 45 years (76.6%), and difference was statistically significant ($p = 0.005$).

Baseline albumin, glycemia, HDL-C, IgM levels, platelet count and Fib-4 score were all significantly correlated with age at diagnosis (Table 2). However, none of that was significantly correlated with either treatment response, liver cirrhosis at entry or liver cirrhosis at the end of follow-up (Table 3).

Both baseline ALP $< 200\%$ULN and ALP $< 300\%$ ULN were associated with treatment response to UDCA ($p < 0.001$ for both cut-offs); on the contrary, liver cirrhosis at entry was associated with failure to achieve treatment response ($p = 0.01$). Patients with liver cirrhosis at the end of follow-up responded worse to UDCA than patients without liver cirrhosis at the end of follow-up ($p = 0.02$) (Table 4).

One-quarter of patients had liver cirrhosis at the end of follow-up (25.4%). None of the patients was diagnosed with hepatocellular carcinoma. During follow-up, 7.1% of patients suffered an adverse event, 1.6% of patients underwent liver transplantation and 5.5% of patients died. Five-year and 10-year liver-related mortalities were 2.7% and 4.3%, respectively (Supplementary Table 6).

Discussion

PBC prevalence is increasing annually, although incidence remains relatively constant. This is explained by reduced mortality and/or earlier diagnosis. Prevalence in the USA increased from 21.7 cases in 2006 to 39.2 cases per

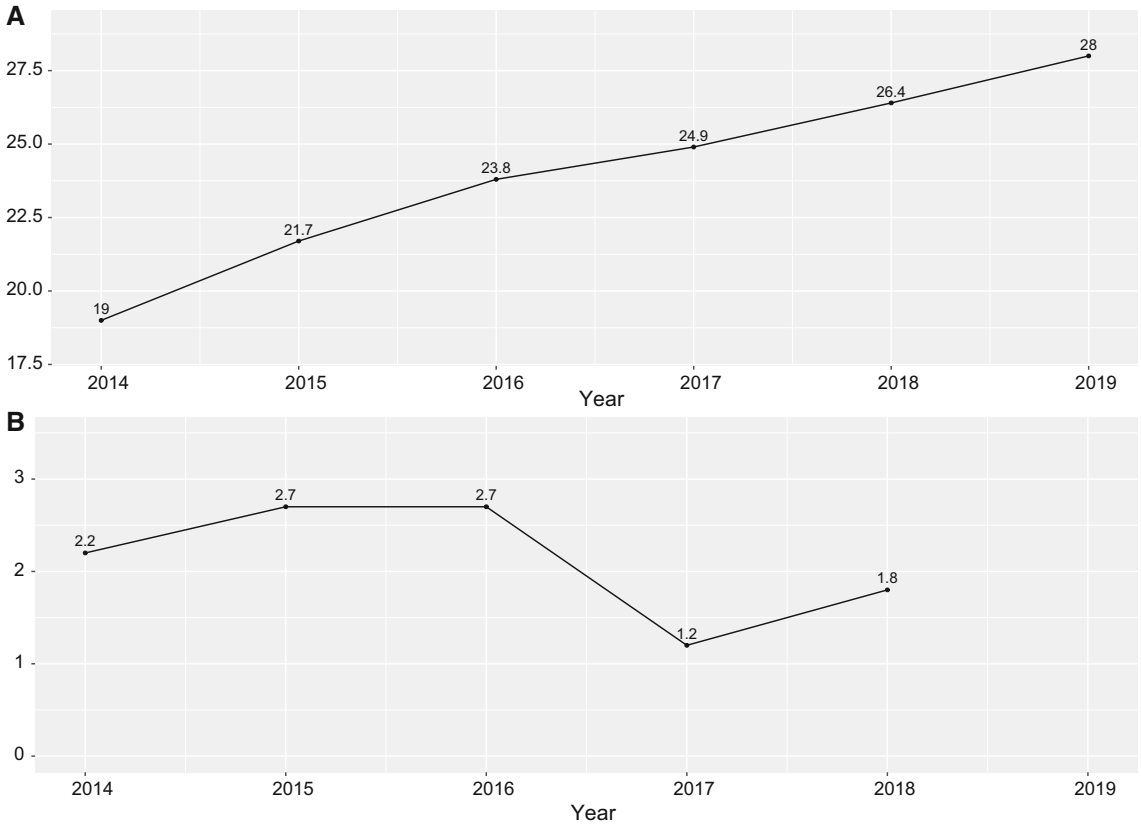

Fig. 2 **a** Prevalence of primary biliary cholangitis in female population in Eastern Slovakia (as of June 2019, cases per 100,000 women). **b** Incidence of primary biliary cholangitis in female population in Eastern Slovakia (cases per 100,000 women per year) (Slovakia, 2019)

100,000 inhabitants in 2014. Incidence did not change significantly during the study period (4.2 and 4.3 cases per 100,000 inhabitants in 2006 and 2014, respectively) (Lu et al. 2018). Similar rise of PBC prevalence has been reported from Europe as well. Prevalence in Sweden has increased from 5.0 in 1987 to 34.6 cases per 100,000 inhabitants in 2014 (Marschall et al. 2019). Prevalence is high in the Scandinavian countries, the USA, Japan and China, and, on the contrary, is very low in Israel, Brunei and South Korea (Boonstra et al. 2012; Chong et al. 2010; Delgado et al. 2005; Kim et al. 2016; Liu et al. 2010; Lu et al. 2018; Marschall et al. 2019; Sakauchi et al. 2005; Tanaka et al. 2016). Prevalence in the USA is the highest in the Caucasian population (46/100,000 persons) and the lowest among African Americans (30.8/100,000 inhabitants). Incidence and prevalence of PBC are not mapped well in Central and Eastern Europe. In a recently published article, average annual PBC incidence for the 11-year period was 0.79 and 0.89 per 100,000 inhabitants per year, whereas the point prevalence was 11.5 and 12.5 per 100,000 inhabitants in the continental and in the coastal Croatian region, respectively (Madir et al. 2019). In our study, annual incidence varied from 0.7 to 1.5 cases per 100,000 during the period from 2014 to 2018 and prevalence increased from 10.2 cases in 2014 to 14.9/100,000 inhabitants in June 2019. In two of the Eastern Slovakian districts, the prevalence in June 2019 was very high (over 50 cases per 100,000 inhabitants). PBC is female predominant, and male patients with PBC make up only 3–24% of all patients. Higher prevalence in the male population is observed in the Scandinavian countries and North America (Boonstra et al. 2012). In our study, women made up 95.7% and men 4.3% of patients with PBC, with female/male gender ratio of 22,3:1. No simple explanation of this comparatively lower prevalence of PBC among men in our study is available. Lower prevalence in the male population was reported only from Spain (Pla et al. 2007). In our study, prevalence in the female population was 29 cases per 100,000 women in June 2019. According to Danish authors, approximately one woman out of 1000 women older than 40 years suffers from PBC (Jepsen et al. 2015). Prevalence in the female population was extremely high (over 100 cases per 100,000 women) in two Eastern Slovakian districts. One of the possible explanations for this kind of difference among districts is that female prevalence is rather high, but a proportion of, particularly asymptomatic, patients are probably underdiagnosed in some districts.

Table 2 Correlation between age at diagnosis and baseline biochemical and hematological characteristics, APRI and Fib-4 scores (Slovakia, 2019)

	Correlation coefficient	*P* value
IgM	**0.164**	**0.029**
Total bilirubin	0.035	0.777
Indirect bilirubin	0.047	0.692
Albumin	**0.25**	**< 0.001**
Platelets	**0.203**	**0.003**
PT	0.081	0.365
Glycemia	**0.213**	**0.002**
ALT	0.119	0.061
AST	0.067	0.295
ALP	0.038	0.55
GGT	0.105	0.095
TC	0.015	0.822
LDL-C	0.034	0.676
HDL-C	**0.236**	**0.002**
TG	0.041	0.57
APRI	0.055	0.425
Fib-4	**0.133**	**0.05**

ALT alanine transaminase; *ALP* alkaline phosphatase; *AST* aspartate transaminase; *GGT* gamma-glutamyl transferase; *HDL-C* high-density lipoprotein cholesterol; *IgM* immunoglobulin M; *LDL-C* low-density lipoprotein cholesterol; *PT* prothrombin time, *TC* total cholesterol; *TG* triglycerides

Although AMA positivity has already been described in 3-year-old child, PBC does not occur in childhood (Invernizzi et al. 2012). Both incidence and prevalence are increasing with age. A study from the USA based on 2014 data reported prevalence of 5.4 cases per 100,000 inhabitants and incidence of 0.8 cases per 100,000 inhabitants per year in population $\leq$ 40 years, but the prevalence was as high as 88.8 cases per 100,000 inhabitants and incidence was 6.7 cases per 100,000 per year in population aged $\geq$ 71 years (Lu et al. 2018). The mean age at diagnosis was in the Scandinavian countries 64 years (Marschall et al. 2019), compared to 56 years in our study. Sixteen percent of patients were younger than 45 years at the time of diagnosis in our study.

Complex interactions between environmental and genetic contributors are responsible for PBC development. Higher prevalence of other autoimmune diseases is reported among patients with PBC, mainly autoimmune thyroiditis, Raynaud and Sjögren syndrome, vitiligo and autoimmune hepatitis. PBC is more prevalent in the first-degree relatives of patients with PBC (Corpechot et al. 2010). Furthermore, PBC is more prevalent in smokers (all active, passive and past smokers) and is associated with various xenobiotics (halogenated compounds, hair dyes, nail polish). PBC occurs more frequently among women on contraceptives or among women who had an ectopic pregnancy, and in people who had been exposed to radiation. Patients with the history of urinary tract infections have also a higher risk of PBC development. Microorganisms might play a role in PBC pathogenesis, which is often explained by molecular mimicry (Kouroumalis 2010). Moreover, vaccination of any type is a protective factor, a fact supporting microbial flora role in PBC pathogenesis.

Patients with PBC have lower annual household income than patients without PBC (Corpechot et al. 2010). We did not evaluate the environmental factors' role in PBC pathogenesis. We believe, however, it would be very interesting to further explore environmental factors in two districts with extremely high prevalence of PBC. Symptomatic patients make 36–89% of all patients with PBC (Lindor et al. 2018). In our study, patients with either or both itching and fatigue make up approximately three-quarters of all patients. The remainder of patients were asymptomatic and referred to gastroenterology or hepatology centers for further investigation of laboratory

Table 3 Laboratory markers significantly correlated with age at diagnosis and their relation to achieving long-term treatment response, liver cirrhosis at entry and liver cirrhosis at the end of follow-up (Slovakia, 2019)

			Response (n = 163)	Liver cirrhosis at entry (n = 26)	Liver cirrhosis at the end of follow-up (n = 65)
IgM	> 100%ULN	*n* (%), p	85 (52.1), 0.47	11 (42.3), 0.57	32 (49.2), 1
	> 150%ULN	*n* (%), p	51 (31.3), 0.87	4 (15.4), 0.94	18 (27.7), 0.57
HDL-C	> 100%ULN	*n* (%), p	85 (52.1), 0.84	14 (53.8), 1	32 (49.2), 0.87
Glycemia	> 5.6 mmol	*n* (%), p	41 (25.2), 0.26	7 (27.0), 1	20 (30.8), 0.75
	> 7.0 mmol		13 (8.0), 0.64	20 (77.0), 0.22	3 (4.6), 0.31
Platelets	$< 150\times10^9$	*n* (%), p	21 (12.9), 0.90		
Albumin	< 35 g/l	*n* (%), p	20 (12.3), 1		
Fib-4 score	< 3.25	*n* (%), p	124 (76.0), 0.89		

g/l grams per liter; *HDL-C* high-density lipoprotein cholesterol; *IgM* Immunoglobulin M; *mmol/l* millimoles per liter; *n* number; *ULN* upper limit of normal

Table 4 Differences in clinical and demographic characteristics between responders and nonresponders (Slovakia, 2019)

	Responders	Nonresponders	*P*	RR (95%CI)
ALP < 200%ULN at baseline	108	21	< 0.001	0.38 (0.2391–0.5913)
ALP > 200%ULN at baseline	55	42		
ALP < 300%ULN at baseline	138	37	< 0.001	0.41 (0.2800–0.6143)
ALP > 300%ULN at baseline	25	26		
Liver cirrhosis at entry	13	13	0.01	2.0 (1.2712–3.1466)
Absence of liver cirrhosis at entry	150	50		
Liver cirrhosis at the end of follow-up	40	25	0.02	1.63 (1.0766–2.4665)
Absence of liver cirrhosis at the end of follow-up	123	38		

ALP alkaline phosphatase; *RR* risk ratio; *ULN* upper limit of normal, 95% CI 95% confidence interval

cholestasis. Approximately 10% of all patients had liver cirrhosis at entry.

AMA-positive and AMA-negative patients respond to UDCA similarly; however, a difference in prognosis remains to be defined yet (Lindor et al. 2018). Nevertheless, AMA-negative patients have a worse health-related quality of life in social and emotional domains (Raszeja-Wyszomirska et al. 2016).

The treatment aims to slow down or completely stop PBC progression, to reduce mortality and to improve health-related quality of life. UDCA remains the gold standard as the first-line therapy, and it reduces liver-related mortality by 43% (Lu et al. 2018). There are several definitions of response to UDCA (Angulo et al. 1999; Corpechot et al. 2008, 2011; Kuiper et al. 2009; Kumagi et al. 2010; Pares et al. 2006; Zhang et al. 2013). Patients who achieve biochemical response to UDCA have similar estimated survival as healthy controls, and nonresponders have considerably shorter transplantation-free survival (Pares et al. 2006). We used modified Toronto criteria (Kumagi et al. 2010) to define the treatment response. These criteria are used for the second-line therapy indication. Complete response was defined as normalization of both ALP and bilirubin during UDCA treatment (Jorgensen et al. 1995). Seventy-two percent of patients treated with UDCA responded to treatment and more than half of them responded to treatment completely. Both male and young female patients respond worse to UDCA than middle-aged female patients (Lu et al. 2018); however, this was not significant in male patients in our case and that may be attributed to small sample size in this category. Patients with higher baseline ALP levels (cut-offs both 200% and 300% of ULN), patients with liver cirrhosis at entry, patients with liver cirrhosis at the end of follow-up and women < 45 years responded significantly worse to UDCA. If patients fail to achieve optimal treatment response to UDCA, the second-line therapy (OCA or bezafibrate) is introduced in addition to UDCA (Corpechot et al. 2018; Nevens et al. 2016). The addition of second-line therapy may further increase the response rate and slow down or stop disease progression in a subset of nonresponders to UDCA monotherapy, thus prolonging their transplant-free survival. Neither OCA nor bezafibrate was reimbursed in Slovakia during our study, and none of the patients were treated either by OCA or bezafibrate. Second-line therapy shows promising results. Nonetheless, there are still some patients, who fail to respond even to the second-line therapy. In that case, PBC progresses to liver cirrhosis and its complications, decompensated liver cirrhosis and/or hepatocellular carcinoma. The estimated annual incidence of hepatocellular cancer in England is 0.36 cases per 100 persons with PBC (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2017). Risk factors for HCC are male gender, alcohol consumption, smoking and any neoplasia among relatives (Zhang et al. 2015). We identified zero cases of hepatocellular carcinoma in our cohort. Histological features of the PBC are predictive of the prognosis. Liver cirrhosis, interface hepatitis and ductopenia in the liver histology are risk factors for progressive disease (Al-Harthy and Kumagi 2012; Kumagi et al. 2010). We were unable to evaluate the prognosis based on the liver histology due to small number of biopsies available. Besides histology, two more continuous scoring systems are used for the calculation of transplant-free survival prediction: The GLOBE score and The UK-PBC risk score (Carbone et al. 2016; Lammers et al. 2015). Both require baseline data and biochemical and hematological results after one year of UDCA treatment. We did not calculate GLOBE or the UK-PBC risk scores because no data about 1-year treatment response were available. During follow-up, 5.5% of patients died from liver-related causes and 1.6% underwent liver transplantation.

Quality of life is determined not only by the advanced stage of the disease, but also by complications and other concomitant diseases. Besides improving the prognosis, adequate PBC treatment will also ameliorate multiple PBC symptoms, including itching, fatigue, sicca syndrome and osteoporosis. Quality-of-life data were not available in our study due to its retrospective design.

Presented epidemiological study has few limitations. Some of the limitations are retrospective design, size of the underlying population (1,600,000 inhabitants) and limited sample size (256 patients were included). The small number of patients in specific groups (male patients, young female patients, patients with liver cirrhosis at entry) limits the power and significance of statistical analysis. Variations of PBC prevalence among districts could be attributed also to different diagnostic skills among gastroenterologists. We did not evaluate environmental factors as possible triggers of PBC, neither did we evaluate treatment of complications nor the quality of life. We did not identify any case of hepatocellular carcinoma and that might be attributed to a low quality of sonography screening. However, major advantage of our study is that most of the patients with PBC were identified early and approximately three-quarters responded to UDCA treatment.

Conclusion

Despite steady incidence, we detected a rising prevalence of PBC in Eastern Slovakia. The low proportion of male patients was quite unexpected. Seventy-two percent of patients responded to UDCA treatment. Worse treatment response was observed in patients with higher baseline ALP or liver cirrhosis (at the time of diagnosis or at the end of follow-up) and women < 45 years. Second-line therapy (OCA or bezafibrate) addition may improve the prognosis of nonresponders to UDCA.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol is in accordance with the 1964 Helsinki Declaration and its later amendments and was approved by the Ethical committee of Poprad Hospital, a.s., on May 5, 2019.

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Affiliations

Sylvia Drazilova[1] · Ingrid Babinska[2] · Jakub Gazda[3] · Monika Halanova[2] · Martin Janicko[3] · Branislav Kucinsky[3] · Dominik Safcak[3,4] · Dominika Martinkova[1] · Lucia Tarbajova[1] · Anna Cekanova[3] · Peter Jarcuska[3] · Eastern Slovakia PBC Group

✉ Ingrid Babinska
ingrid.babinska@upjs.sk

Sylvia Drazilova
drazilova.s@nemonicapp.sk

Jakub Gazda
jkgazda@gmail.com

Monika Halanova
monika.halanova@upjs.sk

Martin Janicko
martin.janicko@gmail.com

Branislav Kucinsky
brano1989@gmail.com

Dominik Safcak
saffkov@gmail.com

Dominika Martinkova
martinkova.d@nemocnicapp.sk

Lucia Tarbajova
tarbajova.l@nemocnicapp.sk

Anna Cekanova
a.cekanova18@gmail.com

Peter Jarcuska
peter.jarcuska@upjs.sk

[1] Department of Internal Medicine, Hospital Poprad, Poprad, Slovakia

[2] Department of Epidemiology, PJ Safarik University, Faculty of Medicine, Kosice, Slovakia

[3] 2nd Department of Internal Medicine, Faculty of Medicine and L Pasteur University Hospital, PJ Safarik University, Kosice, Slovakia

[4] Department of Radiotherapy and Oncology, Faculty of Medicine and Eastern Slovakia Institute of Oncology Kosice, PJ Safarik University, Kosice, Slovakia