Serum IgG4 cut-off of 70 mg/dL is associated with a shorter time to cirrhosis decompensation and liver transplantation in primary sclerosing cholangitis patients

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ABSTRACT

BACKGROUND: Primary sclerosing cholangitis (PSC) is an immune-mediated biliary disorder of unknown etiology with no effective treatment. The purpose of this study was to better prognosticate the development of cirrhosis, decompensation, and requirement for liver transplantation (LT) in PSC patients based on serum immunoglobulin G4 (IgG4) levels.

METHODS: A retrospective chart review was conducted on PSC patients seen at the University of Alberta Hospital between 2002 and 2017. PSC patients were categorized as high IgG4 group (≥70 mg/dL) or normal IgG4 group (<70 mg/dL). Laboratory parameters, clinical characteristics, and outcomes were compared between the groups.

RESULTS: One hundred and ten patients were followed over a mean period of 7.3 (SD 5) years. Seventy-two patients (66%) were male, the mean age at diagnosis of PSC was 35 (SD 15) years, and inflammatory bowel disease (IBD) was present in 80 patients (73%). High IgG4 levels were found in 37 patients (34%). PSC patients with high IgG4 had a shorter mean cholangitis-free survival time (5.3 versus 10.4 years, \(p = 0.02\)), cirrhosis-free survival time (8.7 versus 13.0 years, \(p = 0.02\)), and LT-free survival time (9.3 years versus 18.9 years, \(p <0.001\)). IgG4 ≥70 mg/dL was independently associated with liver decompensation and LT-free outcomes. A cut-off IgG4 value of ≥70 mg/dL performed better than a cut-off value of ≥140 mg/dL to predict time to LT (area under the curve [AUC] 0.68, \(p = 0.03\), sensitivity 72%, specificity 78%).

CONCLUSIONS: Serum IgG4 ≥70 mg/dL in PSC predicts a shorter time to cirrhosis decompensation and LT.

KEYWORDS: autoimmune liver disease; cirrhosis; liver transplantation; primary sclerosing cholangitis; prognostication

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a progressive chronic liver disease that leads to destruction of the biliary tract, chronic cholestasis, multifocal biliary strictures, and cirrhosis (1). The incidence rate of PSC is 0.77 per 100,000 person-years, and up to 70% of PSC patients suffer from concomitant inflammatory bowel disease (IBD) (2,3). In the absence of effective therapy, over 50% of patients require liver transplantation (LT) within 10–15 years of symptom onset (4). Furthermore, 20%–25% of PSC patients will exhibit recurrence 10 years post-LT (5).

As the disease course is variable and most PSC patients will progress to LT, several prognostic models for predicting clinical outcomes in PSC have been developed. The revised Mayo risk score is the most commonly used model; however, it has inherent limitations (1,6). Other models incorporating non-invasive fibrosis biomarkers and magnetic resonance imaging (MRI)/elastography also exist (7–9). In 2006, Mendes et al demonstrated that PSC patients with an elevated serum IgG4 had higher bilirubin, alkaline phosphatase, PSC Mayo risk scores, and a shorter time to LT (1.7 versus 6.5 years, \( p = 0.0009 \)) (10).

PSC patients with elevated serum immunoglobulin G4 (IgG4) levels likely represent a PSC subtype, which can be identified in 9%–22% of PSC patients depending on the cut-off level used to demarcate an elevated IgG4 (11). While some population-based studies have supported the use of serum IgG4 as a prognostic marker for liver outcomes in PSC patients, others have not (11–14). Due to the inconsistency and relative lack of reports, we aimed to better define the relevance of assessing IgG4 levels in PSC patients. Specifically, the primary purpose of this study was to prognosticate the development of complications related to portal hypertension and the requirement for LT in PSC patients based on the hypothesis that PSC patients with elevated serum IgG4 levels have worse outcomes and more aggressive disease.

METHODS

Study patients

A retrospective chart review was conducted on PSC patients followed at the University of Alberta between 2002 and 2017. The University of Alberta’s human research ethics board approved this study in January 2017 (Pro00069785). PSC diagnosis was based on standard criteria including (1) cholestatic liver enzyme elevation, (2) characteristic magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography findings, and (3) exclusion of secondary causes of cholangitis (15). A diagnosis of PSC was confirmed on chart review if no other typical features of IgG4-related disease were present. PSC patients who had at least one serum IgG4 level prior to LT or last follow-up were included in the study. In patients with multiple IgG4 levels, the maximum IgG4 level was chosen. Serum anti-smooth muscle antibody (positive titre defined by at least 1:20), IgG, IgG4, aspartate aminotransferase (AST), aspartate aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, international normalized ratio (INR), albumin, creatinine, platelet count, and concomitant IBD were recorded. Moreover, PSC phenotype (intrahepatic/extrahepatic involvement), first episode of cholangitis (defined as abdominal pain, fever, jaundice, and a dilated common bile duct on imaging), initial requirement for biliary endoscopic treatment, and development of cholangiocarcinoma (CCA), as well as the presence of cirrhosis, liver decompensation, and the requirement for LT, were also documented.

The presence of cirrhosis was defined by histological cirrhosis in liver tissue examination with demonstration of a complete regenerative nodule (16), an increased FibroScan reading (>14 kPa) (FibroScan, Echosens, Paris, France), radiological findings of cirrhosis by computed tomography (CT) or MRI, and/or the development of portal hypertension or its complications. Decompensation date was recorded as the first episode of variceal bleeding, ascites, or hepatic encephalopathy. Model for end-stage liver disease (MELD) scores and PSC Mayo risk scores were calculated at the time of max IgG4 ±1 month (ie, within either 4 weeks prior to the time when max IgG4 level was drawn or within 4 weeks after it was drawn). The PSC Mayo risk score was calculated as per http://www.mayoclinic.org/gi-rst/mayomodel3.html. Patients with autoimmune pancreatitis (AIP), IgG4 associated cholangitis (IAC), primary biliary cholangitis (PBC), or overlap syndrome with autoimmune hepatitis were excluded (17).

IgG4 determination

IgG4 levels at the University of Alberta were quantified by the nephelometric method using Binding
Serum IgG4 is associated with PSC liver outcomes

RESULTS

Patient characteristics
During this period, we evaluated 445 PSC patients seen in our autoimmune liver disease clinic. A total of 325 of the 445 patients were excluded as they did not have at least one IgG4 test. After chart review, 10 more patients were excluded as they had diagnoses of autoimmune pancreatitis (1), PBC (1), IgG4 associated cholangitis (3), and autoimmune overlap (5) (Figure 1). Since a significant number of patients were not eligible for inclusion, we briefly analyzed patients included (n = 110) and excluded (n = 335) from this study. We did not find significant differences in relation to age at PSC diagnosis (mean 34.9 [SD 15.3] years versus mean 37.0 [SD 16.2] years, \( p = 0.3 \)), male gender (66% versus 67%, \( p = 0.8 \)) and LT-free mean survival time (15.63 [SD 1.31] years versus 18.46 [SD 1.19] years, \( p = 0.3 \)).

Statistical analysis
Data are reported as mean and standard deviation (SD) for continuous variables and as a percentage for categorical variables. Time to cholangitis, biliary endoscopic treatment, CCA, portal hypertensive complications, cirrhosis, and LT-free survival were calculated by Kaplan–Meier methods and compared by the log-rank (Mantel–Cox) test. Significant predictors of the outcomes were determined using univariate and multivariate Cox proportional hazard models, and the results were reported as hazard ratios (HR) with 95% CIs. A receiver operating characteristics (ROC) curve was plotted to measure how serum IgG4 performed in predicting LT within 10 years. Model capability to distinguish between outcome groups was assessed using the AUC. The value with the highest Youden index (sensitivity + specificity − 1) was considered as the optimal cut-off.

PSC phenotype
The presence of dominant strictures, the location of biliary involvement, the prevalence of cholangitis and the need for endoscopic intervention did not differ between PSC patients with high IgG4 and PSC patients with normal IgG4 (Table 1).
Table 1: PSC patient demographics and characteristics

| Characteristic                                                      | All patients; n = 110 | High IgG4 (≥70 mg/dL); n = 37 | Normal IgG4 (<70 mg/dL); n = 73 | P       |
|--------------------------------------------------------------------|-----------------------|-------------------------------|--------------------------------|---------|
| Age at PSC diagnosis, y, mean (SD)                                 | 34.9 (15.3)           | 29.9 (15.4)                   | 37.3 (14.9)                   | 0.04    |
| Gender, male                                                       | 72 (66)               | 26 (70)                       | 46 (63)                       | 0.5     |
| Max IgG4, mg/dL, mean (SD)                                         | 69.2 (67.5)           | 147.4 (60.3)                  | 29.5 (18.3)                   | <0.001  |
| Time from PSC diagnosis to max IgG4, y, mean (SD)                  | 10.5 (11.9)           | 9.2 (8.6)                     | 11.2 (8.6)                    | 0.4     |
| Inflammatory bowel disease                                        | 80 (73)               | 26 (70)                       | 54 (74)                       | 0.8     |
| Ulcerative colitis                                                | 54 (48)               | 18 (69)                       | 36 (67)                       | 0.9     |
| Crohn’s disease                                                   | 22 (27)               | 7 (27)                        | 15 (28)                       |         |
| Inflammatory bowel disease, type unclassified                     | 4 (5)                 | 1 (4)                         | 3 (5)                         |         |
| Pancreatic involvement†                                            | 4 (4)                 | 1 (3)                         | 3 (4)                         | 0.6     |
| Dominant stricture                                                | 37 (34)               | 11 (30)                       | 23 (32)                       | 1.0     |
| Biliary involvement                                               |                       |                               |                               |         |
| Intrahepatic                                                      | 38 (35)               | 13 (35)                       | 25 (34)                       |         |
| Extrahepatic                                                      | 0 (0)                 | 0 (0)                         | 0 (0)                         | 0.4     |
| Intra/extrahepatic                                                | 72 (65)               | 24 (65)                       | 48 (66)                       | 0.07    |
| Cholangitis                                                        | 29 (26)               | 14 (38)                       | 15 (21)                       |         |
| Endoscopic intervention                                           | 29 (26)               | 9 (24)                        | 20 (27)                       | 0.8     |
| Cholangiocarcinoma                                                | 6 (5)                 | 2 (5)                         | 4 (5)                         | 1.0     |

Note: Boldface indicates statistically significant at P <0.05
* Unless otherwise indicated
† Pancreatic involvement was defined as pancreatic duct strictures or parenchymal enlargement on imaging
PSC = Primary sclerosing cholangitis; IgG4 = Immunoglobulin G4

IgG4 results

The mean number of IgG4 determinations was 2.4 (SD 2) (range 1–8), and 92% of PSC patients had IgG4 determinations drawn with the reference range 7–74 mg/dL (4–164 mg/dL – 2%, 3–200 mg/dL – 5%, <139 mg/dL – 1%). Of the 37 patients who had a max IgG4 ≥70 mg/dL, over the follow-up period, 10 patients (27%) changed from having an elevated IgG4 to a normal IgG4. At the time of max IgG4 determination, patients with high IgG4 had higher alkaline phosphatase (436 [SD 311] U/L versus 279 [SD 271] U/L, p = 0.009), higher INR (1.2 [SD 0.3] versus 1.1 [SD 0.1], p = 0.04), higher IgG (15.4 [SD 4.9] g/L versus 13.3 [SD 4.9] g/L, p = 0.03), lower albumin (36 [SD 9] g/L versus 40 [SD 6] g/L, p = 0.02), and higher MELD scores (11.4 [SD 4.9] versus 8.6 [SD 4.2], p = 0.006) (Table 2). A cut-off IgG4 value of ≥70 mg/dL performed better than a cut-off value of ≥140 mg/dL in predicting the need for LT within 10 years of diagnosis (AUC 0.68, p = 0.03, sensitivity 72%, specificity 78% versus sensitivity 33%, specificity 85%, Figure 2).

Cholangitis, endoscopic treatment, and cholangiocarcinoma

The mean cholangitis-free survival time in patients with high serum IgG4 was 5.3 years (95% CI 3.9–10.8 years) compared to 10.4 years (95% CI 9.1–11.8 years) in those with normal IgG4 levels (Figure 3a, p = 0.02). On univariate analysis, a higher risk of cholangitis was associated with high serum IgG4 (HR 2.68, 95% CI 1.16–6.22, p = 0.02),
Serum IgG4 is associated with PSC liver outcomes

### Table 2: Laboratory parameters and clinical scores at the time of max IgG4 determination

| Laboratory parameter | Mean (SD)* | P   |
|----------------------|------------|-----|
| All patients; n = 110 |            |     |
| High IgG4 (≥70 mg/dL); n = 37 |       |     |
| Normal IgG4 (<70 mg/dL); n = 73 |       |     |
| ALT, U/L             | 100 (121)  | 0.2 |
| AST, U/L             | 87 (130)   | 0.1 |
| ALP, U/L             | 331 (294)  | 0.01|
| Bilirubin, µmol/L    | 41 (66)    | 0.07|
| INR                  | 1.1 (0.2)  | 0.04|
| Albumin, g/L         | 39 (7)     | 0.02|
| Platelets, ×10⁹/L    | 222 (96)   | 0.9 |
| SMA, no. (%)         | 19 (17)    | 0.4 |
| IgG, g/L             | 13.9 (5.0) | 0.03|
| MELD                 | 9.6 (4.6)  | 0.01|
| PSC Mayo risk score  | 0.31 (1.5) | 0.06|

Note: Boldface indicates statistically significant at P < 0.05
* Unless otherwise indicated

IgG4 = Immunoglobulin G4; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ALP = Alkaline phosphatase; INR = International normalized ratio; SMA = Anti-smooth muscle antibodies; MELD = Model for end-stage liver disease; PSC = Primary sclerosing cholangitis

PSC Mayo risk score (HR 1.71, 95% CI 1.32–2.21, p < 0.001), and MELD score (HR 1.16, 95% CI 1.08–1.24, p < 0.001). Multivariate analysis revealed these three variables were not independently associated with the outcome of cholangitis (Appendix 1, Supplemental Table 1). The mean survival-free times for biliary endoscopic treatment [7.5 years (95% CI 7.1–11.1) versus 8.7 years (95% CI 6.6–10.9), p = 0.21] and CCA development [7.7 years (95% CI 7.1–8.4) versus 12.1 years (95% CI 11.4–12.8), p = 0.89] did not differ between the high and normal IgG4 groups respectively.

### Development of cirrhosis, liver decompensation, and requirement for liver transplantation

The mean cirrhosis-free survival time in patients with elevated IgG4 levels was 8.7 years (95% CI 7.3–10.1) compared to 13.0 years (95% CI 10.7–15.3) in those with normal IgG4 levels, p = 0.02 (Figure 3b). On univariate analysis, shorter cirrhosis-free survival times were associated with age at diagnosis (HR 1.03, 95% CI 1.01–1.05, p = 0.04), high serum IgG4 (HR 2.07, 95% CI 1.14–3.78, p = 0.02), PSC Mayo risk score (HR 1.62, 95% CI 1.31–1.99, p < 0.001) and MELD score (HR 1.09, 95% CI 1.04–1.16, p = 0.001) (Appendix 1, Supplemental Table 2). Multivariate analysis revealed that only the PSC Mayo risk score was independently associated with the outcome of cirrhosis development (HR 2.28, 95% CI 1.26–4.14, p = 0.007).

There was a statistical trend toward shorter liver decompensation-free survival in patients with elevated serum IgG4 compared to those with normal serum IgG4 (8.4 years [95% CI 6.5–10.2] versus 15.5 years [95% CI 12.8–18.1], p = 0.06) (Figure 3c). On univariate analysis, risk of liver decompensation was associated with age at diagnosis (HR 1.03, 95% CI 1.01–1.05, p = 0.04), high serum IgG4 (HR 2.84, 95% CI 1.17–6.88, p = 0.02), PSC Mayo risk score (HR 1.85, 95% CI 1.37–2.50, p < 0.001), and MELD score (HR 1.11, 95% CI 1.02–1.20, p = 0.01) (Appendix 1, Supplemental Table 3). Multivariate analysis revealed that only high serum IgG4 (HR 7.44, 95% CI 1.49–37.1, p = 0.01), and the PSC Mayo risk score (HR 2.84, 95% CI 1.15–7.05, p = 0.02) were independently associated with liver decompensation.

Last, the mean LT-free survival in patients with elevated IgG4 was 9.3 years (95% CI 8.0–10.7)
higher INR, higher IgG, lower albumin, and higher MELD scores. Furthermore, a serum IgG4 level ≥70 mg/dL predicted a shorter time to cholangitis, cirrhosis, and LT as well as was independently associated with cirrhosis decompensation and LT outcomes. Contrary to serum IgG4 cut-offs published previously in the literature (Table 3), a serum IgG4 ≥70 mg/dL better predicted a shorter time to LT within 10 years from the time of PSC diagnosis compared to 18.9 years (95% CI 15.7–22.1) in PSC patients with normal IgG4, $p < 0.001$ (Figure 3d).

On univariate analysis, shorter LT-free survival times were associated with serum IgG4 (HR 1.01, 95% CI 1.00–1.01, $p = 0.004$), high serum IgG4 (HR 5.66, 95% CI 2.40–13.35, $p < 0.001$), PSC Mayo risk score (HR 1.90, 95% CI 1.44–2.52, $p < 0.001$), and MELD score (HR 1.12, 95% CI 1.05–1.20, $p = 0.001$) (Appendix 1, Supplemental Table 4). Multivariate analysis revealed that high serum IgG4 (HR 3.68, 95% CI 1.27–10.65, $p = 0.02$) and PSC Mayo risk score (HR 2.44, 95% CI 1.50–3.96, $p < 0.001$) were independently associated with LT-free survival.

**DISCUSSION**

In our cohort of PSC patients, we identified that patients with a serum IgG4 ≥70 mg/dL had a younger age at diagnosis, higher alkaline phosphatase, compared to 18.9 years (95% CI 15.7–22.1) in PSC patients with normal IgG4, $p < 0.001$ (Figure 3d). On univariate analysis, shorter LT-free survival times were associated with serum IgG4 (HR 1.01, 95% CI 1.00–1.01, $p = 0.004$), high serum IgG4 (HR 5.66, 95% CI 2.40–13.35, $p < 0.001$), PSC Mayo risk score (HR 1.90, 95% CI 1.44–2.52, $p < 0.001$), and MELD score (HR 1.12, 95% CI 1.05–1.20, $p = 0.001$) (Appendix 1, Supplemental Table 4). Multivariate analysis revealed that high serum IgG4 (HR 3.68, 95% CI 1.27–10.65, $p = 0.02$) and PSC Mayo risk score (HR 2.44, 95% CI 1.50–3.96, $p < 0.001$) were independently associated with LT-free survival.

**DISCUSSION**

In our cohort of PSC patients, we identified that patients with a serum IgG4 ≥70 mg/dL had a younger age at diagnosis, higher alkaline phosphatase, higher INR, higher IgG, lower albumin, and higher MELD scores. Furthermore, a serum IgG4 level ≥70 mg/dL predicted a shorter time to cholangitis, cirrhosis, and LT as well as was independently associated with cirrhosis decompensation and LT outcomes. Contrary to serum IgG4 cut-offs published previously in the literature (Table 3), a serum IgG4 ≥70 mg/dL better predicted a shorter time to LT within 10 years from the time of PSC diagnosis compared to a serum IgG4 ≥140 mg/dL.

Our study confirms that there is a subset of PSC patients with elevated serum IgG4 who do not meet the criteria for IAC and may have a worse prognosis. As in Mendes et al (10) and Berntsen et al (13), our PSC patients with an elevated IgG4 had a shorter time to LT [(9 [SD 1] years versus 19 [SD 2] years, HR 5.66 (2.40–13.35)]. Nevertheless, in a large retrospective cohort analysis of 435 Japanese
Table 3: Serum IgG4 association with liver outcomes in primary sclerosing cholangitis

| Study                  | Country             | Patients (no.) | IgG4 threshold (mg/dL) | Elevated IgG4 (%) | Outcome                                                                 |
|------------------------|---------------------|----------------|------------------------|-------------------|-------------------------------------------------------------------------|
| Mendes et al, 2006 (10) | United States       | 127            | >140                   | 9                 | Higher bilirubin, PSC Mayo risk score and decreased transplant-free survival |
| Zhang et al, 2010 (20)  | United States       | 81             | ≥140                   | 22                | No difference                                                           |
| Bjornsson et al, 2011 (26) | United States     | 285            | >140                   | 12                | NA                                                                      |
| Alswat et al, 2012 (12) | Canada              | 101*           | 104                    | 22                | Higher alkaline phosphatase and higher PSC Mayo risk score              |
| Vosskuhl et al, 2012 (29) | Germany             | 23             | >140                   | 26                | NA                                                                      |
| Boonstra et al, 2014 (14) | Netherlands, England | 310         | >140                   | 15                | Lower albumin                                                          |
| Benito de Valle et al, 2014 (30) | Germany, Sweden | 345          | >140                   | 10                | Higher bilirubin and alkaline phosphatase                               |
| Berntsen et al, 2015 (13) | Norway              | 263            | ≥135                   | 18                | Higher PSC Mayo risk score and decreased transplant-free survival       |
| Tanaka et al, 2016 (11)  | Japan               | 216            | ≥135                   | 13                | Lower albumin                                                          |
| Moon et al, 2017 (19)   | South Korea         | 47             | ≥135                   | 17                | NA                                                                      |

* Total patient number reflects sclerosing cholangitis from various etiologies including PSC

IgG4 = Immunoglobulin G4; PSC = Primary sclerosing cholangitis; NA = Not applicable

PSC patients, elevated serum IgG4 levels at diagnosis did not portend a worse prognosis (11). Although the time to LT did not differ based on serum IgG4 levels, PSC patients with an elevated IgG4 trended toward being more likely to undergo LT (11% versus 3%, \( p = 0.054 \)); however, this association became less strong after controlling for confounding variables. A couple of factors could have contributed to these discrepant findings. First, an elevated serum IgG4 was defined as a value ≥135 mg/dL compared to ≥70 mg/dL. Second, IBD was only present in 40% of patients, similar to other countries in East Asia (19), potentially suggesting a different PSC phenotype in Japan.

While most studies have explored the prognostic significance of serum IgG4 in PSC, Zhang et al investigated the significance of IgG4 positive plasma cells in liver explants of PSC patients (20). They demonstrated that PSC patients with increased IgG4 positive plasma cells were more likely to display recurrence of disease post-transplant and had a significantly shorter time to transplant. In contrast, although nearly half (58/122) of PSC liver explants from a Canadian cohort had evidence of hilar IgG4-positive staining, PSC patients with increased IgG4 staining were not predisposed to increased recurrence post-transplantation (21). The potential role of IgG4 in PSC, whether it be in serum or tissue, is still debatable. IgG4 may play a pathogenic role, such as in pemphigus vulgaris, or reflect an epiphenomenon of an inflammatory response (22). Interestingly, studies have also demonstrated that IAC and PSC have contrasting host-microbe interactions that may be involved in disease pathogenesis (23). The higher levels of IgG4 may possibly reflect changes in the bile microbiota and subclinical cholangitis in patients with more advanced liver disease.

One of the strengths of our study was that we had a well-phenotyped cohort of PSC patients followed for almost a decade. Although there is a possibility that IgG4-associated cholangitis (IAC) patients were misclassified as PSC patients with elevated IgG4 in our population, it is reassuring that the mean age of diagnosis of our patients was 35 years, with 73% of patients having concomitant IBD and less than 5% of patients having pancreatic involvement, which is more reflective of PSC patients rather than IAC patients (19,24). Furthermore, we are the first group to observe the
In summary, we have demonstrated that a serum IgG4 ≥70 mg/dL in PSC patients is a non-invasive prognostication marker that predicts worse liver outcomes and, more specifically, a shorter time to cirrhosis decompensation and LT. Moreover, our findings suggest that the definition of what constitutes an elevated IgG4 in PSC patients should not be directly extrapolated from criteria developed for IgG4-related disease. It is evident that an elevated IgG4 >140 mg/dL used for diagnostic purposes in IAC may not be the best predictor of poor prognosis in PSC patients. As this is a single-centre cohort study, these results will need to be replicated in other centres and ideally in a prospective multicentre trial. While the significance of IgG4 remains speculative, we propose that serum IgG4 be used as risk stratification in therapeutic trials to potentially help PSC patients with a more aggressive phenotype.

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ETHICS APPROVAL: The University of Alberta’s human research ethics board approved this study in January 2017 (Pro00069785). The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The ethics certificate information is available upon request.

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Serum IgG4 is associated with PSC liver outcomes

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APPENDIX 1

**Supplemental Table 1:** Features associated with cholangitis by univariate and multivariate Cox proportional hazards analysis

| Characteristics       | Univariate     | Multivariate |          |          |
|-----------------------|----------------|--------------|----------|----------|
|                       | HR (95% CI)    | P            | HR (95% CI) | P        |
| Gender (male)         | 0.94 (0.38–2.30) | 0.9          | –         | –        |
| Age at diagnosis, y   | 0.99 (0.96–1.02) | 0.5          | –         | –        |
| IBD                   | 0.81 (0.33–2.03) | 0.7          | –         | –        |
| IgG4^* , mg/dL        | 1.002 (0.99–1.01) | 0.4          | –         | –        |
| High IgG4 (≥70 mg/dL) | 2.68 (1.16–6.22) | **0.02**     | 1.04 (0.32–3.39) | 0.9 |
| PSC Mayo risk score   | 1.71 (1.32–2.21) | **<0.001**   | 1.37 (0.78–2.42) | 0.3 |
| MELD score            | 1.16 (1.08–1.24) | **<0.001**   | 1.07 (0.91–1.27) | 0.4 |

Note: Boldface indicates statistically significant at P <0.05

* Max IgG4 (throughout the patient’s history until last follow-up)

HR = Hazard ratio; IBD = Inflammatory bowel disease; IgG4 = Immunoglobulin G4; PSC = Primary sclerosing cholangitis; MELD = Model for end-stage liver disease

**Supplemental Table 2:** Features associated with the development of cirrhosis by univariate and multivariate Cox proportional hazards analysis

| Characteristics       | Univariate     | Multivariate |          |          |
|-----------------------|----------------|--------------|----------|----------|
|                       | HR (95% CI)    | P            | HR (95% CI) | P        |
| Gender (male)         | 1.42 (0.78–2.59) | 0.3          | –         | –        |
| Age at diagnosis, y   | 1.03 (1.01–1.05) | **0.04**     | 1.00 (0.97–1.03) | 0.85 |
| IBD                   | 0.67 (0.36–1.25) | 0.2          | –         | –        |
| IgG4^* , mg/dL        | 1.01 (0.99–1.01) | 0.09         | –         | –        |
| High IgG4 (≥70 mg/dL) | 2.07 (1.14–3.78) | **0.02**     | 1.82 (0.65–5.09) | 0.25 |
| PSC Mayo risk score   | 1.62 (1.31–1.99) | **<0.001**   | 2.28 (1.26–4.14) | **0.01** |
| MELD score            | 1.09 (1.04–1.16) | **0.001**    | 0.99 (0.88–1.11) | 0.84 |

Note: Boldface indicates statistically significant at P <0.05

* Max IgG4 (throughout the patient’s history until last follow-up)

HR = Hazard ratio; IBD = Inflammatory bowel disease; IgG4 = Immunoglobulin G4; PSC = Primary sclerosing cholangitis; MELD = Model for end-stage liver disease
### Supplemental Table 3: Features associated with liver decompensation-free survival by univariate and multivariate Cox proportional hazards analysis

| Characteristics | Univariate | P | Multivariate | P |
|-----------------|------------|---|--------------|---|
| Gender (male)   | 0.75 (0.27–2.06) | 0.6 | – | – |
| Age at diagnosis, y | 1.03 (1.01–1.05) | 0.04 | 1.02 (0.98–1.06) | 0.3 |
| IBD             | 0.86 (0.34–2.21) | 0.8 | – | – |
| IgG4*, mg/dL    | 1.01 (1.00–1.013) | 0.08 | – | – |
| High IgG4 (≥70 mg/dL) | 2.84 (1.17–6.88) | 0.02 | 7.44 (1.49–37.1) | 0.01 |
| PSC Mayo risk score | 1.85 (1.37–2.50) | <0.001 | 2.84 (1.15–7.05) | 0.02 |
| MELD score      | 1.11 (1.02–1.20) | 0.01 | 0.97 (0.81–1.16) | 0.7 |

Note: Boldface indicates statistically significant at P <0.05
* Max IgG4 (throughout the patient’s history until last follow-up)

IgG4 = Immunoglobulin G4; HR = Hazard ratio; IBD = Inflammatory bowel disease; PSC = Primary sclerosing cholangitis; MELD = Model for end-stage liver disease

### Supplemental Table 4: Features associated with liver transplant-free survival by univariate and multivariate Cox proportional hazards analysis

| Characteristics | Univariate | P | Multivariate | P |
|-----------------|------------|---|--------------|---|
| Gender (male)   | 1.56 (0.68–3.55) | 0.3 | – | – |
| Age at diagnosis, y | 1.01 (0.98–1.05) | 0.5 | – | – |
| IBD             | 0.62 (2.66–1.47) | 0.3 | – | – |
| IgG4*, mg/dL    | 1.01 (1.00–1.013) | 0.004 | – | – |
| High IgG4 (≥70 mg/dL) | 5.66 (2.40–13.35) | <0.001 | 3.68 (1.27–10.65) | 0.02 |
| PSC Mayo risk score | 1.90 (1.44–2.52) | <0.001 | 2.44 (1.50–3.96) | <0.001 |
| MELD score      | 1.12 (1.05–1.20) | 0.001 | 0.92 (0.82–1.03) | 0.2 |

Note: Boldface indicates statistically significant at P <0.05
* Max IgG4 (throughout the patient’s history until last follow-up)

IgG4 = Immunoglobulin G4; HR = Hazard ratio; IBD = Inflammatory bowel disease; PSC = Primary sclerosing cholangitis; MELD = Model for end-stage liver disease