Primary sclerosing cholangitis with moderately elevated serum-IgG4 – characterization and outcome of a distinct variant phenotype

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Handling Editor: Ana Lleo

Abstract

Background and aims: Immunoglobulin G4-associated cholangitis (IAC) is characterized by distinctly elevated immunoglobulin G4 in serum (slgG4) and responds well to corticosteroid therapy. Primary Sclerosing Cholangitis (PSC) is a progressive liver disease without causal treatment options usually not responding to immunosuppression. Increased serum levels of slgG4 in patients with PSC, that do not meet criteria of IAC, have been reported in 10%-25%. Therefore, we aimed to characterize this subgroup of patients in a retrospective, multicenter study.

Methods: slgG4 values of 289 patients with PSC from three German university hospitals were analysed. Patients with elevated slgG4 levels were identified and further characterized by clinical and biochemical parameters and by cholangiographic presentation. Clinical endpoints, death and liver transplantation were compared between groups. Parameters associated with outcome were identified with Cox regression analysis.

Results: 14.5% of patients with PSC showed increased slgG4 levels (PSC-IgG4), presented with significantly higher (P < .02) albumin, aspartate-aminotransferase, bilirubin and alkaline phosphatase and had a significant lower prevalence of a concomitant autoimmune hepatitis (P = .025). Cholangiogram obtained via ERC showed extrahepatic dominant strictures more often in the PSC-IgG4 subgroup (P = .047). The disease severity models Amsterdam-Oxford-Score (P = .018) and Mayo-Risk-Score (P = .025) predicted lower survival rates for the PSC-IgG4 subgroup. Transplant-free survival after first diagnosis of PSC was shorter in patients with elevated slgG4 (11.6 vs 15.1 years, P = .001).

Abbreviations: AIH, autoimmune hepatitis; AOM, Amsterdam Oxford model; CCA, cholangiocarcinoma; CD, Crohn’s disease; ERC, endoscopic retrograde cholangiography; HBM, hepatobiliary malignancy; IAC, immunoglobulin (Ig)-G4-associated cholangitis; IBD, inflammatory bowel disease; LT, liver transplantation; MELD, model for end-stage liver disease; MRC, magnetic resonance cholangiography; PSC, primary sclerosing cholangitis; PSC-IgG4, subgroup with elevated IgG4; PSC-N, subgroup with normal IgG4-values; sdPSC, small duct PSC; slgG4, serum-IgG4; SUMI-HDEHD, sum of the intrahepatic scoring and the modified extrahepatic scoring; UC, ulcerative colitis; ULN, upper limit of the normal range.

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1 INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare progressive liver disease frequently leading to biliary cirrhosis and is associated with an increased risk of cholangiocarcinoma (CCA). PSC is usually categorized as autoimmune liver disease alongside autoimmune hepatitis, primary biliary cirrhosis and IgG4-associated cholangitis (IAC).2,3 Pathophysiology of PSC is widely unknown resulting in limited causal therapeutic options. Several pathomechanisms have been thoroughly investigated proposing a multifactorial etiology for PSC, reflecting the interface of microbiological, genetic and immunological dysregulations.10-12 The clinical course of this cholestatic liver disease can be extremely variable. Modifiable risk factors accelerating disease progression are not sufficiently identified yet. Useful laboratory parameters for monitoring disease severity are cholestasis parameters like alkaline phosphatase.13,14 In the initial diagnostic work-up of PSC, autoantibodies like antimitochondrial antibodies, anti-nuclear antibodies, smooth muscle antibodies, soluble-liver-antigen antibodies, liver kidney microsomal antigen antibodies, anti-neutrophil cytoplasmic antibodies and serum-IgG4 should be determined in addition to distinguish PSC from the other autoimmune liver diseases. Differentiating between those entities can pose a significant clinical challenge. Especially IAC can mimic PSC phenotypically and clinically rendering correct diagnosis difficult in clinical practice15,16; but prognosis and therapeutic strategies of the two diseases differ profoundly. IAC as a hepatobiliary manifestation of IgG4-associated diseases usually presents with unambiguously increased IgG4-serum concentrations and responds well to corticosteroid therapy.17 IgG4-associated cholangitis is a separate disease entity within the known cholangiopathies, characterized by typical findings according to HISORt or Japanese criteria.15 Patients suffering from PSC typically show strong associations with inflammatory bowel disease (IBD), are of younger age and are highly susceptible for CCA and colorectal carcinomas and do not respond to corticosteroids.18 Whereas Jaundice, abdominal pain and autoimmune pancreatitis or other IgG4-associated diseases occur more often in IAC. Patients with AIC seem to have a much lower risk to develop CCA, when compared with PSC.17,19,20 Prognosis of IAC is therefore better as compared to PSC. Incidental findings of elevated serum-IgG4 (sIgG4) in PSC patients have been reported16,21,22 and could influence transplant-free survival.21 An IgG4-PSC subgroup has therefore been suggested.21 Standard recommended therapeutic strategies for these patients do not exist and the significance of treatment with corticosteroids remains elusive.23

We have therefore conducted a large multicenter retrospective clinical study with 289 PSC patients from three German university hospitals with a long-term follow-up to analyse the role of serum-IgG4 in the disease course of PSC patients and its correlation with specific clinical phenotypes.

2 PATIENTS AND METHODS

2.1 Patients

289 patients with well-characterized PSC from three German university hospitals and with at least one measurement of their serum IgG4-values were included in this retrospective multicenter study.

Patient characteristics like age at PSC diagnosis, gender, subtype of PSC, date of diagnosis and subtype of inflammatory bowel disease, colorectal and hepatobiliary malignancies, death, liver transplantation or last follow-up alive and biochemical parameters were obtained from each clinic’s database. Baseline laboratory parameters

Conclusion: Patients with PSC and elevated sIgG4 should be considered as a distinct subgroup, characterized by different clinical and cholangiographical features and are associated with an inferior outcome.

KEYWORDS

immunoglobulin G4, immunoglobulin G4-related disease, primary sclerosing cholangitis, survival

Lay summary

Primary sclerosing cholangitis (PSC) is a rare biliary liver disease frequently progressing to liver failure and/or cancer, without a causal treatment and with only limited options to slow down disease progression. Immunoglobulin G4 (IgG4)-related disease is a systemic disease affecting many organ systems, including bile ducts. In the present study, we identify specific differences in clinical presentation and bile duct alterations in PSC patients with borderline- or moderately elevated IgG4 compared to those with normal IgG4. Furthermore, we confirm that this specific subgroup of PSC patients has a significantly decreased transplant-free survival. Hence, we suggest PSC patients with elevated IgG4 being viewed as a specific subgroup when designing future PSC studies. In addition, there is an urgent need to evaluate prospectively, whether these patients could benefit from early immunosuppressive therapy.
were determined at time point of first IgG4-measurement and were available for the Bonn and Hannover cohort. Detailed information on the cholangiographic presentation and variceal status of the esophagus was available for patients from Bonn and Hannover. Clinical information about administered steroid therapy was available for the Bonn cohort. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Medical Faculty of the University of Bonn (approval number 003/21).

2.2 | Statistical analyses

Data were analysed using the SPSS 22.0 software package for Windows (SPSS Inc.). Continuous variables are presented as means or medians and were compared by Mann-Whitney U-test. Categorical variables were compared by chi-squared test. Univariable and multivariable Cox regression analyses were fit to assess the impact of individual covariates on the instantaneous rate of clinical events. The actuarial survival free of liver transplantation rate was estimated by Kaplan-Meier survival analysis. The differences between the actuarial estimates were analysed using the log-rank test. All tests were two-tailed and a P-value of .05 or less was considered statistically significant.

2.3 | Diagnostic criteria

All patients were diagnosed with PSC in accordance with the current European or German guidelines. Cases showing typical histological findings in line with PSC, but lacking bile duct changes in magnetic resonance cholangiography (MRC) or endoscopic retrograde cholangiography (ERC) were classified as small duct PSC (sPSC). Additionally, PSC patients with biochemical, serological and/or histological features of autoimmune hepatitis (AIH) were diagnosed as PSC/AIH variant-phenotype. IBD phenotypes were determined according to local expertise and were classified as ulcerative colitis (UC), Crohn’s disease (CD), or indeterminate colitis, in keeping with current consensus guidelines.

2.4 | IgG4-Measurement

Serum-IgG4-values were available for all included patients. Firstly, routinely documented IgG4-measurements were chosen for our analyses. Cases with first IgG4 value determined after liver transplantation (LT) or more than 6 months previous to or 15 years after the date of first diagnosis of PSC were excluded. In a subset of 27 patients subsequent IgG4-measurements were available.

In the Hannover cohort, IgG4 was determined via immunoturbidimetry using assays by Siemens Healthcare Diagnostics. The normal value range for these patients was set from 0.08 to 1.4 g/L according to the laboratory’s specifications. The assays used in the University hospitals Essen and Bonn based on immunonephelometry by Siemens Healthcare Diagnostics to determine IgG4 in serum with normal values ranging from 0.03 to 2.01 g/L. After 2017 diagnostics in Bonn were changed to turbidimetric immunoassays from Binding Site with lower normal range values from 39 to 864 mg/L.

The patient-subgroup with elevated IgG4 (PSC-IgG4) was defined as that the first serum-IgG4 exceeded the upper limit of the normal range (ULN) according to the respective assay in these patients. Accordingly, the group of patients with normal IgG4-values is referred to as PSC-N. Since unit of measurement as well as normal range values differed between assay and centres the ratio of first measured Ig4 in relation to ULN was determined for non-parametric comparison.

3 | RESULTS

3.1 | Patient characteristics

Median age of PSC patients at time of diagnosis was 35 years and 66.4% were male. Concomitant IBD was diagnosed in 61.2% of PSC patients. Because of LT in 10% patients and death before LT in 9% patients the median transplant-free survival time after PSC diagnosis was 14.7 years. Median time of follow-up was 6.5 years (range 0.02-19 years).

3.2 | Subgroup of PSC patients with elevated IgG4-serum-concentrations

The mean ratio of IgG4 in relation to the ULN in the entire cohort was 36%. Increased IgG4 serum-levels were observed in 14.5% of PSC patients (PSC-IgG4). Mean IgG4-level was 132% of the ULN in these patients. (see Figure 1). Sequential measurements of IgG4 at different time points during disease course were available in 27 patients (median: two measurements). IgG4 remained stable in 25 patients. One patient with IgG4 within normal range in the first measurement developed a slightly increased IgG4 value of 880 mg/L (cut off 864 mg/L) at a later time point. In another patient, IgG4 decreased from elevated IgG4 to a borderline normal value of 852 mg/L (Cut-off 864 mg/L).

IgG4 was measured with a median time of 3.8 years after first diagnosis of PSC (range −0.4-14.9 years). There was a trend towards earlier measurements during disease course in patients with elevated IgG4 (median time in PSC-IgG4 = 761 days vs median time in PSC-N 1461 days.) (P = .088). In a subgroup analysis of 112 patients with IgG4 measurements within 6 months prior to diagnosis and 2 years after diagnosis of PSC median time from first diagnosis to IgG4 measurement was 100 days in PSC-N vs 1 day in PSC-IgG4 (P = .2). (Table S1).

The histogram of IgG4 distribution (Figure 1) shows two separate peaks around the median of 0.3 for the PSC-N group and 1.32, respectively, reflecting the PSC-IgG4 group. The nadir in between.
peaks is set at a value of 0.9. When using 0.9 of the ULN instead of the ULN as cut-off value 15.9% of the patients in our cohort were identified as IgG4 (0.9) - PSC patients. Distribution of age, gender, presence of an IBD (see Table 1) or IBD subgroup (CD, CU, Indeterminate colitis) (see Table 1) as well as small duct-phenotype were comparable between PSC-IgG4 and PSC-N groups (see Table 1). There were significantly less patients with IgG4-values above the ULN in the subgroup of patients with an AIH-phenotype (see Table 1).

Clinical data concerning concomitant medication were available for 100 patients of the Bonn and Hannover cohort. Corticosteroids were administered in 6.6% of all patients. Patients with PSC/AIH-phenotype received systemic steroid therapy (75%) at time of first IgG4 measurement significantly more often than PSC patients without AIH-phenotype (11.4%) ($P < .01$). In cases of concomitant IBD 21.9% were treated with corticosteroids at time of first IgG4-measurement. Patient treated with corticosteroids at time of IgG4 measurement, regardless of the indication for steroid therapy, had a significantly lower IgG4 ratio ($P = .033$).

AST, Bilirubin and alkaline phosphatase were significantly higher, and albumin was significantly lower in IgG4- PSC group (see Table 1).

### 3.3 Risk models for disease severity predict lower survival rates in IgG4-PSC patients

Today, for estimating survival rates based on clinical and laboratory values two models, the revised Natural History Model for Primary Sclerosing Cholangitis (Mayo-Risk-score) and the Amsterdam-Oxford-score are established in clinical practice. Furthermore, the model for End-Stage Liver Disease (MELD) represents a validated scoring system for severity of chronic liver diseases and is used to estimate urgency for liver transplantation in many regions. We calculated those risk models for the patients from the Bonn and Hannover cohort (Figure 2).

Mayo risk score (Figure 2A) was calculated in 125 patients (including 19 PSC-IgG4 patients) with a median score of 0.218 (predicting a 4-year survival rate of 92%) in PSC-IgG4 patients, which was significantly higher compared to median value of – 0.540 (predicting a 4-year survival rate of 96%) in PSC-N group ($P = .025$).

Similarly, Amsterdam Oxford Model (Figure 2B) was applied to 124 patients (including 20 PSC-IgG4 patients). Calculated risk score in PSC-IgG4 group was 1.88. Estimated transplant-free survival rate is about 74% in 10 years or 61% in 15 years. PSC-N patients showed a significantly lower Amsterdam- Oxford score of 1.34 ($P = .018$). Corresponding survival rates are about 84% in 10 years or 75% in 15 years.

Parameters for assessing MELD-score (Figure 2C) were available for 198 patients (including 35 PSC-IgG4 patients) and indicated a trend towards more advanced disease stage for PSC-IgG4 with a median MELD of 8.7 in comparison to PSC-N patients (median MELD 6.7) ($P = .056$).

With a lower cut-off ratio at 0.9-fold of the ULN not only Mayo risk score (PSC-IgG4(0.9) 0.22 vs PSC-N(0.9) -0.54; $P = .011$) but also Amsterdam Oxford Model (PSC-IgG4(0.9) 1.88 vs PSC-N(0.9) 1.33, $P = .007$) showed even more pronounced and significant differences between PSC-N(0.9) and PSC-IgG4(0.9). Only with the lower cut-off

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**FIGURE 1** Distribution of IgG4 ratio between PSC-N (ratio ≤ 1) and PSC-IgG4 (ratio > 1) with median ratio of each group

**TABLE 1** Patient characteristics of PSC-N compared to PSC-IgG4; median values are presented for age and laboratory parameters. Distribution of gender, AIH phenotype and sdPSC are given in percentage. $P$-values are calculated with Kruskal-Wallis Test for *<0.05; **<0.01; ***<0.001.

| Parameter | PSC-N | PSC-IgG4 | $P$ value |
|-----------|-------|----------|-----------|
| Gender    | 64.8% male | 76.2% male | .162 |
| Age at Diagnosis | 34 years | 37 years | .532 |
| Small duct PSC | 3.2% | none | .608 |
| AIH phenotype | 18.2% | 4.3% | .025* |
| IBD       | 61% | 64.3% | .734 |
| Ulcerative colitis | –48.4% | –52.4% | .626 |
| Crohn’s disease | –10.6% | –7.1% | |
| Indeterminate colitis | –2.0% | –4.8% | |
| ALT       | 51 | 53 | .574 |
| AST       | 38 | 55 | .015* |
| INR       | 1.00 | 1.03 | .364 |
| Bilirubin | 0.64 | 1.00 | .016* |
| ALP       | 143 | 235 | .008** |
| gGT       | 116 | 202 | .215 |
| Creatinine | 0.78 | 0.75 | .642 |
| WBC       | 6.6 | 6.5 | .569 |
| PC        | 257 | 238 | .451 |
| CRP       | 3.0 | 5.5 | .150 |
| IgG       | 13.1 g/L | 15.1 g/L | <.001*** |
| Albumin   | 41 | 39 | .006** |
ratio MELD reached a statistical significant difference ($P = .014$) between PSC-IgG4 (MELD 9.3) and PSC-N (MELD 6.6).

Similarly, results regarding prognostic scores within the subgroup of patients with IgG4 measurement within a more limited time-frame showed significantly higher scores in PSC-IgG4 (see Table S1).

### 3.4 Elevated IgG4 is associated with inferior transplant-free survival

To analyse the impact of different IgG4-levels on the combined endpoint liver transplantation or death, Kaplan-Meier estimates of transplant-free survival were compared by log-rank test. Patients with IgG4-serum values above the respective ULN had a significant inferior transplant-free survival compared to PSC patients with normal IgG4-levels ($P = .001$) (see Figure 3). Results were still significant when excluding patients with IgG4-measurement later than 2 years after PSC diagnosis (see Table S1). 17.4% of the PSC-IgG4 group underwent liver transplantation and another 17.4% died during follow-up vs 8.5% and 7.5%, respectively, for the PSC-N group. The median transplant-free survival in PSC patients with normal IgG4-values was 15.1 years. Patients with higher IgG4 had a significantly shorter transplant-free survival of 11.6 years. 5-year and 10-year survival rates were 77% and 67% in PSC-IgG4 patients vs 94% and 85% in PSC-N patients.

In univariable analyses, apart from IgG4, parameters like bilirubin, alkaline phosphatase, AST, albumin, age at first diagnosis PSC, Amsterdam Oxford Model, Mayo Risk Score and MELD were associated with survival (see Table 2). AIH-phenotype, small-duct PSC, concomitant IBD or dominant stricture ($P = .1$) did not have an impact on transplant-free survival rates (see Table 2). A trend towards inferior transplant-free survival for patients with extrahepatic dominant strictures could be observed ($P = .078$). Steroid administration at time of first IgG4-measurement did not influence transplant-free survival rates, neither did steroid therapy during any time in course of disease (see Table 2).

In multivariable Cox regression with IgG4, bilirubin, ALP, AST, albumin, age at diagnosis of PSC and MELD, only ALP (0.016) and age at diagnosis of PSC ($P = .006$) proved to be independent risk factors for survival. Since AOM and Mayo risk score are comprised of the individual biochemical parameters both models were excluded from the regression analysis to avoid redundancy.

PSC-IgG4 had a significant shorter transplant-free survival time in univariable ($P = .021$; HR 2.09, CI 1.12-3.92) Cox regression analysis as well.

### 3.5 IgG4-concentrations are not associated with PSC-related malignancies

Hepatobiliary malignancy (HBM), defined as cholangiocellular carcinoma (=13/247) or gallbladder cancer (=4/247) developed in 6.9% of the PSC-N patients. Patients of the PSC-IgG4 group were diagnosed...
2929

ZHOU et al.

with hepatobiliary malignancies in 11.9%. (CCA = 4/24; gallbladder CA = 1/42). Compared to the PSC-N group these frequencies did not differ statistically ($P = .34$) (see Table 3).

Colorectal cancer could be observed in 4.1% of all patients. The frequency of colorectal malignancy was also not statistically different between patients with physiological IgG4- serum concentrations ($n = 10/209$) and PSC patients with elevated IgG4- values (none) (see Table 3).

3.6 | PSC-IgG4 mainly presents with extrahepatic dominant strictures

116 patients of the MHH and Bonn cohort underwent ERC at time of first IgG4 measurement.

There was a statistical trend towards a higher frequency of overall high-grade biliary strictures in PSC-IgG4 (76.9% = 10/13) compared to PSC-N (51.9% = 40/77) ($P = .133$).

Furthermore, patients with IgG4-Levels above the norm presented with isolated extrahepatic dominant strictures (strictures <1.5 mm in the hilum, the common hepatic duct and/or the common bile duct) significantly more often (53.8% = 7/13) than patients with low IgG4-concentrations (24.7% = 19/77) ($P = .047$).

When setting the cut-off point at 0.9-fold of the ULN 78.6% (11/14) of PSC-IgG4(0.9) patients displayed high-grade strictures overall compared to 51.3% (39/76) of PSC-N(0.9) patients ($P = .08$).

Likewise, extrahepatic dominant strictures were observed even more frequently in the PSC-IgG4(0.9) group (57.1% = 8/14) than in the PSC-N(0.9) group (23.7% = 18/76) when distinguishing serum-IgG4 at a lower cut-off ratio of 0.9 ($P = .021$).

Amsterdam cholangiographic classification of PSC was used to separately describe extrahepatic and intrahepatic changes of bile ducts. The sum of the intrahepatic scoring and the modified extra-hepatic scoring (SUMIHDEHD-score") is calculated based on the Amsterdam classification taking overall bile duct alterations into account. Results did not differ between patients with IgG4- levels above or below the ULN with a score of 3 being the most frequent classification in both groups regardless of chosen cut-off point ($p(1.0-fold) = 0.851$ (see Table 4); $p(0.9-fold) = 0.736$ (data not shown)). Choledocholithiasis occurred in 8.9% in PSC-N group and 15.4% in PSC-IgG4 group ($P = .610$).

4 | DISCUSSION

Elevated Serum-IgG4 has been described in patients with PSC before.21,22,28,29 Studies regarding clinical relevance of IgG4-elevation

### TABLE 2

|                | Univariable Cox regression analysis | Multivariable Cox regression analysis |
|----------------|------------------------------------|--------------------------------------|
|                | Hazard ratio | 95 % CI | $P$-value | Hazard ratio | 95 % CI | $P$-value |
| PSC-IgG4 subgroup | 2.40 | 1.28-4.50 | .06 | 0.45 | 0.17-1.19 | .11 |
| Steroid therapy |  |  |  |  |  |  |
| At time of first IgG4 | 1.11 |  | .895 | 1.11 | 1.00-1.23 | .053 |
| At any time | 1.64 |  | .416 | 1.00 | 1.001-1.005 | .016 |
| Age at first diagnosis PSC | 1.05 | 1.02-1.07 | <.001 | 1.06 | 1.02-1.09 | .001 |
| AIH phenotype | 0.85 |  | .678 | 1.00 | 1.001-1.005 | .013 |
| Small duct PSC | 0.05 |  | .581 | 1.00 | 1.001-1.005 | .013 |
| IBD | 0.91 |  | .727 | 1.00 | 1.001-1.005 | .013 |
| Bilirubin | 1.15 | 1.1-1.2 | <.001 | 1.11 | 1.00-1.23 | .053 |
| Alkaline phosphatase | 1.00 | 1.002-1.004 | <.001 | 1.00 | 1.001-1.005 | .016 |
| AST | 1.00 | 1.001-1.005 | <.001 | 1.00 | 1.001-1.005 | .016 |
| Albumin | 0.88 | 0.83-0.93 | <.001 | 1.03 | 0.94-1.2 | .574 |
| Mayo risk score | 1.60 | 1.13-2.25 | .007 | 1.00 | 0.94-1.2 | .574 |
| Amsterdam oxford score | 1.91 | 1.08-3.36 | <.001 | 1.00 | 0.9-2.13 | .274 |

Significant $P$-values (<.05) are marked in bold.

### TABLE 3

Frequency of colorectal or hepatobiliary malignancies in PSC patients according to IgG4 measurement. $P$- value was calculated with Chi-squared test

|                | PSC-N | PSC-IgG4 | $P$ value |
|----------------|-------|----------|-----------|
| CRC            | 4.8%  | none     | .367      |
| HBM            | 6.9%  | 11.9%    | .340      |
| Gallbladder cancer | -1.6% | -2.4%    |           |
| Cholangiocellular carcinoma | -5.3% | -9.5%    |           |

With hepatobiliary malignancies in 11.9%. (CCA = 4/24; gallbladder CA = 1/42). Compared to the PSC-N group these frequencies did not differ statistically ($P = .34$) (see Table 3).

Colorectal cancer could be observed in 4.1% of all patients. The frequency of colorectal malignancy was also not statistically different between patients with physiological IgG4- serumconcentrations ($n = 10/209$) and PSC patients with elevated IgG4-values (none) (see Table 3).
in PSC present different, and partially contradicting, findings and hypotheses. Incidences of 10%-25% have been reported. In most studies serum concentrations between 100-140 mg/dL were chosen as cut-off values to distinguish PSC patients with normal IgG4-values from a subgroup of patients with high IgG4. Since methods of quantitative analysis differed between centres in our cohort with distinct reference ranges of serum IgG4 we consider the use of relative values to be more appropriate.

Here, we report in a large and representative multicenter cohort of 289 patients from three German liver transplantation centres IgG4-levels above the normal range in 14.5% of the PSC patients (PSC-IgG4). IgG4-values were only moderately elevated (median at 1.3-fold) in our cohort as opposed to highly increased values to be more appropriate.

The separating line between those two peaks was determined at 0.9-fold of the ULN, thus suggesting that a slightly lower cut-off value might be more suitable to distinguish the subgroup of PSC-IgG4 patients from classical PSC patients.

IBD is typically associated with PSC, and also a risk factor for disease progression or recurrence after transplantation. It was therefore noteworthy that we could not confirm previous observations on a reduced prevalence of IBD in PSC-IgG4 compared to classical PSC. Navaneethan et al. did also not observe higher incidence of IBD but different UC patterns and higher inflammatory bowel disease activity, resulting in shorter colectomy-free time. Unfortunately, in our cohort activity of IBD was not assessed.

We observed a significant lower frequency of elevated IgG4-levels in patients with the autoimmune hepatitis variant phenotype of PSC. Recent reports showed that IgG4-expression can be associated with AIH as well, leading to speculations whether AIH might be the hepatic manifestation of IgG4-related diseases. Pathophysiologically, it therefore seemed unlikely for PSC/AIH-phenotype to function as a protective factor for IgG4-elevation. When further investigating this subgroup, it was apparent that patients with PSC/AIH-phenotype received systemic steroid therapy at the time of IgG4-measurement significantly more often (75%) than PSC patients without concomitant AIH (11.4%). On the other hand, only one patient treated with steroids had increased IgG4-values. It is well-known that in IgG4-related diseases and moreover in PSC patients with the AIH variant phenotype. In a prospective study from Björansson et al. a small number of PSC patients with elevated IgG4-values were treated with prednisolone and responded with significant decrease of ALP and IgG4 in serum. Nevertheless, controlled, randomized studies with well-defined clinical endpoints and assessment of endoscopic response are urgently needed to evaluate the relevance of immunosuppressive therapy.

One of the main findings of this retrospective multicenter study was the significantly lower transplant-free survival of patients with elevated serum IgG4. These findings are similar to the results of Mendes et al.  and Culver et al. or the borderline significant univariate analyses of the Japanese study by Tanaka et al. Whereas in a recent study including 123 patients from the region of Götaland in Sweden and 222 patients from Berlin, Germany, de Valle et al. could not confirm elevated IgG4-values to be associated with outcome in PSC patients. Of note, the latter study included also patients from a population-based study and not only from transplant centres. All studies showing an impact of IgG4 on survival in PSC (including the present analysis) were from transplant centres only. It is well-known that the mean survival of PSC patients in population based studies is markedly longer than in studies that include only patients from transplant centres. We therefore assume that the impact of IgG4 on transplant-free survival is somewhat exaggerated in these high-risk cohorts, while in population-based studies it only manifests statistically in much larger cohorts.

Our data did not show any evidence that malignancy could be the main reason of shorter transplant-free survival in PSC-IgG4, as the incidence of neither colorectal nor hepatobiliary malignancies was significantly associated with increased IgG4-levels. According to previous reports, IAC is not strongly associated with a higher risk for CCA although two studies suggested that patients with IgG4-related disease might have a higher risk to develop pancreaticobiliary malignancies.

To further investigate inferior survival rates in this subgroup we analysed the baseline biochemical parameters and found that PSC-IgG4 patients presented with significantly higher levels for bilirubin and ALP. These findings are mostly in line with the previous studies. Additionally, we found that AST was significantly higher and albumin was significantly lower in PSC-IgG4 as well. Altogether these findings reflect a more severe stage of PSC regarding cholestasis and inflammatory activity in the PSC-IgG4 subgroup. An important and well validated prognostic tool is the Amsterdam Oxford Model (AOM). It comprises of laboratory surrogate parameters reflecting cholestasis, liver function and portal hypertension, most of which were significantly associated with transplant-free survival in Cox regression analysis in our cohort. Consequently, calculated AOM-scores were significantly higher in PSC-IgG4 compared to PSC patients without IgG4-elevation, predicting a lower transplant-free

| Score of 1 | Score of 2 | Score of 3 | Score of 4 | Score of 5 |
|------------|------------|------------|------------|------------|
| PSC        | 8.2% (6)   | 17.8% (13) | 53.4% (39) | 15.1% (11) | 5.5% (4)   |
| IgG4-PSC   | 14.3% (2)  | 21.4% (3)  | 35.7% (5)  | 28.6% (4)  | None       |

Table 4: Summary of IgG4-PSC and IgG4-PSC with elevated levels
survival. Furthermore, clinical aspects of progressive cirrhosis as variceal bleeding expressed by the Mayo risk score predicted a lower probability of survival for PSC-IgG4. These results are consistent with previous reports\(^2^{,29}\) and suggest that IgG4-associated inferior survival most likely results from more severe cholestasis, progressing to biliary cirrhosis and leading to impaired liver function. It is important to note, that in line with the results from our multivariable regression analyses IgG4 does not resemble an independent, direct prognostic parameter such as the Mayo risk score, the Amsterdam-Oxford score or MELD. Instead of applying IgG4 as a continuous variable to predict outcome, IgG4 in relation to the normal range should be viewed as a discriminator to distinguish an immunological variant form of PSC patients with a less favourable outcome because of a more progressive disease course.

Biliary strictures as visualized in the cholangiogram are the main characteristic feature of PSC and of IAC and have been proven to be of prognostic relevance as well. Patients with higher serum-IgG4 levels presented with a different cholangiogram in ERC compared to PSC-N. Whilst overall biliary involvement assessed via the Amsterdam ERC classification score (SUMIHDEH)\(^{41}\) was comparable between groups, the PSC-IgG4 group had a significantly increased prevalence of extrahepatic dominant strictures compared to PSC-N. Therefore, our data describe for the first time that the PSC-IgG4 subgroup presents with a distinct cholangiographic pattern that is characterized by more extrahepatic dominant strictures. The latter, as well as the trend towards higher prevalence of high-grade strictures overall in our cohort, might be one factor contributing to inferior outcome of PSC-IgG4. Dominant strictures are a known risk factor for a more severe disease course with faster progression to cirrhosis\(^42\) and have been described in context with plasma cell infiltration in explant livers of PSC patients before.\(^43\)

Interestingly, when analysing frequency distribution of IgG4-concentrations the separating line between high and normal IgG4-values was observed at 0.9-fold of the ULN. Our analyses showed that with a slightly lower cut-off value of 0.9-fold the differences regarding the prevalence of extrahepatic dominant strictures and high-grade strictures overall were even more pronounced with 78.6% and 58.1% in the PSC-IgG4\(_{(0.9)}\) group compared to 76.9% and 53.8%, respectively, in the PSC-IgG4 group. Prognostic scores were indicating inferior outcome or more advanced liver impairment, respectively, in PSC-IgG4 for both cut-off values, but the lower cut-off MELD was significantly different between PSC-IgG4\(_{(0.9)}\) (MELD 8.7) and PSC-N\(_{(0.9)}\) (MELD 6.7). These findings might suggest that bile duct alterations and consecutively prognosis are affected already at what is conventionally considered as borderline elevated serum-IgG4. For future trials it should therefore be considered to define the specific subgroup of PSC with elevated IgG4 with an even lower cut-off of 0.9 of the ULN of the respective test for measurement of IgG4.

In summary, our data provide additional evidence that besides the well-known phenotypic variations, small-duct PSC and PSC-AIH-variant, there are further subgroup of PSC patients with elevated IgG4-levels that presents with a distinct cholangiographic phenotype. This subgroup presents with a more advanced disease stage at first diagnosis as reflected by biochemical surrogate parameters of cholestasis and impaired liver function. Consecutively, this subgroup of PSC with elevated IgG4-values has a significantly inferior transplant-free survival. In contrast with prognostic models high IgG4 in PSC should not be valued as a predictor for death or transplant but as a parameter to identify a variant form with a more aggressive disease course.

Since all our patients were treated at transplant centres, we cannot rule out a certain selection bias, particularly with regard to disease stage. Furthermore, on account of the retrospective study design time points of IgG4 measurements were not standardized, which is a limiting factor when interpreting the implications of IgG4 in the disease course of PSC. However, considering the robust results from the analyses including only IgG4 measurement that were determined in early disease course as well as the observations from sequential IgG4 measurements in a subgroup analysis we assume that IgG4 might be a rather stable parameter during natural disease course of PSC.

Nevertheless, we strongly suggest including routine IgG4 measurement in the standard-work-up of PSC at first diagnosis and to include this parameter for patient stratification in future therapeutic studies. Administration of corticosteroids was associated with lower levels of serum-IgG4 and therefore systemic corticosteroid-therapy might have positive effects on diseases progression, analogue to IAC. Hence, there is a strong need to investigate further the therapeutic value of corticosteroid use for this subgroup. Identifying PSC patients who could profit from immunosuppression would offer treatment options in this otherwise continuously progressive disease.

ACKNOWLEDGEMENT
None.

CONFLICT OF INTEREST
None.

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SUPPORTING INFORMATION

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**How to cite this article:** Zhou T, Lenzen H, Dold L, et al. Primary sclerosing cholangitis with moderately elevated serum-IgG4 – characterization and outcome of a distinct variant phenotype. *Liver Int.* 2021;41:2924–2933. https://doi.org/10.1111/liv.15028