J Gastroenterol
DOI 10.1007/s00535-016-1246-5

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Development of a scoring system for differentiating IgG4-related sclerosing cholangitis from primary sclerosing cholangitis

Sung-Hoon Moon[1] · Myung-Hwan Kim[2] · Jong Kyun Lee[3] · Seunghee Baek[4] · Young Sik Woo[3] · Dong Hui Cho[2] · Dongwook Oh[2] · Tae Jun Song[2] · Do Hyun Park[2] · Sang Soo Lee[2] · Dong Wan Seo[2] · Sung Koo Lee[2]

Received: 10 May 2016 / Accepted: 17 July 2016

Abstract

Background Recent research has shown that a substantial number of patients with primary sclerosing cholangitis (PSC) can also have elevated serum/tissue IgG4. The aim of our study was to develop a simple scoring system for the discrimination of IgG4-related sclerosing cholangits (IgG4-SC) from PSC.

Methods Patients with IgG4-SC ($n = 39$) and PSC ($n = 76$) who had intrahepatic/hilar strictures were included. Candidate-differentiating variables included patient age, other organ involvement (OOI), inflammatory bowel disease, serum IgG4, and cholangiographic features. A scoring system was developed on the basis of these variables, and its performance was internally validated using a bootstrapping-based method.

Results The scoring system in the final model included age (<30 years, 0 points; 30–39 years, 1 point; 40–49 years, 2 points; 50–59 years, 3 points; ≥60 years, 4 points), OOI (no, 0 points; yes, 3 points), and beaded appearance (yes, 0 points; no, 2 points). The patients were classified according to their total score into three categories: 0–4 points, probable PSC; 5–6 points, indicating diagnostic steroid trial; 7–9 points, probable IgG4-SC. The discrimination between IgG4-SC and PSC using the scoring system was excellent (area under the receiver operating characteristic curve, 0.986).

Conclusions A reliable differentiation of IgG4-SC from PSC can be made using the scoring system presented here. We suggest the diagnosis of IgG4-SC at a cutoff of 7 points or higher and the indication of diagnostic steroid trial at 5 or 6 points. External validation of our scoring system is warranted.

Keywords IgG4-related sclerosing cholangitis · Primary sclerosing cholangitis · Diagnosis · Scoring system

Introduction

Primary sclerosing cholangitis (PSC) is a chronic progressive disease of unknown etiology, characterized by fibrosis and strictures involving the intra- and extrahepatic bile ducts [1–3]. The natural history of PSC is highly variable, but the disorder eventually develops into liver cirrhosis and hepatic failure in the majority of patients [3–5]. The diagnosis of PSC depends on exclusion of secondary sclerosing cholangitis (SSC) as well as discrimination of typical cholangiographic features in patients

M.-H. Kim and J. K. Lee contributed equally to this work as corresponding authors.

Electronic supplementary material The online version of this article (doi:10.1007/s00535-016-1246-5) contains supplementary material, which is available to authorized users.

✉ Myung-Hwan Kim
mhkim@amc.seoul.kr

✉ Jong Kyun Lee
jongk.lee@samsung.com

[1] Department of Internal Medicine, Hallym University College of Medicine, Hallym University Sacred Heart Hospital, Anyang, South Korea

[2] Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Asanbyeongwon-Gil 86, Songpa-gu, Seoul 138-736, South Korea

[3] Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, 81 Irwon-Ro, Gangnam-Gu, Seoul, South Korea

[4] Department of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Published online: 28 July 2016

with cholestatic biochemical profiles that are not otherwise explained [1–5]. The secondary causes of sclerosing cholangitis that must be excluded are infection, intrabiliary stones, parasites, surgical biliary trauma, ischemic injury, acquired immune deficiency syndrome, and the recently highlighted immunoglobulin G4 (IgG4)-related sclerosing cholangitis (IgG4-SC) [1, 3, 6, 7]. The latest addition of steroid-responsive IgG4-SC to the spectrum of chronic cholangiopathies has triggered hot debate regarding the differential diagnosis of PSC [3, 6, 8, 9].

Discerning between IgG4-SC and PSC is essential because of the significant differences in treatment responses and prognosis, particularly as treatment of IgG4-SC can consist simply of corticosteroids administration, while that of PSC is ultimately liver transplantation. Timely diagnosis of IgG4-SC can lead clinicians to prescribe adequate corticosteroid therapy that can reverse bile duct strictures/wall thickening and cholestatic liver dysfunction, and could potentially prevent future advanced liver disease [6, 9, 10]. A proper diagnosis of PSC, in turn, is crucial for optimizing the surveillance of the disease progression to hepatic decompensation, and the need for liver transplantation [8]. Interval screening for cholangiocarcinoma is also recommended for patients with PSC because this disorder is associated with a lifetime risk of cholangiocarcinoma of around 7–14 % [11]. In contrast, IgG4-SC is very rarely associated with cholangiocarcinoma even considering the paucity of long-term follow-up description in the current literature [12, 13].

The 2015 clinical guideline of the American College of Gastroenterology recommends the measurement of serum IgG4 levels in all patients with possible PSC to exclude IgG4-SC [5]. However, the disease nomenclature of "IgG4"-SC creates somewhat of a dilemma, as the assessment of serum/tissue IgG4, in isolation, does not straightforwardly differentiate IgG4-SC from PSC. Recent research has revealed that 9–26 % of patients with clear-cut PSC also had elevated serum IgG4 levels [8, 14–18]. Moreover, 23 % of the liver explants from patients with PSC who underwent liver transplantation showed periductal infiltration of IgG4-positive plasma cells, despite the absence of any classic histological features of IgG4-SC [18]. On the other hand, some patients with IgG4-SC may show normal levels of serum IgG4, despite the presence of the classic histopathological changes and/or they may show negative IgG4 immunostaining of biopsy specimens [19, 20].

Serum/tissue IgG4 should therefore be interpreted prudently in the appropriate clinical context on the basis of clinical features, biliary imaging, histopathological appearance, and coexistent IgG4-related diseases [2, 6, 21]. A correct diagnosis occasionally requires a constellation of multidisciplinary investigation based on extensive amounts of experience, especially when serum/tissue IgG4 is elevated in a patient with presumed PSC or when IgG4 is normal in a patient with presumed IgG4-SC. The aim of the current study was to develop a simple scoring system that would aid in the discrimination of IgG4-SC from PSC in daily practice. We also wanted to propose a clinical algorithm for distinguishing IgG4-SC from PSC based on our scoring system.

Patients and methods

Patients with IgG4-SC ($n = 39$) and PSC ($n = 76$) who had multifocal intrahepatic/hilar strictures with or without common bile duct (CBD) involvement were included in the study. Patient data were collected from two tertiary academic centers that specialize in biliary and pancreatic diseases (Asan Medical Center and Samsung Medical Center, Seoul, Korea). The study was approved by our institutional review board.

Case ascertainment of PSC

Patients with PSC were collected by a search of the medical records for PSC from January 2001 to December 2013. The diagnosis of PSC was based on (1) elevated alkaline phosphatase and gamma-glutamyltransferase that was otherwise unexplained, (2) the presence of characteristic bile duct changes with multifocal strictures on magnetic resonance cholangiography (MRC) or endoscopic retrograde cholangiography (ERC), and (3) no evidence of SSC [2, 3, 5, 8]. The clinical courses favoring PSC, such as end-stage liver disease needing liver transplantation, were also considered for confirming PSC. Any patient who had a single/localized short stricture, an overt hepatic parenchymal mass, intrabiliary stones or parasites at the initial presentation, small duct PSC, or a history of transarterial chemoembolization was excluded from the study. When elevated serum/tissue IgG4 was found in patients with PSC, comprehensive review of individual patients was performed to exclude IgG4-SC.

Case ascertainment of IgG4-SC

Patients with IgG4-SC were collected from a prospectively maintained autoimmune pancreatitis (AIP)/IgG4-SC database from January 2003 to December 2013. This database of 250 patients with AIP/IgG4-SC contained data for 120 patients with bile duct stricture(s) associated with bile duct wall thickening (Fig. 1). Any patient with an isolated CBD stricture ($n = 81$) was excluded from the study because this feature is generally considered to be a part of AIP rather than a true IgG4-SC [12, 22, 23]. Moreover, PSC is rarely confined to the extrahepatic bile duct alone (<5 %) [3]. Ultimately, this study included a cohort of 39 patients

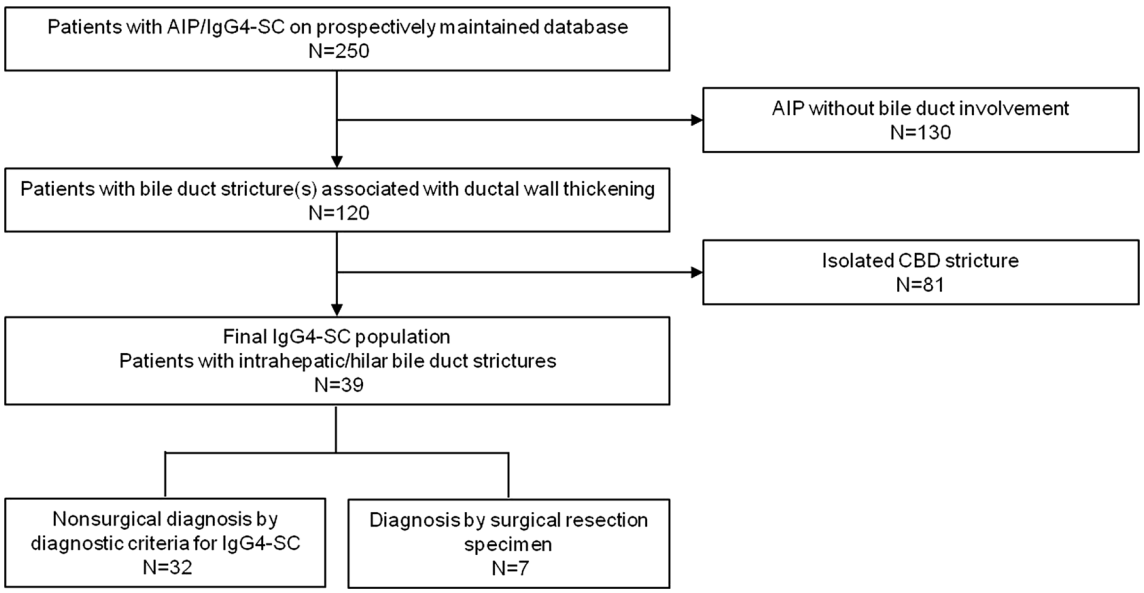

Fig. 1 Flow chart for study population recruitment for IgG4-SC. *IgG4-SC* IgG4-related sclerosing cholangitis, *AIP* autoimmune pancreatitis

with IgG4-SC who had intrahepatic/hilar strictures and who had disease consistent with the Japanese clinical diagnostic criteria [21].

Candidate-differentiating factors between IgG4-SC and PSC

Candidate-differentiating factors for the scoring system were determined on the basis of previous research. Clinical data from chart reviews included the following variables: age of presentation, gender, other organ involvement (OOI), initial manifestations, and coexistent inflammatory bowel disease (IBD). The OOI included possible involvement of previous or concurrent IgG4-related extrabiliary lesions: (1) the pancreas (defined as diffuse or focal enlargement of the pancreas); (2) the kidney (usually multiple renal parenchymal mass lesions including round, wedge-shaped, or diffuse patchy involvement); (3) the salivary gland (evident as symmetrical salivary gland enlargement by physical or radiological examination); and (4) the retroperitoneum (determined as a soft-tissue mass surrounding the abdominal aorta and/or inferior vena cava). The OOI in this study was confined to these four organs because they are most commonly associated IgG4-related extrabiliary lesions, and also located within the scope of abdominal CT scan or detected by physical examination.

Radiological variables included each of the imaging characteristics of PSC and of IgG4-SC based mainly on cholangiography (MRC or ERC). The cholangiographic characteristics of PSC included a beaded appearance (short and annular strictures alternating with normal or minimally dilated segments), a pruned tree appearance (diminished arborization of the intrahepatic ducts and pruning), and diverticulum-like outpouching (outpouching resembling diverticula) [24]. The imaging characteristics favoring IgG4-SC rather than PSC included a long stricture (>10 mm in length) with prestenotic dilatation, a distal CBD stricture appearing as a skipped lesion, and associated extrahepatic bile duct wall thickening (more than 1 mm) extended to suprapancreatic portion [24, 25]. The cholangiographic findings were reviewed in consensus by three gastroenterologists (M.H.K., S.H.M., and T.J.S.) on a picture archiving and communication system. The reviewers were blinded to the diagnosis of PSC/IgG4-SC; however, they had participated in previous patient care.

Positive tissue IgG4 was determined by a consensus statement on the pathology of IgG4-related disease [26]; the cutoff points were (1) 10 IgG4-positive plasma cells per high-power field (HPF) for biopsy from the bile duct, ampulla, and liver, and (2) 50 IgG4-positive plasma cells/HPF for hepatic resection specimens. Positive steroid responsiveness was defined as radiographic resolution or marked improvement in the bile duct strictures and wall thickening after steroid therapy. Biochemical response alone after steroid therapy was not designated as positive steroid responsiveness.

Statistical analysis

Univariate and multivariate logistic regression were performed to predict whether patients were diagnosed with IgG4-SC or PSC. The Hosmer–Lemeshow goodness-of-fit statistic was used to evaluate the agreement between the observed and expected number of patients with IgG4-SC or

PSC across all strata, given the probabilities of having IgG4-SC as estimated from the prediction model. Internal validation was performed using the bootstrap validation algorithm [27]. Bootstrap resampling started by fitting the logistic model in a bootstrap sample of the same number of subjects in the original sample ($n = 115$), which was drawn with replacement from the original sample. The averages of performance measures, explained as a *C* statistic [or the area under the receiver operating characteristic curve (AUC)], were taken over 200 repetitions. We used the selected variables with internal validation to develop a scoring system by adopting the model parameter estimates according to Sullivan et al. [28]. The *C* statistic of the scoring system was calculated to estimate its discriminating ability, while the Hosmer–Lemeshow goodness-of-fit statistic was used to describe the calibration ability. A *p* value less than 0.05 was considered statistically significant and all statistical analyses were done using SPSS version 20.0 (IBM Corp., Armonk, NY, USA) and R 3.0.2 (free software that can be downloaded from http://www.r-project.org) with the packages 'boot' and 'PredictABEL'.

Results

Baseline characteristics

IgG4-SC

The 39 patients with IgG4-SC (35 men, 4 women) ranged in age from 40 to 81 years [median, 61 years; interquartile range (IQR), 50–71 years]. Seven patients were diagnosed with IgG4-SC after surgical resection under a clinical diagnosis of cholangiocarcinoma, whereas the remaining 32 patients were diagnosed on the basis of the diagnostic criteria without the aid of surgery. Most patients (87 %, 34 of 39) had a previous or concurrent IgG4-related disease; this was most frequently AIP (72 %, 28 of 39). Among the five patients with isolated IgG4-SC, four (80 %) needed surgical resection for the diagnosis of IgG4-SC.

The clinical presentations of IgG4-SC were as follows: abdominal pain/discomfort (41 %), jaundice (31 %), asymptomatic cholestatic liver dysfunction (15 %), and weight loss (15 %). No patient had a history of IBD. During a median follow-up of 34 months (range 6–134 months), no patient needed liver transplantation due to hepatic failure occurrence. One patient died from a non-hepatobiliary complication (pneumonia) during follow-up.

The serum IgG4 level was elevated above the upper limit of normal (ULN $\geq$ 135 mg/dL) in 58 % of the patients, and greater than twice the ULN ($\geq$270 mg/dL) in 37 % (Table 1). The serum levels of CA 19-9 were elevated (>37 U/mL) in 31 % of the patients. Positive IgG4 immunostaining was found in 70 % of the biopsy specimens from bile duct/ampulla and in 100 % of the surgical specimens. On a per-person basis, 23 (77 %) of the 30 patients showed positive IgG4 immunostaining. Corticosteroid treatment was given to 31 of 32 IgG4-SC patients who were diagnosed without the aid of surgery. After steroid therapy, all patients showed resolution or marked improvement of bile duct strictures and wall thickening. The one remaining patient with a previous history of autoimmune pancreatitis refused corticosteroid therapy because the symptoms were mild. This patient showed no further abnormality of the liver function test during follow-up.

PSC

The 76 patients with PSC (42 men, 34 women) ranged in age from 18 to 73 years (median, 34 years; IQR 24.5–46.5 years). Thirty-one patients (41 %) had a history of IBD (30 patients, ulcerative colitis; 1 patient, Crohn's disease). Two patients had a history of diffuse pancreatic enlargement, which was eventually diagnosed as drug-induced acute pancreatitis.

The clinical presentations of PSC were as follows: asymptomatic cholestatic liver dysfunction (47 %), abdominal pain/discomfort (29 %), jaundice (13 %), and pruritus (7 %). During a median follow-up of 52 months (range 6–174 months), 15 patients (20 %) underwent liver transplantation due to the occurrence of hepatic failure. Four patients died from hepatic failure: one who did not undergo liver transplantation and three who had undergone liver transplantation. Two additional patients died from pneumonia ($n = 1$) or cholangiocarcinoma ($n = 1$).

The serum IgG4 level was elevated above the ULN in 17 % of the patients, and greater than twice the ULN in 4 %. The serum levels of CA 19-9 were elevated in 11 %. Nineteen PSC patients underwent histopathological examination with IgG4 immunohistochemistry for 22 biopsies—from ampulla, bile duct, or liver—and from six explanted livers. Positive IgG4 immunostaining was found in 18 % of the biopsies, but in 67 % of the surgical specimens. On a per-patient basis, seven patients (37 %) had positive IgG4 immunostaining in any specimen. A trial of corticosteroid therapy was administered to 11 patients, mostly because of the elevated serum/tissue IgG4. However, no patient with PSC showed improvement of biliary strictures after steroid therapy.

Scoring system for differentiating between IgG4-SC and PSC

Univariate logistic regression analysis revealed 12 factors that were significantly associated with a differentiation of

Table 1 Baseline characteristics

Variables	IgG4-SC	PSC	*p* value
Patient number	39	76	
Age (years)[a]	61 (50–71)	34 (24.5–46.5)	<0.0001
Male sex[b]	89.7 % (35/39)	55.3 %(42/76)	0.0002
Elevated serum IgG4 (>ULN)[b]	57.9 % (22/38)	17.0 % (8/47)	0.0001
Positive tissue IgG4[b]	76.7 % (23/30)	36.8 % (7/19)	0.0053
Other organ involvement[b]	87.2 % (34/39)	2.6 % (2/76)[d]	<0.0001
Inflammatory bowel disease[b]	0 % (0/39)	40.8 % (31/76)	<0.0001
Long stricture with prestenotic dilatation[b]	69.2 % (27/39)	21.1 % (16/76)	<0.0001
Distal CBD stricture as a skipped lesion[b]	59.0 % (23/39)	10.5 % (8/76)	<0.0001
Extrahepatic biliary wall thickening (> 1 mm)[b,c]	64.1 % (25/39)	43.4 % (33/76)	0.0357
Beaded appearance[b]	5.1 % (2/39)	56.6 % (43/76)	<0.0001
Pruned tree appearance[b]	12.8 % (5/39)	30.3 % (23/76)	0.0357
Diverticulum-like outpouching[b]	2.6 % (1/39)	10.5 % (8/76)	0.1323
Positive ANA[b]	16.7 % (4/24)	27.1 % (16/59)	0.1189
Positive ANCA[b]	8.3 % (1/12)	53.1 % (26/49)	0.0002
AST (IU/L)[a]	59 (37–87)	64.5 (36.5–106.5)	0.5726
ALT (IU/L)[a]	78 (35–144)	73 (36–139)	0.9929
ALP (U/L)[a]	293 (127–377)	366 (184–615.5)	0.019
Bilirubin (mg/dL)[a]	1.2 (0.8–4.9)	1.2 (0.7–2.55)	0.4614
CA 19-9 (U/mL)[a]	18.5 (7.6–42.9)	19.5 (8.2–30.1)	0.6961

IgG4-SC IgG4-related sclerosing cholangitis, *PSC* primary sclerosing cholangitis, *CI* confidence interval, *ULN* upper limit of normal, *ANA* antinuclear antibody, *ANCA* antineutrophil cytoplasmic antibody, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CA 19-9* carbohydrate antigen 19-9

[a] Data are presented as median (interquartile range)

[b] Data are presented as percentage (number of positive result/number of total patient)

[c] Extrahepatic biliary wall thickening (>1 mm) extended to suprapancreatic portion

[d] Two patients had a history of diffuse pancreatic swelling. These events were diagnosed as drug-induced acute pancreatitis and not associated with true IgG4-related disease

IgG4-SC from PSC (Supplementary Table 1). On multivariate logistic regression analysis, OOI, a beaded appearance, and patient age were selected for our predictive model by stepwise elimination (Supplementary Table 2). Excellent discrimination between IgG4-SC and PSC was obtained in our cohort using this predictive model ($C = 0.989$). Internal validation using the bootstrap method gave an excellent optimism-corrected AUC ($C = 0.9895$).

Scores of variables were assigned to each of the three factors according to the estimated regression unit in the final model (Supplementary Table 3): OOI (yes, 3 points; no, 0 points), beaded appearance on cholangiography (yes, 0 points; no, 2 points), and age (<30 years, 0 points; 30–39 years, 1 point; 40–49 years, 2 points; 50–59 years, 3 points; ≥60 years, 4 points). A diagnostic scoring system, designated as the Kim score, was defined as the sum of each score. The patients were classified according to their Kim scores into three categories: 0–4 points, probable PSC; 5–6 points, indicating diagnostic steroid trial; 7–9 points, probable IgG4-SC (Table 2). A Hosmer–Lemeshow goodness-of-fit statistic of the scoring system showed a good fit ($p = 0.9859$), indicating good calibration of the model. The distribution of patients according to Kim scores is shown in Supplementary Table 4. The discrimination between IgG4-SC and PSC using the scoring system was excellent ($C = 0.986$; Supplementary Fig. 1). Even in IgG4-SC patients with normal serum IgG4 levels or in PSC patients with elevated serum IgG4 levels, our scoring system consistently stratified patients into three groups (Table 3).

Proposal of strategy for patients presenting with multifocal intrahepatic/hilar biliary strictures, with a focus on distinguishing IgG4-SC from PSC

On the basis of the developed scoring system, we propose a clinical algorithm for patients with multifocal intrahepatic/hilar biliary strictures, with a focus on the differentiation between IgG4-SC and PSC (Fig. 2). The exclusion of cholangiocarcinoma is the step of utmost importance, because some imaging features of IgG4-SC overlap those of cholangiocarcinoma and PSC is associated with a

Table 2 New scoring system for the differentiation of IgG4-SC and PSC

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 scores	Diagnosis	
0–4	Probable PSC	
5–6	Indicating diagnostic steroid trial	
7–9	Probable IgG4-SC	

Other organ involvement includes the presence of IgG4-related extrabiliary lesions

This scoring system can be used in patients who have intrahepatic/hilar stricture after exclusion of cholangiocarcinoma or other secondary sclerosing cholangitis

potential risk of cholangiocarcinoma. An endobiliary biopsy should be routinely performed at the time of endoscopic retrograde cholangiopancreatography (ERCP) in the setting of obstructive jaundice/cholangitis, or dominant stricture. A liver biopsy can be performed in the presence of a tumefactive periductal nodule/mass. Serum CA 19-9 should be serially measured at baseline and during follow-up. Evident SSC can be excluded by personalized evaluation given the array of secondary etiologies, starting with careful listening to the patient's history [29].

In the next stage of evaluation, patients should undergo serum IgG4 measurement. If serum IgG4 level shows elevation greater than twofold, a steroid trial (steroid use as a diagnostic trial) is indicated. If serum IgG4 level shows normal or elevation less than twofold, our scoring system is applied to these patients (Fig. 3). Steroid responsiveness should be assessed on the basis of follow-up imaging and CA 19-9 level. When a diagnostic steroid trial results in no response on imaging, an endobiliary/liver biopsy with IgG4 immunostaining could be considered. When serum CA 19-9 rises even after biliary decompression, cholangiocarcinoma should be differentiated by means of a meticulous rebiopsy.

Discussion

The emergence of the new disease entity of "steroid-responsive" IgG4-SC has made diagnosis of PSC more challenging and critical for clinicians because of the vast difference in treatment modalities and prognosis between these two sclerosing cholangiopathies. The increased awareness of IgG4-SC may lead to its early recognition and management with corticosteroids, and can eventually prevent organ failure that could possibly result from a delayed diagnosis. On the contrary, a misclassification of PSC as IgG4-SC may result in inadvertent corticosteroid treatment and delay the optimal surveillance [8]. Differential

Table 3 Distribution of patients according to scoring system

	IgG4-SC ($n = 39$)	IgG4-SC with normal serum IgG4 ($n = 16$)	PSC ($n = 76$)	PSC with elevated serum IgG4 ($n = 8$)
Total score				
0	0 (0 %)	0 (0 %)	17 (22.4 %)	0 (0 %)
1	0 (0 %)	0 (0 %)	11 (14.5 %)	0 (0 %)
2	0 (0 %)	0 (0 %)	18 (23.7 %)	3 (37.5 %)
3	0 (0 %)	0 (0 %)	7 (9.2 %)	2 (25.0 %)
4	1 (2.6 %)	1 (6.3 %)	14 (18.4 %)	2 (25.0 %)
5	4 (10.3 %)	2 (12.5 %)	6 (7.9 %)	1 (12.5 %)
6	1 (2.6 %)	0 (0 %)	3 (3.9 %)	0 (0 %)
7	9 (23.1 %)	6 (37.5 %)	0 (0 %)	0 (0 %)
8	5 (12.8 %)	1 (6.3 %)	0 (0 %)	0 (0 %)
9	19 (48.7 %)	6 (37.5 %)	0 (0 %)	0 (0 %)
Score categories				
0–4	1 (2.6 %)	1 (6.3 %)	67 (88.2 %)	7 (87.5 %)
5–6	5 (12.8 %)	2 (12.5 %)	9 (11.8 %)	1 (12.5 %)
7–9	33 (84.6 %)	13 (81.3 %)	0 (0 %)	0 (0 %)

IgG4-SC IgG4-related sclerosing cholangitis, *PSC* primary sclerosing cholangitis

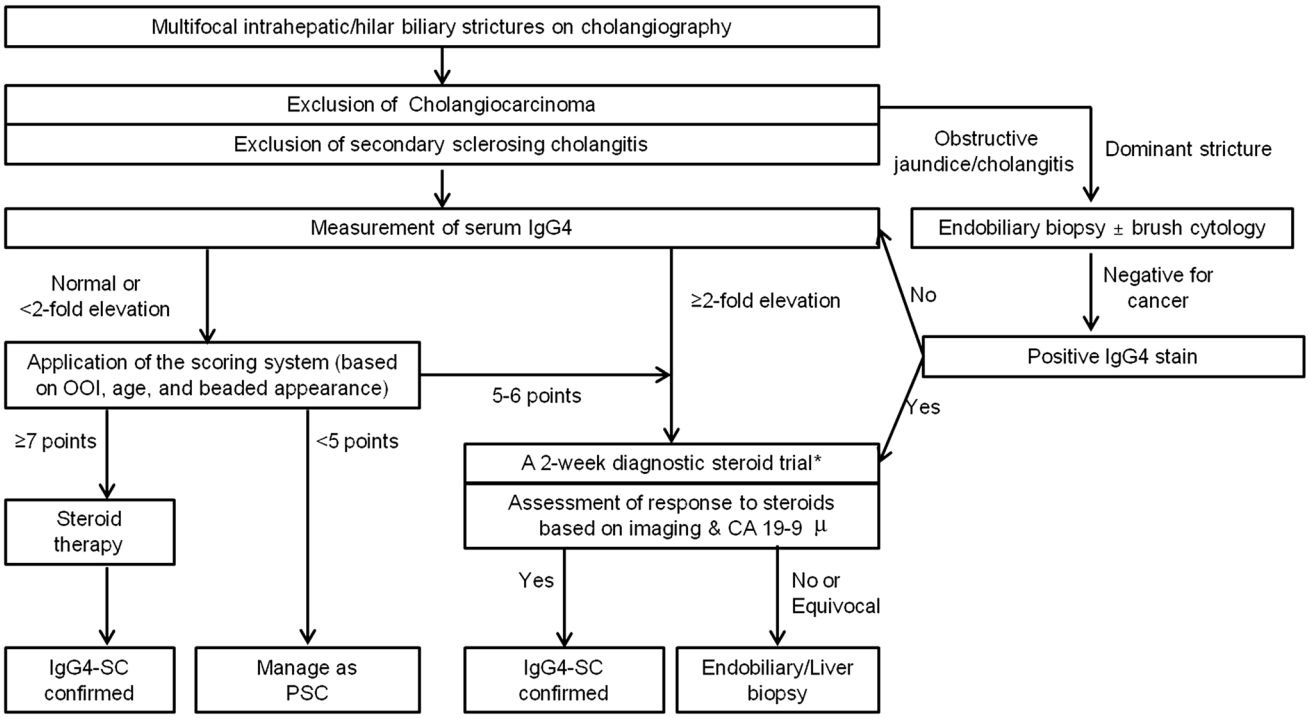

Fig. 2 Clinical algorithm for distinguishing IgG4-SC from PSC. *IgG4-SC* IgG4-related sclerosing cholangitis, *AIP* autoimmune pancreatitis, *OOI* other organ involvement (presence of IgG4-related extrabiliary lesions). *Prednisone 0.6–1.0 mg/kg × 2 weeks. *μ*: response to steroids should be evaluated at a minimum by cross-sectional imaging, cholangiography, and follow-up of serum CA 19-9. When serum CA 19-9 increases even after biliary decompression, cholangiocarcinoma should be differentiated by means of a meticulous rebiopsy

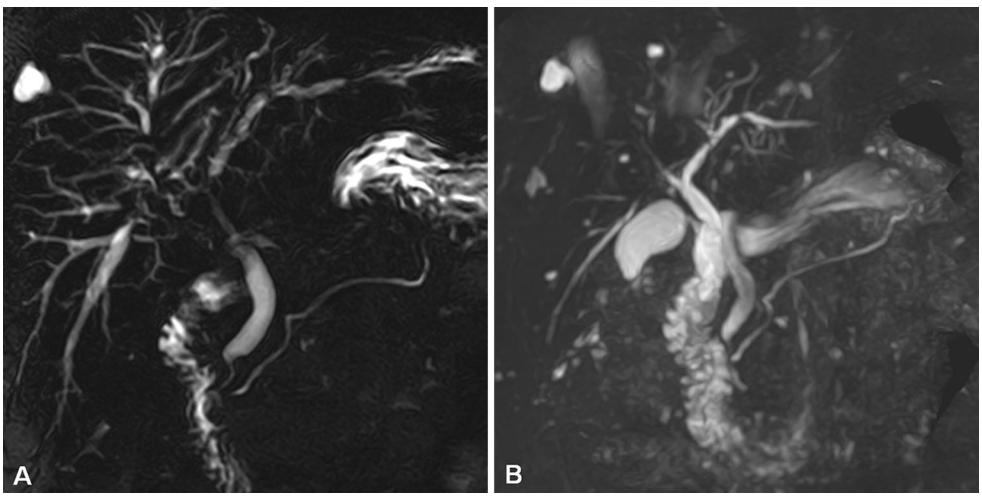

Fig. 3 Serial images from a 79-year-old woman with serum IgG4 level of 136 mg/dL and the Kim score of 6 points (age 4 points, other organ involvement 0 points, and absence of beaded appearance 2 points) who was finally diagnosed as having IgG4-related sclerosing cholangitis after a diagnostic steroid trial. **a** Pretreatment: magnetic resonance cholangiopancreatography showed multifocal intrahepatic/hilar bile duct strictures. **b** Post-treatment: after the 2-week steroid trial, hilar/intrahepatic bile duct strictures improved to almost normal

diagnosis between these two diseases can be confusing because of their similar manifestations, such as male predominance, cholestatic liver dysfunction of unknown etiology, and frequent stenosis of both the intrahepatic and extrahepatic bile ducts [1, 3, 4, 10, 12]. Our study suggested an algorithm to differentiate between IgG4-SC and PSC based on a scoring system using patient age, OOI, and a beaded appearance on cholangiography.

The Western literature indicates that PSC tends to be a disease of young adults and middle-aged persons [4]. The

median age at diagnosis for PSC ranged from 35 to 41 years in Western countries [14, 30, 31]. Interestingly, a Japanese nationwide survey for PSC demonstrated two unique peaks in age distribution (the first at 35–40 years and the second at 65–70 years) [17]. The age distribution of our Korean patients with PSC corresponded to that of the Western population, rather than the Japanese population, as our patients had a median age of 34 years and showed no second peak at older age. One plausible explanation for this discrepancy between Japan and Korea is that many older patients diagnosed with PSC in Japan might actually represent IgG4-SC patients, because the nationwide survey included various gastroenterologists with varying experience in PSC/IgG4-SC [17, 32].

IgG4-SC tends to present at an older age than is observed with PSC. The age of presentation in IgG4-SC is mostly over 50 years, with a median age of 59–69 years [10, 17, 33, 34]. In contrast, very few cases have been reported in young adults less than 40 years of age (0–10 %) [17, 33]. Our study confirmed this result, as most of our patients with IgG4-SC (77 %) were older than 50 years, whereas none were younger than 40 years. Taken together, these differences in age distribution partitioned the patients with sclerosing cholangitis who were under the age of 40 years and without an evident secondary cause as almost always PSC, whereas a patient age more than 60 years favored IgG4-SC. Our scoring system incorporated this age factor with a range from 0 to 4 points, as this differences in age of presentation plays a big role in the differentiation.

IgG4-SC lies within a spectrum of IgG4-related disease, with the pancreas most commonly involved. According to the literature, AIP was associated with 87–100 % of the IgG4-SC patient population [10, 33, 35, 36]. This association with AIP was relatively low in our IgG4-SC patients (72 %), most likely because our study excluded 81 AIP patients with CBD stricture alone. The definition of IgG4-SC can affect the number and characteristics of the study population whether isolated CBD stricture is included or not. Our patients with IgG4-SC are a relatively large population, when considering that our IgG4-SC group did not include isolated CBD stricture. Unlike IgG4-SC, PSC is seldom associated with pancreatic involvement [17, 37]. Although two of our PSC patients had a history of pancreatic enlargement, this appeared to be drug-induced pancreatitis, rather than a true association with the pancreas. Multifocal biliary strictures that coexist with evident IgG4-related disease may lead to a straightforward diagnosis of IgG4-SC, whereas diagnosis of isolated IgG4-SC needs endobiliary biopsy and steroid trial for nonoperative diagnosis [38]. Our scoring system gave other organ involvement of IgG4-related disease a value of 3 points.

Characteristic cholangiographic features may allow discrimination of IgG4-SC from PSC [24, 39]. Beaded appearance, diverticulum-like outpouching, and pruned tree appearance are typical for PSC, whereas distal CBD stricture, longer stricture, and more prestenotic dilatation favor IgG4-SC [20, 24, 39]. However, typical cholangiographic features of PSC are usually found in less than 50 % of PSC patients [40]. Cholangiographic criteria could also be observer-dependent; a beaded appearance is determined by subjective assessment and a pruned tree appearance is affected by the pressure of injected contrast. Actually, a previous blinded multicenter study, which tested 17 worldwide specialists, revealed a poor sensitivity (45 %), high specificity (88 %), and slight interobserver agreement (kappa 0.18) for the diagnosis of IgG4-SC [41]. This poor sensitivity of the ERC findings for the diagnosis of IgG4-SC suggests that many patients with IgG4-SC may be misdiagnosed with PSC or cholangiocarcinoma. Our data showed that beaded appearance and pruned tree appearance were characteristics of PSC, whereas a long stricture with prestenotic dilatation and skipped distal CBD stricture were characteristics of IgG4-SC. Our multivariate analysis supported the inclusion of the beaded appearance in our scoring system, with a value of 2 points.

The recent guidelines suggested measuring serum IgG4 levels to exclude IgG4-SC for all patients with possible PSC [3, 5]. However, the IgG4 molecule is not specific for IgG4-SC, as recent research has demonstrated that 9–26 % of clear-cut PSC cases showed elevated serum IgG4 levels [8, 14–18, 42]. Our study confirmed this finding, as 17 % of our PSC patients had elevated serum IgG4 levels. An elevation of the cutoff value used for serum IgG4 levels could increase the specificity for diagnosing IgG4-SC [36], but this could resultantly decrease its current sensitivities of 74–90 % [8, 10, 17]. The serum IgG4 level alone, therefore, cannot be used specifically to discriminate IgG4-SC from PSC.

IgG4 immunostaining of a bile duct/liver biopsy specimen can be used to support the diagnosis of IgG4-SC [38]. The small sample size and possible patchy involvement, however, can result in variable sensitivities of IgG4 immunostaining in biopsies, which can range from 18 to 88 % [20]. Our data confirmed the moderate sensitivity (70 %) of IgG4 immunostaining of biopsies in IgG4-SC patients. Recent research demonstrated cases of PSC with tissue IgG4 positivity in 17 % of the biopsy specimens and 23 % of the liver explants [18, 43]. Our data confirmed this tissue IgG4 positivity of PSC, as 18 % of our biopsies showed positive IgG4 immunostaining. Isolated findings of increased tissue IgG4 therefore should not be used for the differentiation of IgG4-SC from PSC. Moreover, endobiliary biopsy with endoscopic retrograde cholangiopancreatography is not mandatory for all cases with multifocal biliary stricture in this era of magnetic resonance cholangiopancreatography [44]. We recommend an endobiliary

biopsy in the setting of obstructive jaundice, dominant stricture, or suspected isolated IgG4-SC.

The majority of PSC patients have concomitant IBD, at a rate of 60–80 % in Western countries [4, 5, 37, 40] and 30–50 % in Japan [13]. The coexistence of IBD in our Korean patients with PSC corresponded to that of the Japanese population, as 41 % of our PSC patients had IBD. In contrast, IBD is seldom associated with IgG4-SC patients (0–10 %) [10, 33, 35, 36]. Our IgG4-SC patients also had no coexistent IBD. The presence of IBD may therefore favor the diagnosis of PSC. Although our results did not incorporate the coexistent IBD in the scoring system, enrichment of the study populations with more coexistent IBD would likely influence the statistical significance.

Steroid responsiveness may deserve to be used as an important diagnostic tool, since the biliary stricture of IgG4-SC responds to corticosteroid therapy, while that of PSC does not [6, 12, 38]. Although the current guidelines state that corticosteroid treatment has not demonstrated any improvement in disease activity or in the outcome of classic PSC [2, 3, 5], some researchers have argued that a small portion of PSC patients show positive steroid responsiveness [15, 45–47]. A literature analysis of the cited research shows that the reported positive steroid responsiveness of PSC is mostly a biochemical response, occurring especially in patients with overlap syndrome [15, 45–47]. A radiographic response of the biliary strictures to corticosteroids, therefore, is extremely indicative of IgG4-SC; however, the inverse of this statement is not always true. This is because burnt-out IgG4-SC may not show steroid responsiveness [12, 48] and some IgG4-SC that is refractory to steroids may respond to rituximab. In addition, 2 or 3 weeks of steroids treatment may not adversely affect the overall outcome of steroid-administered PSC patients. On the basis of our scoring system, we recommend a diagnostic steroid trial in patients with Kim scores of 5 or 6 points, whereas we recommend a steroid therapy in patients with Kim scores of 7 points or more.

Recent research used new modalities such as serum IgG1, intraductal ultrasonography, or bile IgG4 for more accurate differentiation of IgG4-SC from PSC [8, 49, 50]. In contrast, our scoring system adopts three factors commonly assessed in workups for differentiation between IgG4-SC and PSC: OOI, beaded appearance, and patient age. Our scoring system does not adopt the use of serum IgG4 per se; nevertheless, we recommend measurement of serum IgG4 levels in all patients with possible PSC (Fig. 2). The basis for the inclusion of serum IgG4 in our algorithm is as follows. First, current PSC guidelines recommend the measurement of serum IgG4 in all patients with possible PSC [3, 5], and measuring serum IgG4 is very simple. Second, serum IgG4 is one of the diagnostic criteria for IgG4-SC and for extrabiliary IgG4-related disease. Lastly, patients showing an elevation of serum IgG4 to a level more than two twice the ULN might benefit from a short-term steroid trial. Moreover, accumulation of the data for PSC with elevated serum IgG4 might contribute to the future clinical guidelines for PSC.

One limitation of this study is that our cohorts do not include any SSCs other than IgG4-SC. Our scoring system therefore may only be useful for the differentiation of IgG4-SC from PSC after the exclusion of evident SSCs. The relatively small population with PSC is another limitation of our study. Clinicians must also be aware that our scoring system cannot discriminate cholangiocarcinoma from IgG4-SC and must remember that cholangiocarcinoma is a much more common disease than PSC or IgG4-SC. Actually, cholangiocarcinomas (excluding distal common bile duct cancer) were diagnosed in 7948 patients, and 1628 patients underwent major hepatobiliary surgery for cholangiocarcinoma during the study period. The thorough exclusion of cholangiocarcinoma by liver/endobiliary biopsy should be emphasized in cases with any features suspicious of cholangiocarcinoma, such as rising serum CA 19-9, tumefactive liver nodule/mass, dominant stricture, obstructive jaundice, and asymmetric/irregular bile duct wall thickening.

In conclusion, we established a scoring system for differentiating IgG4-SC from PSC that can be readily applied in clinical practice, with the incorporation of OOI, beaded appearance, and patient age. The scoring system defined the indications for diagnostic steroid trial for the differentiation of IgG4-SC from PSC. Our suggested algorithm based on the scoring system and steroid trial may reliably differentiate IgG4-SC from PSC in clinical practice. However, cholangiocarcinoma is the important differential diagnosis, even in the setting of multifocal intrahepatic/hilar biliary strictures. External validation of our scoring system is now warranted.

Compliance with ethical standards

Funding No financial or other support was granted for this study.

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

References

1. Karlsen TH, Boberg KM. Update on primary sclerosing cholangitis. J Hepatol. 2013;59:571–82.
2. European Association for the Study of the Liver. EASL clinical practice guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51:237–67.
3. Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51:660–78.

4. Hirschfield GM, Karlsen TH, Lindor KD, et al. Primary sclerosing cholangitis. Lancet. 2013;382:1587–99.
5. Lindor KD, Kowdley KV, Harrison ME. ACG Clinical Guideline: primary sclerosing cholangitis. Am J Gastroenterol. 2015;110:646–59.
6. Okazaki K, Uchida K, Koyabu M, et al. IgG4 cholangiopathy—current concept, diagnosis, and pathogenesis. J Hepatol. 2014;61:690–5.
7. Ponsioen CY. Diagnosis, differential diagnosis, and epidemiology of primary sclerosing cholangitis. Dig Dis. 2015;33(Suppl 2):134–9.
8. Boonstra K, Culver EL, de Buy Wenniger LM, et al. Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. Hepatology. 2014;59:1954–63.
9. Culver EL, Chapman RW. Systematic review: management options for primary sclerosing cholangitis and its variant forms—IgG4-associated cholangitis and overlap with autoimmune hepatitis. Aliment Pharmacol Ther. 2011;33:1273–91.
10. Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology. 2008;134:706–15.
11. Bonato G, Cristoferi L, Strazzabosco M, et al. Malignancies in primary sclerosing cholangitis—a continuing threat. Dig Dis. 2015;33(Suppl 2):140–8.
12. Bjornsson E, Chari ST, Smyrk TC, et al. Immunoglobulin G4 associated cholangitis: description of an emerging clinical entity based on review of the literature. Hepatology. 2007;45:1547–54.
13. Takikawa H, Takamori Y, Tanaka A, et al. Analysis of 388 cases of primary sclerosing cholangitis in Japan; presence of a subgroup without pancreatic involvement in older patients. Hepatol Res. 2004;29:153–9.
14. de Valle MB, Muller T, Bjornsson E, et al. The impact of elevated serum IgG4 levels in patients with primary sclerosing cholangitis. Dig Liver Dis. 2014;46:903–8.
15. Bjornsson E, Chari S, Silveira M, et al. Primary sclerosing cholangitis associated with elevated immunoglobulin G4: clinical characteristics and response to therapy. Am J Ther. 2011;18:198–205.
16. Mendes FD, Jorgensen R, Keach J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol. 2006;101:2070–5.
17. Tanaka A, Tazuma S, Okazaki K, et al. Nationwide survey for primary sclerosing cholangitis and IgG4-related sclerosing cholangitis in Japan. J Hepatobiliary Pancreat Sci. 2014;21:43–50.
18. Zhang L, Lewis JT, Abraham SC, et al. IgG4+ plasma cell infiltrates in liver explants with primary sclerosing cholangitis. Am J Surg Pathol. 2010;34:88–94.
19. Deheragoda MG, Church NI, Rodriguez-Justo M, et al. The use of immunoglobulin g4 immunostaining in diagnosing pancreatic and extrapancreatic involvement in autoimmune pancreatitis. Clin Gastroenterol Hepatol. 2007;5:1229–34.
20. Moon SH, Kim MH. The role of endoscopy in the diagnosis of autoimmune pancreatitis. Gastrointest Endosc. 2012;76:645–56.
21. Ohara H, Okazaki K, Tsubouchi H, et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci. 2012;19:536–42.
22. Park DH, Kim MH. Intrapancreatic common bile duct involvement of autoimmune pancreatitis: is it really IgG4-associated cholangitis? Gastroenterology. 2008;135:324–5.
23. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol. 2006;4:1010–6 (quiz 934).
24. Nakazawa T, Ohara H, Sano H, et al. Cholangiography can discriminate sclerosing cholangitis with autoimmune pancreatitis from primary sclerosing cholangitis. Gastrointest Endosc. 2004;60:937–44.
25. Kim JH, Byun JH, Kim SY, et al. Sclerosing cholangitis with autoimmune pancreatitis versus primary sclerosing cholangitis: comparison on endoscopic retrograde cholangiography, MR cholangiography, CT, and MRI. Acta Radiol. 2013;54:601–7.
26. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25:1181–92.
27. Steyerberg EW, Harrell FE Jr, Borsboom GJ, et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54:774–81.
28. Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: the Framingham study risk score functions. Stat Med. 2004;23:1631–60.
29. Abdalian R, Heathcote EJ. Sclerosing cholangitis: a focus on secondary causes. Hepatology. 2006;44:1063–74.
30. Boonstra K, Weersma RK, van Erpecum KJ, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology. 2013;58:2045–55.
31. Molodecky NA, Kareemi H, Parab R, et al. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. Hepatology. 2011;53:1590–9.
32. Kamisawa T, Egawa N, Tsuruta K, et al. Primary sclerosing cholangitis may be overestimated in Japan. J Gastroenterol. 2005;40:318–9.
33. van Buuren HR, Vleggaar FP, Willemien Erkelens G, et al. Autoimmune pancreatocholangitis: a series of ten patients. Scand J Gastroenterol. 2006;41(Suppl 243):70–8.
34. Beuers U, Hubers LM, Doorenspleet M, et al. IgG4-associated cholangitis—a mimic of PSC. Dig Dis. 2015;33(Suppl 2):176–80.
35. Huggett MT, Culver EL, Kumar M, et al. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. Am J Gastroenterol. 2014;109:1675–83.
36. Ohara H, Nakazawa T, Kawa S, et al. Establishment of a serum IgG4 cut-off value for the differential diagnosis of IgG4-related sclerosing cholangitis: a Japanese cohort. J Gastroenterol Hepatol. 2013;28:1247–51.
37. Eaton JE, Talwalkar JA, Lazaridis KN, et al. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. Gastroenterology. 2013;145:521–36.
38. Kamisawa T, Zen Y, Pillai S, et al. IgG4-related disease. Lancet. 2015;385:1460–71.
39. Nakazawa T, Naitoh I, Hayashi K, et al. Diagnostic criteria for IgG4-related sclerosing cholangitis based on cholangiographic classification. J Gastroenterol. 2012;47:79–87.
40. Ponsioen CY, Vrouenraets SM, Prawirodirdjo W, et al. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. Gut. 2002;51:562–6.
41. Kalaitzakis E, Levy M, Kamisawa T, et al. Endoscopic retrograde cholangiography does not reliably distinguish IgG4-associated cholangitis from primary sclerosing cholangitis or cholangiocarcinoma. Clin Gastroenterol Hepatol. 2011;9(800–3):e2.
42. Parhizkar B, Mohammad Alizadeh AH, Asadzadeh Aghdaee H, Malekpour H, Entezari AH. Primary sclerosing cholangitis associated with elevated immunoglobulin-G4: a preliminary study. ISRN Gastroenterol. 2012;2012:325743.
43. Kawakami H, Zen Y, Kuwatani M, et al. IgG4-related sclerosing cholangitis and autoimmune pancreatitis: histological assessment of biopsies from Vater's ampulla and the bile duct. J Gastroenterol Hepatol. 2010;25:1648–55.
44. Dave M, Elmunzer BJ, Dwamena BA, et al. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. Radiology. 2010;256:387–96.

45. Boberg KM, Chapman RW, Hirschfield GM, et al. Overlap syndromes: the international autoimmune hepatitis group (IAIHG) position statement on a controversial issue. J Hepatol. 2011;54:374–85.
46. Parkes M, Booth JC, Pillai G, et al. Do steroids help jaundice caused by primary sclerosing cholangitis? J Clin Gastroenterol. 2001;33:319–22.
47. Zenouzi R, Lohse AW. Long-term outcome in PSC/AIH "overlap syndrome": does immunosuppression also treat the PSC component? J Hepatol. 2014;61:1189–91.
48. Nakazawa T, Naitoh I, Ando T, et al. A case of advanced-stage sclerosing cholangitis with autoimmune pancreatitis not responsive to steroid therapy. JOP. 2010;11:58–60.
49. Vosskuhl K, Negm AA, Framke T, et al. Measurement of IgG4 in bile: a new approach for the diagnosis of IgG4-associated cholangiopathy. Endoscopy. 2012;44:48–52.
50. Naitoh I, Nakazawa T, Hayashi K, et al. Comparison of intraductal ultrasonography findings between primary sclerosing cholangitis and IgG4-related sclerosing cholangitis. J Gastroenterol Hepatol. 2015;30:1104–9.