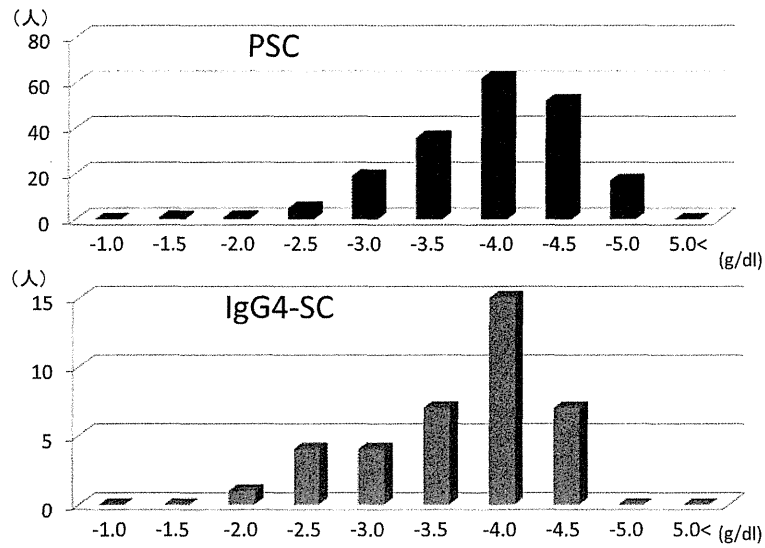


図２　PSC・IgG4-SC の血清アルブミン値の分布

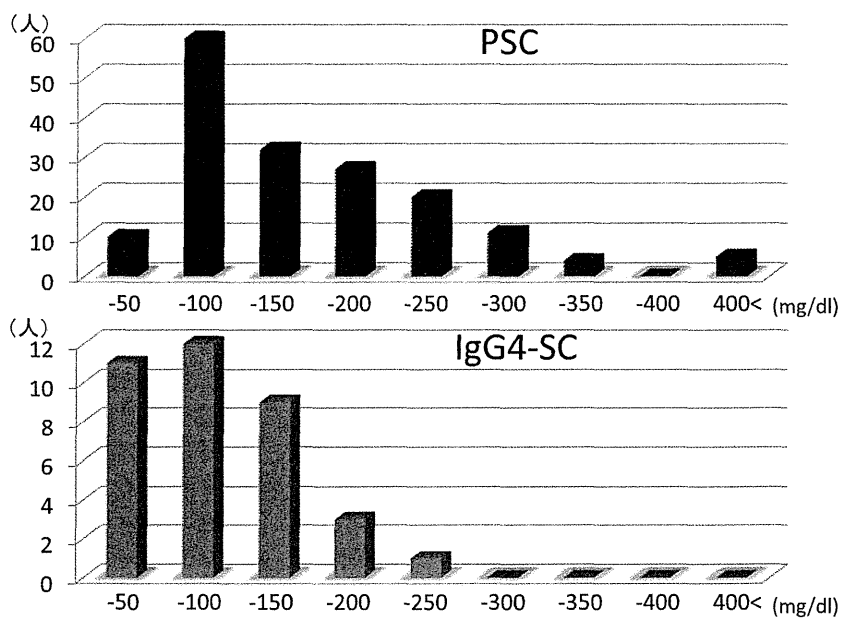


図３　PSC・IgG4-SC の血清 IgM 値の分布

われていた．PSC の Ludwig 分類では，I 期・II 期・III 期・IV 期それぞれ，24 例・23 例・18 例・5 例であった．IgG4-SC の胆管像分類では，今回 AIP を合併していない症例を対象としたこともあり，Type I～Type III は比較的少数であり，Type IV がもっとも高頻度であった（43 例中 22 例，51%）（図 7）．

**PSC の合併症**

PSC における炎症性腸疾患（inflammatory bowel diseases；IBD）の有無については，IBD の合併ありとの回答は 68 例で，PSC 全体の 34% にとどまっていた（図 8）．大腸内視鏡検査（colonofiberscopy；CF）を施行した上で IBD が確認されなかった症例は 46 例（23%），

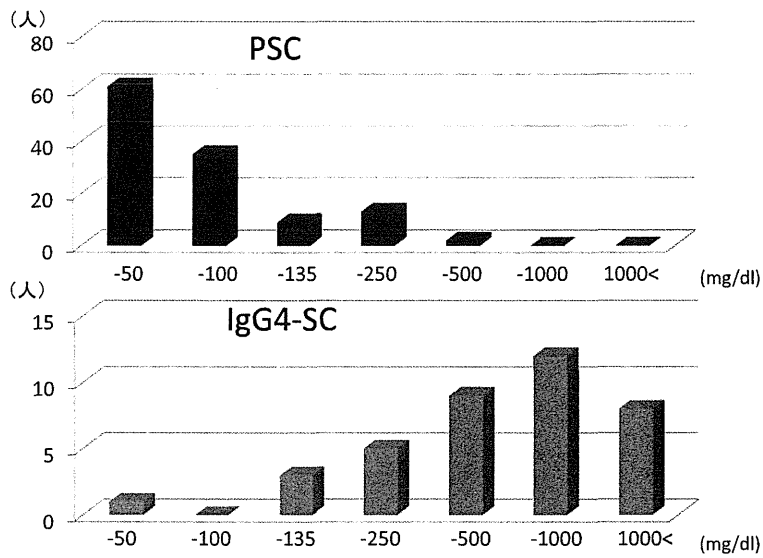


図4　PSC・IgG4-SCの血清IgG4値の分布

表2　PSCとIgG4-SCにおける血清IgG4値の比較

| | PSC | IgG4-SC |
|---|---|---|
| ≦135mg/dl | 105 | 4 |
| ＞135mg/dl | 15 | 34 |

CFを行わずIBDなしとした症例が41例(21%)であった．IBDの具体的な診断名は，潰瘍性大腸炎（ulcerative colitis；UC)が55例，非特異性腸炎が10例，記載のなかったものが3例であった．その他PSCの合併症として肝胆道系疾患および結腸癌について回答を求めたところ，胆管細胞癌が14例（7.3%），胆嚢・胆管結石36例（19%），胆嚢ポリープ3例（2%），結腸癌4例（2%）であった．胆嚢癌の合併例はなかった．PSCとの診断から胆管細胞癌との診断までの期間の分布を図9に示す．胆管癌発症時期の記載のあった13例のうち，11例ではPSCとの診断後1年以内に胆管細胞癌の診断がなされていた．結腸癌4例のうち，2例はUCを合併していたが，1例はCFを施行した上でIBD合併なし，1例はCF施行なしでIBD合併なしとの症例であった．

**IgG4-SCの合併症**

IgG4-SCの合併症としては，IgG4関連疾患である涙腺・唾液腺炎，および後腹膜線維症がそれぞれ6例(14%)，4例（9%）に合併していた．胆嚢・胆管結石と胆嚢ポリープはそれぞれ1例のみ，胆道系悪性腫瘍の合併はなかった．

**薬物治療**

PSCでは，197例のうち159例(81%)で何らかの薬物治療がなされているという記載があった(表3)．もっとも高頻度だったのはウルソデオキシコール酸(ursodeoxycholic acid；UDCA）単独投与であり，次いでUDCA＋ベザフィブラート併用であったが，UDCA＋ステロイドがその次に多かった．UDCAはPSC全体のうち150例（76%）で使用されており，ステロイドは40例(20%)，ベザフィブラートは39例(20%)であった．ただし，ステロイド投与40例のうち18例はUCを合併していた．

IgG4-SCについては，薬物治療についての回答のあった36例中27例（75%）でステロイドが投与されていた．初期投与量は30mgが最も多く20例，40mgが5例，15mgとミニパルスとの回答が各1例であった．治療効果は，記載のあった23例全例で「あり」という回答であった．

**内視鏡的治療**

PSCでは24例で内視鏡的胆管拡張術，46例でステント挿入が行われ，内視鏡的治療効果について記載された52例中39例で良好な結果であった．一方IgG4-SCでも4例で胆管拡張術，15例でステント挿入がなされ，14例中12例で結果は良好と記載されていた（表4)．

**予後**

2005年以降の診断例に限定したこともあり，今回集

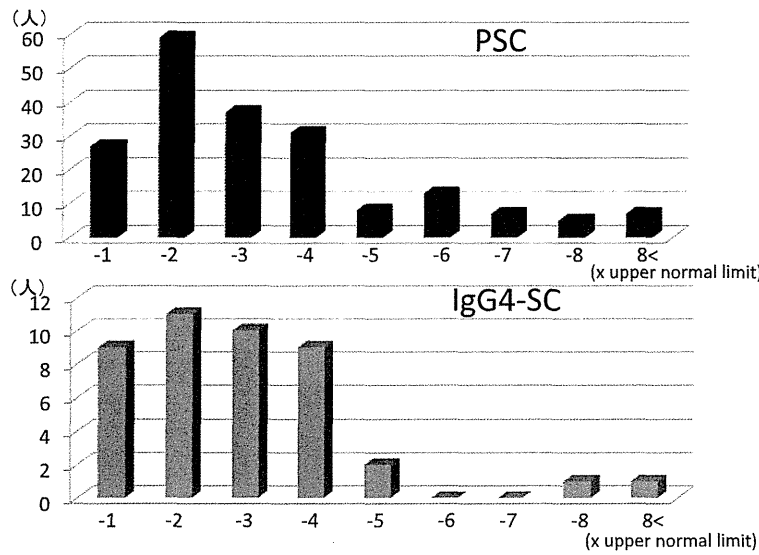


図5　PSC・IgG4-SC の血清 ALP 値の分布

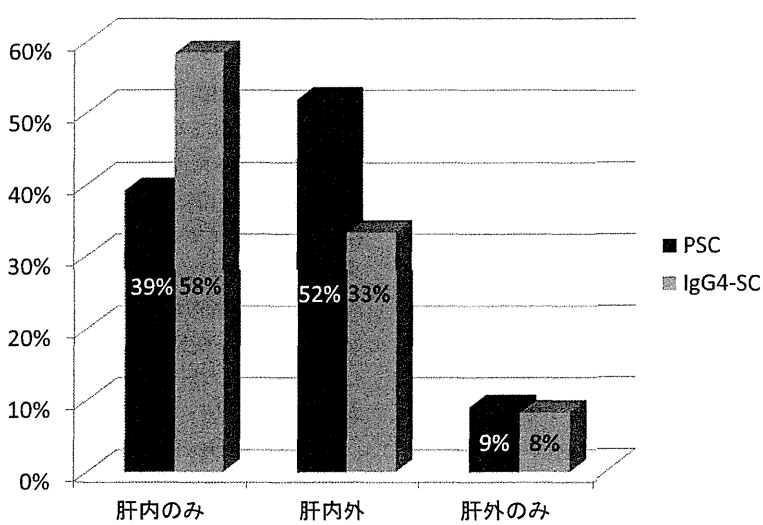


図6　PSC・IgG4-SC の病変部位

積された症例の平均観察期間は比較的短く，PSC では 2.74±2.00 年，IgG4-SC では 2.29±1.80 年であった．PSC の累積生存曲線を図 10A に示す．3 年生存率は 85.0%，5 年生存率は 71.5% であった．肝移植は PSC 197 例中 20 例で施行されており，エンドポイントを死亡＋肝移植とした場合の生存曲線を図 10B に示す．この場合 3 年生存率は 77.3%，5 年生存率は 66.0% となった．一方 IgG4-SC ではもともと症例数が少ないため 5 年生存率の計算はできないが，3 年生存率は 90.0% となった（図 10C）．最終転帰確認時に死亡と報告された症例は 3 例であり，診断時からの経過年数および死因は，それぞれ 0.7 年（乳房外 Paget 病），1.4 年（膵癌），1.7 年（感染症）であった．

## 考　察

今回の全国調査では PSC 197 例，AIP を合併していない IgG4-SC 43 例が集積された．われわれが行った前々回・前回の PSC 全国調査ではそれぞれ 192 例・388

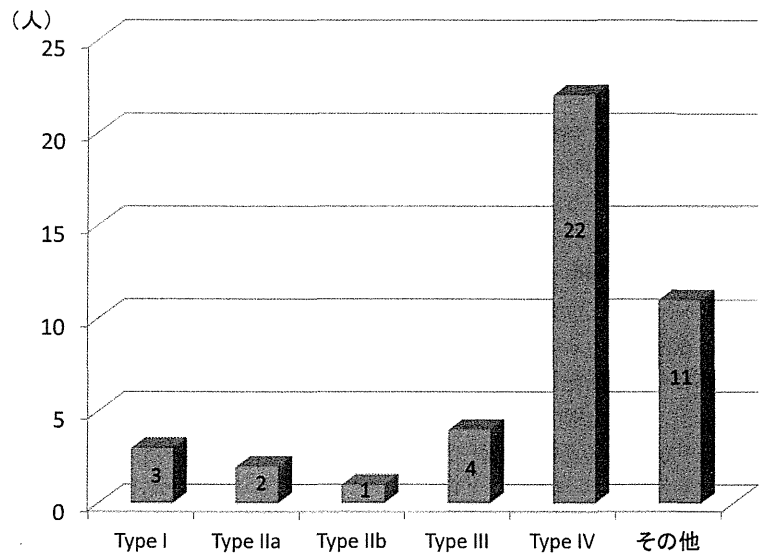


図7　IgG4-SC の病型分類

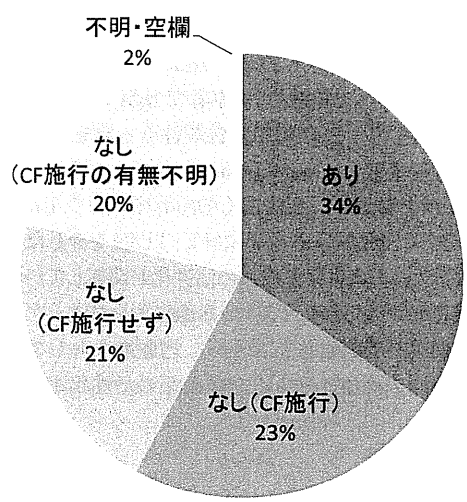


図8　PSC における IBD の有無

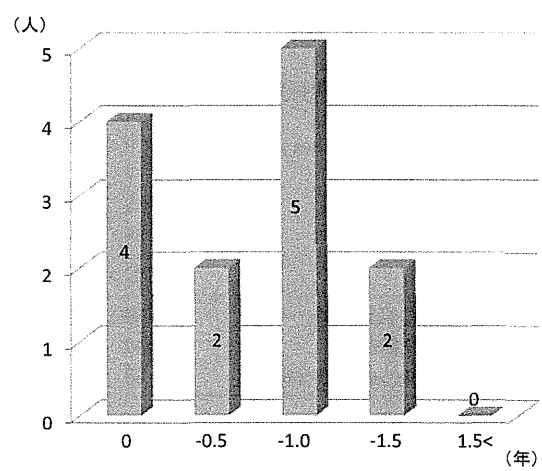


図9　PSC における PSC 診断から胆管癌診断までの期間

例が集積された[2)3)]が，この中には IgG4-SC が混入していた可能性が否定できず，IgG4-SC を除外した上での PSC の実態調査としてはこの調査がはじめてである．IgG4-SC としては，過去最も多くの症例を集積し検討したのは 2008 年の Mayo clinic からの報告であり，53 例が対象となっている[8)]．しかしこのうち 49 例は AIP 合併例であり，PSC，あるいは胆管癌との鑑別診断が困難となる AIP を合併していない IgG4-SC の検討としては，今回の調査がもっとも多くの症例を集積としたものである．

今回の調査でいくつかの興味深い点が明らかになった．まず，PSC については，前回・前々回で確認された，欧米からの報告では見られない本邦の PSC の特徴が再び確認された．すなわち，二峰性の年齢分布が IgG4-SC を除外した上でも依然として存在していたこと，IBD の合併が比較的少ないこと，の 2 点である．欧米の報告では唯一カナダからの population-based study が 65 歳超の高齢者にも発症のピークが存在することを報告

している[13]以外，概ね若年者のみで発症リスクが高いことを示している[14)~17)]．また，PSCにおけるIBDの合併頻度も欧米の報告では60-80%とされ[18)19)]，最近のオランダからのpopulation-based studyでも66%と報告されている[20)]．しかし，本邦のPSCにおけるIBDの合併頻度は，われわれの前回調査では37%(125/388)にとどまり[3)]，今回も34%(68/197)であった．大腸内視鏡検査施行と記載されていたのは197例中114例であったが，今回アンケート調査を送付した施設はERCPなど内視鏡検査を積極的に施行している施設であり，IBDの疑いがあるにもかかわらず大腸内視鏡検査を施行しなかったとは考えにくく，もし全例で大腸内視鏡検査が施行されていたとしてもIBDの合併頻度が大きく上昇する可能性はないと思われる．興味深いことに，やはりアジアからの報告であるシンガポールにおける調査では，症例数は少ないもののIBDの合併頻度は20%(2/20)と低率にとどまっている[21)]．PSCの臨床像が本当に本邦，あるいはアジアと欧米とで異なるのかどうかについて結論を出すためには，今後アジアの他国からの疫学研究，および本邦のPSCにおける疾患感受性遺伝子についての研究などが必要であると思われる．

PSCとIgG4-SCの鑑別という重要な問題についても，今回の調査はいくつかの示唆を与える．まず，臨床現場で頻用されている血清IgG4値については，カットオフ値を135mg/dlとした場合，IgG4-SCの診断における感度・特異度はそれぞれ89.5%，87.6%となり，満足すべき数字であった．また，血清IgM値がPSCで高値となっており，IgMのカットオフ値を200mg/dlとすると，これを超えていたのはPSCでは169例中40例(24%)存在したのに対し，IgG4-SCでは36例中1例のみであった．われわれの検索した限りPSCで血清IgMが上昇するとした報告はなく，唯一高齢者と比較して若年者のPSCではIgMが高値となる傾向を示唆した本邦からのHiranoらによる報告があるのみである[22)]．この報告では，症例数は少ないものの，18例の若年PSCと10例の高齢PSCとを比較し，若年者でIgMが高い傾向にあるとしている．PSC同様慢性胆汁うっ滞を示す原発性胆汁性肝硬変(primary biliary cirrhosis；PBC)で血清IgMが上昇することはよく知られている[23)]．KikuchiらはPBCにおけるIgM上昇に対し，TLR9を介したbacterial CpGによる自然免疫系の活性化が関与していることを報告した[24)]．近年，PSCの病態においても，ゲノムワイド関連分析の結果などから，門脈血を介して肝に移行した腸内細菌による自然免疫系の活性化が重要で

表3　PSCに対する薬物治療

| 薬物治療の内容 | 例数 |
|---|---|
| UDCA単剤 | 89 |
| UDCA＋bezafibrate | 28 |
| UDCA＋PSL | 24 |
| UDCA＋PSL＋bezafibrate | 9 |
| PSL mono | 7 |
| beza mono | 2 |
| 記載なし | 38 |
| 計 | 197 |
| UDCA投与症例 | 150 |
| PSL投与症例 | 40 |
| bezafibrate投与症例 | 39 |

表4　内視鏡的治療の内容とその効果

| | PSC（n＝197） | IgG4-SC（n＝43） |
|---|---|---|
| 内視鏡的胆管拡張 | | |
| あり | 24（12%） | 4（ 9%） |
| なし | 157（80%） | 35（81%） |
| 不明・空欄 | 16 | 4 |
| ステント挿入 | | |
| あり | 46（23%） | 15（35%） |
| なし | 110（56%） | 17（40%） |
| 不明・空欄 | 41 | 11 |
| 内視鏡治療の効果 | | |
| 良好（excellent＋fair） | 39 | 12 |
| 不良（poor）・不明（undetermined） | 13 | 2 |
| 不明・空欄 | 145 | 29 |

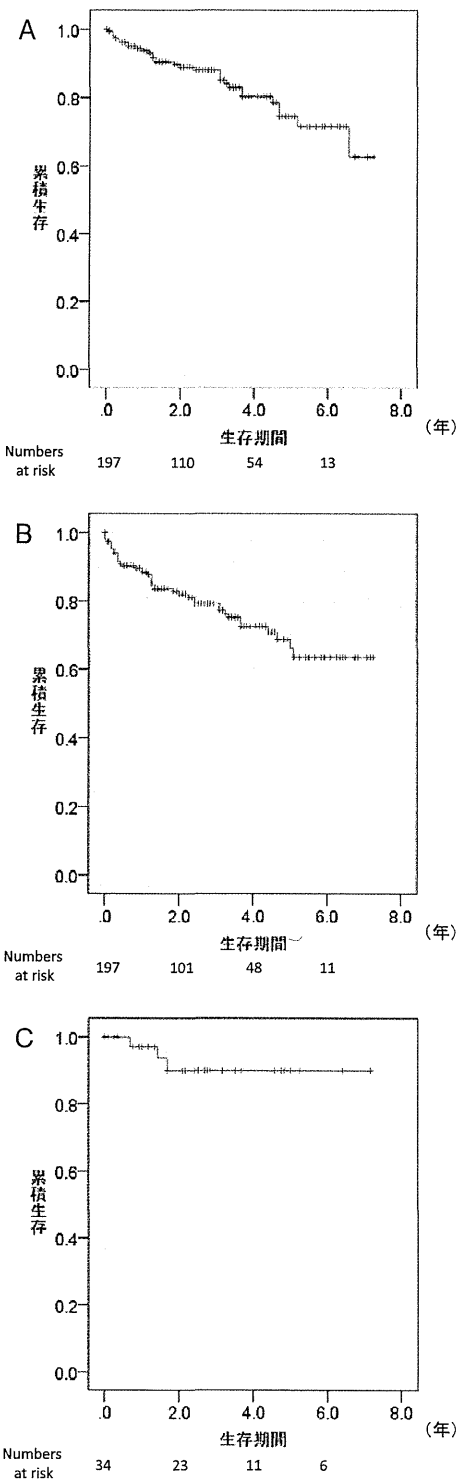


図10　累積生存期間．A, PSCにおける生存期間．B, PSCにおける移植なし生存期間．C, IgG4-SCにおける生存期間．

あるという報告がなされており[25][26]，PBCと同様のメカニズムが働いてIgMが高値となっている可能性がある．さらにHiranoらは，高齢者PSCではIgEが有意に高かったとも報告している[22]．今回のわれわれの検討では，IgEが測定されていた症例数が少なく有意とはならなかったものの，IgEがIgG4-SCでは高い傾向にあった．IgG4-SCは高齢者に多いことを考え合わせると，高齢者のPSCにはやはりIgG4-SCと鑑別が困難な症例が存在しており，その結果IgEが高いという結果となったという解釈が可能かもしれない．

今回の調査は胆道専門医の勤務している全国144施設に対するアンケート調査という方式によって症例を収集した．したがって，PSC・IgG4-SCの診断，およびAIPの除外診断は，各施設の胆道専門医によって行われている．2012年に発表されたIgG4-SCの診断基準は主に血清IgG4値に加え，主に画像・病理組織診断に依拠しており[11]，画像や病理組織所見の解釈において施設間にある程度のばらつきが存在する可能性がある．AIP合併例の除外という点においても同様である．この結果，今回の調査でも前回同様，やはりPSC症例中にある程度IgG4-SC症例が混入している可能性を完全には否定できないと思われる．事実，前回調査同様PSC症例の年齢分布が二峰性となっており，高齢者に発症の一つのピークがみられることは，欧米では見られない本邦のPSCの一つの特徴である可能性はあるものの，反面，高齢者中心に発症するIgG4-SCが混入した結果である可能性はやはり残る．またPSC症例でも，IBDを合併していないにもかかわらずステロイド治療例が存在することは，診療に当たっている主治医がIgG4-SCの可能性を完全には否定できなかった表れかもしれない．今回集積された症例のうち，画像診断はほぼ全例で行われていると思われるし，病理組織診断もPSCでは125例，IgG4-SCでは31例において行われている．全症例の臨床情報のみならず画像・病理組織をも収集し，一括して診断を行うことができれば，診断上のばらつきの問題は解決されるが，アンケート調査ではこのような一括診断は不可能であり，この点が本研究の限界である．

以上，PSCとIgG4-SCについての全国調査の結果を報告した．今回の結果から，PSCとIgG4-SCとを比較した場合，PSCは男性に多いこと，年齢分布に若年層・高齢層と2つのピークがあること，血液検査でIgM・アルブミンが低値，IgG・IgG4が高値であること，といった特徴が明らかにされた．ことにIgG4-SCと比較

してPSCでIgMが上昇するという所見は今回の調査で初めて明らかにされた結果であり，今後さらなる検討が必要である．また，今回は画像所見や病理組織の検討は行っておらず，集積された症例，ことに高齢者のPSCおよびIgG4-SCについて，画像所見や病理組織所見を収集し，一括して解析する必要がある．あわせて，今回の検討では平均観察期間が短く予後についての解析が不十分であり，今後これらの症例を長期追跡して，PSCとIgG4-SCについての治療内容および予後についての検討を加えていきたい．

謝辞

今回の全国調査に当たり，下記施設・先生方から調査票をご返送いただきました．謹んでお礼を申し上げます(敬称略)．

手稲渓仁会病院消化器病センター(金俊文，真口宏介)，札幌医科大学公衆衛生(野島正寛)，北海道大学消化器内科(河上洋)，岩手医科大学消化器・肝臓内科(宮本康弘)，仙台市医療センター仙台オープン病院消化器内科(野田裕)，東北大学消化器内科(下瀬川徹，菅野敦)，山形大学消化器内科(牧野直彦，池田祐之)，山形大学第一外科(木村理，平井一郎)，福島県立医科大学消化器・リウマチ膠原病内科(大平弘正，高橋敦史)，茨城県立中央病院診療情報室(須能まゆみ)，茨城県立中央病院・茨城県地域がんセンター(永井秀雄)，埼玉医科大学消化器内科・肝臓内科(持田智)，千葉県がんセンター消化器外科(有光秀仁)，千葉大学腫瘍内科学(横須賀收，露口利夫)，順天堂大学消化器画像診断研究室(崔仁煥)，東京医科大学消化器内科(糸井隆生，辻修二郎)，東京大学消化器内科(平野賢二，水野卓)，東邦大学医療センター大橋病院消化器内科(齋藤倫寛)，昭和大学内科消化器内科(吉田仁)，東京大学人工臓器移植外科(菅原寧彦)，東京都立駒込病院内科(神澤輝実)，東海大学消化器内科(川口義明)，済生会横浜市東部病院こどもセンター肝臓・消化器部門(十河剛，乾あやの)，新潟大学消化器内科(山際訓)，金沢大学消化器外科(北川裕久)，信州大学総合健康安全センター(川茂幸)，信州大学消化器内科(村木崇)，長野市民病院消化器内科(長谷部修)，名古屋大学腫瘍外科(菅原元)，名古屋大学消化器内科(川嶋啓揮)，名古屋大学病院光学医療診療部(廣岡芳樹)，名古屋市立大学消化器・代謝内科(中沢貴宏)，藤田保健衛生大学坂文種報徳会病院消化器内科(山本智支)，名古屋大学消化器内科膵臓研究室・国立長寿医療研究センター消化機能診療科(洪繁)，岐阜大学第一内科(土井晋平)，京都大学肝膵胆・移植外科(上本伸二，伊藤孝司)，国立病院機構京都医療センター臨床研究センター(島津章)，国立病院機構京都医療センター消化器内科(遠藤文司)，関西医科大学消化器肝臓内科(内田一茂)，大阪大学消化器内科学(竹原徹郎，江崎久男)，神戸大学肝胆膵外科(味木徹夫，吉田優子)，神戸大学消化器内科(増田充弘，久津見弘)，岡山大学消化器・肝臓内科(山本直樹)，広島大学総合内科・総合診療科(山本隆一)，愛媛大学第三内科(畔元信明)，九州大学第三内科(伊藤鉄英，五十嵐久人)，九州大学消化器総合外科(調憲)，久留米大学外科(川原隆一)，久留米大学消化器内科(岡部義信)，長崎医療センター臨床研究センター(小森敦正)

## 文　献

1) Nguyen D. Primary sclerosing cholangitis. In: Schiff E, ed. Schiff's Disease of the Liver. Philadelphia: Wiley-Blackwell, 2012: 477—488
2) Takikawa H, Manabe T. Primary sclerosing cholangitis in Japan - analysis of 192 cases. J Gastroenterol 1997; 32: 134—137
3) 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—159
4) Hamano H, Kawa S, Uehara T, et al. Immunoglobulin G4-related lymphoplasmacytic sclerosing cholangitis that mimics infiltrating hilar cholangiocarcinoma: part of a spectrum of autoimmune pancreatitis? Gastrointest Endosc 2005; 62: 152—157
5) Hamano H, Umemura T, Uehara T, et al. IgG4-related sclerosing cholangitis should be included as an exclusion criterion for the diagnosis of primary sclerosing cholangitis. Am J Gastroenterol 2007; 102: 691—692
6) Uehara T, Hamano H, Kawa S, et al. Distinct clinicopathological entity 'autoimmune pancreatitis-associated sclerosing cholangitis'. Pathol Int 2005; 55: 405—411
7) Zen Y, Harada K, Sasaki M, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol 2004; 28: 1193—1203
8) Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology 2008; 134: 706—715
9) Nakazawa T, Ohara H, Sano H, et al. Clinical differences between primary sclerosing cholangitis and sclerosing cholangitis with autoimmune pancreatitis. Pancreas 2005; 30: 20—25
10) Nakazawa T, Ohara H, Sano H, et al. Schematic classification of sclerosing cholangitis with autoimmune pancreatitis by cholangiography. Pancreas 2006; 32: 229

11) 岡崎和一，川茂　幸，乾　和郎，ほか．IgG4関連硬化性胆管炎臨床診断基準2012．胆道　2012；26：59—63
12) 滝川　一．原発性硬化性胆管炎．「消化器病診療」編集委員会　編：消化器病診療　—よきインフォームド・コンセントに向けて—．東京：日本消化器病学会，2004
13) Kaplan G, Laupland K, Butzner D, et al. The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. Am J Gastroenterol 2007; 102: 1042—1049
14) Broome U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 1996; 38: 610—615
15) Farrant J, Hayllar K, Wilkinson M, et al. Natural history and prognostic variables in primary sclerosing cholangitis. Ganstroenterology 1991; 100: 1710—1717
16) Schrumpf E, Abdelnoor M, Fausa O, et al. Risk factors in primary sclerosing cholangitis. J Hepatol 1994; 21: 1061—1066
17) Wiesner R, Grambsch P, Dickson E, et al. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. Hepatology 1989; 10: 430—436
18) EASL. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009; 51: 237—267
19) Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology 2010; 51: 660—678
20) Boonstra K, van Erpecum KJ, van Nieuwkerk KM, et al. Primary sclerosing cholangitis is associated with a distinct phenotype of inflammatory bowel disease. Inflamm Bowel Dis 2012; 18: 2270—2276
21) Ang TL, Fock KM, Ng TM, et al. Clinical profile of primary sclerosing cholangitis in Singapore. J Gastroenterol Hepatol 2002; 17: 908—913
22) Hirano K, Tada M, Isayama H, et al. Clinical features of primary sclerosing cholangitis with onset age above 50 years. J Gastroenterol 2008; 43: 729—733
23) Selmi C, Bowlus CL, Gershwin ME, et al. Primary biliary cirrhosis. Lancet 2011; 377: 1600—1609
24) Kikuchi K, Lian ZX, Yang GX, et al. Bacterial CpG induces hyper-IgM production in CD27 (+) memory B cells in primary biliary cirrhosis. Gastroenterology 2005; 128: 304—312
25) Bowlus CL. Cutting edge issues in primary sclerosing cholangitis. Clin Rev Allergy Immunol 2011; 41: 139—150
26) Folseraas T, Melum E, Rausch P, et al. Extended analysis of a genome-wide association study in primary sclerosing cholangitis detects multiple novel risk loci. J Hepatol 2012; 57: 366—375

# A nation-wide survey of sclerosing cholangitis

Atsushi Tanaka[1], Susumu Tazuma[2], Kazuichi Okazaki[3],
Hirohito Tsubouchi[4], Kazuo Inui[5], Hajime Takikawa[1]

We conducted a nation-wide survey to elucidate the characteristics of PSC as well as IgG4-SC without apparent pancreatic involvement diagnosed after 2005, by sending questionnaires. One-hundred and ninty-seven patients with PSC and 43 patients with IgG4-SC were identified. Compared to PSC, IgG4-SC was male-dominant and developed in older patients. There were two peaks in the age distribution of PSC patients, as demonstrated in the previous nation-wide surveys. The main location of involved bile ducts was both intra and extrahepatic in PSC and intrahepatic in IgG4-SC. Inflammatory bowel diseases was noticed in 68/197 (34%) of PSC, relatively low as shown in the previous surveys. Three-year survival rate were 85.0% in PSC and 90.0% in IgG4-SC, suggesting better prognosis of IgG4-SC.

*JJBA* 2013; 27: 176—187

[1] Teikyo University School of Medicine (Tokyo)
[2] Department of General Medicine, Hiroshima University, Graduate School of Medical Science, Programs of Applied Medicine, Clinical Pharmacotherapy (Hiroshima)
[3] The Third Department of Internal Medicine, Kansai Medical University (Hirakata)
[4] Digestive and Lifestyle Diseases, Kagoshima University, Graduate School of Medical and Dental Sciences (Kagoshima)
[5] Department of Internal Medicine, Second Teaching Hospital, Fujita Health University (Nagoya)

**Key Words**: primary sclerosing cholangitis, IgG4-related, autoimmune pancreatitis

Journal of Autoimmunity 46 (2013) 35–40

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review

# Geoepidemiology of primary sclerosing cholangitis: A critical review

Atsushi Tanaka*, Hajime Takikawa

*Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan*

ARTICLE INFO

*Article history:*
Received 8 July 2013
Accepted 11 July 2013

*Keywords:*
Epidemiology
Incidence
Prevalence
IgG4-sclerosing cholangitis

ABSTRACT

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown origin, characterized by progressive destruction of bile ducts caused by diffuse inflammation and fibrosis. Previous epidemiological studies in Northern Europe and North America demonstrated that incidence and prevalence rates are ranging from 0.5 to 1.3 and from 3.85 to 16.2 per 100,000 inhabitants per year, respectively. It is of note that the incidence of PSC appears to be gradually increasing. We have extensively reviewed the geoepidemiology of PSC and attempted to place it in context with the incidence in Japan. In 2012, the clinical diagnostic criteria of IgG4-SC were established and published by the Japan Biliary Association, rendering it possible for physicians to clinically differentiate PSC from IgG4-SC. We conducted a new nationwide survey for PSC as well as IgG4-SC, and have identified 197 patients with PSC and 43 patients with IgG4-SC without pancreatic involvement. In this survey we estimated prevalence rate of PSC in Japan as 0.95, lower than those in North America and European countries. Also we identified other unique features of Japanese PSC patients, including 2 peaks in age distribution at diagnosis and fewer presences of comorbid inflammatory bowel diseases, occurring in only 34% of PSC. This data is placed in the perspective of the international experience on PSC.



## 1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown origin, characterized by the progressive destruction of bile ducts caused by diffuse inflammation and fibrosis that eventually leads to liver cirrhosis [1]. The etiopathogenesis of PSC has not been fully understood, and therefore epidemiological studies of PSC are of vital importance to reduce a significant burden to the health care system posed by PSC [2,3]. So far several epidemiological studies have been performed mainly in Northern Europe and North America to elucidate the incidence and prevalence of PSC, and revealed high prevalence rates of PSC in these areas [4–12]. Also recent studies consistently demonstrated that a significant increase over time in the incidence of PSC [3,7,12]. However, epidemiological data of PSC were lacking for regions of low prevalence areas, including Japan and other countries in Asia.

In Japan PSC was recognized as an uncommon liver disorder until the early 1990s, yet the number of reported cases of PSC was increasing. We conducted nationwide retrospective surveys to elucidate the characteristics of PSC in Japan in 1997 and 2003 [13,14] and demonstrated the presence of unique features of Japanese PSC patients as compared to those in patients from North America and European countries, including 2 peaks in age distribution and fewer presences of inflammatory bowel diseases as comorbidities, occurring in only 37% of PSC patients. Meanwhile, accumulating evidences, mainly originating from Japan, suggested the presence of a different clinical entity of sclerosing cholangitis with elevated serum IgG4 levels, complicated with/without autoimmune pancreatitis (AIP) [15–17]; this disorder is now defined as IgG4-related sclerosing cholangitis (IgG4-SC) [18]. In 2012, the clinical diagnostic criteria of IgG4-SC were established in Japan [19], based mainly on cholangiographic findings. It was thus possible to discriminate PSC from IgG4-SC using these criteria; therefore, we conducted the third nationwide survey to investigate the characteristics of PSC as well as IgG4-SC lacking pancreatic involvement [20]. Furthermore, we performed an epidemiological study of PSC in Japan in 2007 based on the data from national surveys and estimated the prevalence of PSC in this country [21], and as far as we know this study still remains the only epidemiological data of PSC in Asia.

In this review, first we summarized the geoepidemiological data of PSC, mainly focusing on the comparison between Europe/North America and Japan. Next, we describe the unique features of Japanese patients with PSC identified in nationwide surveys along with a focus on patients with IgG4-SC.

*Abbreviations:* PSC, primary sclerosing cholangitis; AIP, autoimmune pancreatitis; IgG4-SCI, gG4-related sclerosing cholangitis; IBD, inflammatory bowel diseases; CCA, cholangiocarcinoma; UC, ulcerative colitis.

* Corresponding author. Department of Medicine, Teikyo University School of Medicine, 2-11-1, Kaga, Itabashi-ku, Tokyo 173-8605, Japan. Tel.: +81 3 3964 1211; fax: +81 3 3964 6627.
*E-mail address:* a-tanaka@med.teikyo-u.ac.jp (A. Tanaka).

0896-8411/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jaut.2013.07.005

## 2. Geoepidemiology of PSC

To our knowledge, there have been 10 epidemiological studies indicating incidence and prevalence of PSC from 1984 to 2007, including our study [4–12,21]. The results of these studies are summarized in Table 1. The incidence rates (IR) are ranging from 0.07 to 1.3 per 100,000 inhabitants per year; almost similar IR among North America and Northern Europe, while an IR was 0.07 and exceptionally low in Spain [9]. The prevalence rate also varies, ranging from 0.22 to 16.2. In Spain a prevalence rate was the lowest, 0.22 per 100,000 inhabitants per year.

The epidemiological study conducted in Japan in 2007 was a questionnaires-based retrospective design. A questionnaire was circulated to 1910 tertiary referral centers all over in Japan, covering 43,875,000 populations of Japan. The diagnosis of PSC was made in each referral center, according to the diagnostic criteria proposed by Lindor et al. [22], mainly depending on cholangiographic studies, biochemical and histological findings, and exclusion of other possible causes. The response was obtained from 1355 centers (71%) and 415 patients with PSC were identified. Based on these figures we estimated the prevalence of PSC in Japan was 0.95 (95% CI; 0.61–1.29) [21]. Although IR was lacking in our epidemiological study, the prevalence rate of in Japan is relatively low compared to Northern Europe and North America, supporting the demographic diversity of PSC.

The difference in the prevalence of PSC between Japan and Europe/North America may be partly explained by the study design. Our study is a questionnaires-based retrospective design recruiting tertiary referral centers, not a population-based epidemiological study. As a result the number of PSC patients might be underestimated in this study by a referral or diagnostic bias. However, we sent a questionnaire to quite large numbers of tertiary referral centers all over in Japan, covering almost one-third populations of this country. Furthermore, a diagnosis of PSC is well known among gastroenterologists, and cholangiographic studies (ERCP and/or MRCP) are routinely performed in Japan. Rather, a primary factor playing a significant role in the global distribution of PSC is genetic diversity among ethnic groups. The population-based epidemiological studies in Japan and other Asian countries may help to resolve this issue.

It is of note that the incidence of PSC appears to be increasing. Recent two large cohort studies demonstrated a significant increase in IR of PSC over time [7,12]; average annual percent change (AAPC) was reported to be 3.06 (95% CI 0.01–6.20) in one study [12]. Another study also reported a tendency toward increasing incidence, although not significant [8]. Although we failed to estimate an IR in our study in Japan, the reported number of patients with PSC nearly doubled between two national surveys, 192 in 1997 [13] and 388 patients in 2003 [14]. Since a questionnaire was similarly sent to referral centers in both surveys, the increase in the number of PSC patients may reflect a real increase of IR of PSC in Japan. It remains unsolved why incidence of PSC is increasing recently. Escorsell et al. reported that although no geographical difference in incidence was found there was a trend to detect more PSC cases in industrial regions [9]. Epidemiological studies of PSC in developing countries with identical ethnic backgrounds to North America/Europe are required to solve whether this hypothesis is the case or not. Earlier diagnosis of PSC with better recognition of the disease among clinicians and better diagnostic devices may be another reason for increased IRs. However, Boonstra et al. recently demonstrated that serum bilirubin levels at diagnosis remained stable over time while incidence was rising during the same period, and denied the possibility that earlier diagnosis underlay the increase [7]. We agree this view because no significant difference in clinical profiles was noted as well between two national surveys we performed.

## 3. Characteristics of Japanese PSC patients as compared to those in Europe and North America

In addition to lower prevalence of PSC in Japan, we noticed several characteristic features of Japanese PSC patients in previous nationwide surveys, which had been scarcely demonstrated before by epidemiological studies from other countries. First, there were 2 peaks in the age distribution at diagnosis, i.e., in the 3rd and 7th decades of life (Fig. 1). Most previous epidemiological studies from North America and Europe indicated a single age category as the highest risk for developing PSC [23–26], except for a recent study in Canada which suggested two categories, 18–35 and >65, are higher risk groups than another categories, similar to Japanese studies [10]. Interestingly, the age distribution of PSC complicated with inflammatory bowel diseases (IBD) demonstrated a single peak in the twenties, while patients with AIP exhibited a small peak in the sixties. At this point, PSC patients with AIP are not considered to have "true" PSC, but rather are diagnosed as IgG4-SC. Although it is notable that the peak in the sixties persists even if patients with AIP are eliminated, it remains possible that IgG4-SC patients without pancreatic involvement may be misdiagnosed as PSC and thus comprise the second peak in the elderly.

Second, the prevalence of IBD as comorbidity appears to be lower in Japanese PSC patients. In various case series from North America and Northern Europe, IBD was a complication in 47–76% of PSC patients [4,6–12] (Table 2). However, in Japanese PSC patients, the presence of IBD was restricted to only 37% (125/388) patients in 2003 survey [14]. In general, total colonoscopy is frequently performed in Japanese facilities where PSC is diagnosed by endoscopic retrograde cholangiography (ERC); therefore, a lack of a thorough examination of the colon is not a plausible reason for the lower prevalence of IBD. Indeed, total colonoscopy was performed in 53%

**Table 1**
Incidence and prevalence of PSC.

| Author [Ref.] | Country | Study period | Method of case ascertainment | No. of cases | Incidence[a] (95% CI) | Prevalence[a] (95% CI) |
|---|---|---|---|---|---|---|
| Escorsell et al. [9] | Spain | 1984–1988 | Questionnaires | 43 | 0.07 | 0.22 |
| Berdal et al. [5] | Norway | 1985–1994 | ICD codes | 12 | 0.7 | 5.6 |
| Boberg et al. [6] | Norway | 1986–1995 | Prospective cohort | 17 | 1.3(0.8–2.1) | 8.5 (2.8–14.2) |
| Bambna et al. [4] | US | 1976–2000 | Medical records linkage system | 22 | 0.9 | 13.6 |
| Card et al. [8] | UK | 1987–2002 | General Practice Research Database | 149 | 0.41(0.34–0.48) | 3.85 (3.04–4.80) |
| Kingham et al. [11] | UK | 1984–2003 | Prospective cohort | 46 | 0.91 | 12.7 |
| Lindkvist et al. [12] | Sweden | 1992–2005 | ICD codes | 199 | 1.22 | 16.2 |
| Kaplan et al. [10] | Canada | 2000–2005 | Retrospective cohort | 49 | 0.92 | N/A |
| Boonstra et al. [7] | Netherlands | 2000–2007 | Retrospective cohort | 519 | 0.5 | 6.0 |
| Tanaka et al. [21] | Japan | 2007 | Questionnaires | 415 | N/A | 0.95 (0.61–1.29) |

N/A, not available.
[a] Per 100,000 inhabitants.

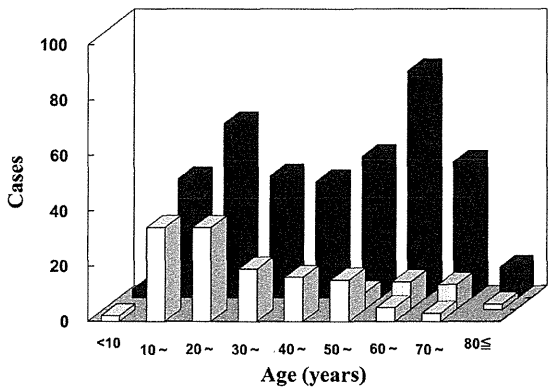


**Fig. 1.** Age distribution of patients with PSC in the 2003 survey in Japan [3]. Black columns, total PSC cases ($n$ = 388); white columns, PSC cases with IBD ($n$ = 125); dotted columns, PSC cases with AIP ($n$ = 28).

(206/388) of the PSC patients in our case series [14], suggesting that almost all PSC patients with any bowel symptoms were examined by total colonoscopy. Even after considering that IBD may be present with little or no clinical bowel symptoms in PSC patients, it is unlikely that the prevalence of IBD in Japanese PSC patients could reach 60–80%, even with colonoscopy performed for all PSC patients. Interestingly, another epidemiological study from Asia also demonstrated a lower prevalence of IBD in PSC patients (2/10; 20%) [27], although the number of patients was relatively small. Further, in Japanese PSC patients with IBD, several unique features were noted, such as rectal sparing and right-sided dominance, similar to those observed in PSC-IBD patients from North America and European countries but in contrast to IBD occurring in non-PSC patients. A retrospective cohort of IBD patients in Korea also demonstrated that PSC-IBD patients share features similar to the Japanese patients [28]. Thus, the atypical presentation of IBD in PSC patients appears to be a general phenomenon worldwide.

## 4. IgG4-sclerosing cholangitis: how to differentiate it from PSC?

We have described above the apparent unique clinical features observed in Japanese PSC patients. However, these features may not result from special characteristics of Japanese PSC itself; rather, they may be explained by "contamination" of the PSC population with IgG4-SC patients. We therefore need to discuss the clinical entity of IgG4-SC, focusing on how IgG4-SC can be differentiated from PSC.

Clinical researchers in Japan, both endoscopists and pathologists, have greatly contributed to the establishment of the concept of IgG4-SC. In 2001, the first report of sclerosing pancreatitis with elevated serum IgG4 levels was published by Hamano et al. [29]. Subsequently it was reported that bile duct lesions—or sclerosing cholangitis—were associated with sclerosing pancreatitis; these conditions were termed as "sclerosing pancreato-cholangitis" [30,31]. In 2004, similar cases with dominant biliary lesions but without pancreatic involvement were reported [15,17]; these were characterized by high serum IgG4 levels and dense infiltration of IgG4-positive plasma cells in the bile duct lesions, and this clinical entity was first termed as IgG4-SC [17]. The clinical importance of IgG4-SC lies in its excellent response to corticosteroid treatment; it is therefore crucial to differentiate IgG4-SC from PSC or CCA, both of which do not respond to corticosteroids at all and are not expected to have favorable prognosis [32]. Nevertheless, the cholangiographic features of IgG4-SC widely vary and closely resemble those of PSC and CCA, and the diagnosis of IgG4-SC at presentation, especially in cases without pancreatic lesions, is very challenging. In the largest retrospective cases series of IgG4-SC patients, diagnosis was essentially based on the presence of complicated AIP or using bile duct histopathological examination of resected materials following surgical treatment [33]. Further, serum IgG4 levels were demonstrated to not necessarily be elevated in all IgG4-SC patients; in fact, serum IgG4 levels have been reported to be high even in certain PSC cases [34].

To clarify the differences in IgG4-SC and PSC, the Japanese Biliary Association launched a working group in 2010 and established the clinical diagnostic criteria of IgG4-SC in 2012 [19]. The criteria mainly consist of the following 4 items: (1) characteristic cholangiographic findings, (2) elevated serum IgG4 levels, (3) coexistence of IgG4-related diseases in other parts, and (4) histopathological findings compatible with IgG4-SC; the effectiveness of corticosteroid therapy is an additional option. However, the most important criterion among these is cholangiographic findings [35]. Nakazawa et al. demonstrated that IgG4-SC with or without AIP could be discriminated from PSC based on cholangiographic findings [36]. They suggested that "dilation after confluent stricture" and "stricture of lower common bile duct" were typical findings in IgG4-SC, whereas band-like stricture, beaded appearance, pruned-tree appearance, and diverticulum-like outpouching were seen in PSC (Fig. 2). Based on these findings, they proposed a schematic classification of cholangiographic findings of IgG4-SC [37], which was employed in the clinical diagnostic criteria.

However, the concept that cholangiographic findings can discriminate IgG4-SC from PSC or CCA is not supported worldwide; the reliability of ERC could not be confirmed by researchers enrolled from several countries, including Japan [38]. The validity and universality of the clinical diagnostic criteria of IgG4-SC

**Table 2**
Summary of clinical profiles of PSC.

| Author [Ref.] | Country | No. of cases | Male (%) | Age at diagnosis, median (yrs) | Age category at highest risk | IBD (%) |
|---|---|---|---|---|---|---|
| Escorsell et al. [9] | Spain | 43 | 60 | 42.3[a] | N/A | 47 |
| Berdal et al. [5] | Norway | 12 | 58 | 43[a] | N/A | N/A |
| Boberg et al. [6] | Norway | 17 | 71 | 37 | N/A | 71 |
| Bambna et al. [4] | US | 22 | 68 | 40 | N/A | 73 |
| Card et al. [8] | UK | 149 | 63.5 | 55 | 65–74 | 48 |
| Kingham et al. [11] | UK | 53[b] | 62 | 52 | N/A | 62 |
| Lindkvist et al. [12] | Sweden | 199 | 71 | 38.5 | N/A | 76 |
| Kaplan et al. [10] | Canada | 49 | 55 | 41 | 18–35, >65 | 67 |
| Boonstra et al. [7] | Netherlands | 590 | 64 | 38.9[a] | 40–49 | 68 |
| Tanaka et al. [20] | Japan | 197 | 54 | 48.1 | 35–40, 65–70 | 34 |

N/A, not available.
[a] Mean.
[b] Seven patients in this study were excluded for estimation of incidence and prevalence since they lived just outside this demarcation.

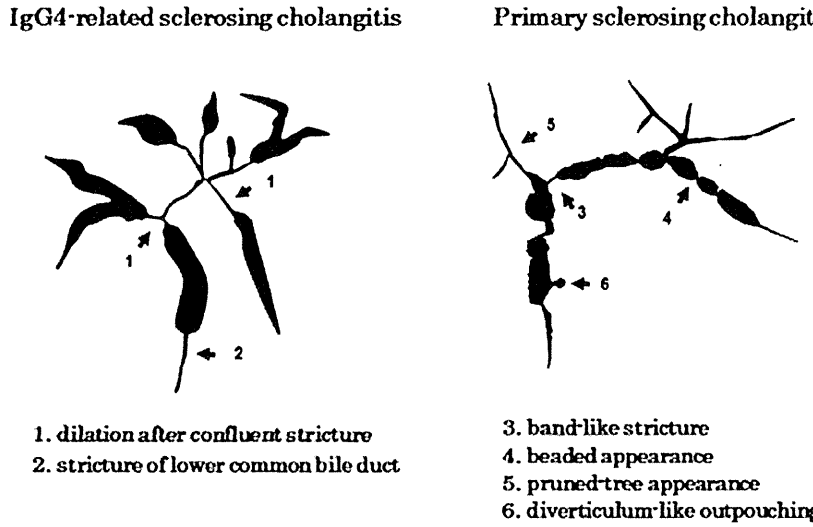


**Fig. 2.** The schematic comparison of cholangiographic findings of IgG4-SC and PSC [8]. Dilation after confluent stricture and stricture of lower common bile duct were typical findings in IgG4-SC, whereas band-like stricture, beaded appearance, pruned-tree appearance, and diverticulum-like outpouching were seen in PSC.

therefore needs to be examined in other cohorts of IgG4-SC patients with disease controls that include PSC and CCA, especially in Europe and North America.

### 5. The recent nationwide survey of patients with PSC and IgG4-SC without AIP in Japan

Based on the diagnostic criteria for IgG4-SC, clinical researchers in Japan are now able to correctly diagnose and differentiate between PSC and IgG4-SC; the misdiagnosis of IgG4-SC as PSC can thus be avoided. In 2012, we conducted a third nationwide survey for PSC and IgG4-SC patients diagnosed after 2005, when IgG4-SC was better known among clinicians in Japan as compared to that in 2003. Since the differential diagnosis of IgG4-SC from PSC is not problematic when AIP is coexistent with IgG4-SC, we enrolled only cases with IgG4-SC apparently lacking pancreatic lesions.

Overall, we enrolled 197 PSC and 43 IgG4-SC patients with no or little pancreatic lesions. The male/female ratio was 54%/46% in PSC and 77%/23% in IgG4-SC, indicating that male dominance was more evident in IgG4-SC. The age distribution is shown in Figs. 3 and 4. Two peaks in age distribution, one at 35–40 years and the other at 65–70 years, were clearly observed in the current study, even after patients with IgG4-SC lacking pancreatic involvement were carefully excluded (Fig. 3). Thus, it was confirmed again that elderly patients (>65 years) are at high risk for developing PSC in Japan. In contrast, IgG4-SC was not diagnosed in any patient younger than 45 years of age; therefore, the elderly population is also considered to be at high risk for IgG4-SC (Fig. 4). Symptoms at presentation were comparable in both groups, and patients presented as asymptomatic (PSC 58%, IgG4-SC 56%), with jaundice (24%, 23%), and with itching (17, 19%). Serum IgG4 levels at diagnosis (normal range; <135 mg/dL) were elevated in 12/121 PSC (12.4%) and in 34/38 IgG4-SC (89.5%) patients. Thus, serum IgG4 levels were significantly higher in patients with IgG4-SC ($p < 0.0001$), and the sensitivity and specificity of serum IgG4 levels for diagnosing IgG4-SC without AIP were 89.5% and 87.6%, respectively. Thus, although some PSC patients had elevated serum IgG4 levels, as reported previously, both the sensitivity and the specificity of serum IgG4 with a cut-off level at 135 mg/dL for IgG4-SC were fairly acceptable.

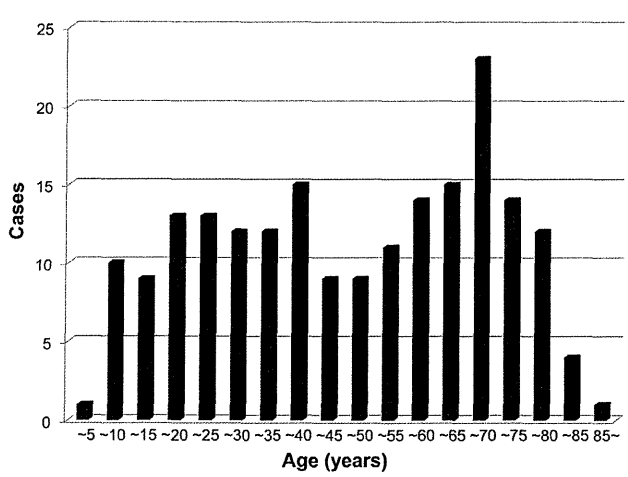


**Fig. 3.** Age distribution of patients with PSC in the 2012 survey in Japan.

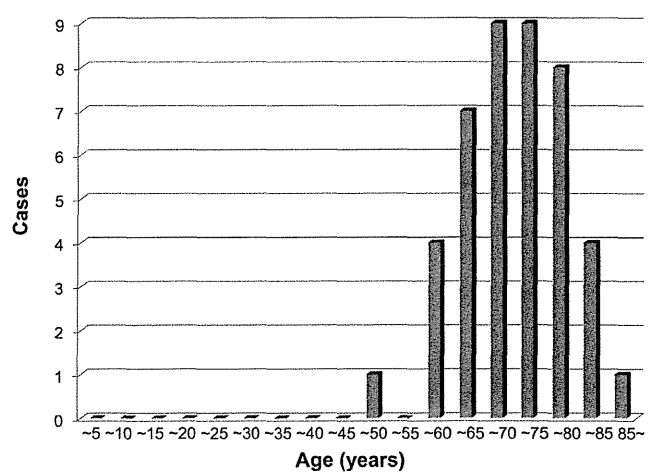


**Fig. 4.** Age distribution of patients with IgG4-SC lacking apparent pancreatic involvement in the 2012 survey in Japan.

With respect to complications, IBD was detected in 68/197 PSC patients (34%), again indicating a relatively low prevalence of IBD in Japanese PSC patients. IBD was diagnosed as ulcerative colitis (UC) and non-specific colitis in 55 and 10 patients, respectively. Crohn's disease was not reported in any patient. CCA was found in 14/197 PSC (7.3%), which was higher than the prevalence observed in our previous surveys in Japan. While neither IBD nor CCA was noted in patients with IgG4-SC, other IgG4-related diseases, i.e., dacryoadenitis/sialadenitis and retroperitoneal fibrosis, were detected in 6/43 (14%) and 4/43 (9%) patients, respectively.

Since we limited the subjects to those diagnosed after 2005 in the current survey, the median follow-up period was relatively short, being 2.7 ± 2.0 years for PSC patients and 2.3 ± 1.8 years for IgG4-SC patients. The 5-year survival and transplantation-free rate was 66.0% for PSC and 90.0% for IgG4-SC, indicating that the prognosis of IgG4-SC was considerably better than that of PSC, probably due to the excellent response to corticosteroid therapy observed in IgG4-SC patients. Liver transplantation was not required in any of the IgG4-SC patients.

## 6. Concluding remarks

The third nationwide survey in 2012 has provided several interesting clinical details regarding the apparent differences of PSC in Japanese patients and those from Europe/North America. First, it was confirmed that there were 2 peaks in age distribution, which have not been prominently observed in epidemiological studies from Europe and North America. Second, the prevalence of IBD was shown to be consistently lower in Japanese PSC patients as compared to similar patients from North America and European countries. However, it remains unclear whether Japanese PSC is truly characterized by differing clinical features as compared to those in patients from other countries or if these apparent differences are only due to the "contamination" of the cohort by IgG4-SC patients even after careful exclusion of IgG4-SC cases.

In this regard, we need to carefully confirm whether PSC patients from the elderly population are "true" PSC patients by histopathological studies. Since diagnoses were made separately in each facility, the cholangiographic findings of such cases should be reexamined. In addition, it should be validated whether the clinical diagnostic criteria for IgG4-SC as proposed in Japan are appropriate for patients from Europe and North America. Interestingly, the characteristics of IgG4-SC patients observed in the current survey appear to closely resemble those in IgG4-SC patients in the Mayo clinic [33], suggesting that the Japanese diagnostic criteria may be comparable for both populations. Finally, genetic studies to investigate the susceptible genes that contribute to the development of PSC in Japanese patients are needed in order to clarify whether the genetic background of PSC is similar between Japan and Europe/North America. One major shortcoming of studies of PSC throughout the world has been the relative lack of study of the role of gender and sex hormones. Although the incidence of PSC is higher in males, the mechanisms for this are unknown. We note a recent symposium on gender hormones and autoimmunity and note that amongst the various papers highlighted, the subject of PSC is virtually ignored [39–53]. Indeed, there is only one recent study which focuses on the molecular basis of gender specificity in PSC [54]. Taken together, extensive cross-examination studies between the East and West are strongly warranted to solve this interesting and challenging issue of whether PSC is a different clinical entity in the East.

## References


[1] Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. Lancet 2013 [Epub ahead of print].

[2] Karlsen TH, Boberg KM. Update on primary sclerosing cholangitis. J Hepatol 2013 [Epub ahead of print].

[3] Molodecky NA, Kareemi H, Parab R, Barkema HW, Quan H, Myers RP, et al. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. Hepatology 2011;53:1590–9.

[4] Bambha K, Kim WR, Talwalkar J, Torgerson H, Benson JT, Therneau TM, et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. Gastroenterology 2003;125:1364–9.

[5] Berdal JE, Ebbesen J, Rydning A. Incidence and prevalence of autoimmune liver diseases. Tidsskr Nor Laegeforen 1998;118:4517–9.

[6] Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol 1998;33:99–103.

[7] Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, et al. Population-based epidemiology, malignancy risk and outcome of primary sclerosing cholangitis. Hepatology 2013 [Epub ahead of print].

[8] Card TR, Solaymani-Dodaran M, West J. Incidence and mortality of primary sclerosing cholangitis in the UK: a population-based cohort study. J Hepatol 2008;48:939–44.

[9] Escorsell A, Pares A, Rodes J, Solis-Herruzo JA, Miras M, de la Morena E. Epidemiology of primary sclerosing cholangitis in Spain. Spanish Association for the Study of the Liver. J Hepatol 1994;21:787–91.

[10] Kaplan G, Laupland K, Butzner D, Urbanski S, Lee S. The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. Am J Gastroenterol 2007;102:1042–9.

[11] Kingham JG, Kochar N, Gravenor MB. Incidence, clinical patterns, and outcomes of primary sclerosing cholangitis in South Wales, United Kingdom. Gastroenterology 2004;126:1929–30.

[12] Lindkvist B, Benito de Valle M, Gullberg B, Bjornsson E. Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden. Hepatology 2010;52:571–7.

[13] Takikawa H, Manabe T. Primary sclerosing cholangitis in Japan – analysis of 192 cases. J Gastroenterol 1997;32:134–7.

[14] Takikawa H, Takamori Y, Tanaka A, Kurihara H, Nakanuma Y. 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.

[15] Hamano H, Kawa S, Uehara T, Ochi Y, Takayama M, Komatsu K, et al. Immunoglobulin G4-related lymphoplasmacytic sclerosing cholangitis that mimics infiltrating hilar cholangiocarcinoma: part of a spectrum of autoimmune pancreatitis? Gastrointest Endosc 2005;62:152–7.

[16] Uehara T, Hamano H, Kawa S, Sano K, Honda T, Ota H. Distinct clinicopathological entity 'autoimmune pancreatitis-associated sclerosing cholangitis'. Pathol Int 2005;55:405–11.

[17] Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol 2004;28:1193–203.

[18] Hamano H, Umemura T, Uehara T, Kawa S, Kiyosawa K. IgG4-related sclerosing cholangitis should be included as an exclusion criterion for the diagnosis of primary sclerosing cholangitis. Am J Gastroenterol 2007;102:691–2.

[19] Ohara H, Okazaki K, Tsubouchi H, Inui K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci 2012;19:536–42.

[20] Tanaka A, Tazuma S, Okazaki K, Tsubouchi H, Inui K, Takikawa H. A nationwide survey of primary sclerosing cholangitis and IgG4-related sclerosing cholangitis in Japan. Submitted for publication.

[21] Tanaka A. The epidemiological study of PSC in Japan. Health Labour Sciences Research Grant from Research on Measures for Intractable Diseases, the intractable hepato-biliary disease study group in Japan [in Japanese]; 2008.

[22] Lindor K, LaRusso N. Primary sclerosing cholangitis. In: Schiff E, editor. Schiff's disease of the liver. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 673–84.

[23] Broome U, Olsson R, Loof L, Bodemar G, Hultcrantz R, Danielsson A, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 1996;38:610–5.

[24] Farrant J, Hayllar K, Wilkinson M, Karani J, Portmann B, Westaby D, et al. Natural history and prognostic variables in primary sclerosing cholangitis. Ganstroenterology 1991;100:1710–7.

[25] Schrumpf E, Abdelnoor M, Fausa O, Elgjo K, Jenssen E, Kolmannskog F. Risk factors in primary sclerosing cholangitis. J Hepatol 1994;21:1061–6.

[26] Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, et al. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. Hepatology 1989;10:430–6.

[27] Ang TL, Fock KM, Ng TM, Teo EK, Chua TS, Tan JY. Clinical profile of primary sclerosing cholangitis in Singapore. J Gastroenterol Hepatol 2002;17:908–13.

[28] Ye BD, Yang SK, Boo SJ, Cho YK, Yang DH, Yoon SM, et al. Clinical characteristics of ulcerative colitis associated with primary sclerosing cholangitis in Korea. Inflamm Bowel Dis 2011;17:1901–6.

[29] Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344:732–8.

[30] Erkelens G, Vleggaar F, Lesterhuis W, van Buuren H, van der Werf S. Sclerosing pancreato-cholangitis responsive to steroid therapy. Lancet 1999;354:43–4.

[31] Horiuchi A, Kawa S, Hamano H, Ochi Y, Kiyosawa K. Sclerosing pancreatocholangitis responsive to corticosteroid therapy: report of 2 case reports and review. Gastrointest Endosc 2001;53:518–22.
[32] Kamisawa T, Tabata T. IgG4-related sclerosing cholangitis. Ann Hepatol 2011;10:552–5.
[33] Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology 2008;134:706–15.
[34] Mendes F, Jorgensen R, Keach J, Katzmann J, Smyrk T, Donlinger J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol 2006;101:2070–5.
[35] Nakazawa T, Naitoh I, Hayashi K, Okumura F, Miyabe K, Yoshida M, et al. Diagnostic criteria for IgG4-related sclerosing cholangitis based on cholangiographic classification. J Gastroenterol 2012;47:79–87.
[36] Nakazawa T, Ohara H, Sano H, Ando T, Aoki S, Kobayashi S, et al. Clinical differences between primary sclerosing cholangitis and sclerosing cholangitis with autoimmune pancreatitis. Pancreas 2005;30:20–5.
[37] Nakazawa T, Ohara H, Sano H, Ando T, Joh T. Schematic classification of sclerosing cholangitis with autoimmune pancreatitis by cholangiography. Pancreas 2006;32:229.
[38] Kalaitzakis E, Levy M, Kamisawa T, Johnson GJ, Baron TH, Topazian MD, 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.
[39] Shoenfeld Y, Tincani A, Gershwin ME. Sex gender and autoimmunity. J Autoimmun 2012;38:J71–3.
[40] Rogers MA, Levine DA, Blumberg N, Fisher GG, Kabeto M, Langa KM. Antigenic challenge in the etiology of autoimmune disease in women. J Autoimmun 2012;38:J97–102.
[41] Quintero OL, Amador-Patarroyo MJ, Montoya-Ortiz G, Rojas-Villarraga A, Anaya JM. Autoimmune disease and gender: plausible mechanisms for the female predominance of autoimmunity. J Autoimmun 2012;38:J109–19.
[42] Dillon SP, Kurien BT, Li S, Bruner GR, Kaufman KM, Harley JB, et al. Sex chromosome aneuploidies among men with systemic lupus erythematosus. J Autoimmun 2012;38:J129–34.
[43] Menon R, Di Dario M, Cordiglieri C, Musio S, La Mantia L, Milanese C, et al. Gender-based blood transcriptomes and interactomes in multiple sclerosis: involvement of SP1 dependent gene transcription. J Autoimmun 2012;38:J144–55.
[44] Bogdanos DP, Smyk DS, Rigopoulou EI, Mytilinaiou MG, Heneghan MA, Selmi C, et al. Twin studies in autoimmune disease: genetics, gender and environment. J Autoimmun 2012;38:J156–69.
[45] Pollard KM. Gender differences in autoimmunity associated with exposure to environmental factors. J Autoimmun 2012;38:J177–86.
[46] Borchers AT, Gershwin ME. Sociological differences between women and men: implications for autoimmunity. Autoimmun Rev 2012;11:A413–21.
[47] Selmi C, Brunetta E, Raimondo MG, Meroni PL. The X chromosome and the sex ratio of autoimmunity. Autoimmun Rev 2012;11:A531–7.
[48] Pan Z, Chang C. Gender and the regulation of longevity: implications for autoimmunity. Autoimmun Rev 2012;11:A393–403.
[49] Lee TP, Chiang BL. Sex differences in spontaneous versus induced animal models of autoimmunity. Autoimmun Rev 2012;11:A422–9.
[50] Gatto M, Iaccarino L, Canova M, Zen M, Nalotto L, Ramonda R, et al. Pregnancy and vasculitis: a systematic review of the literature. Autoimmun Rev 2012;11:A447–59.
[51] Bianchi I, Lleo A, Gershwin ME, Invernizzi P. The X chromosome and immune associated genes. J Autoimmun 2012;38:J187–92.
[52] Amur S, Parekh A, Mummaneni P. Sex differences and genomics in autoimmune diseases. J Autoimmun 2012;38:J254–65.
[53] Pennell LM, Galligan CL, Fish EN. Sex affects immunity. J Autoimmun 2012;38:J282–91.
[54] Friedrich K, Rupp C, Hov JR, Steinebrunner N, Weiss KH, Stiehl A, et al. A frequent PNPLA3 variant is a sex specific disease modifier in PSC patients with bile duct stenosis. PloS One 2013;8:e58734.

J Hepatobiliary Pancreat Sci (2014) 21:43–50
DOI: 10.1002/jhbp.50

TOPICS

# Nationwide survey for primary sclerosing cholangitis and IgG4-related sclerosing cholangitis in Japan

**Atsushi Tanaka · Susumu Tazuma · Kazuichi Okazaki · Hirohito Tsubouchi · Kazuo Inui · Hajime Takikawa**

Published online: 29 October 2013


**Abstract**
*Background* We previously conducted nationwide surveys for primary sclerosing cholangitis (PSC) in Japan, and demonstrated several characteristic features of Japanese PSC patients, yet patients with IgG4-related sclerosing cholangitis (IgG4-SC) might be misdiagnosed as PSC. Since the clinical diagnostic criteria of IgG4-SC were established in 2012, we again conducted a nationwide survey to investigate the characteristics of PSC and IgG4-SC lacking pancreatic involvement.
*Methods* The design was a questionnaire-based, multicenter retrospective study. The enrolled subjects were patients with PSC and IgG4-SC without pancreatic involvement diagnosed after 2005.
*Results* We enrolled 197 PSC and 43 IgG4-SC patients without pancreatic lesions. The male dominance was significantly evident in IgG4-SC ($P = 0.006$). In patients with PSC, two peaks in age distribution were clearly observed. IgG4-SC was not detected in any patient younger than 45 years of age. At presentation, serum albumin and IgM were significantly higher in PSC, while serum IgG and IgG4 were significantly elevated in IgG4-SC. Inflammatory bowel disease (IBD) was detected in only 68/197 PSC patients (34%). The prognosis of IgG4-SC was considerably better than that of PSC.
*Conclusion* We confirmed several interesting clinical details of PSC in Japanese patients: two peaks in the age distribution and lower prevalence of IBD.

**Keywords** Autoimmune pancreatitis · Inflammatory bowel diseases · Nationwide survey · Prednisolone · Ursodeoxycholic acid

A. Tanaka (✉) · H. Takikawa
Department of Medicine, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan
e-mail: a-tanaka@med.teikyo-u.ac.jp

S. Tazuma
Department of General Medicine, Hiroshima University Graduate School of Medical Science, Programs of Applied Medicine, Clinical Pharmacotherapy, Hiroshima, Japan

K. Okazaki
Third Department of Internal Medicine, Kansai Medical University, Hirakata, Japan

H. Tsubouchi
Digestive and Lifestyle Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

K. Inui
Department of Internal Medicine, Second Teaching Hospital, Fujita Health University, Nagoya, Japan

This article is a secondary publication based on a study first reported in the *Journal of Japan Biliary Association* (JBA 2013;27:176–187).

## Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown origin, characterized by the progressive destruction of bile ducts caused by diffuse inflammation and fibrosis that eventually leads to liver cirrhosis [1]. The etiopathogenesis of PSC has not been fully understood, and therefore epidemiological studies of PSC are of vital importance to reduce a significant burden to the health care system posed by PSC [2, 3]. We conducted questionnaire-based nationwide retrospective surveys to elucidate the characteristics of PSC in Japan in 1997 and 2003 [4, 5] and demonstrated several characteristic features of Japanese PSC patients, which had been scarcely reported before by epidemiological studies from Europe and North America. In particular, it is notable that there were two peaks in the age distribution at diagnosis, that is, in the 3rd and 7th decades of life, in Japanese patients with PSC [4, 5]. Most previous epidemiological studies from North America and Europe indicated a single age category as the highest risk for developing PSC [6–9]. Interestingly, the age distribution of PSC complicated with inflammatory bowel diseases (IBD) demonstrated a single peak in the 20s, while patients with AIP exhibited a small peak in the 60s.

Meanwhile, accumulating evidence suggested the presence of a different clinical entity of sclerosing cholangitis with elevated serum IgG4 levels, complicated with/without autoimmune pancreatitis (AIP) [10–12]; this disorder is now defined as IgG4-related sclerosing cholangitis (IgG4-SC) [13]. At the time of 2003 when we conducted the nationwide survey for PSC, the concept of IgG4-SC was not well known among physicians and therefore it was likely that patients with IgG4-SC might be misdiagnosed as PSC in the survey. Indeed, not a few PSC patients consisting of the peak at 60s were reported to be complicated with pancreatitis, indicating that these patients should be considered to be IgG4-SC complicating with AIP, not PSC. This was confirmed by the fact that these patients were reported to have good responses to corticosteroid treatment. Moreover, it is of note that the peak in the 60s persists even if patients with pancreatitis are eliminated. Thus it remains possible that IgG4-SC patients without pancreatic involvement may be also misdiagnosed as PSC and thus coordinately comprise the second peak in the elderly in the 2003 survey.

In 2012, the clinical diagnostic criteria of IgG4-SC were established in Japan [14], based mainly on cholangiographic findings. It was thus possible to discriminate PSC from IgG4-SC using these criteria. At this moment, we conducted the third nationwide survey to investigate the characteristics of PSC as well as IgG4-SC, especially IgG4-SC lacking pancreatic involvement and we reported the results from elsewhere in Japanese [15]. In this article, we aimed to describe the unique features of Japanese patients with PSC identified in the current nationwide survey along with a focus on patients with IgG4-SC.

## Patients and methods

### Study design and inclusion criteria

This nationwide survey was conducted as a questionnaire-based, multi-center retrospective study as previous surveys in 1997 and 2003. A questionnaire was sent to the 144 facilities in Japan, in which active members of the Japanese Biliary Association, the intractable hepato-biliary disease study group in Japan, and the research committee to establish diagnostic criteria and development of treatment for systemic IgG4-related sclerosing disease in Japan belonged to, and we asked that the questionnaires be sent back when subjects of the study were present in their facilities. The enrolled subjects in this study were patients with PSC and IgG4-SC without pancreatic involvement diagnosed after 2005, when IgG4-SC was supposed to be well known among clinicians in Japan. Since the differential diagnosis of IgG4-SC from PSC is not problematic when AIP is coexistent with IgG4-SC, we enrolled only cases with IgG4-SC apparently lacking pancreatic lesions.

### Diagnosis of PSC/IgG4-SC

The diagnosis of PSC and IgG4-SC was independently performed by physicians of each facility. The diagnosis of PSC basically was made according to the diagnostic criteria proposed by Lindor et al. [16], mainly depending on cholangiographic studies, biochemical findings, and exclusion of other possible causes. The diagnosis of IgG4-SC was made using the clinical diagnostic criteria of IgG4-SC established by the Japanese Biliary Association in 2012 [14]. Schematic classification of cholangiographic findings of IgG4-SC was made according to the work by Nakazawa et al. [17]. The presence of pancreatic involvement in cases with IgG4-SC was determined by imaging studies in each facility.

### Statistical analyses

As for statistical analyses, continuous variables are presented as means ± standard deviations (SD) if they were normally distributed, or medians if not. Comparison between PSC and IgG4-SC was performed using Student's *t*-test for normal distributed variables, or Mann–Whitney *U*-test for non-normal distributed variables. Dichotomous variables were compared using $\chi^2$ test. All tests were two-tailed and conducted at a 1% level of significance, considering multiple comparisons. All statistical analyses in the current study were performed using IBM SPSS Statistics version 19 (IBM Japan, Tokyo, Japan). This study protocol was approved by the ethical board committee of Teikyo University School of Medicine (#11-121).

## Results

### Demographic characteristics

In Table 1, we demonstrate the demographic characteristics of PSC and IgG4-SC without apparent pancreatic involvement. Overall, we enrolled 197 PSC and 43 IgG4-SC patients without pancreatic lesions. The male/female ratio was 106:91 (54%/46%) in PSC and 33:10 (77%/23%) in IgG4-SC, indicating that male dominance was significantly evident in IgG4-SC ($P$ = 0.006). The age distribution (median [min–max]) was 48.1 [4.0–86.3] in PSC and 69.3 [47.6–87.4] in IgG4-SC. In patients with PSC, two peaks in age distribution, one at 35–40 years and the other at 65–70 years, were clearly observed in the current study as well as shown in the previous surveys (Fig. 1A). Thus it was confirmed again that elderly patients (>65 years) are at high risk for developing PSC in Japan. By contrast, IgG4-SC was not detected in any patient younger than 45 years of age; therefore, the elderly population is also considered to be at high risk for IgG4-SC (Fig. 1B). Symptoms at presentation were

**Table 1** Demographic characteristics of primary sclerosing cholangitis (PSC) and IgG4-SC

| | PSC ($n$ = 197) | IgG4-SC ($n$ = 43) | $P$-value |
|---|---|---|---|
| Sex (male : female) | 106:91 | 33:10 | 0.006 |
| Age[a] | 48.1 [4.0–86.3] | 69.3 [47.6–87.4] | <0.001 |
| *Symptoms at presentation* | | | |
| None | 100 (55%) | 22 (54%) | NS |
| Jaundice | 46 (25%) | 9 (22%) | NS |
| Cholangitis | 37 (20%) | 7 (17%) | NS |
| Skin itching | 31 (17%) | 8 (20%) | NS |
| *Laboratory data*[a] | | | |
| TP | 7.5 [4.8–9.8] | 7.7 [6–11.8] | NS |
| Alb | 3.9 [1.3–4.9] | 3.5 [2.2–4.8] | <0.001 |
| T.Bil | 1.0 [0.2–29.4] | 0.9 [0.4–27.2] | NS |
| AST | 55 [10–751] | 44 [17–426] | NS |
| ALT | 60 [7–927] | 42 [7–260] | NS |
| ALP (xUNL) | 2.25 [0.32–17.0] | 2.05 [0.30-13.74] | NS |
| γGTP | 236 [11–2975] | 265.5 [17–1344] | NS |
| IgG | 1623.5 [508–4456] | 2303 [680–6615] | <0.001 |
| IgG4 | 48.9 [3.0–369] | 519.5 [22.2–2470] | <0.001 |
| IgA | 284 [43.2–1597] | 272.5 [53–963] | NS |
| IgM | 119 [24–599] | 80.5 [20–247] | <0.001 |
| IgE | 177 [4–1816] | 703 [20–3550] | NS |
| CEA | 1.99 [0.3–28] | 2.4 [0.7–14.7] | NS |
| CA19-9 | 19.85 [0.6–6957.2] | 31.2 [2–4862] | NS |
| *Detection of autoantibodies*[b] | | | |
| ANA | 58/105 (36%) | 14/17 (45%) | NS |
| pANCA | 2/88 (2%) | 1/11 (8%) | NS |
| cANCA | 3/48 (6%) | 0/4 (0%) | NS |

[a] Expressed as median [minimum–maximum]

[b] Expressed as positive/negative cases (positive rate)

*ALP* alkaline phosphatase, *Alb* albumin, *ALT* alanine aminotransferase, *ANA* anti-nuclear antibodies, *AST* aspartate aminotransferase, *CA19-9* carbohydrate antigen 19-9, *cANCA* c-anti-neutrophil cytoplasmic antibodies, *CEA* carcinoembryonic antigen, *γGTP* gamma-glutamyl transpeptidase, *Ig* immunoglobulin, *pANCA* p-anti-neutrophil cytoplasmic antibodies, *T.Bil* total bilirubin, *TP* total protein

comparable in both groups, and patients presented as asymptomatic (PSC 55%, IgG4-SC 54%), with jaundice (25%, 22%), with cholangitis (20%, 17%) and with itching (17, 20%). The impaired lesions of bile ducts are shown in Figure 2. Extrahepatic bile ducts were mainly affected in PSC, while intrahepatic bile ducts were dominant lesions in IgG4-SC without pancreatic involvement. Cholangiographic classification of IgG4-SC according to the clinical diagnostic criteria of IgG4-SC in 2012 [14] are demonstrated in Figure 3. Type IV was the most common, probably because cases with IgG4-SC without apparent pancreatic involvement were enrolled in this study.

As for laboratory data at diagnosis (Table 1), serum albumin and IgM were significantly higher in patients with PSC. By contrast, serum IgG, in particular IgG4 (Fig. 4A,B), were significantly elevated in IgG4-SC. Serum IgG4 levels at diagnosis (normal range; <135 mg/dL) were elevated in 15/120 PSC (12.5%) and in 34/38 IgG4-SC (89.5%) patients (Table 2). Thus, the sensitivity and specificity of serum IgG4 levels for diagnosing IgG4-SC without AIP were 89.5% and 87.6%, respectively.

## Complications

With respect to complications, IBD was detected in 68/197 PSC patients (34%), indicating a relatively low prevalence of IBD in Japanese PSC patients as demonstrated in the previous surveys (Fig. 5). IBD was diagnosed as ulcerative colitis (UC) and non-specific colitis in 55 and 10 patients, respectively. Crohn's disease was not reported in any patient. Cholangiocarcinoma (CCA) was found in 14/197 PSC (7.3%), which was higher than the prevalence observed in our previous surveys in Japan. The duration between the diagnosis of PSC and development of CCA was shown in Figure 6. It is of note that most cases with CCA (11/14) were found within one year after the diagnosis of PSC. While

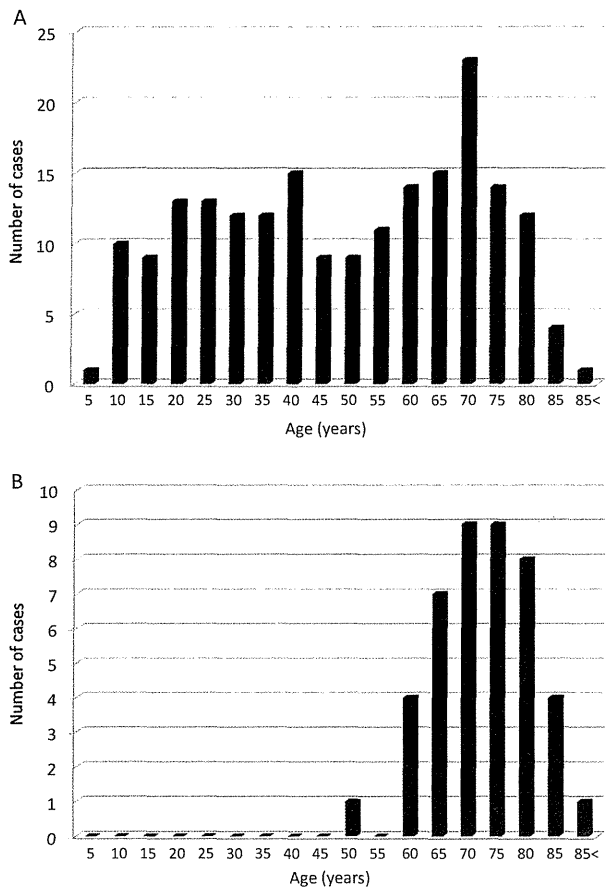


**Fig. 1** The distribution of age at diagnosis of enrolled patients at diagnosis. (**A**) patients with primary sclerosing cholangitis (PSC). (**B**) patients with IgG4-SC lacking apparent pancreatic involvement

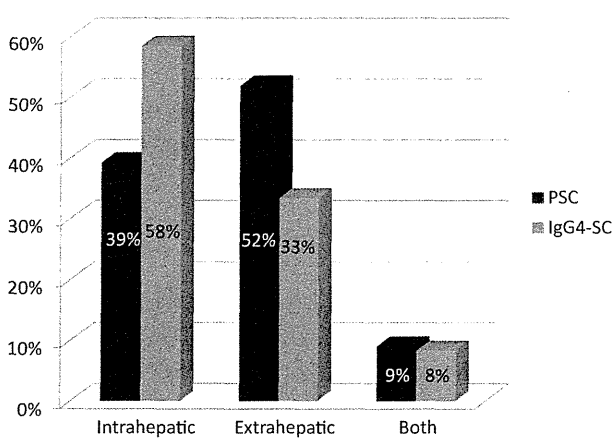


**Fig. 2** The bile duct lesions of primary sclerosing cholangitis (PSC) and IgG4-SC lacking apparent pancreatic involvement

neither IBD nor CCA was noted in patients with IgG4-SC, other IgG4-related diseases, i.e. dacryoadenitis/sialadenitis and retroperitoneal fibrosis, were detected in 6/43 (14%) and 4/43 (9%) patients, respectively.

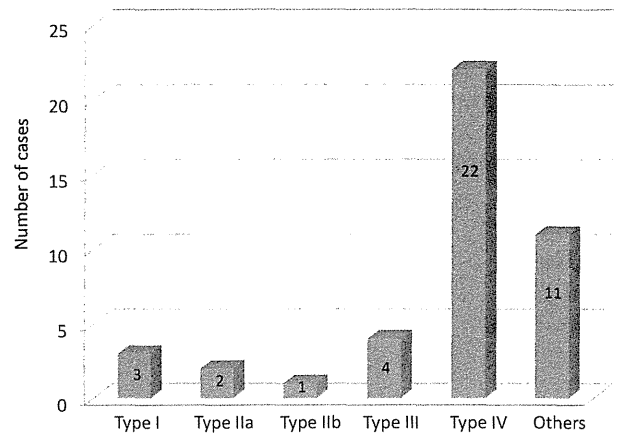


**Fig. 3** Cholangiographic classification of IgG4-SC lacking apparent pancreatic involvement according to the clinical diagnostic criteria of IgG4-SC in 2012 [14]

## Treatment

Medical treatments for PSC are summarized in Table 3. Ursodeoxycholic acid (UDCA) monotherapy was the most frequent choice ($n$ = 89, 45%), followed by combination of UDCA and bezafibrate ($n$ = 28, 14%) and combination of UDCA and prednisolone (PSL; $n$ = 24, 12%). Overall, UDCA, PSL and bezafibrate were used in 150 (76%), 40 (20%) and 39 (20%) out of all PSC cases. Among 40 cases with PSL administration, 18 cases were complicated with ulcerative colitis. As for IgG4-SC, 27 patients out of 36 (75%) in which answers about medical treatment were given were administered with PSL. Initial doses were 30 mg ($n$ = 20), 40 mg ($n$ = 5), 15 mg ($n$ = 1) and mini-pulsed ($n$ = 1). All these cases responded well to PSL.

In Table 4, we summarize endoscopic procedures for patients with PSC and IgG4-SC. Endoscopic dilatation of bile ducts and stenting were performed in 24 (12%) and 46 (23%) PSC patients, respectively. The effect was excellent/fair in 39 and poor/undetermined in 13. In patients with IgG4-SC, dilatation/stenting were performed in four (9%) and 15 (35%) IgG4 patients, respectively. The effect was excellent/fair in 12 and poor/undetermined in two.

## Prognosis

In Figure 7A–C we demonstrated cumulative survival rate of PSC and IgG4-SC. Since we limited the subjects to those diagnosed after 2005 in the current survey, the median follow-up period was relatively short, being 2.7 ± 2.0 years for PSC patients and 2.3 ± 1.8 years for IgG4-SC patients. The 3-year survival rate was 85.0% for PSC and 90.0% for IgG4-SC, and the 3-year transplantation-free survival rate of PSC was 77.3%. Liver transplantation was not performed in

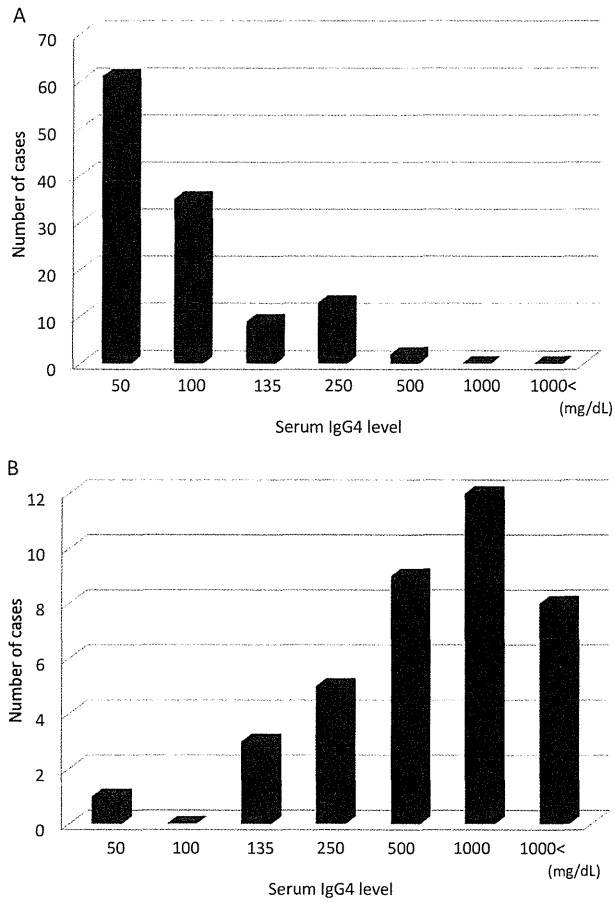


**Fig. 4** The distribution of serum IgG4 level at diagnosis of enrolled patients at diagnosis. (**A**) Patients with primary sclerosing cholangitis (PSC). (**B**) patients with IgG4-SC lacking apparent pancreatic involvement

**Table 2** Comparison of serum IgG4 level between primary sclerosing cholangitis (PSC) and IgG4-S

| | PSC | IgG4-SC |
|---|---|---|
| ≤135 mg/dL | 105 | 4 |
| >135 mg/dL | 15 | 34 |

any of the IgG4-SC patients. These figures indicate that the prognosis of IgG4-SC was considerably better than that of PSC, probably due to the excellent response to corticosteroid therapy observed in IgG4-SC patients.

## Discussion

In the current study we demonstrated the results of a nationwide survey for PSC and IgG4-SC without apparent AIP, and again confirmed the second peak in the elderly of patients with PSC (Fig. 1A). In the previous survey in 2003 when the clinical concept of IgG4-SC was not well known

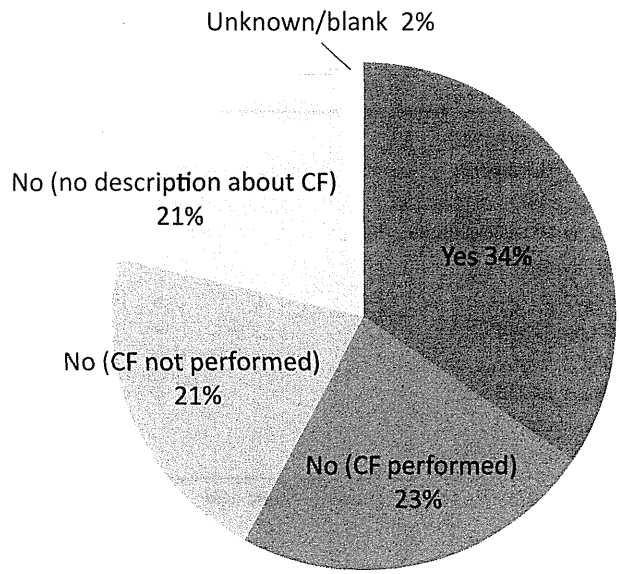


**Fig. 5** Presence of inflammatory bowel diseases (IBD) in cases with primary sclerosing cholangitis (PSC). *CF* colonofiberscopy

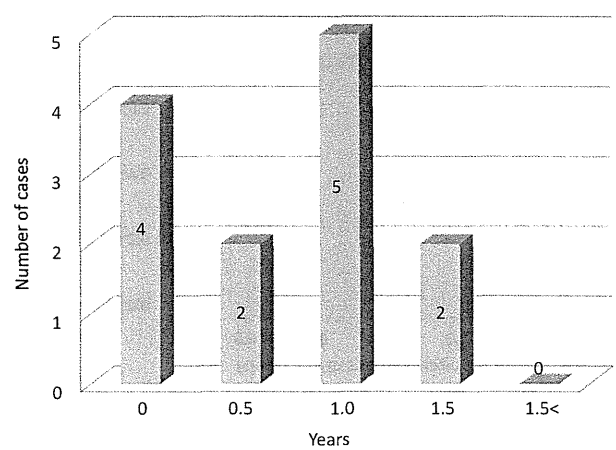


**Fig. 6** Duration between diagnosis of primary sclerosing cholangitis (PSC) and diagnosis of cholangiocarcinoma

among Japanese gastroenterologists, it remained possible that IgG4-SC might be misdiagnosed as PSC and thus compromise the second peak in the elderly. In other words, the second peak in the 60s may not result from special characteristics of Japanese PSC itself; rather, they may be explained by "contamination" of the PSC population with IgG4-SC patients.

Thereafter, based on the great contribution of clinical researchers in Japan, both endoscopists and pathologists, to the establishment of the concept of IgG4-SC, the Japanese Biliary Association established the clinical diagnostic criteria of IgG4-SC in 2012 [14]. The criteria mainly consist of the following four items: (1) characteristic cholangiographic findings; (2) elevated serum IgG4 levels; (3) coexistence of