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Cholestatic Liver Disease: from Pathophysiology to Treatment

Lead Guest Editor: Peter Jarcuska
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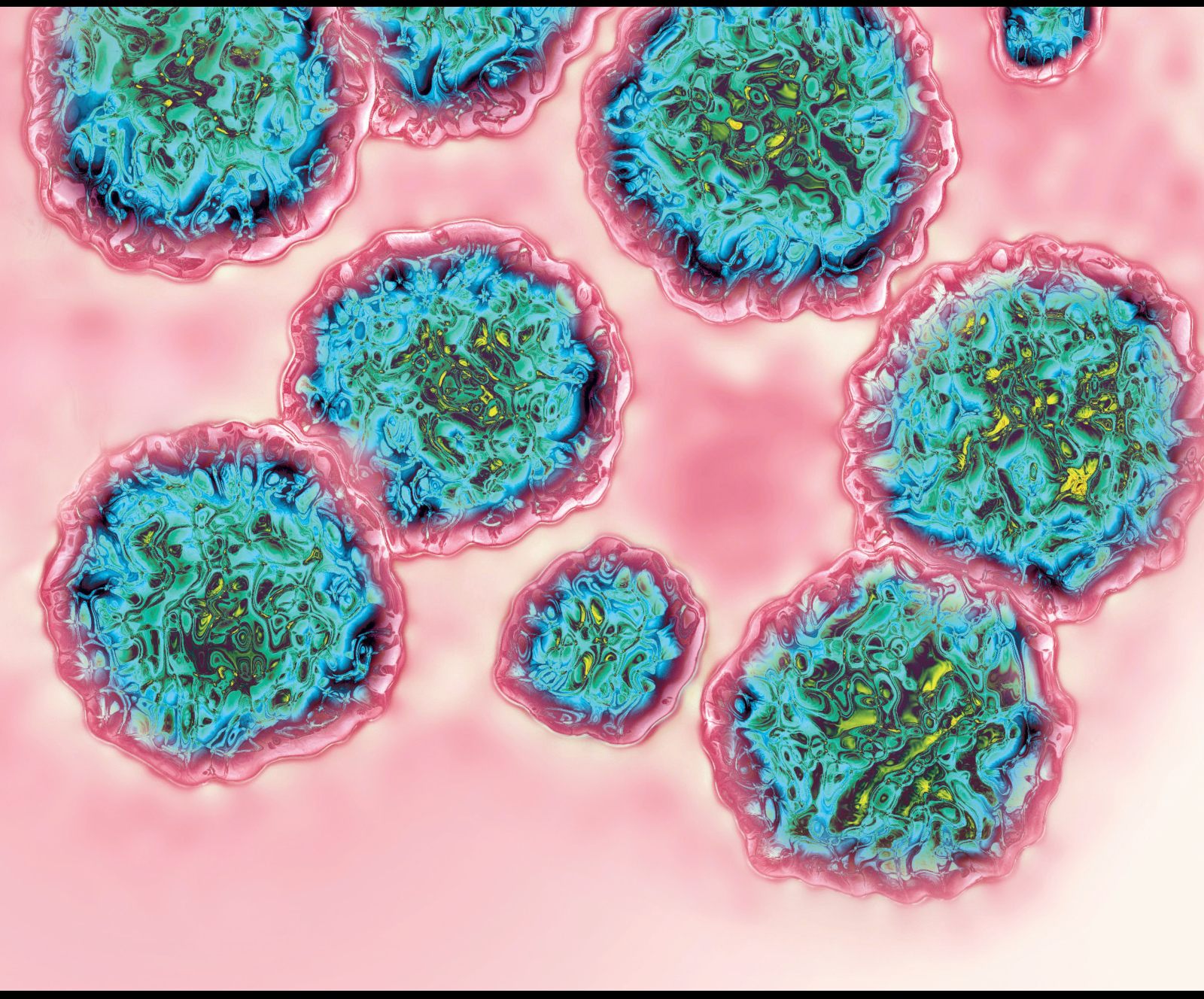

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Contents

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Review Article

Pretransplant Evaluation and Liver Transplantation Outcome in PBC Patients

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Primary biliary cholangitis (PBC) is an autoimmune chronic cholestatic liver disease characterized by progressive cholangiocyte and bile duct destruction leading to fibrosis and finally to liver cirrhosis. The presence of disease-specific serological anti-mitochondrial antibody (AMA) together with elevated alkaline phosphatase (ALP) as a biomarker of cholestasis is sufficient for diagnosis. Ursodeoxycholic acid (UDCA) is the first treatment option for PBC. Up to 40% of patients have an incomplete response to therapy, and over time disease progresses to liver cirrhosis. Several risk scores are proposed for better evaluation of patients before and during treatment to stratify patients at increased risk of disease progression. GLOBE score and UK PBC risk score are used for the evaluation of UDCA treatment and Mayo risk score for transplant-free survival. Liver transplantation (LT) is the only treatment option for end-stage liver disease. More than 10 years after LT, 40% of patients experience recurrence of the disease. A liver biopsy is required to establish rPBC (recurrent primary biliary cholangitis). The only treatment option for rPBC is UDCA, and data show biochemical and clinical improvement, plus potential beneficial effects for use after transplantation for the prevention of rPBC development. Additional studies are required to assess the full impact of rPBC on graft and recipient survival and for treatment options for rPBC.

1. Introduction

Primary biliary cholangitis (PBC) is an autoimmune, chronic, cholestatic liver disease characterized by progressive cholangiocyte destruction, eventually leading to intrahepatic bile duct destruction, fibrosis, and liver cirrhosis [1]. The pathogenesis of the disease is not completely understood but is caused by an interplay of environmental, immunogenetic, and epigenetic factors [1]. In the last decade, published studies gave better insight regarding PBC prevalence and incidence even though the results varied largely depending on the region, local awareness, and diagnostic possibilities. According to available data, the estimated prevalence ranges from 1.9 to 39.2 and incidence from 0.3 to 5.8 per 100,000 population per year in Europe, and the estimated prevalence and incidence for North America range from 2.24 to 40.2 and from 0.33 to 3.03 per 100,000 population per year with reported female-to-male ratio as high as 10 : 1, respectively [2]. It is usually diagnosed in the 5^{th} or 6^{th} decades of life [2]. Increasing prevalence and incidence are mostly due to easier diagnosis of the disease since the discovery of disease-specific serological anti-mitochondrial antibodies (AMAs). The presence of AMA together with elevated alkaline phosphatase (ALP) as a biomarker of cholestasis is sufficient for diagnosis [3]. AMA is detected in approximately 95% of PBC patients, rarely in other diseases, and analysis is available worldwide [1, 3]. Liver biopsy is necessary only in the absence of AMA in cases with a high suspicion of PBC or other chronic parenchymal liver diseases [1]. The natural history of the disease is progressive but unpredictable. Some patients rapidly progress to end-stage liver disease (ESLD), while others remain asymptomatic for decades. Early diagnosis and initiation of therapy can significantly improve the course of

the disease. Ursodeoxycholic acid (UDCA), a natural hydrophilic bile acid, is the first treatment option for PBC, approved for use in 1997 [4]. UDCA improved survival rates for PBC patients and overall prognosis [1, 3, 4]. However, up to 40% of patients have an incomplete response to therapy and over time disease progresses to liver cirrhosis [5, 6]. Liver transplantation (LT) remains the only definitive treatment option for end-stage liver disease and its complications. Before the introduction of UDCA as a standard treatment for PBC patients, LT was the only treatment option for PBC and this chronic liver disease was the most common indication for LT in the 1980s [6]. Nowadays, LT has been used for the treatment of PBC-related cirrhosis and malignancy, a disease refractory to control by medication, or when symptomatic treatments fail to control pruritus [7]. Thus, several scoring systems have been presented to determine clinical outcomes and to stratify patients with increased risk of treatment failure and disease progression to liver cirrhosis. Symptomatic PBC patients have a median survival time of up to 10 years without LT, and once the decompensated disease develops, the median survival time decreases to 3 to 5 years [8].

2. Treatment

During the last two decades, the clinical course of PBC has significantly improved due to earlier disease recognition and widespread use of UDCA [3, 6, 7, 9–14]. Also, more frequent routine tests and improved AMA isolation methods led to the detection of clinically asymptomatic patients with normal liver enzymes. In 2017, European Association for the Study of the Liver (EASL) guidelines stated that AMA reactivity alone is not sufficient to diagnose PBC and recommend follow-up of these patients with annual biochemical reassessment for the presence of liver disease and in case of the biochemical activity or signs of chronic liver disease treatment should be initiated [1]. Many studies have reported that PBC patients who had early liver disease and were not treated with UDCA have a shortened survival in comparison with the healthy population regardless of symptoms [11, 12]. In three contemporary series, asymptomatic patients had a 10-year survival ranging from 50% to 70%. Additionally, symptomatic patients had a median duration of survival from 5 to 8 years from the onset of symptoms [11, 12]. Several trials have reported that UDCA is associated with significant improvement in liver function tests, improvement in histology, and prolonged transplant-free survival [3, 6, 9, 10]. For example, a French randomized trial that was published 20 years ago reported that the risk of progression from stages I-II to stages III-IV was $7\% \pm 2\%$ in UDCA, while in the placebo group it was $34\% \pm 9\%$ [13]. In an early prospective study of 180 patients, the authors investigated the usefulness of UDCA therapy in the prevention of esophageal varices development [14]. Patients received UDCA vs. placebo and were monitored for up to 4 years. The authors reported that the risk of developing varices was 16% for the UDCA-treated patients, while it was 58% for those receiving the placebo [14]. UDCA is a synthetic bile acid that has anti-inflammatory properties, promotes bile excretion, and reduces the severity of cell injury [7].

Current guidelines recommend that the dose for PBC treatment is 13 to 15 mg/kg/d [6]. An ongoing clinical trial (NCT03345589) aims to investigate the efficacy of an intermediate dose of UDCA 18–22 mg/kg/day in comparison with the standard dose over 6 months of therapy. The trial endpoint is biochemical remission [7].

Although UDCA as a first-line treatment option for PBC treatment is associated with slowing the progression of chronic liver disease, this drug is ineffective for the common symptoms of fatigue or pruritus [6]. Moreover, up to 40% of PBC patients have partial or no response to UDCA. Failure to respond to UDCA is defined as a lack of normalization or reduction in ALP by greater than or equal to 40% at 1 year of UDCA treatment [7]. Risk factors that are associated with nonresponse to UDCA are age (females under 45 years), male gender, and the presence of advanced liver disease. Patients who have a poor response to UDCA will have a poor outcome [6].

Due to these limitations of UDCA, in 2016, a new drug named obeticholic acid (OCA) was introduced as a second-line treatment for PBC. OCA is a potent farnesoid X receptor (FXR) agonist [7]. OCA can be used as monotherapy in those PBC patients who do not tolerate UDCA or in combination with UDCA for those who are nonresponsive to UDCA [6, 7]. According to data, OCA is an effective adjunctive treatment for UDCA-refractory or UDCA-intolerant PBC. The current dosing guidelines for OCA were established by the POISE trial phase III, which analyzed 210 patients [15]. In this double-blind, placebo-controlled trial, PBC patients were receiving OCA 5 mg/day titrated to 10 mg after 6 months if lacking clinical benefit, or OCA 10 mg [15]. Patients were treated for one year. In this trial, the primary endpoint was an ALP level of less than 1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline, as well as normal bilirubin levels. The primary endpoint occurred in more PBC patients in the 5–10 mg group and the 10 mg group than in the placebo group ($p < 0.001$ for both groups). On the other hand, there was no significant difference in noninvasive fibrosis markers after 12 months of therapy between groups. Moreover, pruritus was more common with OCA than with placebo. There are still ongoing debates regarding the safety of OCA because there is some evidence that it can cause drug-induced liver injury (DILI), liver decompensation, or acute liver failure requiring LT [7]. So far, it looks like these side effects depend on the dose of the drug and the stage of liver disease [16]. In the ongoing phase 4 COBALT trial, the safety and efficacy of OCA are being investigated. The primary endpoints of this trial (NCT02308111) include death, transplant, and hepatic decompensation [7]. Although studies examining the efficacy of OCA on the survival of patients with PBC are still ongoing, based on the results, the recommended starting dose for patients with preserved synthetic function and in Child-Pugh class A cirrhotic patients is 5 mg daily. After 3 months, the dose can be increased to 10 mg daily if liver chemistries remain abnormal and the patient is tolerating the medication well [17]. On the other hand, Child-Pugh

class B or C cirrhotic patients at the beginning of the trial were dosed at a max of 5 mg weekly. In May 2021, FDA (Food and Drug Administration) issued restrictions for the use of OCA in patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension due to serious liver injury leading to liver decompensation or liver failure. More FXA agonists are under investigation for use in PBC (cilofexor (NCT02943447), tropifexor (NCT02516605), and EDP-305 (NCT03394924)) [18].

Another promising candidate as a second-line treatment for UDCA is fibrates, targeting peroxisome proliferator-activated receptors (PPARs), which affect bile acid synthesis and detoxification [7]. There are three isoforms of PPAR: α, δ, and γ. Several small-sized pilot studies showed an improved biochemical response (reduction in ALP levels to normal ranges and improved ALT levels) with the addition of 160 mg/day of fenofibrate (PPAR-α) to a standard dose UDCA [19]. In the retrospective study published by Cheung and colleagues, 41% of the patients in the fenofibrate and UDCA group met the criteria for clinical response (using Toronto criteria), versus 7% in the UDCA-only group [20]. Exposure to fenofibrate was associated with improved transplant-free and overall survival. On the other hand, more than 20% of patients stopped taking therapy due to side effects and there was a significant increase in bilirubin levels in patients with advanced fibrosis predisposing hepatic decompensation. Of all available studies on fibrates, the most important is the BEZURSO, a double-blind, randomized, placebo-controlled French study, including 100 patients with PBC and incomplete response to UDCA [21]. It demonstrated that a 2-year combination treatment of UDCA and bezafibrate (BZF) at 400 mg/day had a significantly higher rate of complete biochemical response defined by normal levels of ALP, total bilirubin, and aminotransferases (30% vs. none in the placebo group). Also, patients in UDCA and BZF groups had an improvement in liver fibrosis compared with placebo measured via vibration-controlled transient elastography, a decrease of 15% in liver stiffness measurement in the BZF group, compared with an increase of 22% in the placebo group, a difference of 36 percentage points (95% CI, 8–64) [21]. Improvement of symptoms including pruritus was also reported. Since PBC is a slowly progressive chronic disease, it is difficult to prove whether these beneficial effects on liver enzymes and symptoms of the disease can translate into lower overall liver-related mortality or the need for LT. In April 2021, a large retrospective Japanese study was published, in which the use of UDCA-BZF combination therapy, compared with UDCA only, was associated with a significant decrease in all-cause and liver-related mortality or need for LT (adjusted hazard ratios: 0.3253, 95% CI, 0.1936–0.5466 and 0.2748, 95% CI, 0.1336–0.5655, respectively; $p < 0.001$ for both) [22]. The number needed to treat with combination therapy to prevent 1 additional death or LT over 5, 10, and 15 years was 29 (95% CI, 22–46), 14 [10–22], and 8 [6–15], respectively. Fibrates are overall very well tolerated, with minor side effects of heartburn, myalgias, increase in serum creatinine, and transient transaminase elevations reported in clinical trials for PBC [4]. Recently, a dual PPAR-α and PPAR-δ agonist, elafibranor, is investigated as a second-line treatment for PBC patients with incomplete response to UDCA treatment [23]. In phase 2 placebo-controlled trial (NCT03124108), the addition of elafibranor for 12 weeks was found to significantly reduce ALP levels and improve lipid and anti-inflammatory markers [23]. Also, in phase II pruritus was not induced and patients with pruritus at the baseline reported less symptoms at the end of the treatment [23]. The results of phase III global trial are expected to assess the efficacy, safety, and tolerability of elafibranor relative to the currently approved second-line therapy for patients with PBC.

Even though PBC is an autoimmune-mediated liver disease, the addition of immunosuppressants (budesonide, mycophenolate mofetil, azathioprine, methotrexate) did not provide extra treatment benefits so far [18]. New treatment strategies targeting various stages of primary biliary cholangitis pathogenesis are investigated. However, these investigations are limited by the fact that PBC is a heterogeneous disease and hard endpoints take years to develop.

3. Risk Assessment

Risk assessment should evaluate disease severity and activity at baseline and during treatment using static and dynamic markers of the disease. Static markers important for disease prognosis are demographic characteristics (age at the time of diagnosis and sex), serological profiles (AMA or antinuclear antibodies (ANAs) present), laboratory markers of fibrosis (hyaluronic acid, enhanced liver fibrosis (ELF) score, the aspartate aminotransferase-to-platelet ratio index (APRI), noninvasive liver stiffness measurement (LSM), presence of portal hypertension, and histological features at the time of diagnosis. Younger age at the time of diagnosis (less than 45 years) is associated with more symptomatic patients who are less likely to respond to treatment and are at a higher risk of liver-related mortality [24], whereas the male sex is associated with higher age and more advanced disease at the time of diagnosis with a higher risk of hepatocellular carcinoma (HCC) development [25, 26]. Besides AMA, the autoantibody profile of PBC includes antinuclear antibodies (ANAs) also known as PBC-specific ANA (rim-like/membranous patterns (antibodies against gp210) and the multiple nuclear dots (sp100 antigens)) and their positivity strongly suggests the diagnosis of PBC, irrespective of AMA status [27, 28]. The presence of antibodies against gp210 and sp100 antigens is often associated with severe PBC and an unfavorable course of disease [29, 30], but their role as prognostic markers is yet to be determined. Several serum markers of fibrosis showed prognostic ability in PBCs such as hyaluronic acid, ELF score, and APRI index, but there are no data regarding the change in these parameters with time and their relationship with change in the disease characteristics [31]. The best noninvasive surrogate marker for the detection of cirrhosis and advanced fibrosis in patients with PBC is LSM assessed by transient elastography (TE). In 2012, Corpechot et al. showed that baseline values of LSM of 9.6 kPa and yearly LSM increase of 2.1 kPa are associated with a five- and

eightfold increased risk of decompensation, liver transplantation, or death (95% CI: 1.5–15.9; $p < 0.0001$; 95% CI: 3.6–36.0; $p < 0.0001$) [32]. In 2021, EASL guidelines recommend the use of LSM to monitor PBC progression because it was shown that worsening of LSM has a higher predictive value for poor outcome in comparison with the LSM value at the baseline [33]. Another important marker of disease prognosis is the presence of portal hypertension and what we know so far is that portal hypertension can be present in the early stages of the disease long before cirrhosis development, but the underlying pathophysiological mechanism is poorly understood. In the research published by Warnes et al., 82% of the pre-cirrhotic PBC patients had portal hypertension (hepatic venous pressure gradient (HVPG) >5 mmHG) and 34% had HVPG >12 mmHg (clinically significant portal hypertension (CSPH)) [34]. To avoid unnecessary endoscopy screening for esophageal varices or invasive portal pressure gradient measurement, current Baveno VII guidelines recommend using TE and indirect signs of portal hypertension (thrombocytopenia, splenomegaly) to stratify patients who require upper endoscopy. Baveno VII guidelines use the term "compensated advanced chronic liver disease (cACLD)" based on LSM, and values between 10 and 15 kPa are suggestive of cACLD, and values >15 kPa are highly suggestive of cACLD [35]. Therefore, LSM by TE < 15 kPa plus platelet count $>150 \times 10^9$/L rules out CSPH (sensitivity and negative predictive value > 90%) in patients with cACLD. If LSM increases (>20 kPa) or platelet count declines ($<150 \times 10^9$/L), these patients should undergo screening endoscopy [35]. Current EASL guidelines on noninvasive markers suggest using a cutoff value of LSM ≤10 kPa to rule out cACLD in PBC patients [33]. Even though liver biopsy is no longer necessary for PBC diagnosis in the presence of AMA antibody and cholestatic liver biochemistry, it can still be useful in patients who have an inadequate response to UDCA or if there is a clinical suspicion of coexisting disease, especially autoimmune hepatitis. It is shown that certain histological findings are an independent predictor of cirrhosis development and poor response to UDCA treatment, such as the degree of lymphocytic interface hepatitis and the presence of ductopenia [36, 37]. Also, it is important to identify individuals with overlap syndrome because they could benefit from combined treatment with immunosuppressants and UDCA. Up to 10% of PBC patients may present with clinical features of other autoimmune liver diseases, especially autoimmune hepatitis (AIH), known as PBC AIH overlap syndrome [38]. Typical features of AIH can be present at the time of PBC diagnosis but sometimes can present sequentially even years after diagnosis of PBC. Two scoring systems have been used to evaluate patients with PBC AIH overlap syndrome. The first one, published by the International Autoimmune Hepatitis Group, was presented only for the diagnosis of AIH using four criteria (simplified version): autoantibodies, immunoglobulin G, histology, and exclusion of viral hepatitis, and additional studies showed that a score of 7 has overall sensitivity and specificity of 87.1% (95% CI: 84.5–87.6) and 99.6% (95% CI: 98.2–99.9) for AIH diagnosis and can be efficacious also for overlap syndrome [39]. The second one, the Paris criteria, is nowadays mostly used to identify overlap syndrome. According to these criteria, a diagnosis can be made in a patient with PBC with at least two of the following:

(a) Alanine aminotransferase activity >5 times the upper limit of normal

(b) IgG ≥2 times the upper limit of normal and/or positive anti-smooth muscle antibody

(c) Liver biopsy with moderate or severe interface hepatitis

These criteria were incorporated in the latest EASL guidelines for the management of patients with PBC. Both criteria require liver biopsy for the definitive diagnosis.

Since 1983, to estimate the prognosis of patients with PBC and response to UDCA treatment, several risk scores have been made, which could be generally divided into two groups: models that predict the survival of PBC patients in the pre-UDCA era and models of biochemical response predicting clinical outcomes in the UDCA era. Major PBC-specific prognostic models are summarized in Table 1.

3.1. Mayo Risk Score. With the absence of therapeutic intervention in 1983 and 1985, the Yale model and European model were the first PBC-specific prognostic scoring systems. Since none of these models could accurately calculate patient survival and both required liver biopsy, in 1989 Dickson et al. proposed the Mayo score ($R = 0.039 \times$ age in years $+ 0.871 \times \ln$ (bilirubin in mg/dL) $+ 0.859 \times$ edema $- 2.53 \times \ln$ (albumin in gm/dL) $+ 2.38 \times \ln$ (prothrombin time in seconds)) [42]. In the beginning, the model was less useful in predicting survival over time since it was based on baseline characteristics. In 1994, this model was revised and further simplified. The same variables were used (INR instead of PT) to predict short-term survival, described as less than 2 years of survival or time to transplantation at any time point during follow-up. In conclusion, scores greater than 7.8 were associated with a progressively increased post-LT mortality rate [51]. Nowadays, the model contains six variables: age, prothrombin time, bilirubin and albumin levels, presence or absence of edema, and dependence on diuretics. As it can be seen, the Mayo risk score has one great advantage—it does not require liver histology to calculate the risk score, which is among the many reasons why this score is still widely used.

3.2. UDCA Era. In the UDCA era, several groups have published different biochemical response criteria that predict overall survival and progression of liver disease based exclusively on treatment response, i.e., the Barcelona, Paris I, Rotterdam, Toronto, and Paris II criteria. Among all of them, only Toronto criteria were developed comparing histologic disease progression in the paired biopsies from the same patients with biochemical response to UDCA therapy. The Toronto criteria define biochemical response to UDCA as ALP less than 184 IU/L ($1.67 \times$ ULN) after 2 years of treatment. In paired liver biopsies, more than 80% of patients who did not

Table 1: Prognostic models for PBC.

Prognostic models	Year	Settings	Sample size (n)
Pre-UDCA era			
Yale model [40]	1983	USA	280
European model [41]	1985	Denmark	248
Mayo score [42]	1989	USA	418
UDCA era			
Barcelona criteria [43]	2006	Spain	192
Paris I criteria [44]	2008	France	292
Rotterdam criteria [45]	2009	Netherlands	375
Toronto criteria [37]	2010	Canada	69
Paris II criteria [46]	2011	Spain	165
APRI score [47]	2014	Britain	1015
ALBI score [48]	2015	China	61
GLOBE score [49]	2015	Netherlands	4119
UK PBC risk score [50]	2016	UK	1916

respond to UDCA according to the criteria showed histologic progression after 10 years (odds ratio, 12.14; 95% CI, 2.69–54.74) [37]. The biochemical response criteria after 12 months of UDCA treatment are the most validated and easy to use. The Paris I criteria are generally considered the best to predict transplant-free survival for patients with advanced PBC (stages III-IV). Patients with ALP <3 ULN, AST <2 ULN, and bilirubin ≤17 μmol/L after 1 year of UDCA had a 10-year transplant-free survival rate of 90% compared with 51% [44]. To predict the prognosis of patients with early-stage PBC, Paris II criteria were defined as AST and ALP ≤1.5 ULN, with a normal bilirubin level after 1 year of UDCA therapy [46]. French studies showed that among 165 early-stage PBC patients survival rates without adverse outcomes at 5, 10, and 15 years of follow-up were 100% in responders and 93%, 87%, and 74%, respectively, in nonresponders [46].

3.3. GLOBE Score. GLOBE score system was a model made in 2015 by Lammers et al. to predict the outcomes of PBC patients receiving UDCA therapy [49]. It calculates five objective variables including age at the start of UDCA therapy and levels of bilirubin, albumin, ALP, and platelet count (PLT) after 1 year of UDCA. The multicentre meta-analysis included 4119 UDCA-treated patients, at liver centers in 8 European and North American countries [49]. After 1 year of UDCA, a meta-analysis showed that only the levels of bilirubin, albumin, ALP, and PLT were independently associated with death or liver transplantation. In addition, patients with risk scores >0.30 were defined as UDCA nonresponders with significantly shorter transplant-free survival than a matched healthy individual ($p < 0.0001$) [49]. This leads to the idea that using the GLOBE score we can distinguish UDCA nonresponders, who may need second-line treatment options, from those who should continue using UDCA monotherapy. Furthermore, transplant-free survival could still be accurately calculated by the GLOBE score with laboratory values collected at 2–5 years after treatment. The limitation of this study was the exclusion of other potentially relevant PBC laboratory parameters such as prothrombin time, GGT, immunoglobulin M (IgM), or immunoglobulin G (IgG) and its relatively complex calculation [6].

3.4. UK Primary Biliary Cholangitis Risk Score. One year after the GLOBE score was presented, Carbone et al. proposed a scoring system for a long-term prediction of end-stage liver disease (ESLD) in PBC called UK PBC risk score [50]. They analyzed data from more than 3,000 participants at liver centers in Great Britain and Northern Ireland to estimate the absolute risk of developing ESLD requiring liver transplantation at 5, 10, and 15 years from the time of diagnosis. Initial diagnosis of PBC was defined by the date of the first positive test for AMA or by the date of the diagnostic liver biopsy for seronegative patients. ESLD that requires liver transplantation was defined by 3 events: death related to liver disease (liver failure, variceal hemorrhage, or hepatocellular carcinoma (HCC)), liver transplantation for PBC, and for living patients—serum bilirubin greater than or equal to 100 mmol/L. UK PBC score includes levels of bilirubin, AST or ALT, and ALP after 12 months from diagnosis or UDCA treatment and also albumin level and platelet count at baseline as parameters of synthetic liver function and indirect signs of liver fibrosis. Since it calculates the area under the receiver operating characteristic curve (AUC) for each risk score at 5, 10, and 15 years, it is considered superior to existing prognostic models [50]. Its disadvantage could be found in the fact that they did not present a specific threshold for their risk scores. To sum up, by giving individualized, objective, and accurate information on the prognosis, this model could be used for evaluating patients who may be candidates for frequent monitoring and second-line therapies, as well as those who are at low risk of developing ESLD. The algorithm for risk assessment, treatment, and monitoring for PBC patients is presented in Figure 1.

4. Liver Transplantation

The LT treatment procedure includes determining an indication for LT, the process of organ allocation, and a complex surgical procedure followed by lifelong immunosuppressive treatment, whereas the main focus in the posttransplant period is aimed at the treatment of complications of the transplant procedure and immunosuppressive treatment. Since a successful outcome requires optimal patient selection and timing, the issue of which patients to list for LT and when to transplant cirrhotic patients has generated great interest and considerable controversy [51].

LT is nowadays the standard treatment procedure for all patients with end-stage acute or chronic liver failure of various etiologies, i.e., in cases where the limits of medical therapy have been reached. Evaluation for LT should be considered once a patient with end-stage liver disease or cirrhosis has experienced the first complication of portal hypertension or develops hepatocellular dysfunction resulting in a MELD score (model of end-stage liver disease) ≥15. In these patients, LT would extend life expectancy beyond that of the natural history of underlying liver disease and likely improve the quality of life (QoL). There are no uniform allocation rules or systems worldwide. Several organ exchange organizations operate in different countries

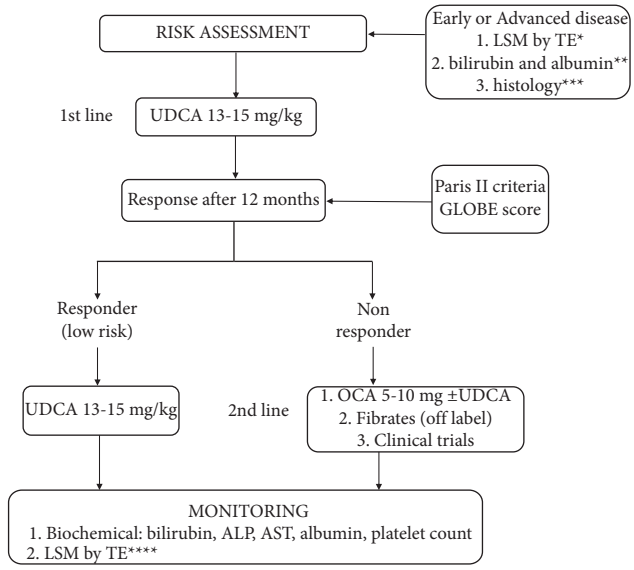

Figure 1: Risk assessment, treatment, and monitoring for PBC patients. *early from advanced disease stage based on LSM by TE (LSM <10 kPa or LSM >10 kPa). **both parameters normal vs. at least 1 parameter abnormal. ***absent or mild fibrosis vs. bridging fibrosis or cirrhosis. ****repeat TE every 2 years in early stage and every year for advanced disease.

and geographical areas. Most organizations have similar rules with the urgent priority group (e.g., for acute hepatic failure, early retransplantation following primary graft nonfunction, hepatic artery, or portal vein thrombosis). In patients with chronic liver diseases, there are some differences related to organizational and allocation policies. MELD score is a good predictor of short-term pretransplant mortality risk in patients with decompensated liver cirrhosis [52]. In many Western transplant centers, the allocation of liver transplants is based on MELD score. However, not all diseases and complications are well reflected by MELD. Those patients (e.g., with HCC, refractory ascites, recurrent bleeding, encephalopathy, or intractable pruritus) should be recognized and treated differently. In most centers, priority is given to these patients by specific rules defined by multidisciplinary expert teams. Depending on the availability of the organ in specific countries and international collaboration, the waiting time on the list significantly varies.

To ensure the forehand and feasible LT, the pretransplant LT candidate workup comprises the evaluation of all potential complications of liver disease (e.g., ascites, varices, hepatic encephalopathy, hepatopulmonary syndrome, portopulmonary hypertension, hepatorenal syndrome, and hepatocellular carcinoma) and all other potential organ comorbidities. Evaluating and selecting a good recipient for LT requires the collaboration of several specialists. The final decision should be made within each expert center among a multidisciplinary team. While a potential candidate is registered on the LT list, all potentially treatable etiologies and components of hepatic decompensation should be treated and regularly evaluated.

Advances in immunosuppressive treatment, organ preservation solutions, anesthesiological and surgical procedures, and better recognition of posttransplant complications significantly improved the patient and graft survival. The average one-year survival of LT recipients is 96%, 5-year 78%, and 10-year 71% [53]. The life expectancy of transplant recipients and grafts is mostly limited by recurrent diseases such as malignant diseases and primary sclerosing cholangitis (PSC) and the occurrence of side effects associated with immunosuppression such as diabetes, chronic renal failure, hyperlipidemia, atherosclerosis, or *de novo* malignancy. For many years, there have been no new immunosuppressive drugs with lower toxicity on the horizon of transplant medicine, which further justifies efforts to better manage existing treatment options. Cholestatic liver diseases, including PBC, are considered favorable indications for LT, with 1- and 5-year patient survival rates reported between 93–94% and 82–90%, respectively. The reported rates of graft survival have been between 85 and 86% within 1 year and 81 and 82% within 5 years and are among the greatest compared with other indications [54]. Recurrence of autoimmune diseases (e.g., AIH, PBC, and PSC) varies between 10 and 50%. The exact rates of recurrence and their impact on graft function and patient survival are obscured by inconsistencies in the diagnostic approaches and criteria employed [55, 56].

5. Liver Transplantation Waiting List and PBC

UDCA as a recognized treatment for PBC patients has improved the natural history of the disease and its survival [57]. As a result, the number of PBC patients requiring LT has dramatically decreased over the last decades to <10% of all indications in Western countries [58].

In many other chronic liver diseases, the most common indications for LT in PBC patients are decompensated liver cirrhosis or complications secondary to portal hypertension, i.e., bleeding from gastroesophageal varices, diuretic-resistant ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and moderate hepatopulmonary syndrome when the expected survival is less than one year (MELD ≥15). Except for MELD score, another option is the Mayo risk score of 7.8 or higher. Uncontrolled and intolerable pruritus refractory to all possible medical therapies, even as an isolated indication, represents the second most common indication for LT because it provides a significant improvement in the QoL of PBC patients after LT. HCC is an exceptionally rare indication for LT in PBC patients. Although fatigue is a distinctly disabling factor, a significant proportion of patients continue to have impaired QoL after LT, and hence, it is not recognized as an indication for LT.

Before registration on the waiting list, the potential LT candidate is evaluated by a multidisciplinary team according to the standard procedure. It includes screening for complications of liver cirrhosis and portal hypertension and extensive workup for comorbidities. Even though there is no formal age limit for potential LT recipients, patients older than 65 years need a special multidisciplinary workup. In the United States, the average age of patients undergoing transplantation for PBC is in the range of 53 to 55 years. Patients are evaluated for the existence of malignant,

cardiovascular, renal, pulmonary, oropharyngeal, urological, gynecological, and psychiatric diseases. Finally, they are evaluated for their nutritional and overall functional status and the presence of osteoporosis (Table 2). PBC patients often have associated autoimmune and metabolic diseases, especially hyperlipidemia and osteoporosis, thyroid disease, keratoconjunctivitis sicca, and xerostomia. Those persist or even may worsen after LT and should be properly treated. Hyperlipidemia in PBC patients is common and yet it has not been shown to carry additional cardiovascular risk in the absence of other risk factors for cardiovascular disease (CVD). Part of the confusion appears from the various effect of PBC on lipid metabolism. In early disease, patients often have elevated levels of LDL (which increases cardiovascular risk) and HDL levels and also levels of adiponectin and lipoprotein X (Lp-X), a circulating lipid particle with a density similar to LDL, which has a cardioprotective effect [60]. Also, PBC therapy impacts lipid metabolism in a way that UDCA increases cholesterol absorption and fibrates are modulating bile acid and cholesterol transportation [60]. Lipid-lowering therapy should be individualized based on CVD risk assessment and comorbidities and currently published guidelines are not offering strong recommendations regarding monitoring or treatment. Statins are the first choice for therapy, and since data on risk stratification within PBC are not available and most studies have only examined moderate-intensity statins (atorvastatin 10–20 mg daily or simvastatin 20–40 mg daily), it is safe at these doses and up titrate as clinically indicated [61, 62]. Although fibrates are a promising therapy for PBC, in the context of hyperlipidemia treatment they have no advantage in lowering overall cardiovascular morbidity and mortality over statins. A meta-analysis of fibrates did show a 10% relative risk reduction (95% CI, 0 to 18) in major cardiac events but did not improve cardiovascular mortality [63]. Metabolic bone disease (osteopenia, osteoporosis) is a common complication of PBC, which increases morbidity and mortality [64, 65]. Therapeutic options are limited and mostly derived from osteoporosis in postmenopausal women. PBC-related osteoporosis is driven primarily by decreased bone formation compared with postmenopausal osteoporosis, which is secondary mostly to increased bone resorption [66]. Patients after liver transplantation are prone to osteopenia and osteoporosis, with an expected bone loss of 8% to 18% in the first 3–6 months after liver transplantation [67, 68] and 20% to 40% incidence of fractures in the first year posttransplant [67, 69]. Prevention and treatment of osteoporosis before and after transplantation are imperative in the overall management of PBC. It is suggested that all patients undergo bone mineral density assessment (dual-energy X-ray absorptiometry (DEXA)) at the time of diagnosis and continue with surveillance between 1 and 5 years later depending on the outcome and general osteoporosis risk [1]. Preventive measures include optimal lifestyle and nutritional support. Supplementation of vitamin D and calcium is recommended by EASL guidelines in all PBC patients without a history of renal stones [1]. Many treatment strategies for osteoporosis in PBC are copied from therapeutic options in postmenopausal osteoporosis. Several trials have demonstrated that bisphosphonates, especially weekly alendronate, and monthly ibandronate, are effective in increasing bone mass in patients with PBC [70]. Additional studies investigating PBC-specific therapies with a focus on improving bone formation are necessary to improve patients' outcome.

Patients with cirrhosis are especially prone to various clinically evident and latent infections that could result in the development of multiple organ failures and death before and after LT. Screening for bacterial, fungal, and viral acute or chronic infections is mandatory before LT. The presence of an active uncontrolled infection contraindicates the procedure. The infectious screening should be performed at all time points in the process of LT: in all LT candidates, in patients eligible for LT at the time of listing, and in patients with risk factors according to their clinical history, comorbidities, and exposure to endemic diseases (Table 2). Regarding vaccination, it is important to make sure that LT candidates are immunized against HAV and HBV, varicella, Pneumococcus, influenza, and tetanus, and concerning the current epidemiological situation, COVID-19.

Pretransplant assessment is not uniform to all transplant teams, and the optimal approach is constantly evaluated and changing in each transplant center. Absolute and relative contraindications to LT are also changing over time and may vary among liver transplant centers, depending on their local expertise.

Patients on the waiting list should be regularly evaluated and properly treated for the consequences of portal hypertension and liver decompensation.

6. Recurrent Primary Biliary Cholangitis

In approximately 21% to 37% of patients who have undergone liver transplantation as the only definitive treatment for PBC, recurrence of the disease was reported after 10 years. [6]. Initial studies showed a lower incidence of disease recurrence, but with long-term follow-up, rPBC was reported by most world centers with growing numbers [71]. Data from multiple studies considering median time to graft loss as a consequence of disease recurrence showed no difference in survival of patients with recurrence of the disease in contrast to those without it. Nevertheless, with time, there is a possibility of this becoming a greater challenge in the long-term treatment of patients [6, 71].

6.1. Diagnosis of Recurrent PBC. Diagnosis of rPBC comes with a set of challenges in comparison with the diagnosis of PBC, which is mainly because clinical and serological findings are not as useful as in diagnosing *de novo* disease so clinicians depend on histopathological findings, which are received with performing invasive procedures and consequently not routinely done. According to the American Association for the Study of Liver Diseases, de novo PBC is diagnosed in case of long-term elevated ALP serum levels in combination with one of the other criteria: either positive AMA antibodies, positive PBC-specific ANA, or histopathological findings affirmative of PBC [3, 6, 71].

Table 2: Comorbidity assessment in liver transplant candidates.

Comorbidity	Procedure	Associated risk
Cardiovascular	ECG, heart ultrasound with Doppler ergometry or pharmacological stress test (>50 years or with multiple cardiovascular risk factors for coronary heart disease), coronary angiography (with positive ergometry test or pharmacological stress test)	In the case of adequately treated coronary heart disease, the risk is equal to the rest of the population, for recipients aged >70 years increased cardiovascular risk
Respiratory	Chest X-ray, spirometry, diffusion capacity for CO, the definition of hepatopulmonary syndrome (HPS; calculation of alveolar/arterial oxygen gradient or contrast echocardiography) and portopulmonary hypertension (PPHTN; mean pulmonary artery pressure—MPAP >30 mmHg, right-sided cardiac catheterization is obligatory)	For HPS and pO2 <50 mmHg without response to 100% oxygen therapy—possible irreversible respiratory failure not corrected with LT, for PPHTN and MPAP ≥35 mmHg not responding to pulmonary vasodilator therapy—high perioperative mortality MPAP 35–50 mmHg—50% risk of mortality after LT [59] MAP >50 mmHg absolute contraindication for LT—100% risk of posttransplantation mortality [59]
Renal	Abdominal and kidney ultrasound, spot urine test, K/Na/protein/creatinine in daily urine, eGFR (MDRD6)	Sevenfold increased perioperative risk recipients with GFR <30 mL/min or hepatorenal syndrome and dialysis >8–12 weeks or >30% glomerulosclerosis or fibrosis on kidney biopsy—simultaneous liver and kidney transplantation indicated
Nutritive status	Body mass index (BMI), prealbumin, psoas thickness (MSCT)	Recipients with a BMI <18.5 or >40 have elevated mortality
Osteoporosis	Densitometry	Osteoporotic fracture (fractures of the hip, vertebrae, and distal forearm are the most common)
Infections	The first level of screening consists of screening for human immunodeficiency virus (HIV) 1 and 2 antibodies, HBV serology, HCV antibodies, HAV antibodies, cytomegalovirus (CMV), and completing a chest X-ray [51] The second level of screening consists of screening for *Mycobacterium tuberculosis* (history + PPD-Mantoux + IFN gamma release assays), Epstein–Barr virus (EBV), human herpes virus 8 (HHV-8), varicella-zoster virus (VZV), herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), urine culture, parasitological examination and stool culture (*Strongyloides stercoralis* serology, *Toxoplasma gondii* IgG, *Treponema pallidum* serology), Immunoenzymatic Assay with Venereal Disease Research Laboratory (VDRL), *Staphylococcus aureus* nasal/axillary swab, and dentist review recipients should receive the vaccine for HAV, HBV, chickenpox, pneumococcus, influenza, tetanus, COVID-19	Uncontrolled sepsis, bacterial, viral, and invasive fungal infections (aspergillosis) are a contraindication for the LT procedure

6.1.1. Clinical Features. Characteristic symptoms of PBC in the native liver are not necessarily present in the recurrent forms of the disease. Moreover, studies show that clinical manifestations of the disease, such as chronic fatigue and pruritus, surface in only 12% of patients with a confirmed diagnosis. Furthermore, concomitant autoimmune diseases (thyroid disease, keratoconjunctivitis sicca, and xerostomia) may persist and/or resolve after transplantation or even from *de novo,* but none of these is a predictive factor for disease recurrence [6, 71, 72].

6.1.2. Serology Features. Persistent elevation of cholestatic parameters such as ALP combined with either positive AMA antibodies or positive PBC-specific ANA is enough for a serologic diagnosis of PBC, however in rPBC that is not the case. Approximately 50% of patients with normal liver biochemistry may have characteristic histology finding on protocol biopsy. Additionally, in cases where the diagnosis was made on histologic findings in the allograft, it was not mirrored by the cholestatic profile of liver enzymes. Another contributing factor to ALP non-specificity is a large number of conditions with ALP elevation after transplantation, including acute and chronic graft rejection, viral infections, graft-versus-host disease, or obstructive cholestasis. AMA nor PBC-specific ANA also cannot be used in the diagnosis of recurrent types of the disease since their role in diagnosing rPBC is limited [6, 27, 28, 73]. After transplantation, there is usually a transient fall in serum levels of both AMA and PBC-specific ANA, but in the long term, their levels in the majority of patients stay elevated [74–76].

6.1.3. Histology Features. Liver biopsy and characteristic histological findings are the only valid parameters for the diagnosis of recurrent PBC. Not all centers require protocol allograft biopsies in long-term follow-up of transplanted patients with PBC, which could falsely lead to lower reported rates of rPBC. A good marker for the necessity of liver biopsy could be the elevation of IgM levels, considering that it has been shown that IgM levels are more likely to be elevated in patients with recurrence of PBC after transplantation than in those without it [6, 71]. Florid duct lesions or destructive lymphocytic cholangitis presence is defined as a histologic hallmark of disease recurrence. To be exact, there are four specific portal tract lesions: damage to the bile ducts, lymphoid aggregate formations, and the presence of mononuclear inflammatory infiltrate or epithelioid granulomas. If two of four of these characteristics are present in the liver biopsy, a diagnosis of rPBC is highly probable. If all of them are recognized, then the diagnosis is definitive [6, 77]. Even with histopathological characteristics of rePBC, other causes of graft failure must be excluded, such as acute and chronic rejection of an allograft, viral infections (CMV, HCV), and graft-versus-host disease. The Birmingham study published in liver transplantation showed that in 13 of 83 biopsy specimens taken from patients transplanted for PBC, a recurrent form of the disease was diagnosed. However, in 12 of them, a histologic stage of 1-2 was established and only one patient developed cirrhosis in the liver allograft. There is the utmost importance of follow-up biopsies in patients with the histological finding of stages 1 and 2 to determine disease progression and timely diagnosis [71]. Sylvestre and colleagues in the study done at the Mayo Clinic have confirmed that one-half to one-third of patients with a definitive histological diagnosis of rPBC had normal ALP levels at the time of biopsy [77].

In summary, diagnostic criteria for rPBC include anamnestic data of liver transplantation for PBC, positive serum levels for AMA or PBC-specific ANA with the existence of mononuclear inflammatory infiltrate, lymphoid aggregates, epithelioid granulomas, and bile duct destruction with pathohistological findings of liver biopsy, all of which is preceded with the exclusion of other causes for graft failure [6, 71, 73, 76].

7. Risk Factors for Recurrence

Over the years, a large number of risk factors for the recurrence of PBC have been analyzed and many of them remain controversial. Patients undergoing liver transplantation for PBC are usually in their 60 s or 70 s. Certain studies showed a positive correlation between younger recipients' age and a higher rate of recurrence, while a study published by Silveira and colleagues saw a greater risk of recurrence in patients who were older at the time of LT [72]. The role of HLA mismatch as a risk factor for PBC recurrence also remains controversial, but Sanchez and colleagues concluded that certain patterns of alleles are found more often in patients with rPBC, such as A1, B57, B58, DR44, DR57, and DR58 in donors and B48 in recipients [78]. According to one Japanese study [79], a small number of mismatches in HLA-A, HLA-B, and HLA-DR were associated with a higher risk of PBC recurrence, and a high number of those are connected to increased mortality 6 months after transplantation. Factors of the donor liver, such as age and warm and cold ischemic time, were also analyzed. In a study published by Silveira and colleagues, a donor older than 65 years was described as a risk factor in the case of tacrolimus immunosuppression. Cold ischemic time was recognized as a risk factor, while warm ischemic time was not described as statistically significant [72]. The use of different calcineurin inhibitors in immunosuppression therapy after transplantation was also evaluated. In a few studies, with the use of tacrolimus, a shorter time from transplantation to recurrence has been described in comparison with cyclosporine [72, 78, 80]. Corticosteroid therapy also seems to have a role in rPBC. Several studies showed that immunosuppressive therapy without corticosteroids may increase the incidence of recurrence [71, 72].

Until recently, the results of several studies showed that rPBC has a limited overall impact on graft or recipient survival and all studies had an evident limitation in the short follow-up period [56, 81, 82]. A retrospective, multicentre study published by Montano et al. [82] was the first to demonstrate that recurrence of PBC was significantly associated with graft loss (HR, 2.01; 95% CI, 1.16–3.51) and death of recipient (HR, 1.72; 95% CI, 1.11–2.65). The same study also showed that the age at diagnosis <50 years, age at

liver transplantation <60 years, use of tacrolimus, and biochemical markers of severe cholestasis (bilirubin >100 mmol or alkaline phosphatase >3-fold the upper limit of normal) at 6 months after liver transplantation were associated with a higher risk of PBC recurrence, while the use of cyclosporine reduced risk of rPBC. The only available treatment option for rPBC is UDCA, and there is numerous observational evidence that re-induction of UDCA leads to biochemical improvement [50]. Some centers started using UDCA preemptively to reduce the incidence of rPBC and biliary complications after LT. In 2015, retrospective multicentre analysis showed that preventive administration of UDCA was associated with a significant reduction (21% vs. 62%) in the risk of PBC recurrence over the 10-year follow-up [83]. The effect of preventive exposure to UDCA on the incidence and long-term impact of rPBC after LT was investigated in the longitudinal retrospective study that included the largest cohort of transplanted patients with PBC to date [84]. The study showed that preventive exposure to UDCA (10–15 mg/kg per day) was associated with reduced risk of rPBC (adjusted HR (aHR) 0.41; 95% CI, 0.28–0.61; $p < 0.0001$), graft loss (aHR, 0.33; 95% CI, 0.13–0.82; $p < 0.05$), liver-related death (aHR, 0.46; 95% CI, 0.22–0.98; $p < 0.05$), and all-cause death (aHR, 0.69; 95% CI, 0.49–0.96; $p < 0.05$). The beneficial effect of cyclosporin over tacrolimus was also confirmed in this study. Moreover, the combination of preventive UDCA and cyclosporine was associated with survival gains of 2.26 years (95% CI, 1.28–3.25) and 3.51 years (95% CI, 2.19–4.82), respectively, over 20 years. The exact mechanism of action involved in the preventive effect of UDCA on rPBC is unclear, but it is assumed to be related to the well-known immunomodulatory and anti-inflammatory properties such as inhibiting prostaglandin E2 (PGE2), thus blocking the propagation of autoimmune liver injury and decreasing the hepatocellular expression of MHC class I and the biliary expression of MHC class II, thus interfering with the autoimmune basic mechanisms [44, 84]. Recurrence of primary biliary cholangitis is relatively common; luckily, many patients are diagnosed with a histologic stage of 1-2 and very rarely there is a need for retransplantation. In a large study including 486 patients who underwent LT for PBC, only 2 of them again reached end-stage liver disease caused due to rPBC and were retransplanted [85], but Corpechot and colleagues have shown that in a prolonged follow-up period, rPBC has a significant impact on graft and recipient survival [84]. Additional studies (preferable randomized clinical trials) are needed to confirm the beneficial effects of UDCA and immunosuppressive regime on rPBC and to explore the usefulness and effects of current second-line therapies for PBC (OCA and fibrates) in the context of rPBC.

8. Conclusion

Diagnosis of PBC can be made using biochemical and serologic findings, and easier diagnostic requirements result in increasing prevalence and incidence of the disease. On the other hand, available treatment options, especially UDCA, changed the clinical course of the disease and prolonged LT-free survival, and there is no increased incidence of patients with PBC added to the waitlist for LT. Several risk scores are proposed for better evaluation of patients before and during treatment to stratify patients at increased risk of disease progression and ESLD development. GLOBE score and UK PBC risk score are widely used for the evaluation of UDCA treatment with the greatest advantage of not needing a liver biopsy to evaluate the treatment's effect, only noninvasive objective data. For UDCA-refractory or UDCA-intolerant PBC, OCA has been approved as a second-line treatment and there are ongoing trials for several new treatment options. LT is the only treatment option in the case of ESLD. Up to 40% of patients experience recurrence of the disease more than 10 years after LT. rPBC is a histological diagnosis, and liver biopsy is required. Several studies highlighted potential risk factors for rPBC such as the role of HLA mismatching, use of corticosteroids after LT, or type of calcineurin inhibitors but with no strong conclusions. Until recently, it was considered that rPBC has a limited overall impact on recipient and graft survival mostly due to the short follow-up period. Now, we have several studies with longer follow-up periods that demonstrated that rPBC is significantly associated with graft loss and death of the recipient. With this in mind, there is a need to find an effective therapy for rPBC and if possible, to prevent disease recurrence. The use of UDCA after rPBC is associated with biochemical and clinical improvement in the majority of patients, and recently published studies even show a beneficial effect of UDCA use after transplantation for the prevention of rPBC development. Further studies are needed to rule on the preventive effect of UDCA on rPBC and to make conclusions on universal prophylactic therapy after LT. LT is a definitive treatment option for ESLD, but the question arises as to what can be done to prevent the progression of the disease. Although the use of UDCA has significantly altered the natural course of PBC, about 40% of patients have an inadequate clinical response and are at high risk of disease progression. Furthermore, currently approved therapies for PBC do not affect frequent clinical symptoms such as pruritus and fatigue, and additional therapy for symptom control is often not enough. Moreover, intractable pruritus with all available symptom control therapies is an indication for liver transplantation. There are multiple ongoing trials to address the lack of treatment options for PBC, and fibrates appear to be the most promising new therapy in achieving PBC treatment endpoints.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

IgG4-Related Sclerosing Cholangitis: Rarely Diagnosed, but not a Rare Disease

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IgG4-related sclerosing cholangitis, a biliary manifestation of an IgG4-related disease, belongs to the spectrum of sclerosing cholangiopathies which result in biliary stenosis. It presents with signs of cholestasis and during differential diagnosis it should be distinguished from cholangiocarcinoma or from other forms of sclerosing cholangitis (primary and secondary sclerosing cholangitis). Despite increasing information and recently established diagnostic criteria, IgG4-related sclerosing cholangitis remains underdiagnosed in routine clinical practice. The diagnosis is based on a combination of the clinical picture, laboratory parameters, histological findings, and a cholangiogram. Increased serum IgG4 levels are nonspecific but are indeed a part of the diagnostic criteria proposed by the Japan Biliary Association and the HISORt criteria for IgG4-SC. High serum IgG4 retains clinical utility depending on the magnitude of elevation. Approximately 90% of patients have concomitant autoimmune pancreatitis, while 10% present with isolated biliary involvement only. About 26% of patients have other organ involvement, such as IgG4-related dacryoadenitis/sialadenitis, IgG4-related retroperitoneal fibrosis, or IgG4-related renal lesions. A full-blown histological finding characterized by IgG4-enriched lymphoplasmacytic infiltrates, obliterative phlebitis, and storiform fibrosis is difficult to capture in practice because of its subepithelial localization. However, the histological yield is increased by immunohistochemistry, with evidence of IgG4-positive plasma cells. Based on a cholangiogram, IgG-4 related sclerosing cholangitis is classified into four subtypes according to the localization of stenoses. The first-line treatment is corticosteroids. The aim of the initial treatment is to induce clinical and laboratory remission and cholangiogram normalization. Even though 30% of patients have a recurrent course, in the literature data, there is no consensus on chronic immunosuppressive maintenance therapy. The disease has a good prognosis when diagnosed early.

1. Definition

IgG4-related sclerosing cholangitis (IgG4-SC) is a biliary manifestation of IgG4-related disease (IgG4-RD). IgG4-RD is an immune-mediated fibroinflammatory disease that can affect almost any organ. The disease may present either as diffuse fibroinflammation or as the formation of inflammatory pseudotumors in the affected organ. Typical histological signs for IgG4 disease are IgG4-enriched lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis, and variable presence of eosinophils in affected organs [1–3]. Most patients have elevated serum IgG4 levels. A good initial response to corticoids is characteristic as well [4]. In IgG4-SC, lymphoplasmacytic inflammation affects

the bile duct wall; however, it usually presents with other organ manifestations, especially with autoimmune pancreatitis [5, 6]. The term IgG4-associated sclerosing cholangitis was replaced with the formal name "IgG4-related sclerosing cholangitis" at the 1st International Symposium on IgG4-related disease [7]. This nomenclature aims to emphasize not only the similarities with primary sclerosing cholangitis (PSC) but also the strong need to distinguish between the two diseases, as they have diametrically different treatment and prognoses.

2. Epidemiology

There are only limited epidemiological data on IgG4-SC, some of which evaluate the occurrence of IgG4-SC only indirectly. There are several reasons for this. IgG4-RD is a new disease, whose diagnostic criteria have only recently been accepted worldwide. This has raised global awareness of the disease, but the disease does not have its own unique International Statistical Classification of Diseases and Related Health Problems (ICD-10) code, which complicates epidemiological studies. The concept of IgG4 disease was preceded by information about its individual organ manifestations. The most studied one is autoimmune pancreatitis (AIP), which IgG4-SC is typically associated with. Most literature data come from Japan. The first mention of AIP dates back to 1995; however, the diagnostic criteria for AIP were first proposed by the Japan Pancreas Society in 2006 [8, 9]. In the same year, the new clinicopathological entity of IgG4-SC associated with autoimmune pancreatitis was proposed by Kamisawa et al. [10]. Epidemiological studies focusing on IgG4-SC's prevalence and incidence have many limitations:

(1) IgG4-RD is a relatively new disease entity with unification of a host of previous clinical entities under the umbrella term "IgG4-RD" only achieved in 2012 [4]

(2) The diagnostic criteria for IgG4-SC have not yet been unified, with the HISORt and Japan Biliary Association criteria sharing many similarities but also some important differences [2, 11]

(3) There is controversy around whether type 1 IgG4-SC should be considered IgG4-SC or simply AIP with associated biliary sclerosis

Another factor that affects epidemiological studies is the interpretation of type 1 IgG4-SC, which is associated with a lower rate of bile duct stenosis and is mostly associated with the AIP. One group of experts does not approve of this type, because it believes that such stenosis could be caused by external compression of the intrapancreatic portion of the bile duct by the inflamed pancreatic tissue and not by inflammation of the bile duct [12].

The other group of experts presumes that type 1 IgG4-SC may occur even without concurrent AIP, which is supported by case series, large series, and even histological findings [3, 13–16].

Exclusion of type 1 IgG4-SC would have a significant impact on epidemiological data, because type 1 IgG4-SC occurs most frequently and according to Tanaka makes up to 64% of all IgG4-SC [17].

These studies have several limitations, and it is generally assumed that they underestimate the real incidence and prevalence. In 2011, Kanno et al. conducted the Nationwide Epidemiological Survey of Autoimmune Pancreatitis in Japan with the following results: the overall prevalence rate of AIP was 4.6 cases per 100,000 inhabitants and the annual incidence rate was 1.4 per 100,000 inhabitants [18]. Based on this information and the fact that IgG4-SC is present in about 40% of patients with AIP, we can indirectly conclude that the incidence of IgG4-SC is approximately 0.5 new cases per 100,000 inhabitants and the prevalence is 1.8 cases per 100,000 inhabitants [19]. On the other hand, approximately 10% of patients with IgG4-SC are not diagnosed with AIP; therefore, the estimated prevalence of IgG4-SC could theoretically be as high as 2.0 cases per 100,000 inhabitants. Finally, in 2020, Tanaka et al. published the first epidemiological study evaluating 1,045 IgG4-SC patients from 532 centers in Japan and showed that the prevalence of IgG4-SC in 2018 was 2.18 (95% confidence interval, 2.13–2.23) per 100,000 inhabitants, which is comparable to other data [20]. Thus, we can conclude that the prevalence of IgG4-SC in Japan is higher than the prevalence of PSC, which in 2016 was 1.80 (95% CI, 1.75–1.85) [21].

An indirect estimate of the prevalence of IgG4-SC can be obtained from case series data on the percentage of IgG4-RD cases with biliary involvement. In 2015, Inoue et al. analyzed a cohort of 235 patients from 8 Japanese IgG4-RD centers, 64% of whom had histologically verified disease. Pancreatic involvement was present in 60% and bile duct involvement in 13% of them [22]. On the other hand, a study published by Chinese authors reports 118 patients with IgG4-RD, 38% of whom had AIP and in 17.8% biliary tree involvement was present [23]. The findings of another Chinese study are similar, where, among 200 patients with IgG4-RD, pancreatic and biliary tract involvement was seen in 38.5% and 19% of patients, respectively [24]. Even lower prevalence of these organ manifestations was observed in a study by Wallace et al. from USA from 2015, which included 125 patients with histologically verified IgG4-RD. Only 19.2% of patients had pancreatic involvement and only 9.6% had biliary tract involvement [25]. If we want to indirectly judge the epidemiology of IgG4-SC in Europe, three works are available. The first included 41 patients with IgG4-RD from Italy. Autoimmune pancreatitis was the most common organ manifestation in 41% of patients, with the biliary tree being affected in 9.8% of patients [26]. The second is from Spain and evaluates 55 patients with IgG4-RD diagnosed in 12 Spanish hospitals. In this study, 16% of patients had pancreas involvement and only 4% had bile duct involvement. The smallest is the study from France, which included 25 patients with IgG4-RD, up to 52% with AIP and up to 32% with IgG4-SC [27], while 10% presented with isolated biliary involvement. The prevalence variability is mainly due to sampling error from these small sample sizes and referral

bias and perhaps due to differences in clinical manifestation in different patient populations (e.g., perhaps due to the differences in HLA serotypes mentioned in the section on pathogenesis). The limited sample size of European studies also prevents the generalization of epidemiological data.

IgG4-SC is a disease of elderly patients. Most patients are diagnosed in the 6th-7th decade; the disease has not yet been described in children and adolescents [28, 29]. Only 0.7% of patients had the disease diagnosed in the second decade of life [20]. The median age at diagnosis in a different case series is comparable and represents 66–67 years in Japan, 62 years in USA, and 61 years in the UK [11, 20, 29, 30]. By contrast, patients with PSC are younger, and their mean age at diagnosis varies in the Western population from 35 to 47 years [31]. Both IgG4-SC and PSC predominantly affect men. Male patients represent 74% to 85% of all IgG4-SC patients. If IgG4-SC occurs in women, the IgG4-SC without AIP is more common [13].

3. Pathogenesis of IgG4-SC

IgG4-SC is a disease of unknown etiology with a multifactorial pathogenesis. IgG4-RD typically presents with polyclonal hypergammaglobulinemia and elevated serum IgG4 levels [32]. Some authors consider IgG4-SC to be an autoimmune disease because some patients have antinuclear antibodies and respond well to corticosteroid treatment or to rituximab [9, 33, 34]. The theory of an autoimmune basis of IgG4-RD is supported by the identification of several autoantigens (galectin-3, laminin 111, and annexin A 11). IgG4 galectin-3 autoantibodies are present in a portion of patients with IgG4-RD and correlate with galectin-3 plasma levels. Anti-laminin-511 E-8 IgG autoantibodies are targeted against laminin 511 in approximately half of patients with AIP. IgG1-mediated proinflammatory autoreactivity against annexin A11 in patients with IgG4-RD may be attenuated by formation of annexin A11-specific IgG4 antibodies in IgG4-SC and AIP patients [35–37].

IgG4 physiologically makes up to 3–6% of the total amount of IgG [28]. We do not know whether IgG4 has a proinflammatory or anti-inflammatory character; evidence suggests that IgG4 has an anti-inflammatory role in allergy, is pathogenic in certain autoimmune conditions (e.g., pemphigus), and supports an immune-tolerant state in helminthic infections [38, 39]. However, IgG4 appears to be a neutralizing antibody that fails to secure a complement, has weak binding to the Fc receptor, and is unable to form large immunocomplexes [38, 40, 41]. Some authors believe that excessive IgG4 production occurs secondarily, with the aim of attenuating the extensive immune response in IgG4-RD. This theory is supported by the fact that IgG4 interacts with the Fc portion of IgG in a way that mimics the rheumatoid factor [42]. In contrast to other autoimmune diseases, men are more commonly affected (80%) with higher mean age [43]. A theory that IgG4-SC should not be considered an autoimmune disease is supported by the finding of increased levels of regulatory T cells (Tregs) in IgG4-SC, whereas, in patients with classic autoimmune diseases, Tregs are reduced [44, 45]. Concerning the "allergic fibrosis theory," the current prevalent approach states that Th2 is prevalent in IG4-RD patients with allergic disease [46]. Most IgG4-RD patients are not atopic, though most of them have eosinophilia and higher levels of IgE in the peripheral blood. These findings may imply that processes inherent to IgG4-RD itself rather than atopy per se contribute to the eosinophilia and IgE elevation [47].

Physiologically, IgG4 is formed as a result of strong or repeated antigen stimulation to induce tolerance [28]. Elevated IgG4 levels may be a protective mechanism for long-term antigen exposure [48]. Furthermore, some authors consider IgG4-SC to be a lymphoproliferative disease [43]; but current consensus does not believe this to be the etiology and no conclusive data is available for any of these possibilities (including lymphoproliferative disorder).

Genetic predisposition plays an important role in the development of IgG4-SC. HLA serotypes DRB1∗0405 and DQB1∗0401 are more common in IgG4-SC in the Japanese population, though not in other ethnic groups [49, 50]. In an English multicentric study, HLA-DRB1∗0301-DQB1∗0201 was found to be more common in patients with IgG4-SC and IgG4-AIP [51]. HLA-B∗07 and DRB1∗15 haplotypes are also more common in IgG4-SC [28]. Five single nucleotide polymorphisms are associated with the occurrence or higher activity of IgG4-SC: cytotoxic T-lymphocyte-associated protein 4 (CTLA4), tumor necrosis factor (TNF), Fc receptor-like 3 (FCRL3), trypsin 1 (PRSS1), and cystic fibrosis transmembrane conductance regulator (CFTR) [52–56]. Further analysis of genome-wide association studies will help determine the genetic risk for IgG4-SC.

The leading theory of the pathogenesis of IgG4-SC is an aberrant interaction between innate immunity, T-cell immunity, and B-cell immunity.

Activation of nucleotide-binding oligomerization domain-containing protein 2 (NOD-2) and toll-like receptor (TLR) on monocytes or basophils of IgG4-AIP patients activates the B-cell-activating factor (BAFF), leading to an enhancement of the IgG4 response. In an animal model, activation of TLR3 and TLR4 leads to immune-mediated cholangitis, pancreatitis, and sialoadenitis [57]. Macrophages, especially the M2 subtype, are abundant in bile duct tissue and can remodel the extracellular matrix of IgG4-SC patients [43]. The role of complement and the formation of circulating immunocomplexes in the pathogenesis of IgG4-RD are controversial. In IgG4-AIP, the level of complement is decreased and the level of circulating immunocomplexes in which IgG4 and its subtypes can be found is increased. However, the classical pathway through IgG1 appears to play a more important role in complement activation compared to the alternative pathway through IgG4 [58]. In patients with IgG4-SC, the Th2 lymphocytes response dominates with the release of IL-4, IL-5, and IL-13 [59]. The Th-2 cellular response generally leads to the maturation and proliferation of B cells and plasmacytes [57]. In IgG4-associated sialodacryoadenitis, IL-21 is released from both Th2 lymphocytes and Th follicular helper cells, leading to germinal center formation, but the incidence of these is lower in IgG4-SC than in IgG4-RD [43, 60, 61]. It should be noted that Th follicular helper cell levels correlate with both the number of

plasmablasts and the serum IgG4 level [62]. These cells play an important role in the interaction of the T-cell and B-cell response in patients with IgG4-RD [43]. Tregs also play a fundamental role in the pathophysiology of IgG4-SC. Circulatory levels of naive CD45RA and Tregs are reduced, while levels of memory CD45RA-Tregs are increased [63]. Memory Tregs can inhibit the inflammatory response in the circulation and peripheral tissues, including bile tissue, while decreased levels of circulatory naive Tregs may lead to a multilocular inflammatory response, which may be pathogenic in patients with IgG4-RD [57]. In patients with IgG4-SC, high concentrations of FOXP3 + CD4 + CD25 + Tregs, which produce IL-10 and tumor growth factor-β (TGF-β), are present in the bile duct tissue. Costimulation of B cells with IL-4 and IL-10 increases IgG4 production [43]. On the other hand, TGF-β overproduction plays a very important role in the fibrogenesis of patients with IgG4-SC [64].

Chemokines play an important role in IgG4-RD. CCR8 expression was detected in half of Th2 lymphocytes and in 60% of FOXP3 Tregs [65]. CCR8-positive lymphocytes are present around bile ducts and peribiliary glands. CCL1 is also expressed in IgG4-SC in the ductal and glandular epithelia. Endothelial cells also express CCL1. The CCR8-CCL1 interaction may lead to obliterative phlebitis, which is a common pathological finding in IgG4-SC [66].

Patients with IgG4-RD have higher counts of plasmablasts and plasma cells but lower counts of $CD19^+$ B-cells, $CD20^+$ B-cells, and naive B-cells compared to the healthy population [67, 68]. IL-10-producing Bregs and circulating plasmablasts form IgG4 to an increased extent [43]. Remission of IgG4-RD on glucocorticoid treatment led to the depletion of naïve B-cells, plasmablasts, and plasma cells, while $CD19^+$ B-cells and $CD20^+$ B-cells were not altered. An increase of memory B-cells was observed only in patients who relapsed within two years of follow-up [68]. Compared to PSC, IgG4-SC has three activated immunological cascades (Fc-gamma receptor-mediated phagocytosis, B-cell receptor signaling pathway, and Fc-epsilon receptor I signaling pathway), and all three immunological pathways are associated with B cells or immunoglobulins, and conversely none of these pathways are directly linked to T cells in proteomic examination. These facts suggest a dominant role for B cells in the pathogenesis of IgG4-SC [43].

Okazaki et al. developed a pathogenic theory of IgG4-SC formation. So far, an imprecisely defined antigenic stimulus (self-antigen or microorganism) causes a decrease in naive Tregs, leading to the induction of a Th-immune response with the release of proinflammatory cytokines (interferon-γ, IL-1β, IL-2, and tumor necrosis factor-α). Subsequently, the Th-2 immune response is activated, leading to disease progression. An increased production of BAFF from monocytes and basophils and IL-10 from memory Tregs leads to increased production of IgG4, while upregulation of TGF-β from memory Tregs leads to fibrogenesis [57]. Cytotoxic T-lymphocytes play a crucial role in the pathogenesis of IgG4-RD. B cells present antigen and activate CD4+ cytotoxic T-lymphocytes; CD4+ cytotoxic lymphocytes dominate in immune cell infiltrate and decrease after targeted therapy [69]. Further studies will be needed to clarify the etiopathogenesis of this disease.

4. Classification

According to the 2019 American College of Rheumatology/European League Against Rheumatism classification criteria, a 3-step classification is recommended for determining a diagnosis of IgG4-RD. First, it must be demonstrated that a potential IgG4-RD case has the involvement of at least one of 11 possible organs in a manner consistent with IgG4-RD. Second, exclusion criteria consisting of a total of 32 clinical, serological, radiological, and pathological items must be applied. Third, eight weighted inclusion criteria domains, addressing clinical findings, serological results, radiological assessments, and pathological interpretations, are applied [70].

The classification of IgG4-SC is based on two clinical features: whether or not it is associated with AIP and the location of the bile duct stenosis. According to the association with AIP, we classify IgG4-SC into the following:

(i) The form associated with AIP

(ii) IgG4-SC without AIP

The subtypes of IgG4-SC based on cholangiography appearance are the following (see Figure 1):

(1) Type 1: the stenosis is located in the distal part of the bile duct. According to recent criteria, only the stenosis of bile duct in its intrapancreatic segment is classified as type 1; otherwise, it is type 4.

(2) Type 2: Diffuse intrahepatic and extrahepatic stenoses are present. It has two subtypes: type 2a with prestenotic dilatations and type 2b without prestenotic dilatations with reduced bile duct branches caused by severe infiltration of plasma cells into the peripheral bile ducts.

(3) Type 3: hilar stenosis + distal choledochal stenosis.

(4) Type 4: isolated hilar stenosis (Figure 1).

Type 1 is mostly associated with AIP and should be distinguished from chronic pancreatitis, pancreatic cancer, and CC. Type 2 imitates PSC. MRCP is often sufficient to differentiate this type, and, in most of the cases, ERCP is not required for the diagnosis. A complementary test is liver biopsy, which verifies small bile duct involvement in PSC and colonoscopy, given the strong association of PSC and inflammatory bowel disease (IBD). Type 3 and type 4, which are associated with hilar stenosis, must be distinguished from CC. Endoscopic retrograde cholangiopancreatography (ERCP) with biliary tract biopsies, or endoscopic ultrasonography (EUS) and intraductal ultrasonography (IDUS), is necessary.

Approximately 90% of IgG4-SC patients have concomitant AIP [11, 29, 30]. The isolated IgG4-SC without AIP is less common, most often type 4. IgG4-SC without AIP type 1 has long been considered rare. Nakazawa et al. diagnosed 5 cases of isolated IgG-4-SC type 1, in three of which the diagnosis was made after surgery [15]. The

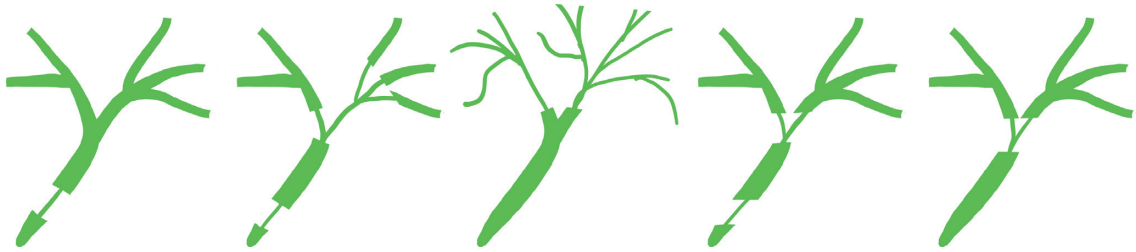

Figure 1: Schematic classification of IgG4-related sclerosing cholangitis by cholangiography.

observations of Naitoh et al. are interesting [13]. In a cohort of 872 patients with IgG4-SC, 62% of patients had type 1, 13.1% had type 2, 9.6% had type 3, 10.3% had type 4, and 3.9% had an unclassified type. Naitoh et al., like their predecessors, confirmed that the most common type of IgG4-SC is type 1, which accounts for more than 60% of patients with IgG4-SC [13, 29]. Naitoh et al. further compared the clinical features of patients with AIP-associated IgG4-SC and IgG4-SC without AIP. IgG4-SC without AIP was present in up to 16.3% (142/872) of IgG4-SC and was more common in women compared to the AIP-associated form. In IgG4-SC without AIP, the most common type was type 4 IgG4-SC, which was present in 30.9%, followed by type 1 in 23.8% of patients. This is the first large case series to report the distribution of stricture types in patients with isolated IgG4-SC. This work confirmed the conclusions from the past that the most common type of IgG4-SC without AIP is type 4 [16]. However, it pointed to a higher number of patients with IgG4-SC without AIP among patients with IgG4-SC and a higher number of patients with type 1 IgG4-SC among patients with IgG4-SC without AIP.

5. Diagnosis

The diagnosis of IgG4-SC is based on a combination of four criteria:

(1) A typical cholangiogram

(2) Laboratory findings of elevated IgG4 antibodies

(3) The presence of a systemic involvement

(4) Histological examination

The aim is not only to determine the diagnosis of IgG4-SC as accurately as possible but also to exclude diseases with diametrically different treatment and prognosis, such as pancreatic cancer, PSC, and CC. Of the diagnostic methods, MRCP is sufficient in some cases; however, in most of the patients, ERCP with biliary tract biopsies, endoscopic ultrasonography-guided fine-needle aspiration of the pancreas or IDUS is required.

Currently, two diagnostic criteria are accepted in the diagnosis of IgG4-SC: the HISORt criteria, which were taken from the AIP diagnostic criteria and found their application mainly in Europe and USA, and the Japan Biliary Association criteria, which are used mainly in Japan and China. Both are based on a combination of the four diagnostic methods mentioned above. However, they differ in the definition of a certain and probable diagnosis of IgG4-SC.

In 2008, Ghazale et al. proposed applying the criteria originally created for the diagnosis of AIP to the diagnosis of IgG4-SC-HISORt [11]. Based on these, the diagnosis can be considered certain in a typical cholangiogram in combination with a laboratory or possibly histological finding. Diagnosis is probable if two of the following criteria are met: Criterion S, Criterion O, partially Criterion H, partially Criterion I. Patients with a probable diagnosis are indicated for trial treatment with corticoids. If they show a therapeutic response, the probable diagnosis can be reevaluated as definitive. Comparison between the HISORt criteria and the Japan Biliary Association criteria is summarized in Table 1.

In 2012, the Japan Biliary Association introduced diagnostic criteria that define a definite, probable, and possible diagnosis. They are listed in Table 2. Compared to the HISORt criteria, typical cholangiogram and elevated IgG4 do not mean a definitive diagnosis of IgG4-SC; only a possible diagnosis that needs to be verified by corticosteroid treatment. If the patient shows a response, the diagnosis should be reevaluated as probable. For a definite diagnosis, either a typical cholangiogram in combination with a precisely defined systemic involvement, a fully developed histological finding, or combination of partial histological findings, elevated serum IgG4 and cholangiogram is needed.

Thus, we can conclude that the HISORt criteria emphasize a typical cholangiogram; a typical histological finding is not necessary for the definitive diagnosis, while serological evidence of elevated IgG4 antibodies has the same diagnostic weight as the histological finding. Systemic impairment is only an additional criterion for a probable diagnosis. On the other hand, the Japanese criteria emphasize the role of histology and in some ways elevate the evidence of a well-defined organ involvement meeting the criteria for IgG4 disease above the elevated serum IgG4 alone.

New diagnostic criteria were published in 2021 by the Japan Biliary Association [71]. These follow the Japanese criteria from 2012 and take into account the Japanese Clinical Diagnostic Criteria for autoimmune pancreatitis from 2018 [72]. The following findings of IgG4-RD should be considered in the diagnosis:

(i) A typical pathological finding is localized subepithelially and leads to a thickening of the biliary tract wall even in sections that appear normal on the cholangiogram.

Table 1: Comparison between the HISORt criteria and the Japan Biliary Association criteria [4, 11].

	HISORt criteria	Japan Biliary Association criteria
(1) Other organ involvement	Extrabiliary manifestations consistent with IgG4-RD, such as pancreas (focal pancreatic mass/enlargement without pancreatic duct dilatation, multiple pancreatic masses, focal pancreatic duct stricture without upstream dilatation, pancreatic atrophy); Retroperitoneal fibrosis; Kidney (single or multiple parenchymal low attenuation lesions: Round, wedge-shaped, or diffuse patchy); Salivary or lacrimal gland (enlargement)	Coexistence of autoimmune pancreatitis, or IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
(2) Histology	Lymphoplasmacytic infiltrate with >10 IgG4+ cells per high-power field within and around bile ducts; Obliterative phlebitis; Storiform fibrosis	(a) Marked lymphocytic and plasmacyte infiltration and fibrosis (b) Infiltration of IgG4-positive plasma cells >10 IgG4-positive plasma cells/HPF (c) Storiform fibrosis, obliterative phlebitis
(3) Serology	Raised serum IgG4 levels (>1.35 g/L)	Elevated serum IgG4 concentrations (≥135 mg/dL)
(4) Imaging	Strictures of the biliary tree including intrahepatic ducts, proximal extrahepatic ducts, intrapancreatic ducts; fleeting and migrating biliary strictures	Diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of bile duct wall
(5) Response to steroids	Normalization of liver enzymes and at least partial stricture resolution after steroid treatment	Effectiveness of steroid therapy
Definite IgG4-SC	2 + 4, 3 + 4	1 + 4, 2a & b+3 + 4, 2a & b & c, 2a & b & d
Probable IgG4-SC	2 of the following: 1, 3, partial 2, partial 4	3 + 4+5
Possible IgG4-SC	N/A	3 + 4

(ii) Almost 90% of patients with IgG4-SC have AIP; therefore, it is necessary to classify IgG4-SC into IgG4-SC associated with AIP and isolated IgG4-SC from the beginning, as both forms have separate diagnostic criteria.

(iii) It is also necessary to classify IgG4-SC according to the cholangiogram from the beginning. IgG4-SC types 1, 2, 3, and 4 differ in differential diagnosis.

(iv) The following organ manifestations are diagnostically significant: sialoadenitis/dacryoadenitis, retroperitoneal fibrosis, and IgG4-related kidney disease.

(v) The importance of ruling out hepatobiliary malignancy was emphasized by adding "no neoplastic cells detected" to the histology criteria.

(vi) Good prognosis is predicted by a good response to corticosteroids, and response to steroids has become a separate diagnostic criterion. Because some malignant lesions may also respond to steroids, cytological or histological examination is always recommended before using steroids. Steroid effectiveness should be assessed based on ERCP and/or MRCP imaging within two weeks after their administration.

(vii) New imaging modalities, such as EUS and IDUS, are important in differential diagnosis.

The Japanese Clinical Diagnostic Criteria for IgG4-related sclerosing cholangitis are listed in Table 2. A significant limit to their application in daily practice will probably be their complexity. The scoring system developed by Moon et al. on a sample of 39 IgG4-SC patients and 76 PSC patients appears to be significantly simpler for daily practice. Based on age, other organ involvement, and beading on the cholangiogram, it reports excellent discrimination (area under the receiver operating curve 0.99) between IgG4-SC and PSC [73]. It is detailed in Table 3.

6. Clinical Picture

IgG4-SC often has a dramatic course but ultimately a good prognosis given a good response to corticosteroids and a comparable risk of developing malignancies as the general population.

The clinical picture is dominated by abdominal pain and jaundice, which is the most common symptom in patients with IgG4-SC. In the above-mentioned retrospective study of Tanaka et al., which evaluated 527 IgG4-SC patients from Japan, 35% of patients had jaundice [29]. Similarly, in an epidemiological study by the same authors from 2020, jaundice was the most common symptom in approximately 40% of patients [20]. The incidence of jaundice was significantly higher in the IgG4-SC-AIP(+) group (42.9%) than in the IgG4-SC-AIP(−) group (31.0%) ($p = 0.010$) [13].

Jaundice was twice as common in IgG4-SC patients in the United States and the United Kingdom, where it occurred in 77% and 74% of patients, respectively [11, 30]. Sudden jaundice, weight loss, and older age at the time of diagnosis mimic hepatobiliary malignancy. A certain portion of patients with IgG4-SC or PSC are asymptomatic at the time of diagnosis; the others suffer from pruritus or fatigue. Paradoxically, approximately 37% of patients with IgG4-SC from a recent study by Tanaka et al. in 2020 were asymptomatic at the time of diagnosis [20].

Table 2: Revised criteria of the Japan Biliary Association [71].

I.	Narrowing of the intrahepatic and/or extrahepatic bile duct	(a) ERC (b) MRCP
II.	Thickening of the bile duct wall	(a) EUS/IDUS (b) CT/MRI/US
III.	Serological findings	Elevated serum IgG4 concentrations (≥135 mg/dL)
IV.	Pathological findings among (i)–(v) listed below	(a) (i), (ii), and (v) are observed (b) (v) is observed (c) All of (i), (ii), and (v) and either or both of (iii) or (iv) are observed (i) Marked lymphoplasmacytic infiltration and fibrosis (ii) More than 10 IgG4-positive plasma cells per high-power microscopic field (iii) Storiform fibrosis (iv) Obliterative phlebitis (v) No neoplastic cells identified
V.	Other organ involvement (OOI)	(a) Type 1 autoimmune pancreatitis (b) IgG4-related dacryoadenitis/sialadenitis, IgG4-related retroperitoneal fibrosis, IgG4-related kidney lesion
VI.	Effectiveness of steroid therapy	
Definite diagnosis IgG4-SC associated with AIP	Types 1, 2 Types 3, 4	Ia/b + IIa/b + III/VI Ia + IIa + IVb + III/VI
Definite diagnosis isolated IgG4-SC	Types 1, 2, 3, 4	Ia + IIa + III + IVa/VI
Probable diagnosis IgG4-SC associated with AIP	Types 1, 2 Types 3, 4	Ia/b + IIa/b Ia + IIa + IVb Ia/b + IIb + VI
Probable diagnosis isolated IgG4-SC	Types 1, 2, 3, 4	Ia + IIa + Iva Ia + IIa + III + IVb Ib + IIa + III + VI
Possible diagnosis IgG4-SC associated with AIP	Types 3, 4	Ia/b + IIa Ib + IIb + III
Possible diagnosis Isolated IgG4-SC	Types 1, 2, 3, 4	Ia + IIa + III/Vb/VI Ib + IIb + III + VI

Table 3: Scoring system for the differentiation of IgG4-SC and PSC [73].

Variable	Category	Points
Other organ involvement	Yes	3
	No	0
Beaded appearance	Yes	0
	No	2
Age	<30 years	0
	30–39 years	1
	40–49 years	2
	50–59 years	3
	>60 years	4
Total score	Diagnosis	
0–4	Probable PSC	
5–6	Indicating diagnostic steroid trial	
7–9	Probable IgG4-SC	

Decompensated liver cirrhosis is rare in IgG4-SC. The most common manifestation in these patients is bleeding from the esophageal varices, which occurred in 0.9% of them [20].

Association with IBD is rare in IgG4-SC; it does not exceed 5% and is usually an intestinal manifestation of IgG4-RD. On the other hand, up to 90% of patients with IgG4-SC have concomitant AIP [11, 29, 30]. The incidence of AIP was slightly lower, 83.7%, in the last work of Tanaka et al. from 2020 [20]. The association of AIP with IgG4-SC is explained by identification of four phenotypes of IgG4-RD: pancreatobiliary, retroperitoneum/aortitis, head and neck limited, and Mikulicz systemic. Patients with the pancreatobiliary phenotype have the highest serum IgG4 and IgE levels and high prevalence of diabetes mellitus [74]. Occasional involvement of the pancreas in PSCs is mostly associated with azathioprine treatment.

AIP is the most common, but not the only, systemic manifestation of IgG4-RD in patients with IgG4-SC. Many of them have extrapancreatic manifestations of IgG4-RD, such as retroperitoneal fibrosis, sialodenitis and dacryoadenitis (Mikulicz disease), mediastinal lymphadenopathy, or renal involvement. Lung involvement is manifested with nodule creation, pulmonary fibrosis, or interstitial lung disease. Retro-orbital disease, aortic involvement, and neurological symptoms, such as progressive encephalitis and pituitary mass causing hypopituitarism, are rare. Based on recent data, approximately 26% of IgG4-SC patients had extrapancreatic manifestations, with a higher rate in those with concomitant AIP [13, 20]. IgG4-related organ disease (OOI) is also an important diagnostic criterion for patients with IgG4-SC without AIP, as up to 18.5% of these patients had some of the types of IgG4-related OOI included in the Japanese Clinical Diagnostic Criteria for AIP 2018 [13]. In 2017, Tanaka et al. showed that the most common extrapancreatic manifestation in IgG4-SC patients was sialadenitis or dacryoadenitis manifesting in symmetrical bilateral swelling in 15% of IgG4-SC patients, followed by retroperitoneal fibrosis in 7% [29]. Lung, aorta, and kidney involvements were each found in 1% of patients with IgG4-SC. These statistics were similar in a follow-up study in 2020 [20]. The results of Ghazale et al. are different, where up to 26% of patients had renal impairment, 9% retroperitoneal fibrosis, 6% sialadenitis or dacryoadenitis, and 4% lung involvement and mediastinal lymphadenopathy [11]. It is more difficult to interpret the UK study in this regard, as it assesses the incidence of extrapancreatic manifestations in a cohort of patients with AIP and IgG4-SC [30]. IgG4-related sialadenitis was found in 18%, renal infiltrates or masses in 9%, lung involvement in 6%, retroperitoneal fibrosis in 3%, ocular manifestations in 2%, and neurological sequelae in 2%. The results of this work also reflect recent Japanese diagnostic criteria that define the following diagnostically significant organ manifestations: sialoadenitis/dacryoadenitis, retroperitoneal fibrosis, and IgG4-related kidney disease.

The incidence of CC is low in patients with IgG4-SC and varies from 0.09% to 0.7% in individual studies. This stands in contrast to PSC patients who have a 160-fold higher risk of CC compared to the general population and lifetime prevalence of 5–10% [29, 75–78].

6.1. IgG4 in Serum. The IgG4 antibody is one of the four subclasses of immunoglobulin G. Normally, it accounts for less than 5% of the total IgG value. According to some authors, 74–88% of patients with IgG4-SC have elevated serum IgG4 levels (higher than the upper limit of normal value (ULN) of 1.35 g/L) [4, 11, 13, 29, 79]. Both the American and European Association for the Study of Liver Diseases practice guidelines on the diagnosis and management of PSC suggest measuring IgG4 in all patients with possible PSC to exclude IgG4-SC [80, 81].

Not only are IgG4 antibodies specific for IgG4-RD but also they are elevated in some patients with bronchial asthma, pemphigus, and atopic dermatitis. Elevated serum IgG4 levels are also present in some patients with PSC and in some patients with hepatobiliary malignancies, which complicates differential diagnosis. For PSCs, elevated serum IgG4 levels were present in 9–26% of patients [73, 82–91]. In CC, 8–14% of patients have elevated serum IgG4 levels, especially those who have CC in the field of PSC. On the other hand, about 10% of IGG4-SC patients with a typical histological finding have normal serum IgG4 levels [85, 92, 93].

These facts have led to the dilemma of whether the cutoff for IgG4 is set correctly, especially for the differential diagnosis of IgG4-SC from CC. The most problematic group in this respect appears to be patients with IgG4-SC types 3 and 4, without AIP, but it turns out that a cutoff of 1.35 g/L is not sufficient even to distinguish IgG4-SC from PSC. Boonstra et al. showed that the ULN cutoff for IgG4 (1.4 g/L) yields a sensitivity of 90% with a specificity of 85% for IgG4-SC. Increasing the cutoff level to $2 \times$ ULN increased the specificity to 98%; however, it decreased the sensitivity of IgG4 to 70%. The highest specificity for IgG4-SC was achieved when applying the $4 \times$ ULN (sIgG4 > 5.6 g/L) cutoff with a sensitivity of 42% [85].

Ohara et al. evaluated the cutoff values for IgG4 between each cholangiographic type of IgG4-SC and patients with other diagnoses: pancreatic carcinoma (PCa), PSC, and CC. The cutoff values were 1.19 g/dL for type 1 IgG4-SC versus

PCa (sensitivity 90.2%, specificity 93.9%), 1.25 g/dL for type 2 IgG4-SC versus PSC (sensitivity 96.4%, specificity 87.6%), and 1.82 g/dL for types 3 and 4 IgG4-SC versus CC (sensitivity 85.7%, specificity 96.6%). Increasing the cutoff to 2.08 g/dL increased the sensitivity for IgG4-SC types 3 and 4 to 100% [92]. Differential diagnosis of IgG4-SC and CC was also addressed by Oseini et al. who compared sIgG4 levels in a test cohort of 126 patients with CC and 50 patients with IgG4-SC as well as in a validation cohort of 161 patients with CC and 47 patients with IgG4-SC and showed 100% sensitivity for IgG4-SC at a cutoff $4 \times$ ULN (sIgG4 > 5.6 g/L) [93].

Therefore, other laboratory differential diagnostic markers were sought. Boonstra et al. used individual IgG subtypes for differential diagnosis. In patients with an sIgG4 >1.4 and <2.8 g/L, incorporating the IgG4/IgG1 ratio with a cutoff at 0.24 in the diagnostic algorithm significantly improved specificity and allows one to distinguish IgG4-SC from PSC [85].

Literature data on IgG4 levels in patients with IgG4-SC without AIP and IgG4-SC + AIP differ. While Nakazawa et al., Graham et al., and Takagi et al. have sporadically shown that patients with the isolated IgG4-SC form have lower serum IgG4 levels, in a recent study by Naitoh et al., patients with IgG4-SC associated with AIP had serum IgG4 levels that were comparable to those of patients with IgG4-SC without AIP [13, 15, 94, 95]. However, if patients with IgG4-SC and AIP have a different OOI at the same time, their serum IgG4 levels are significantly higher than those in patients with IgG4-SC and AIP without another organ impairment. When looking at individual IgG4-SC types according to the cholangiogram, the highest serum IgG4 values were found in type 4 patients, regardless of whether it was IgG4-SC + AIP or IgG4-SC without AIP [13].

Unlike PSC and CC, patients with IgG4-SC have elevated IgG4 levels not only in serum but also in bile. A cutoff of 113 mg/dl has 100% sensitivity and specificity for IgG4-SC [96].

6.2. Imaging Methods. Bile duct visualization is the key in the differential diagnosis of bile duct stenoses. As a rule, it reflects the basic morphological changes in the bile duct wall which accompany stenoses. In the case of IgG4-SC, there is diffuse subepithelial lymphoplasmacytic inflammation of the wall of both intra- and extrahepatic bile ducts with fibrosis, with a preserved epithelial layer [97]. This pathological correlate is manifested in the imaging method by two typical characteristics: segmental and long strictures with prestenotic dilation and diffuse thickening of the bile duct wall, which exceeds the extent of stenosis [13]. Of the imaging methods, computed tomography (CT), MRCP, and ERCP play a key role in the diagnosis of IgG4-SC as methods that are generally available. The cholangiogram is clearer with ERCP than with MRCP, and ERCP remains the gold standard in the differential diagnosis of bile duct stenoses. MRCP can replace ERCP in the diagnosis of some cases of IgG4-SC types 1 and 2, and it is important in assessing changes in the pancreatic duct with irregular narrowing of the main pancreatic duct signaling AIP. The quality of the examination is tied to MRI magnet strength and imaging sequences used. The use of 3 Tesla MRI scanners allows a detailed evaluation of the biliary tree comparable to ERCP. IDUS and EUS are of increasing importance, as they more accurately show the thickening of the bile duct wall. The limit for their use is poorer availability in routine clinical practice.

6.3. Cholangiogram. The most common findings on cholangiogram are segmental (>3 mm) and long (>10 mm) strictures with prestenotic dilatation and stricture of the distal common bile duct [13, 98, 99]. In contrast, stenoses in PSC are short (1-2 mm), mostly affecting both the intra- and extrahepatic bile ducts. Stenoses in PSC alternate with short normal sections, creating a typical beaded necklace image. In addition to band-like strictures, beaded and pruned-tree appearance and diverticulum-like formation are typical of PSCs [73, 98]. Nakazawa et al. noted segmental stricture and long stricture with prestenotic dilation in 100% (26/26) and 42% (11/26), respectively, of cases with IgG4-SC with AIP [98]. No patient with IgG4-SC with AIP was found to have a band-like stricture, beaded appearance, or diverticulum-like formation [98]. Nishino et al. retrospectively evaluated the cholangiogram in 24 patients with IgG4-SC with AIP and their conclusions were similar: 100% (24/24) of patients with IgG4-SC with AIP had segmental strictures, and a long stricture with prestenotic dilation was found in 12.5% (3/24) of patients. No patient with IgG4-SC with AIP was found to have a band-like stricture, beaded appearance, or diverticulum-like formation [99].

A long stricture and segmental stricture were the most common findings on the cholangiogram in patients with IgG4-SC without AIP. Naitoh et al. reported these findings in 65.1% of patients with IgG4-SC without AIP. On the other hand, these patients had a relatively high band-like stricture and pruned-tree appearance (11.4% and 4.1%) typical of PSCs, making it difficult to diagnose IgG4-SC without AIP [13].

6.4. Thickening of the Bile Duct Wall. The thickening of the bile duct wall in IgG4-SC is circular, usually extends beyond the extent of the stenosis, and has a smooth inner and outer edge. It is visible in CT scans and on MRCP but is more precisely diagnosed by IDUS and EUS, allowing reliable differential diagnosis with CC. Wall thickening in the stricture-free area was found to be significantly more common in patients with IgG4-SC on IDUS than on EUS (80.9% versus 73.8%; $p = 0.045$) [13]. Naitoh et al. documented IDUS IgG4-SC properties in a cohort of 23 IgG4-SC patients with AIP. The control group consisted of 11 patients with CC. The circularly symmetrical wall thickness, smooth outer and inner edge, and homogeneous inner echo in the stricture were significantly higher in IgG4-SC than in CC ($p < 0.01$). An important diagnostic feature is the wall thickness in IgG4-SC in areas without stricture on the cholangiogram, which was significantly greater than that in the case of CC ($p < 0.0001$). This study provided evidence

for the inclusion of type 1 IgG4-SC: it showed that, in most patients with IgG4-SC type 1 with AIP, stenosis is due to thickening of the inflamed wall (73% of patients) and not external compression by the inflamed pancreatic tissue [14].

The same authors in another paper showed that more than 50% of patients with IgG4-SC without AIP have wall thickening at a nonstricture region. This number is significantly lower than that in patients with IgG4-SC with AIP; however, wall thickening at a nonstricture region is useful for diagnosing IgG4-SC without AIP [13].

6.5. Histological Findings. The aim of the histological examination is not only to confirm IgG4-SC but also above all to rule out malignant stenosis. To exclude cancers, it is important to perform a transampullary bile duct biopsy and bile duct brushing cytology [71]. Immunohistochemistry for IgG and IgG4 is an essential part of the histological examination, which is usually not sufficient on its own to establish a definitive diagnosis.

IgG4-SC is characterized by the following histological findings:

(i) Marked lymphoplasmacytic infiltration
(ii) Eosinophilic infiltration
(iii) More than 10 IgG4-positive plasma cells per high-power microscopic field in biopsy and >50 per high-power field in resection specimens
(iv) A high IgG4/IgG-positive cell ratio (>40%)
(v) Storiform fibrosis which often contains lymphocytes and plasma cells
(vi) Obliterative phlebitis, in which the venous lumen is closed by inflammatory cells and fibrosis [28, 71]

The histological criteria are the same for patients with IgG4-SC with AIP and patients with IgG4-SC without AIP [94]. Bile duct tissue, liver tissue, and the ampulla of Vater can be examined. Naitoh et al. reported more than 10 IgG4-positive plasma cells per high-power microscopic field in 16.9% (56/331) of bile duct biopsies, 15.8% (9/58) of liver biopsies, and 36.8% (75/204) of ampullary biopsies in patients with IgG4-SC. Paradoxically, patients with IgG4-SC without AIP had more than 10 IgG4-positive plasma cells per high-power microscopic field more frequently than patients with AIP (29.6% versus 12.8%, $p < 0.001$) [13]. Marked lymphoplasmacytic infiltration and fibrosis were found in 32.9% (109/331) of patients with IgG4-SC. A total of 0.6% (2/331) of patients with IgG4-SC had storiform fibrosis, and no patient had any obliterative phlebitis in this study. In this work, the histological yield from bile duct tissue, including after immunostaining, was relatively low compared to the histological yield from the ampulla of Vater [13]. Other authors came to a similar conclusion [12]. We can explain this fact very easily, as lymphoplasmocyte inflammation is subepithelial and unevenly distributed in the bile ducts, and samples taken from the bile ducts are very small. Epithelial disruption and the presence of inflammatory infiltration in the epithelial layer suggest PSC. Storiform fibrosis, obliterative phlebitis, and high IgG4/IgG-positive ratio are detected almost exclusively by histological examination of bile duct resections, as opposed to biopsies. Kawakami et al. compared the biopsy yield from bile ducts and the ampulla of Vater and found that the criterion of more than 10 IgG4-positive cells/HPF was met in at least one biopsy in 72% (21/29) of patients, while 31% (9/29) met this criterion in both biopsies. This study was limited by a small cohort of patients with IgG4-SC with AIP [100].

Several studies have confirmed a typical histological finding in ampulla of Vater tissue in patients with IgG4-SC with AIP affecting the head of the pancreas [101, 102]. It appears that biopsy of ampulla of Vater and subsequent histological examination is also important in patients with IgG4-SC without AIP, as more than 10 IgG4-positive plasma cells/HPF were found in 23.8% of the IgG4-SC without AIP cases [13]. Papillary biopsy should not be performed separately, however, as papillary biopsy is considered a supplementary method in order to increase the yield of histological findings.

The utility of liver biopsy in the diagnosis of IgG4-SC is relatively low. Lesions of IgG4-SC may be observed in the biopsy specimen, but a fully developed histological finding is rare. An exception is the work of Deshpande et al. who found that 6/10 patients with IgG4-SC had more than 10 IgG4-positive plasma cells/HPF on a liver biopsy and 70% of IgG4-SC patients had intrahepatic biliary strictures. IgG4-SC patients presented higher portal and lobular inflammatory scores compared to PSC patients. Eosinophiles were found in portal-based fibroinflammatory nodules in 50% of IgG4-SC patients [103]. Patients with IgG4-SC have a significantly higher number of IgG4 plasma cells on a liver biopsy than patients with PSC and CC [99, 104]. Despite this, clinicians cannot overly rely on this criterion to make a definitive diagnosis of IgG4-SC. Like elevated serum IgG4 levels, not only is the presence of IgG4 plasma cells specific for IgG4-SC but also it can be detected in patients with PSC and CC [19]. Liver resections had >50 IgG4-positive cells/HPF in 9% of patients with CC. Liver explants had >50 IgG4-positive cells/HPF in 15.6% of patients with PSC [105, 106].

7. Treatment

The following are indications for treatment:

(i) Symptomatic patients
(ii) Asymptomatic patients with cholestasis
(iii) Patients with subclinical disease that can lead to severe or irreversible organ failure [107]

7.1. Corticosteroids. Corticoids are the first line in the treatment of IgG4-SC. The goal of treatment is to induce and maintain remission. This is defined as remission of symptoms, achievement of a biochemical response, decrease of IgG4 levels, and normalization of the cholangiogram. The indication for corticosteroid therapy is unquestionable, with the only exception being perhaps patients whose current health status contraindicates corticosteroid therapy (such as avascular necrosis of the hip, severe psychosis, etc.).

Response to empiric corticosteroid treatment is an auxiliary diagnostic criterion. Corticosteroids also have a place in the treatment of disease relapse.

7.2. Remission Induction. The recommended initial dose of prednisone is 0.6–0.8 mg/kg body weight daily for 2–4 weeks, followed by a reduction of 5 mg/week over 2-3 months [19, 107]. This recommendation is based on the conclusions of the works of Japanese authors. Kamisawa et al. evaluated the effect of steroid therapy in 459 patients with AIP [108]. Most patients were treated with an initial dose of 30 mg and 40 mg of prednisolone daily. Remission on treatment was achieved in 98% of patients, and the time to remission was not significantly different statistically between patients treated with initial doses of 30 mg/d and 40 mg/d ($p = 0.401$). Therefore, the question arises as to whether a lower initial dose should be used in patients at risk for diabetes mellitus. There is no work that specifically targets patients with IgG4-RD and diabetes mellitus. However, we can conclude that the initial dose of corticoids will affect the likelihood of disease relapse. This is confirmed by the findings of a study by Shirakashi et al. who showed using multivariate analysis of data from 152 IgG4-RD patients that patients treated with an initial dose of 0.4–0.69 mg/kg/day of prednisolone showed lower relapse rates than those treated with an initial dose of <0.39 or >0.7 mg/kg/day [109]. The effect of corticosteroid therapy is prompt in most patients, even dramatic, and minimizes the need for bile duct stenting. Some authors recommend the use of i.v. pulse corticoid therapy to achieve a faster response [110].

7.3. Maintaining Remission. The following issues are open questions in the management of IgG4-SC:

(i) The need for maintenance treatment
(ii) Duration of maintenance treatment
(iii) Maintenance dose
(iv) Bile duct stenting before corticosteroid therapy
(v) The role of steroid-sparing therapy

The first three issues arise from two facts. On the one hand, the reduction and discontinuation of corticotherapy lead to a relapse of the disease in about 30% of those with IgG4-SC [107]. Risk factors for relapse are proximal biliary tract involvement, pancreatic involvement, and IgG4 levels above twice the upper limit of normal [11, 79, 95]. On the other hand, long-term treatment with corticoids exerts other effects, including osteoporosis, infections, or steroid diabetes mellitus. This fact is not negligible, because IgG4-SC affects middle-aged and older patients. More information on maintenance treatment can be drawn from the data on patients with AIP. Sah et al. consider maintenance treatment as not required in all patients with AIP [111]. It is only recommended for patients who have already had relapses or are more likely to relapse. In contrast, the need for maintenance treatment in patients with IgG4-SC is signaled by a study from Mayo Clinic, which concludes that, with early discontinuation of corticosteroid therapy after 11 weeks of treatment, 53% of patients relapse within three months [11].

Similar results were reported from a UK cohort in which 97% of patients with AIP, including IgG4-SC with AIP, responded to steroid treatment, but 50% relapsed after cessation of steroids and 2% during steroid therapy [30]. The Japanese authors emphasize that most patients with IgG4-RD require a prednisone dose of 5–10 mg daily to maintain remission [112]. In another study, the risk of relapse in patients with AIP was lowest at a dose of 5 mg/day of prednisone (26.1%); increasing the dose to 7.5 mg or 10 mg/day did not increase the likelihood of maintaining remission [113]. According to recent Japanese data, maintenance treatment in patients with IgG4-SC can be discontinued if remission persists for more than three years [19]. With this conclusion, the current European recommendation is that maintenance therapy with glucocorticoids should be considered only in multiorgan disease or those with a history of relapse [107].

7.4. Relapse Treatment. In case of relapse, reintroduction of corticosteroids is indicated, possibly in combination with other immunosuppressive treatments.

7.5. Other Immunosuppressions. Nonsteroidal immunosuppressants are currently a second-line treatment and are indicated in

(i) Corticosteroid-resistant patients
(ii) Corticosteroid-dependent patients
(iii) Those patients where corticosteroid treatment is limited due to adverse reactions
(iv) The treatment of relapse

The combined use of nonsteroidal immunosuppressants with steroids to induce remission is a matter of debate. The authors of the International Recommendation for the Treatment of IgG4-RD did not find a uniform answer to this question either [114].

Rituximab has been shown to be effective in inducing, maintaining remission, and treating relapse in patients with IgG4-RD, including IgG4-SC. It is a monoclonal anti-CD20 antibody that induces B-cell depletion, which may play a key role in the treatment of IgG4-RD. The effect of rituximab in patients with IgG4-RD is described in case series and case reports; however, no randomized prospective clinical study has been performed yet.

The work of Ebbo et al. which evaluated the effect of rituximab in 33 patients with IgG4-RD in inducing and maintaining remission and treating relapse is valuable. There, 93.5% of patients achieved a clinical response to rituximab treatment, and 51.5% were able to discontinue corticoids. After discontinuation of rituximab, 41.9% of patients relapsed, whereas long-term rituximab treatment was associated with longer relapse-free survival (41 versus 21 months; $p = 0.02$) [115]. Similar are the recent findings of other European authors that have confirmed the role of rituximab in the treatment of difficult-to-treat patients with IgG4-RD [116]. Carruthers et al. evaluated the efficacy of 1000 mg of rituximab in 30 patients with IgG4-SC who were

not treated by corticosteroids. Disease response was seen in 97% of participants; 47% of patients were in complete remission at 6 months, and 12 patients at 12 months. Serum IgG4 level declined from 911 mg/dL (138–4780 mg/dL) to 422 mg/dL (56–2410 mg/dL) at month 6 ($p < 0.05$), though only 42% of patients achieved normal levels [117].

There are controversial views on the use of rituximab in the induction of remission as a first-line treatment in high-risk patients with high IgG4 levels and multiorgan involvement. It can be used as an off-label therapy in corticosteroid-resistant and corticosteroid-dependent patients, as well as corticosteroid-intolerant patients, or for the treatment of relapse. The recommended dose is 1 gram intravenously every 15 days. Maintenance therapy with rituximab is associated with longer relapse-free survival and may represent a novel treatment strategy, especially for difficult-to-treat patients with IgG4-SC. Difficult-to-treat patients should be identified on the basis of the IgG4-responder score, which is a reasonable index to assess disease activity [118]. The score includes clinical presentation, the number and severity of organ involvements, the presence of organ dysfunction, and the urgency of treatment. A recently published meta-analysis showed that therapy of IgG4-related pancreatobiliary disease with rituximab is associated with a high remission rate and a higher relapse rate in the presence of multiorgan involvement, while adverse effects were limited [119].

Azathioprine, 6-mercaptopurine, mycophenolate mofetil, and methotrexate are other second-line treatment options. Their effects in patients with IgG4-RD, including IgG4-SC, are poorly studied; again, available are data mainly in patients with AIP. A Mayo Clinic study evaluated the effect of steroid-sparing immunosuppression, azathioprine 2.0–2.5 mg/kg/day, 6-mercaptopurine 1 mg/kg/day, and mycophenolate 750–1000 mg b. d., in 76 patients with relapse of AIP. Relapse-free survival was similar in patients treated with combination therapy (steroids plus immunosuppressants) compared to patients treated with a steroid in monotherapy ($p = 0.23$). In the follow-up, treatment with steroid-sparing immunosuppressants failed in 45% of patients. Some had a second relapse treated with rituximab. This treatment was successful in 83% of patients [120].

The work of Huggett et al. who evaluated the effect of azathioprine at a dose of 2 mg/kg/day as an add-on therapy to corticoids in the treatment of relapse in patients with AIP was more favorable for second-line treatment. Treatment was ineffective in 19% and azathioprine was not tolerated in 31.7% of patients. In these, mycophenolate 500 mg–1,000 mg b. d., methotrexate 15 mg weekly, or mercaptopurine 1 mg/kg/day was used as an alternative, and the treatment was well tolerated. At the end of follow-up, 58% of patients maintained remission with second-line treatment without corticoids [30].

7.6. Stenting before Corticotherapy. The initial effect of corticoids is very prompt, so most patients do not need bile duct stenting prior to corticotherapy [121, 122]. Exceptions are patients with severe jaundice and cholangitis.

8. Conclusion

IgG4 sclerosing cholangitis is an important part of differential diagnosis of bile duct stenosis. It is a disease with a very good prognosis if the diagnosis is made early. Despite increasing information and recently updated diagnostic criteria, the diagnosis is relatively difficult in routine clinical practice. Initial corticosteroid therapy is effective in inducing remission; maintenance treatment with corticosteroids reduces the likelihood of relapse but does not completely prevent it and is associated with a risk of side effects. Therefore, there is an unmet need for randomized prospective studies to evaluate new maintenance treatment strategies, including the use of steroid-sparing treatment regimens and B-cell reduction therapy to prevent relapse and long-term complications of this disease.

Abbreviations

AIP: Autoimmune pancreatitis
BAFF: B-cell-activating factor
Bregs: Regulatory B cells
CC: Cholangiocarcinoma
CFTR: Cystic fibrosis transmembrane conductance regulator
CT: Computed tomography
CTLA4: Cytotoxic T-lymphocyte-associated protein 4
ERCP: Endoscopic retrograde cholangiopancreatography
EUS: Endoscopic ultrasonography
FCRL3: Fc receptor-like 3
HPF: High-power field
IBD: Inflammatory bowel disease
ICD-10: International Statistical Classification of Diseases and Related Health Problems
IDUS: Intraductal ultrasonography
IgG: Immunoglobulin G
IgG4-RD: IgG4-related disease
IgG4-SC: IgG4-related sclerosing cholangitis
MRCP: Magnetic resonance cholangiopancreatography
NOD-2: Nucleotide-binding oligomerization domain-containing protein 2
PCa: Pancreatic carcinoma
PRSS1: Trypsin 1
PSC: Primary sclerosing cholangitis
sIg: Specific immunoglobulin
TGF-β: Tumor growth factor-β
TLR: Toll-like receptor
TNF: Tumor necrosis factor
Tregs: Regulatory T cells
ULN: Upper limit of normal value.

Data Availability

Studies supporting this review are appropriately cited in the manuscript text and listed in the list of references.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Clinical Features and Outcomes of Primary Sclerosing Cholangitis in the Highly Admixed Brazilian Population

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Background. Primary sclerosing cholangitis (PSC) is associated with a broad phenotypic spectrum in different populations from diverse ethnic and racial backgrounds. This study aimed to describe the clinical characteristics and outcomes of PSC in a multicenter cohort of patients from Brazil. *Methods*. Data from the Brazilian Cholestasis Study Group were retrospectively reviewed to assess demographic information and clinical characteristics of PSC, as well as the outcomes, such as transplantation-free survival. *Results*. This cohort included 210 patients. After excluding 33 (15.7%) patients with PSC and overlap syndrome of autoimmune hepatitis, 177 (97 males, median age 33 (21–42) years) with clear-cut PSC were eligible for this study. Most of the patients ($n = 139$, 78.5%) were

symptomatic, and 104 (58.7%) had advanced PSC at the time of diagnosis. Concurrent inflammatory bowel disease was observed in 78 (58.6%) of the investigated patients ($n = 133$), and most of them had ulcerative colitis ($n = 61$, 78.2%). The 1- and 5-year survival free of liver transplantation or death were $92.3 \pm 2.1\%$ and $66.9 \pm 4.2\%$, respectively, and baseline advanced PSC, pruritus, and elevated bilirubin levels were independent risk factors for the composite adverse outcome. Females were significantly older and had lower bilirubin levels than males at baseline, but survival was not associated with sex. Approximately 12.4% ($n = 22$) of patients with PSC died, and 32.8% ($n = 58$) underwent liver transplantation at a median follow-up time of 5.3 and 3.2 years. *Conclusion*. Multiethnic Brazilian PSC patients exhibited a less pronounced male predominance and a lower frequency of inflammatory bowel disease than Caucasians. Adverse outcomes were more frequent, probably due to advanced disease at baseline.

1. Introduction

Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease of unknown etiology with a wide spectrum of clinical features [1]. Although studies in northern Europe and the United States have extensively characterized the characteristics of PSC in Caucasians [2–6], there is a paucity of data on disease expression in other parts of the world, particularly in the multiracial and highly admixed population of Latin America [7, 8]. With the emergence of several reports from Asia and western and southern European countries, it has been observed that PSC exhibits a much more varied phenotype and lower disease prevalence than those in other geographical areas [9, 10]. Studies from Spain [11], Singapore [12], Korea [13], and Japan [14, 15] have reported a much lower prevalence of disease in the general population compared to previous northern European studies [16] and clinical characteristics that differ from those classically described, such as a bimodal age of distribution [8, 15] and a lower frequency of concurrent inflammatory bowel disease (IBD) [17–22]. Furthermore, the marked male predominance observed in northern European patients with PSC has not been reported in other populations [15, 17, 18]. However, some studies [1, 5, 23] have suggested that PSC in females may be underdiagnosed as it tends to be more quiescent and less aggressive than PSC in males.

To our knowledge, there are no studies from Latin America that describe the clinical characteristics of patients with PSC [8]. Brazil has a population of highly admixed origin, with varying proportions of genetic ancestry of Native American, African, and European origins, shaped by local historical interactions between migrants brought by the slave trade and European settlement and the Amerindian population [24]. To gather data on the clinical characteristics of PSC and primary biliary cholangitis in the country, the Brazilian Society of Hepatology sponsored a multicenter cooperative consortium named the Brazilian Cholestasis Study Group [25]. This study aimed to describe the clinical characteristics and outcomes of PSC in Brazilians and evaluate the influence of sex on disease expression and outcomes.

2. Patients and Methods

2.1. Study Population and Case Definition. Patients diagnosed with PSC between 1991 and 2021 in 23 different hepatology centers across the country were enrolled in this retrospective study. The inclusion criteria were the diagnosis of PSC, which was considered in the presence of cholestasis and compatible imaging characteristics of PSC disclosed either by magnetic resonance imaging or endoscopic retrograde cholangiography, as recommended by national and international guidelines [26–28]. Small duct PSC was considered in the presence of typical histological features of PSCs in patients with IBD with normal bile ducts on cholangiography [26, 27]. In this study, the overlap syndrome of autoimmune hepatitis (AIH) and PSC was defined based on typical findings of PSC in patients with additional diagnostic criteria for AIH, as suggested by the International Autoimmune Study Group [29]. The exclusion criteria included the diagnosis of other concomitant liver diseases, including overlap syndrome. Clinical, endoscopic, cross-sectional imaging, and histological data were used to define IBD and its subtypes according to established guidelines [30, 31]. Advanced PSC was considered based on the presence of Ludwig PSC stages III or IV [32] whenever liver biopsy results were available or in the presence of findings compatible with compensated advanced chronic liver disease, such as the presence of esophagogastric varices, irregular external contour of the liver or evidence of collateral circulation on imaging, splenomegaly and low platelet counts [33], or decompensated cirrhosis with variceal bleeding, hepatic encephalopathy, or ascites.

2.2. Data Collection. Investigators were asked to identify all patients with PSC who had been followed at their center during the time of the survey and to fill in a standardized database provided by the Brazilian Cholestasis Study Group [25]. Data were retrospectively assessed to evaluate demographic, clinical, and laboratory characteristics of PSC, as well as disease outcomes, such as liver transplantation (LT) and death.

Data collected from medical records included sex, age at diagnosis, baseline clinical and laboratory characteristics, presence of concurrent autoimmune diseases and IBD, treatment with ursodeoxycholic acid (UDCA), outcomes, such as LT or death, and last follow-up visit.

This study was approved by the Federal University of Minas Gerais Ethics Committee Board (CAAE 98626218.6.1001.5149) and conducted following the ethical standards of the Helsinki Declaration.

2.3. Statistical Analysis. Statistical analyses were performed using SSPS 25.0 software (IBM, USA). Categorical variables were reported as absolute numbers and percentages. The continuous variable distribution was assessed using the Shapiro–Wilk test, and those with Gaussian distribution were expressed as mean and standard deviation (SD) or as the median and interquartile range (IQR) if the distribution

was skewed. Univariate analysis was performed using the chi-square or Fisher's exact test, as appropriate, for categorical variables. Based on the data distribution, continuous variables were analyzed using Student's *t*-test or Mann–Whitney *U* test. Univariate and multivariable Cox regression analyses were used to assess the impact of covariates on combined adverse events (i.e., LT or death). Variables with a $p < 0.20$ were enrolled in the multivariable Cox regression using the backward method, as long as there was no collinearity between variables (i.e., variance inflation factor < 2.5, tolerance > 0.4), and the results were reported as the hazard ratio and 95% confidence interval (95% CI). The Kaplan–Meier method was used to estimate transplantation-free survival, and the log-rank test was performed to compare the survival distributions between the two groups. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient Characteristics. The initial cohort included 210 patients with PSC. Thirty-three (15.7%) were diagnosed with PSC and AIH overlap syndrome and, therefore, were excluded. The remaining individuals were eligible for inclusion. Table 1 summarizes the clinical and laboratory data of the remaining 177 patients with PSC (54.8% males, median age 33 (21–42) years). Figure 1 shows the age distribution of patients with PSC. The majority of patients were within 20–39 years of age ($n = 81$, 45.8%) and presented symptoms ($n = 139$, 78.5%) at the time of PSC diagnosis, mainly jaundice ($n = 93$, 52.5%) and pruritus ($n = 78$, 44.1%). Supplementary Figure 1 shows the distribution of the study entry decades (i.e., 1991–2001, 2001–2011, and 2011–2021). Most of the patients had large duct PSC ($n = 154$, 87%), and 33 patients were screened for concurrent IBD and 58.6% of them had ulcerative colitis (UC) ($n = 61$), Crohn's disease (CD) ($n = 13$), or indeterminate colitis ($n = 4$). The remaining patients refused to undergo colonoscopy or cross-sectional imaging, mainly due to the absence of symptoms. The mean age at the time of IBD diagnosis was 26 ± 12 years in males and 32 ± 16 years in females ($p = 0.097$). The date of IBD diagnosis was available in 67 of 78 cases of IBD. The diagnosis of IBD was performed at a median 1 year before PSC diagnosis (IQR: 6 years before the diagnosis of PSC to 1-year post-diagnosis). IBD was diagnosed before, at the same time, or after PSC diagnosis in 42/67 (62.7%), 17/67 (25.4%), and 8/67 (11.9%) patients, respectively. Advanced PSC was present at baseline in 104 patients (58.7%). Neoplasms were observed in only 11 patients (6.2%). The majority of the patients ($n = 142$, 80.2%) were treated with UDCA. After a median follow-up of 70 (31–126) months, 22 (12.4%) patients died and 58 (32.7%) underwent LT. The follow-up time to LT or death was 39 (15–74) and 64 ± 51 months, respectively. The Kaplan–Meier survival estimate of the entire cohort is shown in Figure 2. The 1- and 5-year survival rates of these patients were $92.3 \pm 2.1\%$ and $66.9 \pm 4.2\%$, respectively.

3.2. Factors Associated with Sex. Females with PSC had an older age at diagnosis (36 (23–45) vs. 29 (19–40) years in males, $p = 0.046$) and lower baseline bilirubin levels (1.2 (0.6––4.2) vs. 2.3 (0.9––7.6) times the upper limit of normal in males, $p = 0.011$) compared to their counterparts. No other clinical or laboratory characteristics, including IBD and disease outcomes, were associated with sex, except the fact that females had IBD diagnosis more frequently before (79.3% vs. 50.0%; $p = 0.007$) and less frequently after (6.9% vs. 39.5%; $p = 0.007$) the detection of PSC than males.

3.3. Predictors of Adverse Outcomes. Univariate analysis of clinical and laboratory parameters associated with adverse outcomes (death or LT) showed that symptomatic presentation, pruritus, weight loss, alkaline phosphatase, total bilirubin, and advanced PSC at baseline were associated with adverse outcomes. In the multivariable analysis, pruritus, total bilirubin, and advanced PSC were independently associated with mortality or LT (Table 2). Other variables, including sex and the presence of concurrent IBD or UDCA treatment, were not related to death and/or LT. Supplementary Table 1 provides the 5- and 10-year survival free of death and/or LT for each of the categorical variables analyzed in Table 2.

4. Discussion

This study evaluated 177 Brazilian patients diagnosed with PSC. Most patients were aged 20–39 years old, almost half of them were females, and less than 60% had concurrent IBD. The majority of patients had symptoms at presentation and signs of advanced PSC. Females were diagnosed at an older age with lower baseline bilirubin levels. The 1- and 5-year transplantation-free survival rates were 92.3% and 66.9%, respectively, and the outcomes were independently associated with baseline advanced liver disease, pruritus, and elevated bilirubin levels.

To our knowledge, this is the first study from Latin America to describe the demographics, clinical characteristics, and outcomes of patients with PSC [8]. Our findings are divergent from those of previous reports from the United Kingdom [3, 34], the US [2, 35], and Scandinavia [4, 36, 37], which reported a marked male preponderance and a higher frequency of concurrent IBD observed, respectively, in 62–68% and 62–81% of those patients with PSC, but consistent with other studies from western and southern Europe and Asia [15, 22, 38], which have shown a higher frequency of female patients with PSC and a lower prevalence of concurrent IBD. The largest study to date on the phenotype of PSC was conducted by the International PSC Study Group, which evaluated more than 7.000 patients with PSC [5]. In this study, 65.5% of the patients were male, and 70% had concurrent IBD, but most of the patients were recruited from centers in northern Europe, the British Isles, Germany, and North America. Different results were reported by a recent meta-analysis that evaluated the global incidence and prevalence as well as the phenotype of patients with PSC from different parts of the world [8]. The authors have described heterogeneity in incidence and prevalence rates, which were generally much higher in reports from northern Europe and North America than in southern Europe and

Table 1: Demographics, clinical, and laboratory features of patients with PSC according to sex.

Variables	All patients ($n = 177$)	Male ($n = 97$)	Female ($n = 80$)	P value
Age at diagnosis (years)	33 (21–42)	29 (19–40)	36 (23–45)	**0.046**[4]
Smoking	18 (10.2)	13 (13.4)	5 (6.2)	0.107[1]
Baseline clinical features				
Asymptomatic	38 (21.5)	19 (19.6)	19 (23.8)	0.502[1]
Jaundice	93 (52.5)	53 (54.6)	40 (50.4)	0.538[1]
Pruritus	78 (44.1)	39 (40.2)	39 (48.8)	0.255[1]
Fatigue	54 (30.5)	29 (29.9)	25 (31.3)	0.846[1]
Weight loss	44 (24.9)	28 (28.9)	16 (20.0)	0.174[1]
Baseline laboratory results (x ULN)				
Aspartate aminotransferase	1.9 (1.2–3.2)	1.8 (1.3–3.3)	2.1 (1.1–3.2)	0.472[4]
Alanine aminotransferase	1.7 (0.9–3.2)	1.7 (1.0–3.2)	1.7 (0.9–3.2)	0.997[4]
Alkaline phosphatase	2.6 (1.6–4.4)	2.7 (1.5–4.4)	2.4 (1.6–4.5)	0.989[4]
Gamma-glutamyl transferase	5.6 (2.8–11.3)	5.6 (2.7–10.7)	5.6 (2.9–12.1)	0.970[4]
Total bilirubin	1.8 (0.7–6.1)	2.3 (0.9–7.6)	1.2 (0.6–4.2)	**0.011**[4]
Serum albumin (mg/dL)	3.8 (3.1–4.3)	3.8 (2.9–4.4)	3.8 (3.3–4.1)	0.897[4]
Platelets count ($\times 10^9/mm^3$)	205 (120–300)	187 (101–286)	213 (126–314)	0.581[4]
Imaging findings				
Small duct PSC	23 (13.0)	16 (16.5)	7 (8.8)	0.127[1]
Large duct PSC	154 (87.0)	81 (83.5)	73 (91.2)	
IBD investigated	133 (75.1)	73 (75.2)	60 (75.0)	0.968[1]
IBD	78 (58.6)	45 (61.6)	35 (55.0)	0.439[1]
Age at IBD diagnosis (years)	28 ± 14	26 ± 12	32 ± 16	0.097[3]
Ulcerative colitis	61 (78.2)	37 (82.2)	24 (72.7)	0.414[2]
Crohn's disease	13 (16.7)	7 (15.6)	6 (18.2)	
Indeterminate colitis	4 (5.1)	1 (2.2)	3 (9.1)	
Concurrent disorders				
Seronegative rheumatoid arthritis	7 (4.0)	2 (2.1)	5 (6.3)	0.247[2]
Cholelithiasis	29 (16.4)	15 (15.5)	14 (17.5)	0.716[1]
Gallbladder polyps	2 (1.1)	1 (1.0)	1 (1.3)	>0.999[2]
All cancers	11 (6.2)	6 (6.2)	5 (6.3)	>0.999[2]
Colorectal cancer	3 (27.3)	2 (33.3)	1 (20.0)	
Liver and biliary tract	3 (27.3)	1 (16.7)	2 (40.0)	0.673[2]
Others	5 (45.5)	3 (50.0)	2 (40.0)	
UDCA treatment	142 (80.2)	78 (80.4)	64 (80.0)	0.945[1]
Advanced PSC	104 (58.7)	59 (55.7)	38 (53.5)	0.779[1]
Ludwig score III/IV	28/66 (42.4)	18/37 (48.6)	10/29 (34.5)	0.131[2]
Esophagogastric varices	77 (43.5)	47 (48.5)	30 (37.5)	0.143[1]
Splenomegaly	39 (22.0)	22 (22.7)	17 (21.3)	0.819[1]
Low platelet counts	52 (29.4)	29 (29.9)	23 (28.7)	0.868[1]
Variceal bleeding	31 (17.5)	16 (16.5)	15 (18.8)	0.694[1]
Hepatic encephalopathy	26 (14.7)	17 (17.5)	9 (11.3)	0.240[1]
Ascites	54 (30.5)	29 (29.9)	25 (31.3)	0.846[1]
Follow-up time (months)	70 (31–126)	64 (26–115)	76 (40–140)	0.202[4]
Liver transplantation	58 (32.8)	32 (33.0)	26 (32.5)	0.945[1]
Follow-up until transplantation (months)	39 (15–74)	42 (13–76)	33 (16–75)	0.953[4]
Mortality	22 (12.4)	14 (14.4)	8 (10.0)	0.374[1]
Follow-up until death (months)	64 ± 51	54 ± 48	82 ± 58	0.306[3]

Data are expressed as absolute number (percentage), median (interquartile range), or mean ± standard deviation. IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal. [1]Chi-square test. [2]Fisher's exact test. [3]Student's t-test. [4]Mann–Whitney test.

Asia [8]. In these studies, male predominance and frequency of IBD tended to be less marked in low-prevalence regions than in high-prevalence regions such as northern Europe. The lower frequency of concurrent IBD in this study was aligned with studies from southern Europe and Asia [11, 15, 18]. As reported elsewhere [5, 8], UC was much more common than CD; but different from other reports [5, 39], no association was found between sex and the occurrence of concurrent IBD. Mehta et al. also observed the bimodal age distribution of PSC with relative peaks of age between 15 and 35 years [8]. These findings were previously described in Japan, but different age peaks were observed in the third and seventh decades of life. In this study, no bimodal distribution was observed since most of our patients were in the third to fourth decades of life, as previously described elsewhere [1, 3–5]. However, it is impossible to exclude the impact of referral bias, since all of our patients were recruited from hepatology centers that treat with liver disease in adults.

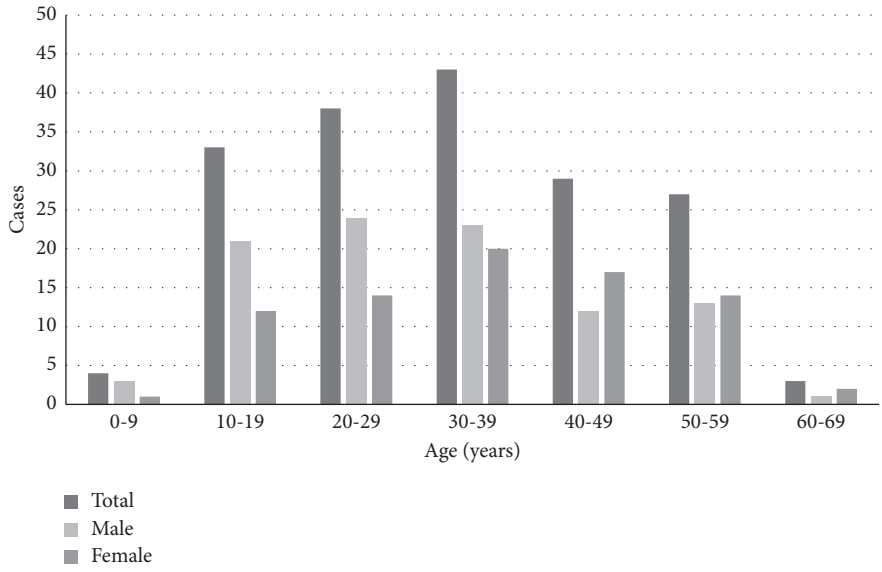

Figure 1: Distribution of patients' age at PSC diagnosis according to sex ($n = 177$).

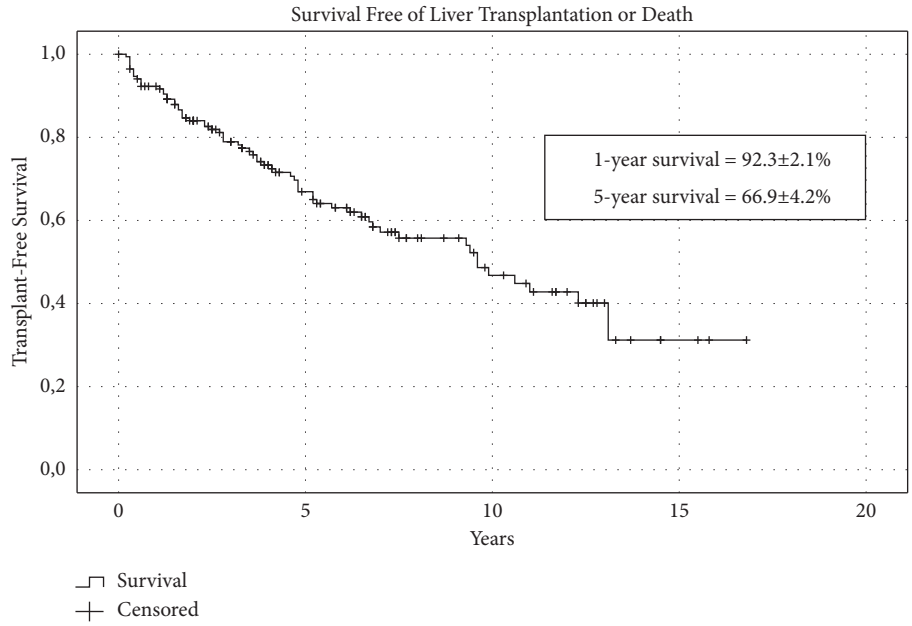

Figure 2: Kaplan–Meier curves of transplant-free survival of patients with PSC ($n = 177$).

In this study, females with PSC were diagnosed at an older age compared to males and probably had less advanced disease, considering their baseline levels of bilirubin. A previous study have reported that females were significantly older at the time of disease presentation than males [5] and had a less severe and progressive disease [5]. Based on these findings, it has been hypothesized that the later onset of the disease and the milder course of PSC observed in females may be due to a slower progression of the disease from subclinical disease to full-blown PSC [1, 5, 8, 23]. However, it must be noted that survival in this study was not associated with sex.

Survival in patients with PSC is highly variable due to several factors, including demographics, the occurrence of symptoms, presence of large duct vs. small duct PSC, concurrent IBD and/or cholangiocarcinoma, baseline bilirubin levels, clinical, biochemical, imaging and/or histological signs of advanced disease, presence of portal hypertension, decompensated liver disease, and access to LT [1, 7, 40, 41]. Few studies have been conducted on the natural history of PSC in Latin America, Africa, and Asia [7], and there is still a gap in the knowledge of disease outcomes in underrepresented regions. This study revealed a lower survival of the disease compared to other cohorts of patients

Table 2: Factors associated with adverse outcomes, either liver transplantation or death, in patients with PSC.

Variables	Univariate		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Female sex	0.82 (0.50–1.33)	0.422		
Age at diagnosis (years)	1.01 (0.99–1.02)	0.399		
Baseline clinical features				
Asymptomatic	0.24 (0.09–0.59)	**0.002**		
Pruritus	2.37 (1.45–3.88)	**0.001**	**1.88 (1.09–3.23)**	**0.023**
Fatigue	1.61 (0.96–2.71)	0.071		
Weight loss	1.95 (1.17–3.25)	**0.011**		
Laboratory at baseline (x ULN)				
Alkaline phosphatase	1.02 (1.00–1.05)	**0.043**		
Total bilirubin	1.10 (1.07–1.14)	**<0.001**	**1.08 (1.05–1.12)**	**<0.001**
Small duct PSC	0.69 (0.31–1.53)	0.369		
IBD	1.39 (0.81–2.39)	0.229		
UDCA treatment	0.70 (0.40–1.23)	0.221		
Advanced PSC	5.89 (2.91–11.93)	**<0.001**	**6.12 (2.73–13.71)**	**<0.001**

Data are expressed as absolute number (percentage) or median (interquartile range). CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal. Cox regression was performed.

[41], particularly in those with advanced PSC, pruritus, and higher baseline bilirubin levels. Compared to other reports [3, 6, 15, 20, 22, 35, 36, 38, 39, 42, 43], a higher percentage of our patients underwent LT due to the presence of advanced disease at baseline or possibly due to referral bias, as some of our patients were enrolled in tertiary care centers with the availability of LT. Taken together, these findings may also highlight that the diagnosis of PSC may be delayed in Brazil or not suspected or screened properly in patients with IBD.

Interestingly, our reported frequency of cholangiocarcinoma was lower than that reported in previous reports [44]. However, the prevalence of cholangiocarcinoma widely varies between different studies, which can be due to the population evaluated (i.e., transplantation centers tend to report a higher number of cases compared to population-based studies) or due to the diagnostic method available in each healthcare facility, as there is a lack of accurate diagnostic modalities to detect early stage cholangiocarcinoma, and surveillance remains controversial between different recommendations [1].

Our study has several limitations, considering its retrospective design and referral bias due to the inclusion of more severe patients from tertiary care centers; however, to our knowledge, this is the first large study addressing PSC characteristics and outcomes in Latin America, with a great contribution not only to local practice but also to the knowledge of PSC expression and outcomes in a multiethnic cohort of patients outside Europe and North America. Although the ethnicity or race of the patients was not reported in this study, it is well described that Brazil has one of the most heterogeneous genetic constitutions in the world, resulting from more than 500 years of interethnic crosses [24]. Furthermore, although our study has assessed factors associated with adverse outcomes in PSC, we did not use previously validated prognostic scores due to their limited usage in clinical practice and lack of validation in the Brazilian population [1, 41], which is characterized for the first time in the literature.

In summary, PSC in Brazilians has a less pronounced male predominance and a lower frequency of concurrent IBD. Females with PSC are diagnosed later in life than males and have a less severe disease at diagnosis, considering baseline bilirubin levels. Survival appeared to be worse, probably due to the more advanced disease at baseline.

Data Availability

The data analyzed during this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they no conflicts of interest.

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Supplementary Materials

Supplementary Figure 1. Description of study entry decades for patients with primary sclerosing cholangitis. Supplementary Table 1. Five and 10-year survival free of liver transplantation or death in patients with PSC. (*Supplementary Materials*)

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Research Article

Conjugated Hyperbilirubinemia in Infants: Is There Still a Role for ERCP?

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Over a twenty-year period, we performed 255 ERCP procedures in infants aged up to 1 year. ERCP was indicated in cholestatic infants with suspicion of biliary obstruction. The most common diagnosis was biliary atresia (48%), choledochal cysts (13%), and choledocholithiasis (4%). The procedure complication rate was 13.7%. Hyperamylasemia occurred in 12.9%. More severe complications were rare-0.8% of ERCP procedure. There were no cases of postprocedural pancreatitis or death. Our study has proved that ERCP is a safe and reliable method in this age group. Its high specificity and negative predictive value for extrahepatic biliary atresia can prevent unnecessary surgeries in patients with normal bile ducts or endoscopically treatable pathologies.

1. Introduction

Cholestasis in children under one year is a serious condition with multiple etiologies. ERCP is one of the diagnostic and potentially therapeutic methods that can distinguish between a surgical and a nonsurgical etiology of cholestasis.

Indications for ERCP differ in various age groups. In the group of children aged less than 1 year, ERCP is a useful method of confirming or excluding biliary atresia and pancreaticobiliary maljunction.

Newborns are indicated mainly for neonatal cholestasis with the goal to exclude or confirm biliary atresia. The unnecessary surgery can be avoided if ERCP fading confirms a normal biliary tract.

The second most frequent indication is suspicion of a choledochal cyst in patients with obstructive jaundice. Typically in these cases, there is a relatively small dilatation of the bile duct, with plugs stemming from protein debris from the wall of the bile duct. Insertion of a biliary stent can postpone the necessity of surgery at an older age.

The aim of this study is to determine the safety of the method and demonstrate its indispensable position/role in the diagnostic algorithm.

2. Patients and Methods

ERCP procedures performed in cholestatic infants aged 1 year or younger, performed from January 2000 till December 2020, were analyzed retrospectively.

ERCP was indicated in a subgroup of cholestatic infants with a suspicion of extrahepatic biliary obstruction. The standardized algorithm of diagnostic workup adopted at our institution was used (Figure 1).

Three outcomes were evaluated: the rate of technical success, the correlation of ERCP findings with the final diagnosis, and the rate of complications. Patients were

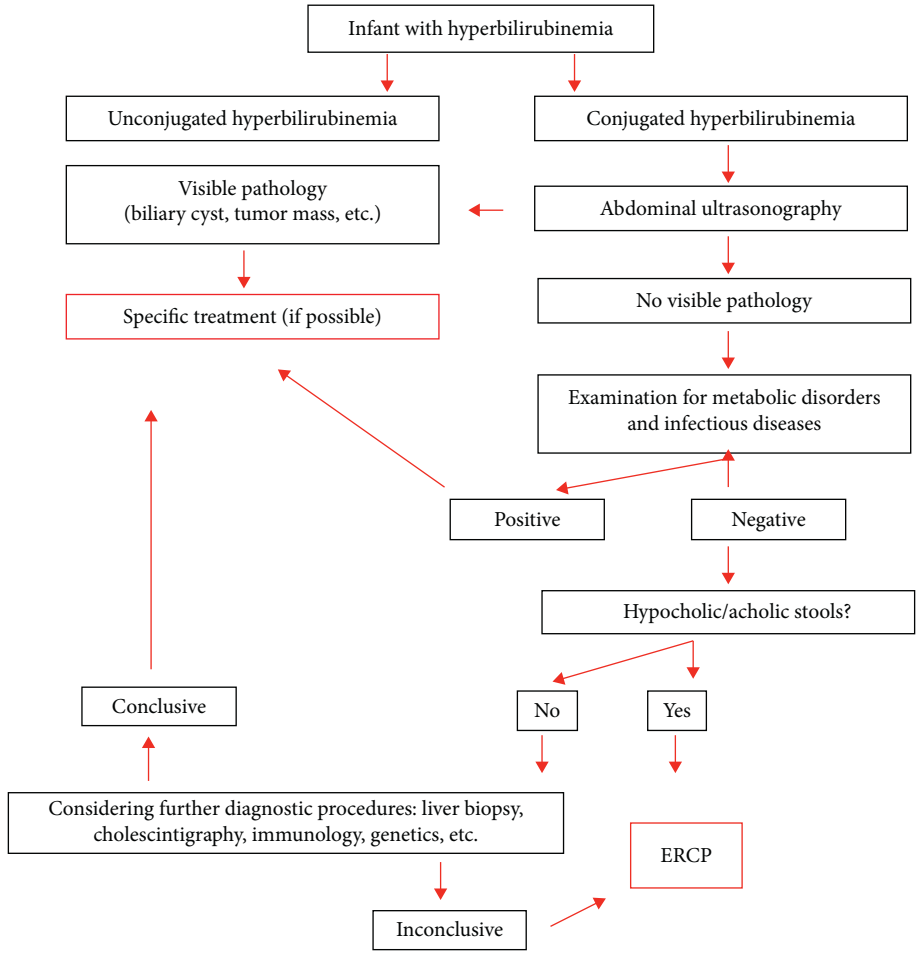

Figure 1: Diagnostic algorithm for conjugated hyperbilirubinemia.

divided into subgroups according to their diagnosis, and these subgroups were analyzed in more detail, including the subgroup of patients with a procedural technical failure. The data were statistically analyzed: sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values were calculated for biliary atresia.

All ERCP procedures were performed by two experienced endoscopists. The examinations were carried out on a fluoroscopic table under general anesthesia, with continuous monitoring of vital functions. In all cases, the pediatric duodenoscope (Olympus PJF) with a 7.5 mm outer diameter and 2 mm working channel was used. The lowest body weight in our cohort was 1.4 kg. Ultrathin handmade cannulas were used for cannulation. For the insertion of stents 5 Fr in diameter, it was necessary to use a double-lumen sphincterotome with an outer diameter of 1.75 mm (MediGlobe RotaCut GSP-21-17-020) and a guide wire with an outer diameter of 0.53 mm (Cook METII-21-480 Tracer Metro Direct Wire Guide). The therapeutic role of ERCP was limited by the fact that, until 2018, sphincterotomy was not performed with the pediatric duodenoscope as the manufacturing company did not recommend it.

In patients with biliary atresia, the findings were divided according to Guelrud's classification [1]: type 1: no visualization of the biliary tree, type 2: opacification of the distal common duct and the gallbladder without visualization of the main hepatic duct, and type 3: opacification of the distal common duct, the gallbladder, and a segment of the main hepatic duct with biliary lakes at the porta hepatis.

Todani classification was used to evaluate biliary cyst findings: type IA: a cystic dilatation of the extrahepatic biliary tree, type IB: a focal, segmental dilatation of the extrahepatic bile duct, type IC: a smooth fusiform dilatation of the entire extrahepatic bile duct, type II: a discrete diverticula of the extrahepatic duct, type III: choledochocoele, type IVA: a combination of intrahepatic and extrahepatic duct dilatation, type IVB: multiple extrahepatic bile duct dilatation, and type V: Caroli disease [2] (Figure 2). The findings of anomalous pancreaticobiliary junction (common channel) were documented, but not further classified.

The retrospective analysis was approved by the Ethics Committee of the University Hospital Motol and 2nd Faculty of Medicine, Charles University in Prague (reference no. EK-1100/18).

3. Results

ERCP procedures were performed on 255 infants (113 girls and 142 boys) aged 1 year and younger between January 2000 and December 2020. The average age of the patients at

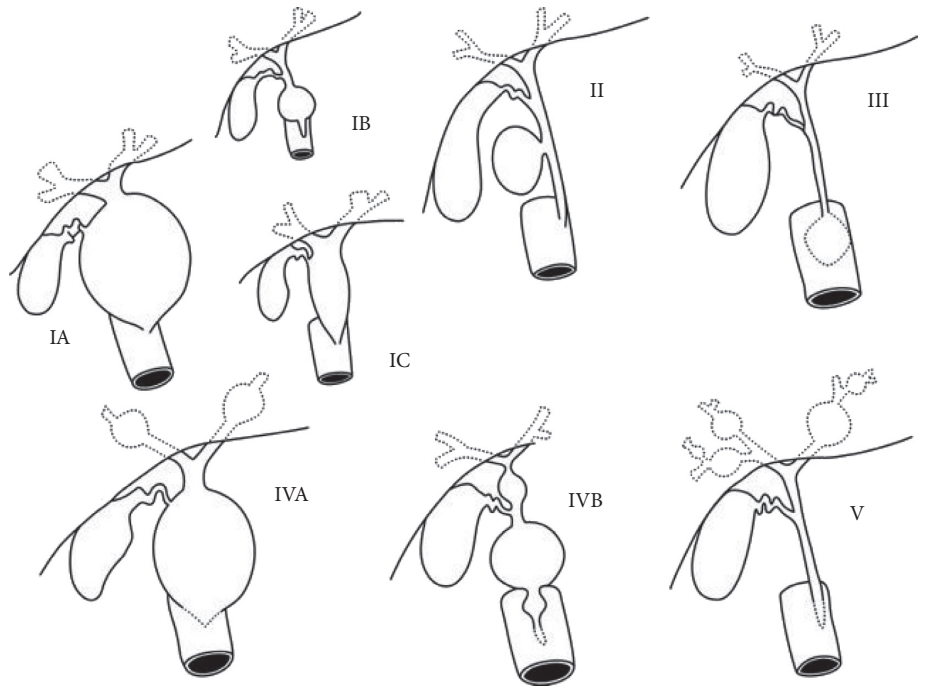

Figure 2: Todani classification of biliary cysts.

the time of procedure was 12.1 weeks. The infants were indicated for ERCP for conjugated hyperbilirubinemia and laboratory signs of cholestasis.

The dominating finding was biliary atresia (BA) (121 children, 48% of all procedures), followed by choledochal cyst (34 children, 13% of all procedures) and choledocholithiasis (9 children, 4% of all procedures) (Table 1). Other findings were marginal.

66 patients (26% of all procedures) had a normal finding.

Biliary atresia was diagnosed in 121 infants. The mean age of these patients at the time of procedure was 8.6 weeks, median: 7.7 weeks. The predominant finding was biliary atresia type I (99 infants, 82%), and biliary atresia type II was found in 22 patients (18%).

The age distribution of children with biliary atresia is shown in Figure 3.

False positive diagnosis of BA was established in 10 patients (8.3%)—5 had cholestasis only, 3 had Alagille syndrome, 1 had bile duct obstruction, and 1 had bile duct hypoplasia. Surgical revision was performed only in 4 of them. Two patients with Alagille syndrome underwent liver transplantation, and 1 infant with Alagille syndrome died before transplantation.

The positive predictive value for BA is 91.8%, the negative predictive value is 100%, specificity is 93.1%, and sensitivity is 100%.

Biliary cyst was diagnosed in 34 kids (13% of all procedures). The mean age of the patients with the biliary cyst finding was 15.9 weeks, median: 10 weeks. Frequency of cyst types according to Todani classification is shown in Table 2.

ERCP procedures failed in 12 patients due to technical reasons. The reasons (for technical failure) were duodenal stenosis (4 patients), a very small or an atypical papilla in an

Table 1: ERCP findings: types and frequency.

ERCP finding	Female	Male	Total
Biliary atresia	61	60	121
Type 1	55	44	99
Type 2	6	16	22
Bile cyst	10	24	34
Lithiasis	5	4	9
Stenosis	2	1	3
Pancreatic pathology	1	0	1
PSC	4	1	5
Postoperative pathology	3	2	5
Normal	19	47	66
Failed	8	4	12
Total	113	142	255

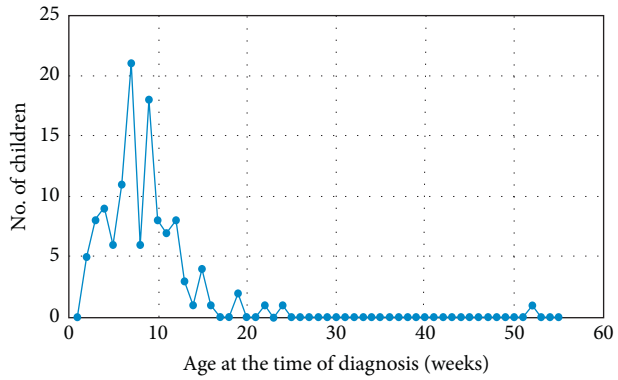

Figure 3: Age distribution of infants with biliary atresia at the time of diagnosis.

Table 2: Frequency of types of the cyst according to Todani classification.

Type of the cyst	No. of patients
Type 1A	7
Type 1B	13
Type IC	12
Type V	2
Total	34

atypical localization (3 patients), a papilla was not found (4 patients), and situs organum viscerum (1 patient).

The overall complication rate was 13.7% of ERCP procedures. Asymptomatic hyperamylasemia occurred in 12.9%. It is questionable if asymptomatic hyperamylasemia should be included in the complication rate. The suspicion of perforation (abdominal pain and elevation of CRP) occurred in one cholestatic infant with a choledochal cyst after an unsuccessful biliary stent insertion. The problem was resolved conservatively with parenteral nutrition and intravenous antibiotic therapy. In one case, a retroperitoneal depot of the contrast medium emerged during the procedure. It was resolved conservatively (parenteral nutrition and antibiotic therapy). There were no cases of ERCP-induced pancreatitis. No mortality was observed after ERCP.

4. Discussion

Fast and correct diagnosis is crucial in the management of infants, mainly neonates, with cholestatic liver disease. The principal moment is most important to exclude extrahepatic biliary atresia in cholestatic infants. In spite of relative invasiveness, ERCP can be a very useful tool to reach this goal with sufficient specificity and sensitivity and a low severe complication rate. High specificity and the negative predictive value of ERCP for extrahepatic biliary atresia indicate a possibility to prevent surgery in patients with normal bile ducts or endoscopically treatable pathology. On the contrary, all papers promoting ERCP for this indication stress the importance of ERCP being performed in large-volume centers by experienced endoscopists.

Historically, the method of choice and the gold standard for the final diagnosis of bile duct atresia were intraoperative cholangiography that definitively demonstrates the anatomy and the patency of the extrahepatic biliary tract. It is recommended to perform intraoperative cholangiography when the liver biopsy findings suggest an obstructive etiology. The cholangiography is also indicated when biopsy results are equivocal or scintiscan fails to demonstrate clear evidence of duodenal bile excretion [3]. This method is more invasive and riskier for infants in comparison with ERCP.

Less-invasive methods used for this indication are no less problematic. Ultrasonography is noninvasive, cheap, and definitely useful to identify anatomic abnormalities, but reported sensitivity as low as 74.9% and specificity at 93.4% [4] were found unreliable in the evaluation of biliary atresia [3]. Triangular cord sign is supposed to be specific for biliary atresia, but its diagnostic usefulness is diminished by its technical difficulty and variability of interpretation of ultrasonographists. Cholescintigraphy possesses high sensitivity in biliary atresia diagnosis, but with low specificity (sensitivity: 93.4% and specificity: 69.2%) [3, 4].

Magnetic resonance cholangiopancreatography (MRCP) requires general anesthesia, even longer compared with ERCP. Technical advancement and clinical experience are necessary before it can be used in the evaluation of cholestatic infants. Sensitivity of MRCP is 89.7%, and specificity is only 64.7% [4]. It is not recommended to use MRCP as a routine test method alone [3].

Meta-analysis of noninvasive diagnostic methods shows growing specificity, and especially, a combination of different methods (ultrasound with MRI or ultrasound with hepatobiliary scintigraphy) might be the future of noninvasive diagnostics [4], but there are still no satisfying data to confirm this hypothesis. None of these methods has a 100% negative predictive value, which is extremely important for the treatment decision.

Diagnosis and treatment in infants aged up to 45 days are important for the best results of hepatic portoenterostomy. The results will progressively get worse if performed at the age of 60–90 days [5]. All patients with biliary atresia in our cohort were diagnosed prior to week 24, ERCP was performed, and diagnosis was established in average at the age of 9 weeks with median 8 weeks, with a peak of cumulation of cases in week 7 (Figure 3). The use of an appropriate and generally accepted diagnostic algorithm for diagnoses can be helpful. There may be some room for improvement in the future. Screening programs for acholic stool exist in some countries. For example, in Taiwan, stool color card screening reduced the age of atresia diagnosis significantly [6]. Stool cards have 76.5% sensitivity and 99.9% specificity for identifying children with biliary atresia [7]. Also, smartphone applications have been developed for this purpose [8].

Some studies have reported the seasonal variation of biliary atresia cases, suggesting a role of viral infections in the etiology of biliary atresia [9]. We looked at the distribution of the month of birth and the month of diagnosis throughout a year. We did not find any significant and repeating occurrence (Figure 4).

Biliary cysts were found in 12.9% of children, which is consistent with our previously published data. Biliary cyst or pathology of the pancreatobiliary junction was found in 10% of children examined by ERCP for cholestasis [10, 11]. ERCP in biliary cyst diagnosis offers therapeutic possibilities—sphincterotomy or stent insertion. Surgical treatment can thus be postponed to older age when surgery is safer and has better results [12]. The bile duct in infants is very narrow and fusiform like. On the contrary, biliary cysts in the infant age look usually just like a relative widening of the bile duct. This finding can be easily confused and described as normal.

Frequency of symptomatic choledochithiasis in patients younger than one year in this cohort is lower than that reported in our older publications, but still relatively high (3.5% versus 7.4%) [9]. The exact epidemiologic data of choledocholithiasis incidence in neonates and infants are missing, but it can be expected to be far less than 1 in 5000 [13], and in most cases, it is asymptomatic. Patients with symptomatic choledocholithiasis benefit from ERCP

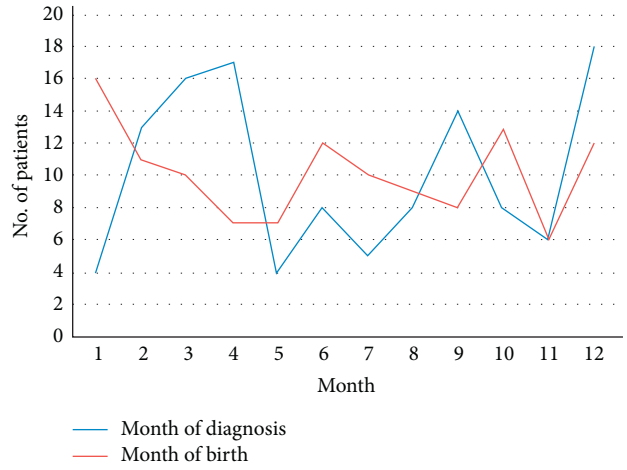

Figure 4: Number of biliary atresia by the month of birth and diagnosis.

availability, and their length of stay in hospitals is shorter than without ERCP therapy [14].

Only 25% of patients had normal bile ducts with no pathology. It indicates a good preselection of patients who were referred to ERCP.

Despite all the positive features described above, the availability of ERCP for infants under one year will probably further decline because of the fact that the production of the pediatric duodenoscope (Olympus PJF) was discontinued in 2013. Several centers no longer have an infant ERCP duodenoscope due to breakdowns and wear [15]. If the production of these endoscopes is not restored, the diagnostic and therapeutic role of ERCP in neonates and infants will be endangered [16].

5. Conclusion

ERCP is a reliable and safe diagnostic method in children younger than one year if it is performed by an experienced endoscopist. It has an indispensable role in the diagnostic algorithm of cholestatic infants. Although specificity and sensitivity of combined noninvasive diagnostic methods are high, ERCP is a unique nonoperative method with 100% negative predictive value for biliary atresia diagnosis. Unfortunately, the termination of the production of pediatric duodenoscopes can lead to lower availability of this procedure in neonates and infants.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

External Validation of UDCA Response Score in Slovak and Croatian Patients with Primary Biliary Cholangitis

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Background. Ursodeoxycholic acid response score (URS) is a prognostic model that estimates the baseline probability of treatment response after 12 months of ursodeoxycholic acid (UDCA) therapy in patients with primary biliary cholangitis (PBC). *Aim*. To independently evaluate the predictive performance of the URS model. *Methods*. We used a cohort of Slovak and Croatian treatment-naïve PBC patients to quantify the discrimination ability using the area under receiver operating characteristic curve (AUROC) and its 95% confidence interval (CI). Furthermore, we evaluated the calibration using calibration belts. The primary outcome was treatment response after 12 months of UDCA therapy defined as values of alkaline phosphatase $\leq 1.67 \times$ upper limit of normal. *Results*. One hundred and ninety-four patients were included. Median pretreatment age was 56 years (interquartile range 49–62). Treatment response was achieved in 79.38% of patients. AUROC of the URS was 0.81 (95% CI 0.73–0.88) and the calibration belt revealed that response rates were correctly estimated by predicted probabilities. *Conclusion*. Our results confirm that the URS can be used in treatment-naïve PBC patients for estimating the treatment response probability after 12 months of UDCA therapy.

1. Introduction

Primary biliary cholangitis (PBC) is a chronic cholestatic autoimmune liver disease. PBC incidence rates range from 0.33 to 5.8 per 100,000 inhabitants/year and prevalence rates range from 1.91 to 40.2 per 100,000 inhabitants and are increasing with time [1]. In Slovakia, annual PBC incidence rates range from 0.7 to 1.5 cases per 100,000 inhabitants/year, and the 2018 point prevalence was 14.1 cases per 100,000 inhabitants [2]. Similarly, in Croatia, PBC incidence rates range from 0.3 to 3.04 cases per 100,000 inhabitants/year and the 2017 point prevalence was 11.5 and 12.5 cases per 100,000 inhabitants in the continental and coastal regions, respectively [3]. Immunological attack on biliary epithelial cells with secondary failure of biliary transporters is, together with epigenetic mechanisms, generally considered to play a major role in the disease's pathogenesis [4]. The hallmark for diagnosis of PBC is serological positivity for antimitochondrial antibodies (AMA) [5]. Furthermore, ancillary markers anti-sp100 and anti-gp210 (antinuclear antibodies) are also used in clinical practice, because their positivity strongly suggests the diagnosis of PBC, irrespective of antimitochondrial antibody status [5]. PBC often results in end-stage liver disease and its associated complications [5]. Progression to the moderate stage occurs in about half of patients with the early stage of the disease. Subsequently, 16% of patients with the moderate stage transit to advanced PBC over a five-year period despite receiving treatment with ursodeoxycholic acid (UDCA) [6]. UDCA increases the proportion of patients with 10-year transplant-free survival by about 20%–40% compared with receiving no treatment or placebo [7, 8]. Patients who achieve treatment response to UDCA therapy in the early stage of the disease have survival rates comparable with the general population [9], and a relatively modest improvement in overall survival is related to a proportion of patients who fail to achieve treatment response. Based on the published data, treatment response is achieved in 46%–74% of all treated patients [10]. Notably, despite its suboptimal efficacy, UDCA remains the first-line treatment option for PBC. Clinical trials have shown that UDCA nonresponders benefit from the addition of either bezafibrate or obeticholic acid [11, 12]. A second-line treatment has already been conditionally approved in combination with UDCA for patients showing an inadequate response to UDCA [5]. Therefore, it is important to identify patients who would not benefit from the first-line treatment, so that they can be offered the second-line treatment whilst still in the early stage of the disease. Additionally, accurate selection of poor first-line treatment responders is also important for the recruitment to clinical trials of new drugs, so they can better demonstrate efficacy compared to UDCA, which is still the standard of care. The UDCA response score (URS) is a recently developed logistic regression model for PBC patients [13]. The URS model was designed to estimate the baseline probability of treatment response after 12 months of UDCA therapy. The authors defined treatment response as $\mathrm{ALP} < 1.67 \times \mathrm{ULN}$ because this was how UDCA response had been defined in clinical trials of second-line agents. The URS is a multivariable prognostic model, which explores the relationship of treatment response and the following independent variables: age at diagnosis (in years; ($\mathrm{age}_{\mathrm{diag}}$)), total bilirubin at diagnosis (in multiples of the upper limit of normal ((×ULN); ($\mathrm{TB}_{\mathrm{diag}}$)), aminotransferase (either aspartate aminotransferase (ASTdiag) or alanine aminotransferase (ALTdiag)) at diagnosis (in ×ULN; ($\mathrm{AT}_{\mathrm{diag}}$)), alkaline phosphatase at diagnosis (in ×ULN; ($\mathrm{ALP}_{\mathrm{diag}}$)), treatment time lag (in years), and change in ALP from diagnosis to start of treatment (ΔALP). The authors used a composite variable AT, which was ALT when available; otherwise, AST was used. Depending on a patient's age at diagnosis and laboratory status only, it precludes any interrater variability in the interpretation of the results. The URS was developed on a well-defined UK-PBC cohort of patients, with good discriminatory ability in the derivation cohort (AUROC 0.87; 95% CI 0·86–0·89). The model was also externally validated on the GLOBE cohort of PBC patients in the original development study (AUROC 0.83; 95% CI 0·79–0·87). Calibration belts revealed that the model was well-calibrated on both the UK-PBC and GLOBE cohorts. A URS calculator is available online (https://www.mat.uniroma2.it/~alenardi/URS.html).

Risk prediction models, such as the URS, can play an essential role in decision-making and future management of patients. It is imperative that these models are transferable and may be used with confidence in any population of patients with the respective medical condition [14]. However, a model might not perform as well as originally reported when it is used in clinical practice due to regional differences in patient populations. Thus, it is important that these risk prediction models are convincingly validated in external cohorts of patients prior to being applied in clinical practice [15]. Aside from the original study, the model's predictive performance has thus far only been evaluated in Japanese PBC patients [16]. In this paper, we aimed to independently evaluate the predictive performance of the URS model on a combined dataset of Slovak and Croatian PBC patients.

2. Methods

We performed an international multicentre retrospective validation study in a cohort of patients who were consecutively diagnosed with PBC and started UDCA treatment at ten hepatology centers in Slovakia (5) and Croatia (5) during the period from 30 June 1999 through 30 June 2019.

The exclusion criteria were as follows: (a) insufficient data for verifying the PBC diagnosis, (b) immunosuppressive or obeticholic acid treatment, (c) liver transplantation after less than 12 months of UDCA treatment, (d) patients with missing data that prevented the assessment of treatment response, and (e) patients with any of the URS predictors missing.

Local investigators completed case report forms (CRF) with on-call assistance from the study coordinators and collected pretreatment (T_0) demographic and clinical information and initial UDCA dosage. To account for interlaboratory variability, TB, AST, ALT, and ALP were all

transformed into a multiple of their respective ULNs. Furthermore, CRF included information on immunosuppressive treatment or obeticholic acid and history of liver transplantation status, and it also contained data necessary for evaluating treatment response after 12 months of UDCA therapy (T_{12}). All centers used immunofluorescence technique to detect AMA, and three of them verified the AMA positivity using western immunoblotting.

Every patient was centrally evaluated for PBC diagnosis following the European Association for the Study of the Liver (EASL) recommendations [5] that states that two out of the three following criteria need to be met: (1) elevated ALP, (2a) the presence of antimitochondrial antibodies (AMA) at a titer >1 : 40 or (2b) the presence of anti-sp100/anti-gp210, and (3) histological signs after liver biopsy.

We used the same Toronto [17] treatment response definition as the one used in the original development study ($\mathrm{ALP} < 1.67 \times \mathrm{ULN}$) and evaluated patients for achieving it after a 12-month course of UDCA.

The baseline UDCA response score was calculated using logistic regression formula provided by Carbone et al.:

$$\begin{aligned}\text{UDCA response score (URS)} = {} & 0.77 + 0.60 \times (\sqrt{\mathrm{TB}_{\mathrm{diag}}})^{-1} - 2.73 \times \ln(\mathrm{ALP}_{\mathrm{diag}}) + 0.35 \times \ln(\mathrm{AT}_{\mathrm{diag}}) \\ & + 0{\cdot}03 \times \text{age} - 0{\cdot}15 \times (\text{treatment time lag}) - 0.56 \times \Delta\mathrm{ALP}.\end{aligned}$$

Slovak and Croatian patients included in the final analyses received UDCA immediately following the diagnosis of PBC ($T_0 = T_{\mathrm{diag}}$). Therefore, we substituted $\mathrm{TB}_{\mathrm{T0}}$ for $\mathrm{TB}_{\mathrm{diag}}$, $\mathrm{ALP}_{\mathrm{T0}}$ for $\mathrm{ALP}_{\mathrm{diag}}$, and $\mathrm{AT}_{\mathrm{T0}}$ for $\mathrm{AT}_{\mathrm{diag}}$ and set both the treatment time lag and ΔALP to 0. We used ALT in the place of the composite AT variable.

We estimated that the pretreatment probability of treatment response achievement after 12 months of UDCA therapy is as follows:

$$\text{Probability} = \mathrm{Exp}\ (\mathrm{URS})/(1 + \mathrm{EXP}\ (\mathrm{URS}))$$

The study protocol is in accordance with the 1964 Declaration of Helsinki and its later amendments and with the principles of good clinical practice. The study protocol was approved by the Ethical Committee of Poprad Hospital, a.s., on 5 May 2019. Due to the retrospective nature of data collection and the complete anonymity of the records even from the principal investigator (only local investigators responsible for the standard of care could identify the patients), the committee waived the need for specific patients' informed consent. All authors had access to the study data and have reviewed and approved the final manuscript.

3. Statistical Analyses

We did not perform formal sample size calculations. However, all eligible data available for the URS model validation were considered to maximize the power and generalizability of the results.

We reported the clinical and demographic characteristics of patients using medians and interquartile ranges (IQR) for the continuous variables and absolute counts and percentages for the categorical variables. Additionally, we used boxplots to visualize the distribution of the continuous variables. Mann–Whitney and χ^2 tests were used to evaluate the statistical significance of differences in continuous and categorical variables, respectively. Furthermore, we compared the patients' characteristics with those from the derivation (UK-PBC) cohort. However, it was impossible to test the significance of differences in the continuous variables, given that only summary statistics (medians and interquartile ranges) are reported in the development study. We considered a p value of ≤0.05 statistically significant.

The predictive ability of the URS model was quantified by examining measures of both calibration and discrimination. Calibration was determined graphically by constructing calibration belts (package givitiR) and analytically using the Hosmer–Lemeshow test. The calibration belts reflect the agreement between predicted probabilities from the URS model with actual outcomes. With respect to other traditional approaches, they offer the possibility of detecting subgroup(s), where the disagreement between predicted probabilities and observed frequencies is significant, and the possibility of determining the direction of miscalibration [18]. Finally, calibration of the model is considered acceptable when the calibration belt encompasses the bisector in the whole 0–1 range. Discrimination was determined by calculating and plotting the AUROC curve (package pROC) and estimating the 95% confidence interval (95% CI) using stratified bootstrapping.

Furthermore, AT is one of the most important independent variables in the URS model. Due to widely reported subpopulations of PBC patients with normal or near-normal baseline AT values, we tried to separately quantify the predictive ability of the URS model in the PBC subpopulations with both normal and increased baseline AT values. Analyses were performed by a biomedical statistician in RStudio (version 1.2.1335).

4. Results

Four hundred seventeen patients were initially evaluated centrally by a joint committee of two study investigators, and 223 patients were excluded based on the selection criteria. We performed a complete-case analysis on 194 patients with primary biliary cholangitis (133 from Slovakia (68.56%) and 61 from Croatia (31.44%)) (Figure 1). One hundred sixty-seven patients were AMA positive (86.08%), and six patients (3.09%), both AMA and ANA negative, were diagnosed by meeting the following criteria only: (1) elevated ALP and (2) histological signs after liver biopsy.

We report baseline clinical and demographic characteristics of both Slovak and Croatian patients together with the baseline characteristics of the derivation (UK-PBC) cohort in Table 1. Slovak and Croatian patients had lower baseline ALP and AT values than those form the UK-PBC cohort. Furthermore, 154 (79.38%) patients achieved a treatment response after 12 months of UDCA therapy (responders) compared with only 1902 (70.4%) patients in the derivation cohort ($p = 0.008$). Median URS in Slovak and Croatian patients was 2.24 (IQR 1.87) in responders and 0.28 (IQR 2.74) in nonresponders ($p < 0.0001$; Figure 2). Slovak

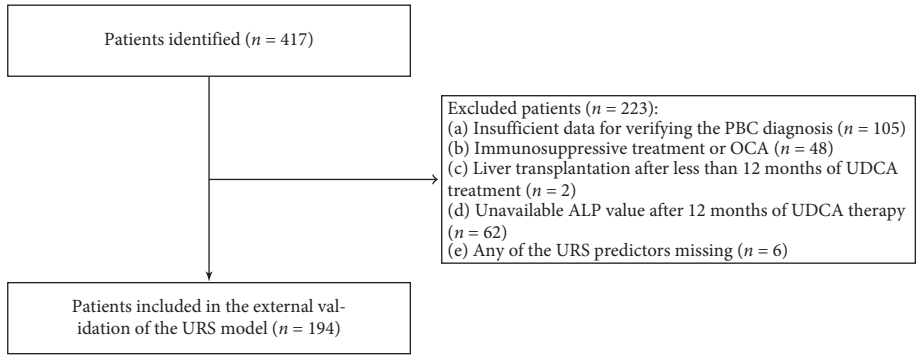

Figure 1: Flowchart of patient recruitment.

Table 1: Baseline clinical and demographic characteristics of both Slovak and Croatian and derivation cohorts.

	Validation cohort (Slovak and Croatian patients, $n = 194$)	Derivation cohort (UK-PBC)
Female patients	165/194 (85.05%)	2409/2703 (89.1)
Age at diagnosis (years)	56.00 (49.00–62.00)	56.80 (49.52–64.16)
Total bilirubin (×ULN)	0.53 (0.43–0.76)	0.53 (0.37–0.76)
Aspartate transaminase (×ULN)	1.13 (0.85–1.67)	1.40 (0.90–2.25) (AT)
Alanine transaminase (×ULN)	1.23 (0.78–1.85)	1.40 (0.90–2.25) (AT)
Alkaline phosphatase (×ULN)	1.66 (1.18–2.54)	1.85 (1.21–3.25)
Gamma-glutamyl transferase (μkat/l)	4.38 (2.34-6.70)	—
Albumin (g/l)	43 (40.16–44.9)	41 (38–44)
Total cholesterol (mmol/l)	5.96 (5.24–6.80)	—
High-density lipoprotein cholesterol (mmol/l)	1.60 (1.31-1.84)	—
Low-density lipoprotein cholesterol (mmol/l)	3.63 (2.94–4.20)	—
Triglycerides (mmol/l)	1.24 (0.98–1.71)	
Ferritin (pmol/l)	66.80 (26.78–118.80)	—
C-reactive protein (mg/l)	4.16 (2.93–8.70)	—
Immunoglobulin *M* (g/l)	3.54 (2.42–5.03)	—
Glycemia (mmol/l)	5.20 (4.83–5.97)	—
Platelets ($\times 10^9$/l)	241.00 (199.25–301.00)	—
Absolute neutrophil/lymphocyte count	1.89 (1.42–2.40)	—
Prothrombin time (INR)	0.99 (0.93–1.05)	—
Ursodeoxycholic acid dosage (mg/d)	1000 (750–1250)	—

Data are presented as median (interquartile ranges) or absolute counts (%). g/l: grams per liter, INR: international normalized ratio, mg/d: milligram per day, mg/l: milligram per liter, mmol/l: millimole per liter, μkat/l: microkatal per liter, *n*: number, pmol: picomole per liter, PT: prothrombin time, and ULN: upper limit of normal.

and Croatian patients were treated with a median of 1000 mg of UDCA per day (IQR 750–1250 mg per day).

We confirmed a high discrimination ability of the URS model (AUROC 0.81; 95% CI 0.73–0.88) for treatment response in a combined cohort of Slovak and Croatian patients. The calibration belt revealed that the response rates were correctly estimated by the predicted probabilities. However, a slight, nonsignificant trend towards underestimating the proportion of responders was present in the lower probabilities range (Figure 3). The Hosmer–Lemeshow test showed no evidence of lack of fit to the data ($p = 0.77$).

Additionally, we quantified predictive performance of the model in patients with normal ($n = 78$ (40.21%)) and increased ($n = 116$ (59.79%)) baseline AT values. Interestingly, the discrimination ability was lower in patients with normal baseline AT values (AUROC 0.73, 95% CI 0.56–0.89) compared with that in patients with increased baseline AT values (AUROC 0.82, 95% CI 0.73–0.90). Despite the presence of wide confidence intervals, the URS model was well calibrated in patients with both normal and increased AT values as the Hosmer–Lemeshow test revealed no evidence of a lack of fit to the data ($p = 0.58$ and $p = 0.99$, respectively) (Figure 4).

5. Discussion

Carbone et al. proposed the URS model to predict treatment response as defined by the Toronto criteria [13]. Although there are several distinctive definitions and continuous scoring systems of the first-line treatment response in PBC patients, the authors chose the Toronto criteria because this was how the treatment response had been defined in clinical trials of the second-line agents [12]. The URS was developed using rigorous logistic regression modelling. The authors used a cohort of PBC patients from the United Kingdom that consisted of 2703 participants and was externally validated on 984 PBC patients from Italy [13]. Further validation in

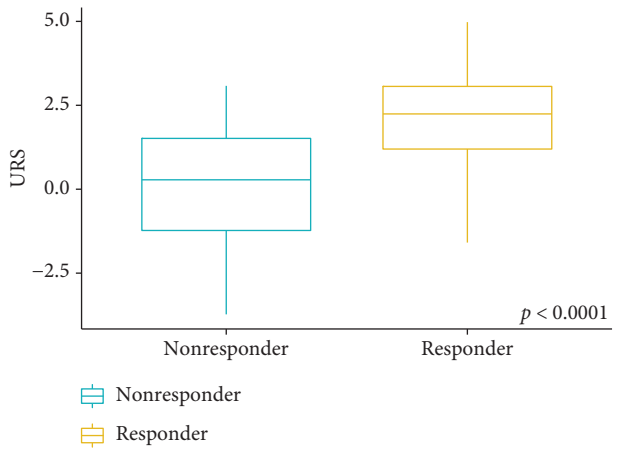

Figure 2: Boxplots of the ursodeoxycholic acid response score in Slovak and Croatian patients.

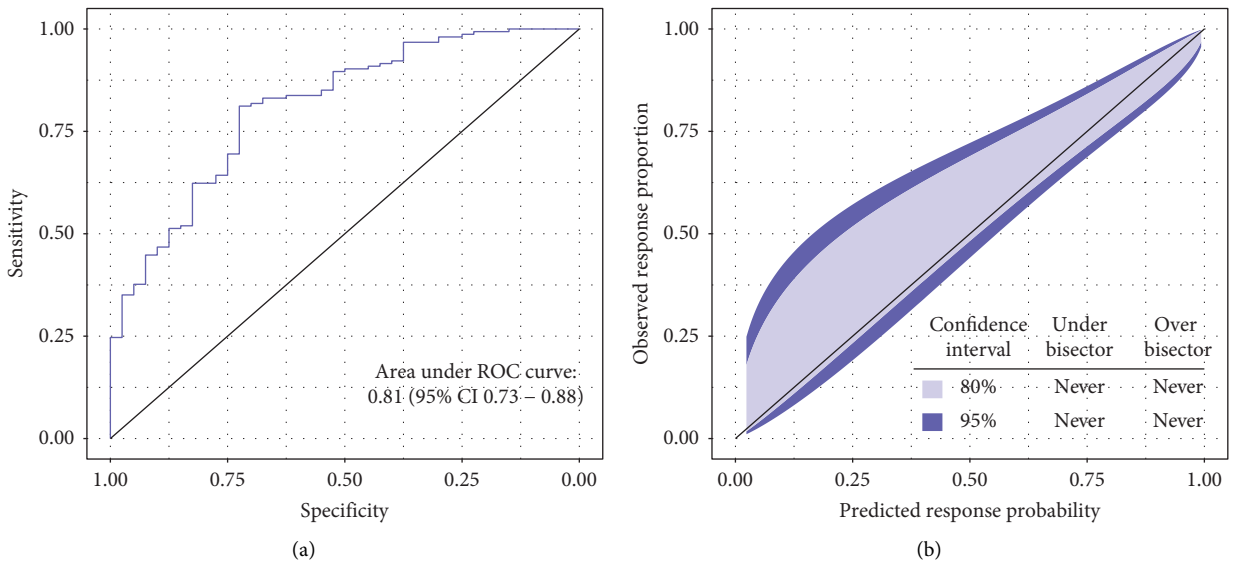

Figure 3: Predictive performance of the URS in Slovak and Croatian PBC patients. (a) AUROC 0.81 (95% CI 0.73–0.88) demonstrates high discrimination ability of the URS model. (b) Calibration belt confirms a well-calibrated URS model.

other geographical regions is essential, however, to universally endorse the URS model. Our results confirm the calibration and discriminatory ability of the URS model as reported in the original study.

Yagi et al. performed the first independent external validation of the URS model on 726 Japanese patients receiving UDCA monotherapy [16]. The authors used ALT instead of the composite AT variable and applied the same treatment response definition (ALP $\leq 1.67 \times$ ULN after 12 months of UDCA therapy). Yagi et al. evaluated the model's discrimination ability using the original and a modified URS equation. The AUROC of the original URS model was 0.77 (95% CI 0.70–0.83), and the AUROC of the modified URS model (using pretreatment data only) was 0.87 (95% CI 0.70–0.83). The authors did not report on any measures of the model's calibration.

Chen et al. proposed another model to estimate the future response to the first-line treatment in PBC patients [19]. In this case, the authors defined the treatment response based on the Barcelona criteria combined with the Paris I criteria. Although similar predictive variables were used, the reported discrimination ability was lower than these of the URS model (AUROC 0.763 (95% CI: 0.701–0.817) and 0.798 (95% CI: 0.681–0.887) in internal and external validation, respectively). The authors did not report on any measures of the model's calibration. We were not able to validate or compare the predictive performance of this model due to the inability to evaluate the treatment response as defined by Paris I criteria.

The Slovak and Croatian cohort of PBC patients has a similar prevalence of AMA negativity and concurrent AMA and ANA negativity as previously reported [20]. In our cohort, both AT and ALP values were numerically lower than in the derivation (UK-PBC) cohort. Four other studies from Western countries have reported similar baseline characteristics as those from our cohort [21–24]. The

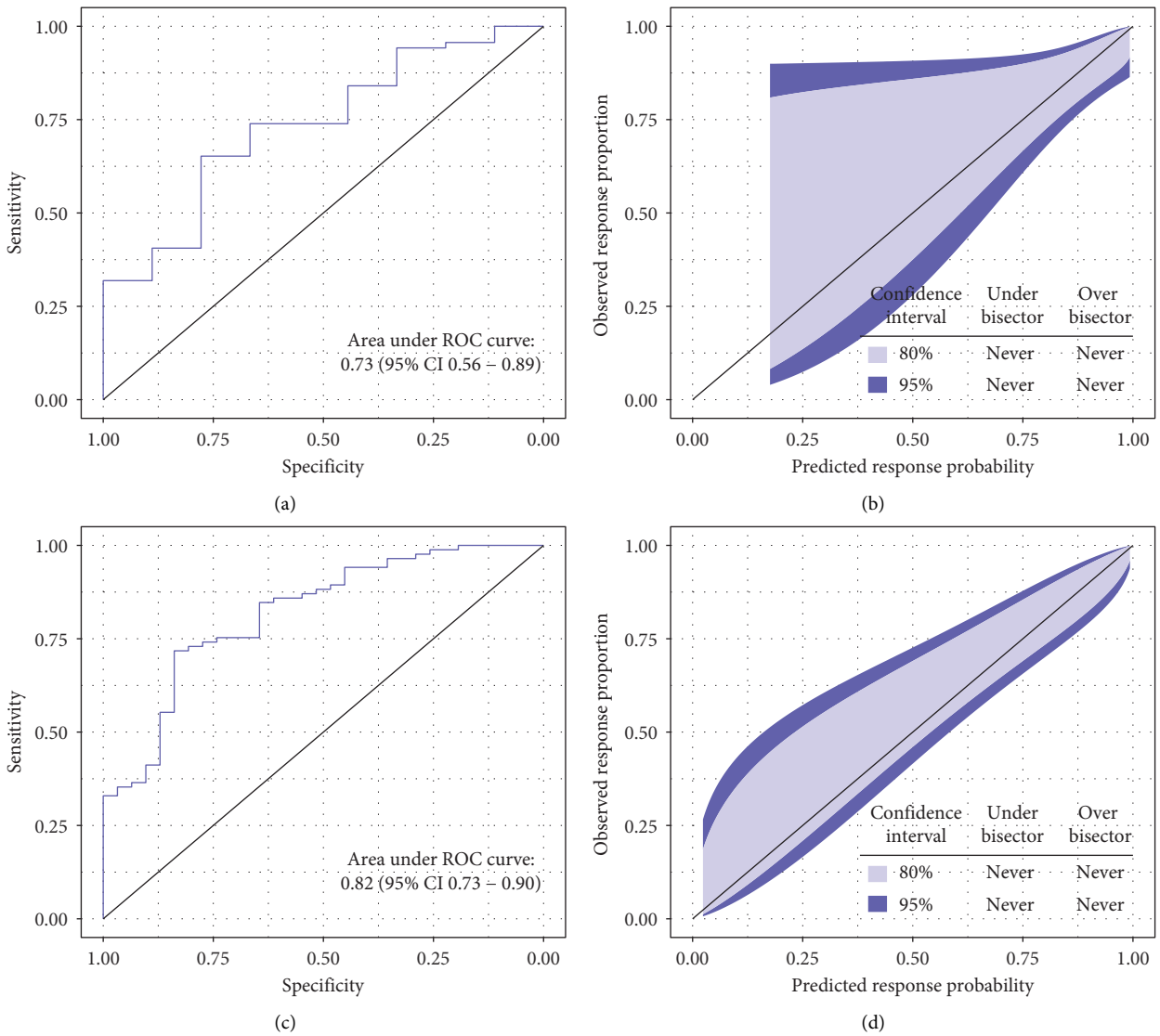

Figure 4: Predictive performance of the URS in patients with normal and increased baseline AT values. (a) Good discrimination ability in patients with normal baseline AT values. (b) Calibration belt in patients with normal baseline AT values characterized by wide confidence intervals in the lower predicted probabilities range. (c) Good discrimination ability in patients with increased baseline AT values. (d) Calibration belt demonstrating good calibration in patients with increased baseline AT values.

proportion of responders was also significantly different between this cohort and the UK-PBC cohort although the reasons for these differences are unclear. The delay in initiating therapy with UDCA in the UK-PBC cohort (median of 75 days) may partially explain this.

Despite the differences, our study shows that the discrimination ability and the model's calibration in the patient cohorts from Slovakia and Croatia are practically identical to these reported in the original study. However, a slight, nonsignificant trend towards underestimating the proportion of the responders is present in the lower probabilities range. This trend is not restricted to Slovakia and Croatian patients only but can be observed in the GLOBE cohort as well.

In general, we demonstrated a good predictive performance of the URS model in a population characterized by a significantly higher proportion of responders than in the UK-PBC or GLOBE cohorts. Furthermore, the evidence presented in this cohort confirms the good predictive ability of the URS model in a PBC population with numerically lower baseline values of both AT and ALP compared with those in the UK-PBC or GLOBE cohorts.

This model showed good discrimination ability, albeit lower AUROC, in the PBC subpopulation with normal baseline AT values. In these patients, the previously mentioned wide calibration belts are probably a result of a truly low proportion of nonresponders rather than poor calibration of the model.

Carbone et al. recognized that the ΔALP and treatment time lag are redundant in clinical practice, but they retained them in the model to emphasize the importance of not delaying effective treatment. In this study, we verified that omitting these variables has practically no impact on the

predictive performance of the model and that individual risk profiles obtained from the URS model can be used to determine a patient's risk of no response after a 12-month course of UDCA. Treatment response evaluations should be recommended for these particular patients earlier than is currently used in clinical practice and also on a regular basis.

Our study has a few limitations. First, the study cohort was recruited retrospectively using archived data, thus creating the possibility of information bias. Second, the sample size was insufficiently large to be truly representative of the whole PBC population in these two countries.

6. Conclusion

We confirmed that the URS model can be used in treatment naïve PBC patients from Eastern Europe for estimating the treatment response probability after 12 months of a UDCA course.

Abbreviations

ALP: Alkaline phosphatase
ALT: Alanine aminotransferase
AMA: Antimitochondrial antibodies
AST: Aspartate aminotransferase
AT: Aminotransferase
AUROC: Area under receiver operating characteristic curve
CI: Confidence interval
CRF: Case report form
EASL: The European Association for the Study of the Liver
g/l: Grams per liter
INR: International normalized ratio
IQR: Interquartile range
mg/d: Milligram per day
mg/l: Milligram per liter
mmol/l: Millimole per liter
n: Number
PBC: Primary biliary cholangitis
PT: Prothrombin time
TB: Total bilirubin
UDCA: Ursodeoxycholic acid
ULN: Upper limit of normal
URS: Ursodeoxycholic acid response score
*μ*kat/l: Microkatal per liter
pmol: Picomole per liter.

Data Availability

The data (in an excel file) used to support the findings of this study are available from the corresponding author upon request.

Disclosure

This research was performed as part of the employment of the authors at Pavol Jozef Safarik University, Comenius University, University of Zagreb School of Medicine, University of Rijeka, and Technical University of Kosice.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

The Epidemiology of Primary Biliary Cholangitis in European Countries: A Systematic Review and Meta-Analysis

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Background. Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease with wide ranges of reported incidence and prevalence. *Aim*. To map the incidence and prevalence of PBC in European countries from 2000 through 2020. *Methods*. Following PRISMA recommendations, we searched the Medline and Scopus databases for studies with information on either the incidence or prevalence of PBC. After data extraction, we used a random-effects model to estimate both the pooled annual incidence rate and pooled point-prevalence rate and performed subgroup analyses to identify components contributing to between-study heterogeneity. *Results*. We performed a qualitative and quantitative analysis of 18 studies. The pooled point-prevalence rate was 22.27 cases per 100,000 inhabitants (95% CI: 17.98–27.01), and the pooled annual incidence rate was 1.87 new cases per 100,000 inhabitants (95% CI: 1.46–2.34). In the subgroup analyses, we proved that a small part of the between-study heterogeneity is significantly associated with a history of being part of the Eastern Bloc.

1. Introduction

Primary biliary cholangitis (PBC) is a chronic inflammatory autoimmune cholestatic liver disease [1]. The aetiology of PBC remains unknown; however, PBC is associated with a myriad of both HLA and non-HLA genes as well as with several environmental factors (socioeconomic status, infectious agents, environmental pollutants, vitamin D, nutrition, drugs, and physical and psychological stresses) [2]. An increased prevalence of PBC has been associated with proximity to waste disposal sites [3, 4], and in the past, it has also been associated with a north-south latitudinal gradient [5, 6]. In the USA, the prevalence increased from 2004 through 2014 despite a steady incidence [7], and the global prevalence and incidence of PBC still vary widely with geographic region. In this meta-analysis, we tried to pool the PBC incidence and prevalence reported from European countries. Furthermore, we investigated the extent to which different components may have contributed to between-study heterogeneity. A similar worldwide study and one particularly from the Asia-Pacific region have recently been reported [8, 9].

2. Materials and Methods

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (https://www.prisma-statement.org/) [10].

2.1. Search Strategy. The Medline and Scopus databases were searched for studies with information on either the incidence or prevalence of PBC. The last search was run on 7 July 2020. A literature review was created using the following search terms: ("epidemiology" or "prevalence" or "incidence") AND ("primary biliary cirrhosis" or "primary biliary cholangitis" or "autoimmune liver disease" or "sclerosing cholangitis" or "biliary liver cirrhosis"). Medical Subject Headings (MESH) were used to increase the precision and efficiency of the search. No language, publication date, or publication status restrictions were imposed. In addition, we expanded the search using the reference lists of relevant review articles identified during the search. Two authors independently screened the literature review using titles and

abstracts and assessed full texts where eligible. Disagreements over the inclusion of articles were resolved by discussion with a senior hepatologist.

2.2. Inclusion and Exclusion Criteria. Studies were included if they met the following criteria: (1) the study was original research; (2) the study reported a prevalence or incidence (or it reported raw data that allowed the calculation of estimates); (3) the study was conducted in Europe; and (4) the study was published in 2000 or later.

Exclusion criteria for the meta-analysis were as follows: (1) the study was a review article; (2) the study was a genome study or an animal study; (3) the study described the epidemiology of PBC among hospitalized patients; and (4) the study did not specifically describe patients with PBC.

2.3. Data Extraction. Two investigators independently performed the data extraction. We developed a data extraction sheet, pilot-tested it on five included studies, and refined it accordingly. Furthermore, we attempted to acquire any missing information by contacting the corresponding authors of two studies; however, neither one responded to our request. Disagreements over extracted information were resolved by discussion with a senior hepatologist. The following information was extracted from each study: (1) the first author, (2) publication year, (3) country of origin, (4) case-finding methods, (5) methods of diagnosis, (6) raw data (underlying population and number of cases), and estimates of incidence and prevalence together with (7) sex-specific estimates, where available. Age-standardized estimates were preferred to crude estimates. Worth noting is that when multiple annual incidence rates were reported in a specific study, the median value for the period was calculated.

2.4. Statistical Analyses. The incidence and prevalence rates were adapted from the original reports. As needed, the underlying population was used to impute the number of cases and vice versa. For sex-specific analyses, the underlying population was divided by two. We used a random-effects model to estimate both the pooled annual incidence rate and the pooled point-prevalence rate (reported per 100,000 inhabitants). The results of meta-analyses are presented graphically using forest plots. We employed the DerSimonian–Laird (DL) approach to estimate the between-study heterogeneity. Two different measures of between-study heterogeneity are reported in this study: (1) Q is a χ^2 statistic; its p value ≤ 0.05 indicates the presence of significant between-study heterogeneity, which requires further investigation, and (2) I^2-statistics (inconsistency), which represents the ratio of between-study variance to the total observed variance. Outlying studies were identified by screening for externally studentized residuals that were larger than three in the absolute value. Furthermore, we assessed the possibility of publication bias by constructing funnel plots, which were assessed both visually and formally with Egger's test. We hypothesized that between-study heterogeneity could be partially associated with the inclusion of studies with different levels of risk of within-study bias. Therefore, we performed prespecified subgroup analyses and multiple metaregressions on the four following components, evaluating their effect on between-study heterogeneity: (1) the number of case-finding methods (cut-off value ≥ 2), (2) diagnostic methods (those complying with the current EASL recommendations were labelled "standard"), and (3) the underlying population (the median of the underlying populations served as the cut-off value). (4) We further investigated whether presence in the former Eastern Bloc may have contributed to different rates when compared to those reported from the former Western Bloc. Choropleth maps with colour progression were used to illustrate annual incidence rates and point-prevalence rates. In the case of multiple reports from the same country, the report based on the largest underlying population was used. All tests were two-sided and performed at the 0.05 significance level. Statistical analyses were performed in RStudio (version 1.2.1335).

3. Results

The electronic search yielded 1,373 records (Medline 1,200; Scopus 173). We identified seven more records reviewing the references of PBC-relevant review articles. No unpublished studies were included. After removing duplicates ($n = 80$), we screened the titles and abstracts of 1,300 records. A total of 93 reports were identified as potentially meeting our inclusion criteria and full-text articles were retrieved and examined in detail. After full-text review, 16 reports were used in subsequent meta-analysis. The PRISMA flow diagram is presented in Figure 1.

3.1. Studies Characteristics. A total of 16 reports on 18 different studies that were conducted in 13 European countries were included in the analysis. The publication dates of all included studies ranged from April 2007 to June 2020. A total of 17 studies (94.44%) reported local prevalence rates (10–58.2 PBC cases per 100,000 inhabitants) and 13 studies (72.22%) reported local incidence rates (0.79–5.31 new PBC cases per 100,000 inhabitants per year). Seven of these studies (38.89%) reported sex-specific rates. Furthermore, seven studies (38.89%) used at least two case-finding methods and 11 studies (61.11%) reported on specific diagnostic criteria (Table 1). A total of 25,343 cases of PBC were identified in the underlying population of 107,578,769 inhabitants.

3.2. Prevalence of PBC in European Countries. In Figure 2, we present a choropleth map of European countries with a colour progression representing PBC point-prevalence rates. Meta-analytic pooling of the prevalence estimates yielded a summary point-prevalence rate of 22.27 cases per 100,000 inhabitants (95% CI: 17.98–27.01; Q: 3168.57, $p < 0.0001$; I^2: 99%, Figure 3). The funnel plot (Figure 4) and Egger's test revealed no publication bias ($p = 0.97$), and no influential studies were identified during the influential analysis. Because of significant heterogeneity, potential moderators were

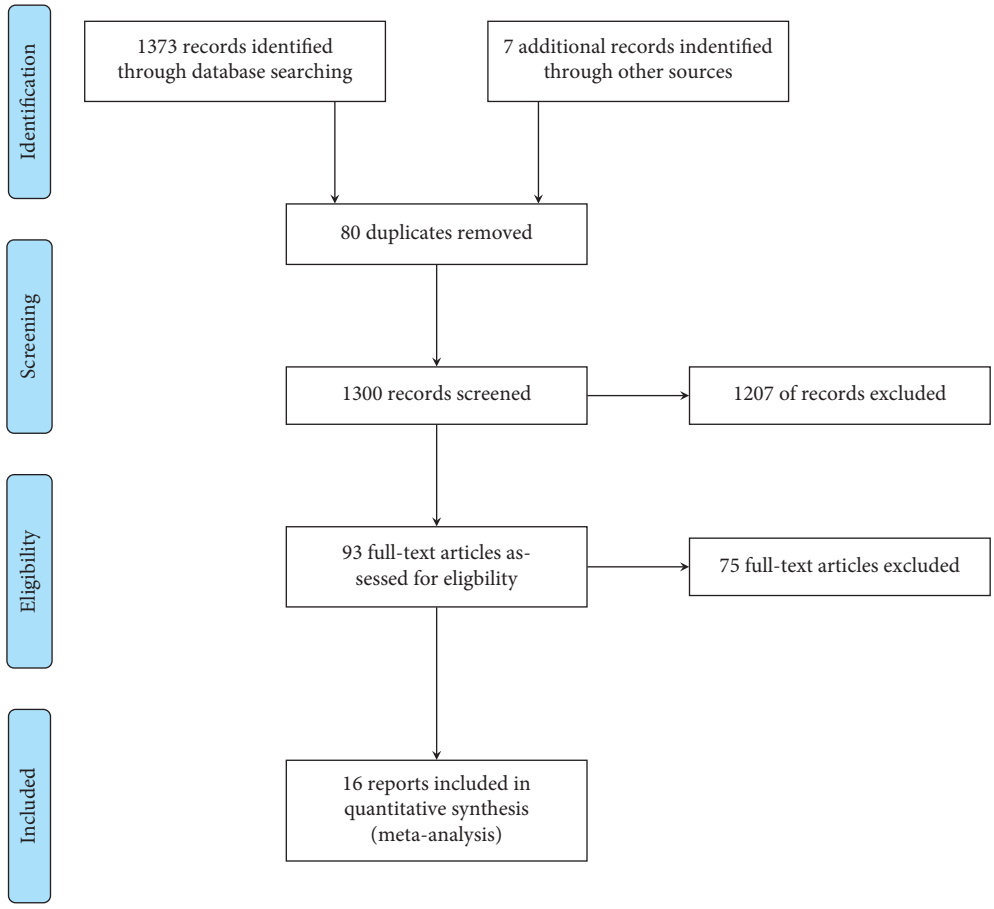


Figure 1: Flowchart of studies inclusion.

explored by subgroup meta-analyses (Figure 5(a)–5(d)) and a multiple metaregression. Neither the diagnostic criteria ($p > 0.05$) and the case-finding methods ($p > 0.05$) nor the underlying population ($p > 0.05$) explained the presence of heterogeneity. However, countries from the former Eastern Bloc had significantly lower point-prevalence rates when compared to those reported from the former Western Bloc (estimate: −0.0071, 95% CI: −0.0127–0.0016, $p < 0.05$). In the female population, the summary point-prevalence rate was 38.07 cases per 100,000 women (95% CI: 22.46–57.75; Q: 831.16, $p < 0.01$; I^2: 99%; Figure 6(a)). In the male population, the summary point-prevalence rate was 7.66 cases per 100,000 men (95% CI: 3.26–13.88; Q:196.23, $p < 0.01$; I^2: 99%; Figure 6(b)).

3.3. Incidence of PBC in European Countries. In Figure 7, we present a choropleth map of European countries with a colour progression representing annual PBC incidence rates. Meta-analytic pooling of the annual incidence estimates yielded a summary annual incidence rate of 1.87 cases per 100,000 inhabitants (95% CI: 1.46–2.34; Q: 1441.68, $p < 0.01$; I^2: 99%; Figure 8). The funnel plot (Figure 9) and Egger's test revealed no publication bias ($p = 0.36$), and no influential studies were identified during the influential analysis. Due to strong evidence of heterogeneity, potential moderators were explored by subgroup meta-analyses (Figure 10(a)–10(d)) and simple metaregressions. However, neither the diagnostic criteria ($p > 0.05$), the case-finding methods ($p > 0.05$), the underlying population ($p > 0.05$), nor the historical presence in either of the Europe's political blocs ($p > 0.05$) explained the presence of heterogeneity. In the female population, the summary annual incidence rate was 2.96 cases per 100,000 women (95% CI: 1.95–4.18; Q: 652.91, $p < 0.01$; I^2: 99%; Figure 11(a)). In the male population, the summary annual incidence rate was 0.70 cases per 100,000 men (95% CI: 0.41–1.07; Q:151.20, $p < 0.01$; I^2: 99%; Figure 11(b)).

4. Discussion

This study aimed to map the incidence and prevalence rate of PBC in Europe. The pooled point-prevalence rate was 22.27 cases per 100,000 inhabitants (95% CI: 17.98–27.01), and the pooled annual incidence rate was 1.87 new cases per 100,000 inhabitants (95% CI: 1.46–2.34). PBC, similarly to other autoimmune disorders, is a female-predominant disease [1]. In Europe, the female prevalence was approximately five times higher compared to estimates from the male population, and the female incidence was four times higher. PBC is associated with lifestyle and both genetic and environmental factors. The population of the first-degree relatives of

Table 1: Reports on PBC incidence and/or prevalence from European countries.

First author	Country	Publication year	Case-finding methods	Diagnostic methods	Population	Prevalence	Female prevalence	Male prevalence	Incidence	Female incidence	Male incidence
Rautiainen et al. [11]	Finland	2007	1, 2, 5, 6	2/3 of a, b, d	2,972,189	18.0	29.2	5.5	1.7	2.7	0.8
Pla et al. [12]	Spain	2007	1, 2, 3, 5	2/3 of a, b/c, d	389,758	19.5	37.02	—	1.72	2.84	—
Eaton et al. [13]	Denmark	2007	2	ICD	5,472,032	12.0	—	—	—	—	—
Baldursdottir et al. [14]	Iceland	2012	1, 2, 3, 5	2/3 of a, b, d	317,630	38.3	64.4	12.5	2.5	4.1	1.0
McNally et al. [15]	England	2014	1, 2, 3, 4, 5	2/3 of a, b, d	2,050,000	—	—	—	4.509	7.668	0.949
Koulentaki et al. [16]	Greece	2014	2	2/3 of a, b, d	600,000	36.5	—	—	2.088	—	—
Boonstra et al. [17]	Netherlands	2014	1, 3, 5, 6, 7	2/3 of a, b, d	5,855,630	13.2	—	—	1.1	1.9	0.3
Heetun et al. [18]	Ireland	2015	2	—	500,000	10.0	—	—	1.4	—	—
Lleo et al. [19]	Italy	2016	2, 7	—	9,742,676	29.5	—	—	1.67	2.19	1.07
Lleo et al. [19]	Denmark	2016	2	—	5,534,738	12.2	20.3	3.5	1.14	1.77	0.47
Gatselis et al. [20]	Greece	2017	8	2/3 of a, b/c, d	750,000	58.2	—	—	—	—	—
Pares et al. [21]	Spain	2018	1 (delphi)	2/3 of a, b, d/US	46,400,000	20.2	—	—	2.2	—	—
Marzioni et al. [22]	Italy	2019	2	ICD	1,204,216	27.9	—	—	5.31	—	—
Madir et al. [23]	Croatia	2019	2	2/3 of a, b, d	331,288	11.5	—	—	0.79	—	—
Madir et al. [23]	Croatia	2019	2	2/3 of a, b, d	296,195	12.5	—	—	0.89	—	—
Marschall et al. [24]	Sweden	2019	2, 4, 7	ICD	8,065,261	34.6	—	—	2.6	—	—
Drazilova et al. [25]	Slovakia	2020	1	2/3 of a, b/c, d	1,600,000	14.9	28.0	—	1.2	2.2	—
Sebode et al. [26]	Germany	2020	7	ICD	8,100,000	36.9	61.2	12.4	—	—	—

The point-prevalence rate is reported as cases per 100,000 inhabitants. The annual incidence rate is reported as new cases per 100,000 inhabitants. Cases-finding methods: (1) survey of physicians, (2) hospital records, (3) laboratory data on antimitochondrial antibody positivity, (4) death notifications, (5) histology data on liver biopsies, (6) liver transplant records, (7) pharmacy or insurance databases or billing system, and (8) prospectively collected registry. Diagnostic methods: (a) cholestatic liver panel, (b) antimitochondrial antibody positivity, (c) antinuclear (anti-gp210/anti-sp100) antibody positivity, (d) compatible liver histology, ICD: International Classification of Diseases, US: abdominal ultrasound.

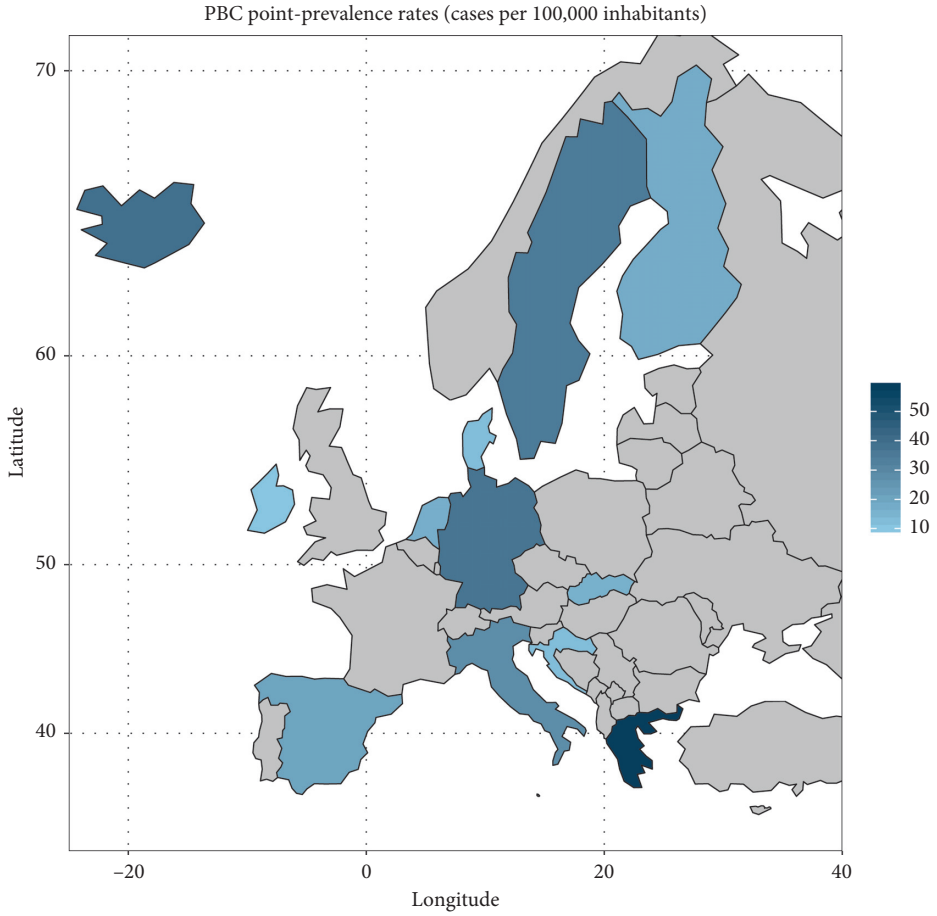


Figure 2: Choropleth map of PBC point-prevalence rates in Europe.

Study	Population	Prevalence	95% CI	Weight (%)
Rautiainen, 2007 (Finland)	2972189	17.97	[16.47; 19.56]	6.0
Pla, 2007 (Spain)	389758	19.50	[15.36; 24.41]	5.7
Eaton, 2007 (Denmark)	5472032	11.99	[11.09; 12.94]	6.0
Baldursdottir, 2012 (Iceland)	317630	38.09	[31.61; 45.52]	5.6
Koulentaki, 2014 (Greece)	600000	36.50	[31.83; 41.67]	5.8
Boonstra, 2014 (Netherlands)	5855630	13.18	[12.27; 14.15]	6.0
Heetun, 2015 (Ireland)	500000	10.00	[7.42; 13.18]	5.8
Lleo, 2016 (Italy)	9742676	29.50	[28.43; 30.60]	6.0
Lleo, 2016 (Denmark)	5534738	12.20	[11.29; 13.15]	6.0
Gatselis, 2017 (Greece)	750000	58.13	[52.81; 63.85]	5.9
Pares, 2018 (Spain)	46400000	20.20	[19.79; 20.61]	6.0
Marzioni, 2019 (Italy)	1204216	27.82	[24.92; 30.96]	5.9
Madir, 2019 (Continental croatia)	331288	11.47	[8.12; 15.74]	5.6
Madir, 2019 (Coastal croatia)	296195	12.49	[8.80; 17.22]	5.6
Marschall, 2019 (Sweden)	15462427	34.59	[33.67; 35.53]	6.0
Drazilova, 2020 (Slovakia)	1600000	14.88	[13.05; 16.89]	6.0
Sebode, 2020 (Germany)	8100000	36.89	[35.58; 38.24]	6.0
Random-effects model		22.27	[17.98; 27.01]	100.0
Heterogeneity: $I^2 = 99\%$, $\tau^2 < 0.0001$, $\chi^2_{16} = 3168.57$ ($p = 0$)				

Figure 3: PBC point-prevalence rates in Europe.

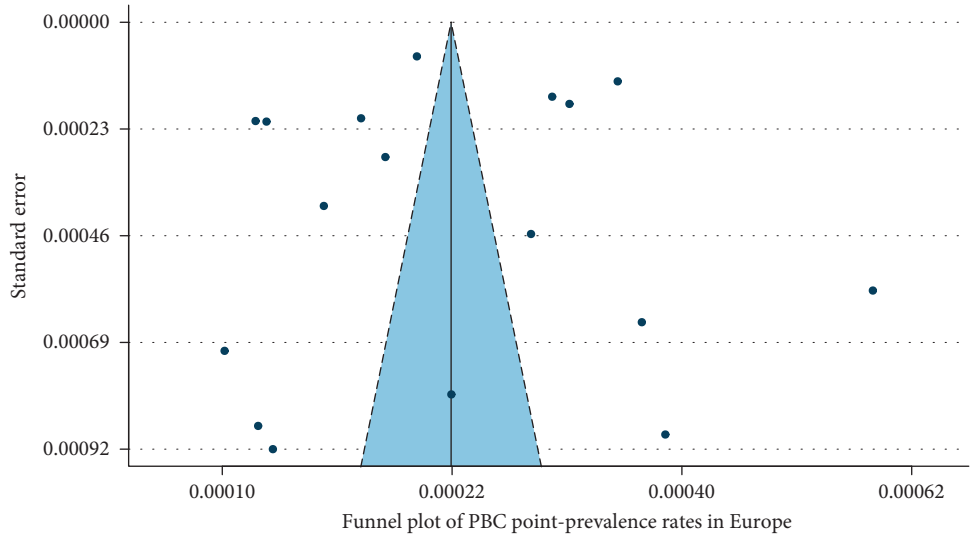


Figure 4: Funnel plot of PBC point-prevalence rates in Europe.

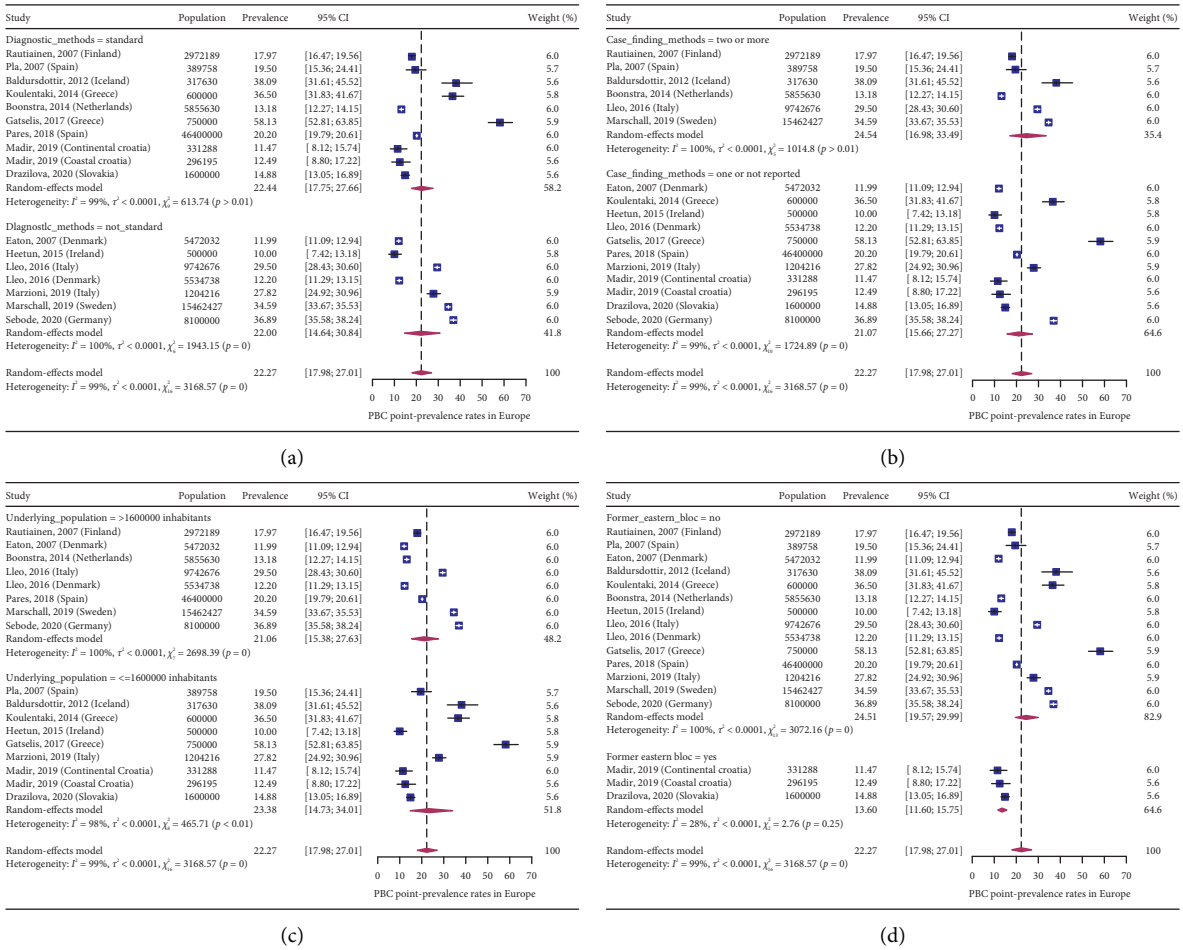
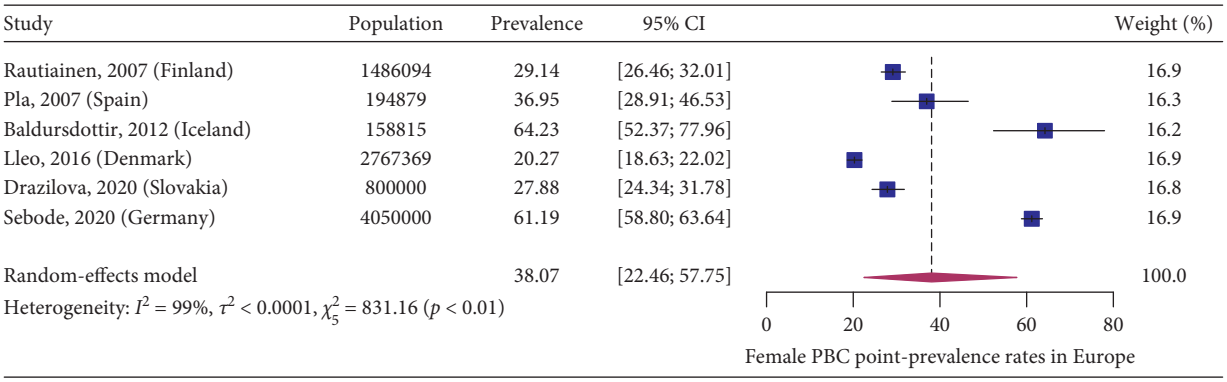
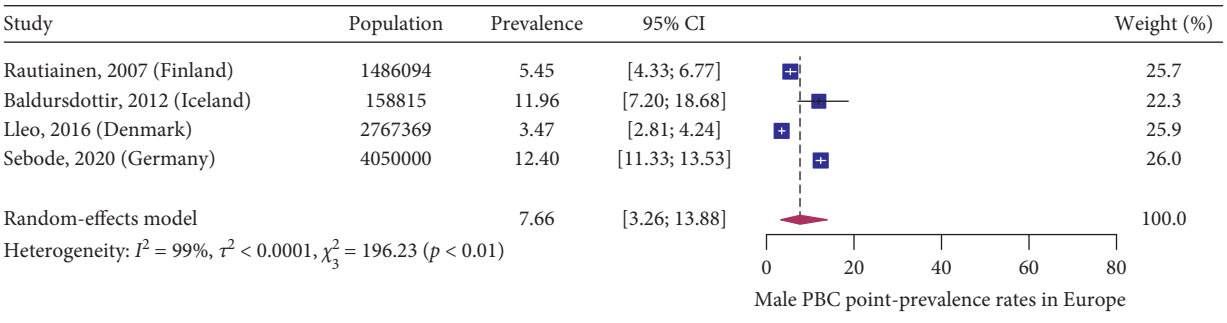


Figure 5: Subgroup analyses of PBC point-prevalence rates. (a) Diagnostic criteria. (b) Case-finding methods. (c) Underlying population. (d) Former Eastern/Western Bloc.

patients with PBC has higher prevalence of the disease when compared to the general population [27]. Smoking, several xenobiotics, oestrogen, hormonal contraception, and proximity to a toxic-waste disposal site are all associated with an increased incidence of PBC [3, 28]. An association with infectious diseases was also reported [28]. However, we



(a)



(b)

Figure 6: (a) Female PBC point-prevalence rates in Europe. (b) Male PBC point-prevalence rates in Europe.

did not analyse the association of these factors and the incidence or prevalence of PBC.

The employment of different case-finding methods may result in different reported rates. We found that both the prevalence (24.54, 95% CI: 16.98–33.49) and the incidence rate (2.15, 95% CI: 1.48–2.94) were higher in studies that reported at least two case-finding methods when compared to studies that did not report any case-finding method or reported only one (prevalence rate: 21.07, 95% CI: 15.66–27.27; incidence rate: 1.63, 95% CI: 1.17–2.16). However, this subgroup analysis did not explain the presence of heterogeneity.

The incidence was relatively stable during the last couple of years. The prevalence, on the other hand, steadily increased [7, 24, 25]. We will try to provide a simple explanation for this phenomenon. (1) Nowadays, awareness about PBC is getting better and diagnostic examinations are more accessible than they were in the past. (2) Advances in pharmacotherapy have resulted in lower liver-related mortality.

Few studies reported a north-south, north-west, or south-east prevalence gradient [23, 29]. Analysing choropleth maps, we did not confirm the existence of such a gradient on the European scale. We did, however, identify a lower incidence and prevalence rate of PBC in former communist states [23, 25] when compared to other European countries. We can explain this phenomenon by the worse awareness of PBC among local physicians. Likewise, Drazilova et al. described significant differences in PBC prevalence among neighbouring counties in Eastern Slovakia [25]. However, even in postcommunist countries, the prevalence is still rising [25].

The European Union, the United Kingdom, Switzerland, and Norway altogether have approximately 527 million inhabitants. When extrapolating from the pooled prevalence rate, roughly 115,000 patients should be diagnosed with PBC in these countries. However, the true number of cases would be significantly higher because a substantial portion of PBC patients, specifically patients with the asymptomatic clinical course, remains undiagnosed. According to one report, approximately one in 1,000 women could be suffering from PBC [30]. Interestingly, we described an even higher prevalence in two counties of eastern Slovakia (10% of counties), even though the overall PBC prevalence in eastern Slovakia was severalfold lower [25]. Ursodeoxycholic acid is the first-line treatment and is well accessible in the European Union [1]. Approximately 70% of patients respond partially or even completely according to the Toronto criteria [25]. The first-line treatment reduces liver-related mortality by about 50% [7]. The only second-line treatment approved by the European Medicines Agency (EMA) for the treatment of PBC is obeticholic acid (OCA), although reports on the effect of bezafibrate are promising as well [31, 32]. OCA is an expensive treatment, and good knowledge of the epidemiological situation can help estimate the cost of such a treatment on a country-wide scale. The systematic mapping of both the incidence and

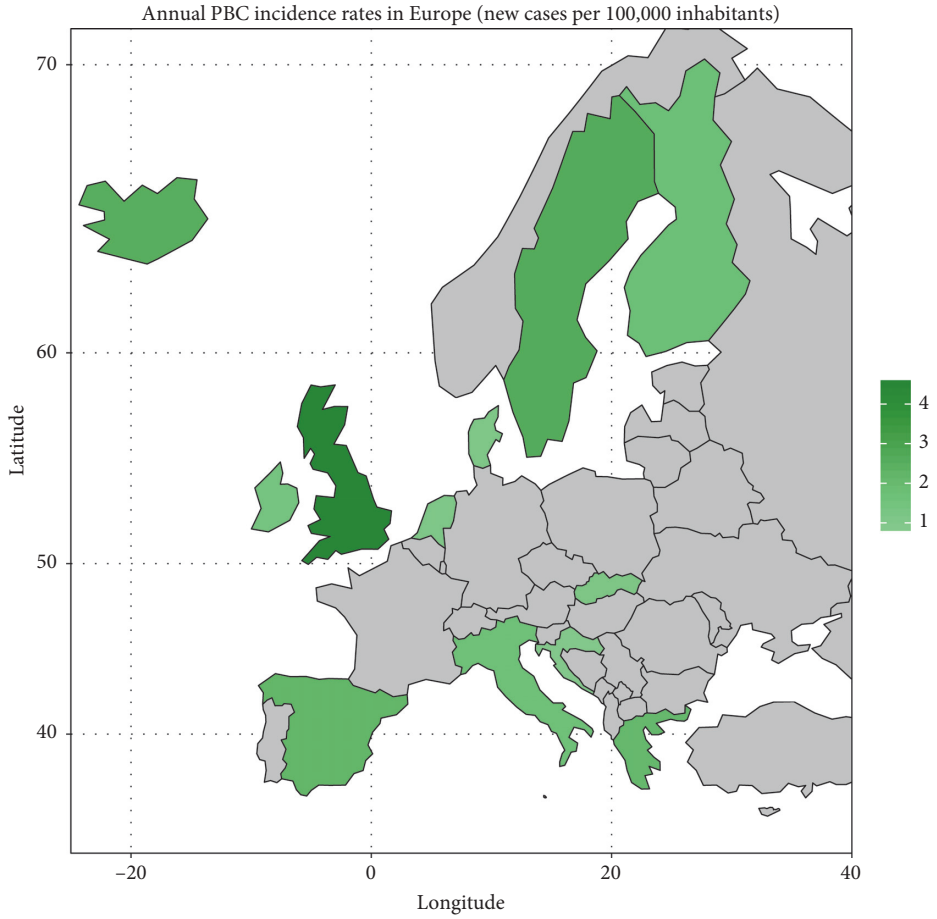


Figure 7: Choropleth map of annual PBC incidence rates in Europe.

Study	Population	Period (years)	Incidence	95% CI	Weight (%)
Rautiainen, 2007 (Finland)	2972189	1	1.68	[1.25; 2.22]	6.4
Pla, 2007 (Spain)	389758	13	1.72	[1.38; 2.12]	6.6
Baldursdottir, 2012 (Iceland)	317630	10	2.49	[1.97; 3.10]	6.4
Koulentaki, 2014 (Greece)	600000	21	2.09	[1.84; 2.36]	6.8
Boonstra, 2014 (Netherlands)	5855630	8	1.10	[1.01; 1.20]	6.9
McNally, 2014 (England)	2050000	9	4.50	[4.20; 4.82]	6.9
Heetun, 2015 (Ireland)	500000	13	1.40	[1.13; 1.72]	6.7
Lleo, 2016 (Denmark)	5534738	10	1.14	[1.05; 1.23]	6.9
Lleo, 2016 (Italy)	9742676	6	1.67	[1.57; 1.78]	6.9
Pares, 2018 (Spain)	46400000	1	2.20	[2.07; 2.34]	6.9
Madir, 2019 (Continental croatia)	331288	12	0.78	[0.53; 1.11]	6.5
Madir, 2019 (Coastal croatia)	296195	12	0.87	[0.59; 1.24]	6.5
Marzioni, 2019 (Italy)	1204216	1	5.23	[4.02; 6.69]	5.7
Marschall, 2019 (Sweden)	8065261	28	2.60	[2.53; 2.67]	7.0
Drazilova, 2020 (Slovakia)	1600000	5	1.20	[0.97; 1.47]	6.7
Random-effects model			1.87	[1.46; 2.34]	100.0

Heterogeneity: $I^2 = 99\%$, $\tau^2 < 0.0001$, $\chi^2_{14} = 1441.68$ ($p > 0.01$)

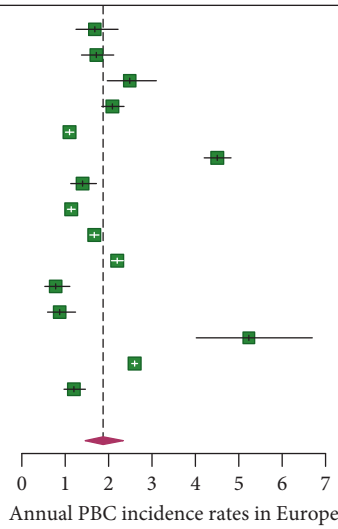


Figure 8: Annual PBC incidence rates in Europe.

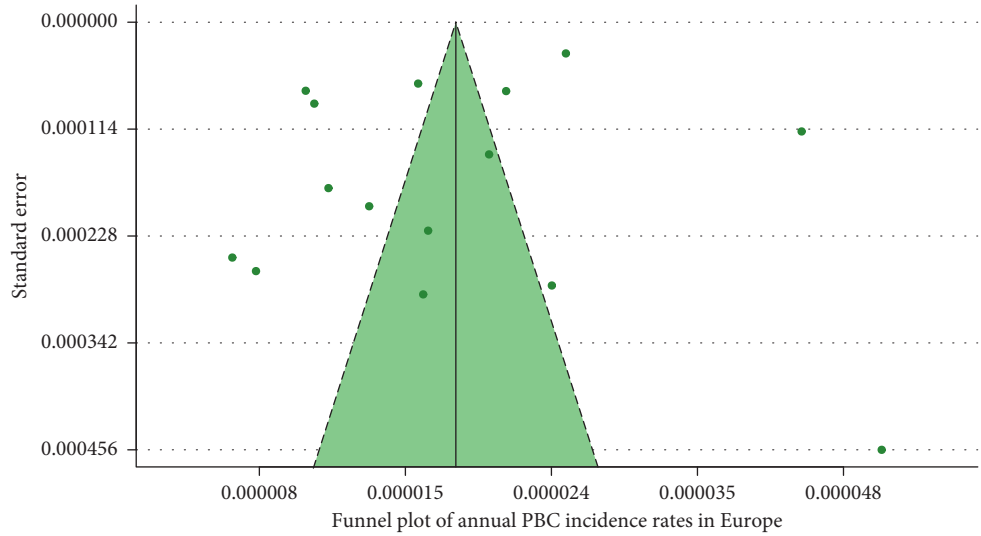


Figure 9: Funnel plot of annual PBC incidence rates in Europe.

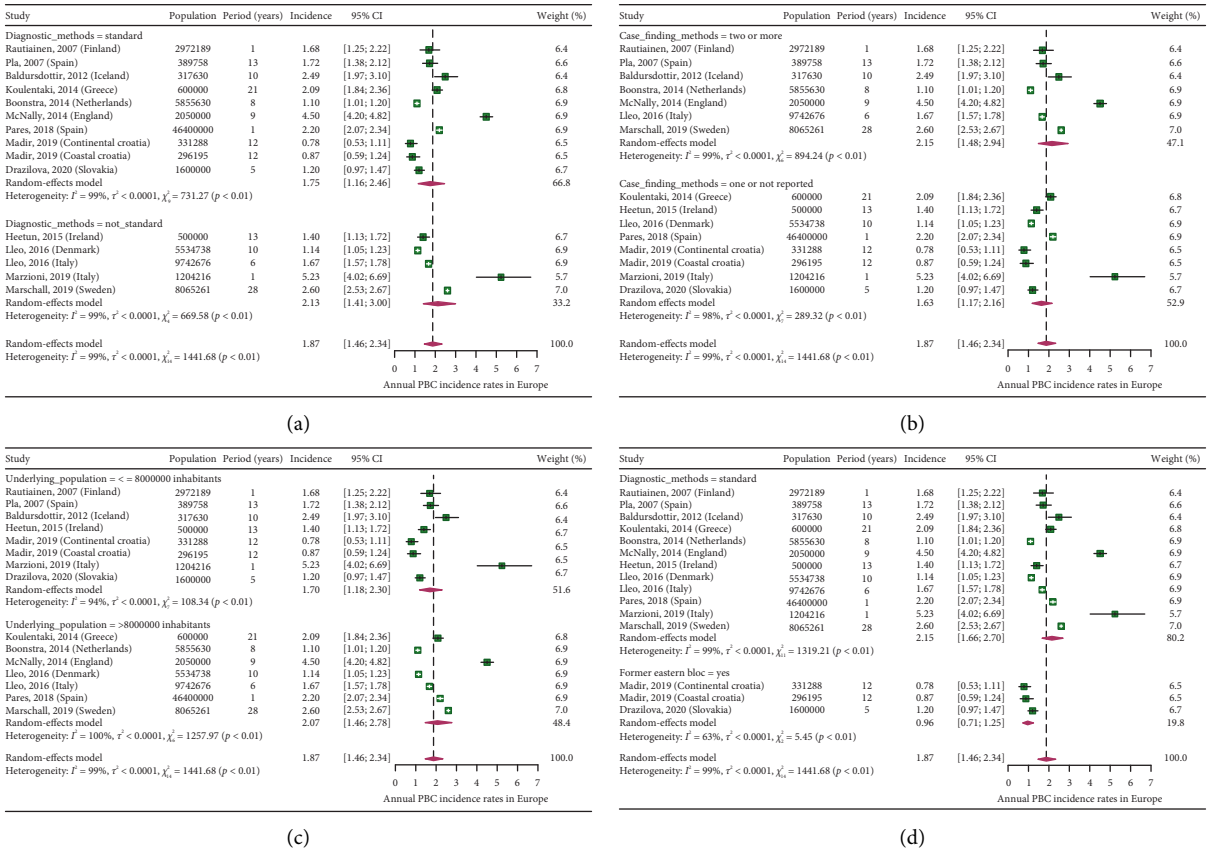
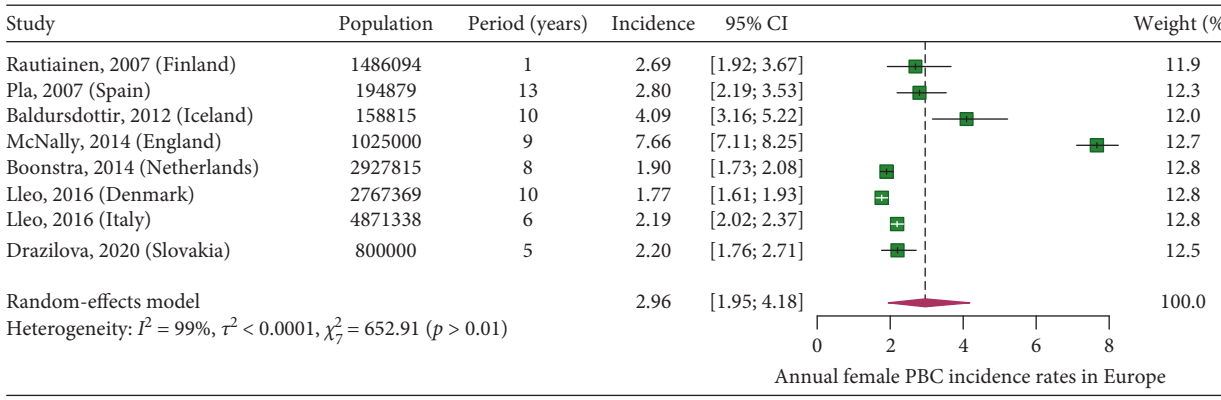
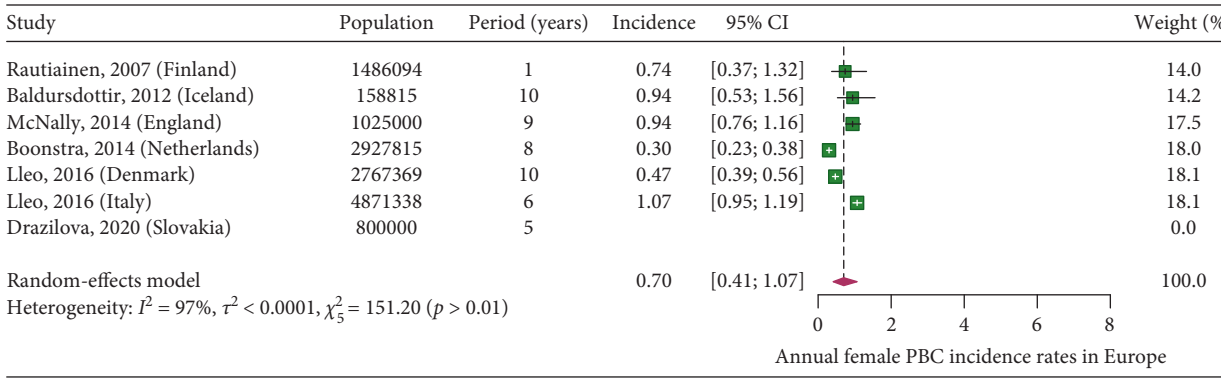


Figure 10: Subgroup analyses of annual PBC incidence rates. (a) Diagnostic criteria. (b) Case-finding methods. (c) Underlying population. (d) Former Eastern/Western Bloc.

prevalence of PBC in the European population is the main advantage of this study. The main limitation of this study is significant between-study heterogeneity. However, we cannot confirm that this heterogeneity is due to either different case-finding methods, diagnostic criteria, or underlying populations.



(a)



(b)

Figure 11: (a) Annual female PBC incidence rates in Europe. (b) Annual male PBC incidence rates in Europe.

5. Conclusion

We describe the incidence and prevalence of PBC in European countries. The true prevalence is probably higher than the reported prevalence, because asymptomatic patients are frequently undiagnosed. Improving awareness of PBC among physicians will catalyse a more effective diagnostic process and will thus result in a higher prevalence of PBC in the European population.

Data Availability

The data (in an excel file) used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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