



Impact of age at diagnosis on disease progression in patients with primary sclerosing cholangitis

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Abstract

Background: The median age of diagnosis of primary sclerosing cholangitis (PSC) is ~30–40 years.

Objective: We aimed to analyse disease progression and liver-dependent survival in patients diagnosed with PSC after 50 years of age.

Methods: Patients with PSC were analysed with regard to their age at diagnosis. Patients with a first diagnosis of PSC after the age of 50 years were considered as the late-onset group.

Results: A total of 32/215 (14.9%) patients were diagnosed with PSC after 50 years of age. The proportion of females was significantly higher among patients with late-onset PSC (48.4 vs. 27.3%; $p = 0.02$). Patients with later diagnosis required dilatation therapy more often due to dominant stenosis (84.2 vs. 53.1%; $p = 0.01$) and suffered from recurrent cholangitis more often (48.3 vs. 21.0%; $p = 0.003$). Patients with late-onset PSC had reduced transplantation-free survival (10.5 ± 0.6 years vs. 20.8 ± 1.7 years, $p < 0.0001$), with progredient liver failure and cholangiocarcinoma as the leading causes of death.

Conclusions: Patients with later age at diagnosis of PSC displayed a different clinical phenotype with a different sex ratio, immune status and an increased risk for progressive liver failure and biliary malignancies.

Keywords

Primary sclerosing cholangitis, immunosenescence, dominant stenosis, cholangiocarcinoma, inflammatory bowel disease, liver transplantation

Received: 16 December 2016; accepted: 29 May 2017

Key summary

- Patients with later age at diagnosis of PSC display a different clinical phenotype with a significantly higher proportion of females.
- Patients with later diagnosis require biliary dilatation therapy more often due to dominant stenosis and restenosis and suffer from recurrent cholangitis more often.
- Patients with late-onset PSC had reduced transplantation-free survival with progredient liver failure and cholangiocarcinoma as the leading causes of death.

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterised by inflammation and stricture formation in the biliary system, progressing to liver cirrhosis in the majority of cases.¹⁻³ The aetiology is still not resolved, but many studies suggest an immunological context.^{4,5} Besides the frequent association with inflammatory bowel disease (IBD) and other immune-mediated diseases,⁶⁻⁸ there is a clear male predominance. The median age at onset of the disease varies between different ethnic groups, but is generally between 30 and 40 years.⁹⁻¹¹ In many cases, time of onset of disease until clinical obvious symptoms is unknown. A recent study found a high prevalence of subclinical PSC in patients with IBD, detected by magnetic resonance cholangiography.¹²

In Japan, a second peak in age distribution was reported, with an onset occurring over 50 years of age. PSC occurring after 50 years of age shows distinct clinical features, such as a weaker association with ulcerative colitis (UC) and lower IgM serum levels.¹³ In many immune-mediated diseases, late onset is associated with a different clinical phenotype.¹⁴ In myasthenia gravis, early onset shows female preponderance, while late-onset patients have a male predominance, and both groups develop different alterations in the thymus tissue.¹⁵ Furthermore, in systemic lupus erythematosus, the sex ratio varies between early- and late-onset cohorts, with a higher mortality in patients with disease onset in childhood.¹⁶ In UC, late-onset disease is associated with higher rates of proctitis and left-sided colitis and an increased risk for cytomegalovirus and herpes virus infections.¹⁷ Changes in immune cell function may explain characteristics of patients with late onset of different immune-mediated diseases.

In this study, we analysed the prevalence of patients with late-onset PSC, defined as a first diagnosis after the age of 50 years, and evaluated their clinical characteristics and immunological activity markers in serum and bile fluids and its impact on liver-dependent survival in a well-characterised cohort of 215 patients that has been prospectively followed for up to 25 years.

Patients and methods

Patients/study design

The prospective cohort for evaluation the effects of first diagnosis of PSC after the age of 50 has already been described.¹⁸ Selection criteria included typical endoscopic retrograde cholangiographic findings, serum alkaline phosphatase activity at least twofold the reference range, negative antimitochondrial antibody results, and liver biopsy findings compatible

with the diagnosis of PSC. Criteria for exclusion were cirrhosis at first presentation, patients in whom liver transplantation was foreseen, and patients with a history of neoplastic disease and/or coexisting hepatic disease. The end points were liver transplantation or death. The study covered the period from May 1987 to September 2012. The outcomes of all patients in the study were followed until May 2013. A total of 66 of 281 consecutive patients who presented at our institutions with PSC were not included according to our exclusion criteria. Eight patients refused to participate in the study; in 22 patients, liver transplantation was foreseen because of the advanced stage of PSC at first visit; 10 had cholangiocarcinoma (CC) diagnosed within 3 months; and one had hepatocellular carcinoma and two had colon carcinoma at first visit. Fifteen patients were lost to follow-up treatment and were not considered in the final evaluation. In eight patients, the diagnosis of PSC was not confirmed. Ten of the excluded patients were 50 years or older at time of first diagnosis. One patient with diagnosis of PSC after the age of 50 refused to participate in the study. Of the 22 patients with end-stage disease at first presentation, three had the diagnosis of PSC after the age of 50. Of the 10 patients excluded due to development of CC, six were older than 50 years. All patients were treated with ursodeoxycholic acid (UDCA) and endoscopic retrograde cholangiography (ERC), as previously reported.¹⁸ Bile samples were routinely collected during endoscopic procedures. Routine laboratory values were determined using standard methods. A dominant stenosis (DS) was defined as a stenosis with a diameter 1.5 mm smaller than that of the common duct or 1.0 mm smaller than that of a hepatic duct (within 2 cm of the bifurcation).¹⁹ Patients with first diagnosis of PSC after the age of 50 years were categorised as late-onset, according to Hirano et al.,¹³ and were compared with patients with earlier onset of disease, meaning before or at the age of 50. In total, 215 patients were included in the final evaluation and followed up until July 2012 (Table 1).

Measurement of serum sCD30 and cytokines in bile fluid

Serum sCD30 at time-point of first diagnosis was quantitated in 50 patients (early-onset = 40, late-onset = 10) by Human sCD30 Instant ELISA (Bender MedSystems, Vienna, Austria) according to the manufacturer's instructions.

In 27 patients (early-onset = 19, late-onset = 8) bile samples from first ERC were available for cytokine analysis. Cytokine levels were measured by mouse cytometric bead array (CBA) Kit (BD Biosciences). Briefly, 50 µl of bile fluid or known concentrations of standard

Table 1. Clinical characteristics of patients with earlier- and later-onset primary sclerosing cholangitis.

	Early onset	Late onset	<i>p</i> -value
Patients	183	32	–
Age at diagnosis [years]	30.1 ± 0.7	57.3 ± 1.3	–
Sex [male %]	133 (72.7)	17 (53.1)	0.02
IBD [yes/no]	122 (66.7)	19 (59.4)	0.4
Overlap with autoimmune hepatitis	11 (6.0)	0 (0.0)	0.2
Dominant stenosis	112 (61.2)	19 (59.4)	0.6
Dominant stenosis at first diagnosis	60 (32.8)	11 (34.4)	0.9
Laboratory parameters at baseline			
Bilirubin [mg/dL]	0.9 ± 0.3	0.8 ± 0.4	0.9
ALT [IU/L]	117.9 ± 11.3	62.3 ± 36.7	0.03
AST [IU/L]	75.0 ± 6.9	44.1 ± 21.0	0.05
AP [IU/L]	298.5 ± 20.9	341.0 ± 52.7	0.2
GGT [IU/L]	320.0 ± 33.2	405.0 ± 61.3	0.6
Albumin [g/dL]	44.0 ± 0.7	41.5 ± 1.2	0.4
Mayo risk score	0.46 ± 0.1	0.69 ± 0.13	0.2
Development of CCA [%]	6 (3.3)	4 (12.5)	0.02
Development of colon cancer	11 (6.0)	2 (6.3)	0.4
Death [%]	7 (3.8)	7 (21.9)	<0.0001
OLT [%]	45 (24.6)	6 (18.8)	0.5
Death/OLT [%]	52 (28.4)	13 (40.6)	0.2
Survival free of liver transplantation [years]	20.8 ± 1.7	10.5 ± 0.6	<0.0001

Data are presented as *n* (%) or as means ± standard deviations.

IBD: inflammatory bowel disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AP: alkaline phosphatase; GGT: gamma-glutamyl transferase; CCA: cholangiocarcinoma; OLT: orthotopic liver transplantation

samples (0–5000 pg/ml) were added to a mixture of 50 µl each of capture antibody bead reagent and phycoerythrin (PE)-conjugated detection antibody. The mixture was incubated at room temperature in the dark for 2 h and then washed to remove unbound detection antibody. Data were acquired using a FACS AriaII flow cytometer and analysed using CBA software 1.1 (BD Biosciences).

Statistical analysis

Calculations were carried out using PASW Statistics 20. Frequencies were compared using a chi-squared test or the Fisher's exact test where appropriate. Continuous data were compared using the nonparametric Wilcoxon rank-sum test. Actuarial transplantation-free survival was estimated using a Kaplan–Meier product limit estimator. Differences between the actuarial estimates were tested using the log rank test. Factors that independently affected the risk of reduced transplantation-free survival were determined using Cox proportional hazard ratio models with simultaneous adjustment for Mayo risk score (MRS), sex, late-onset disease,

presence of IBD, and presence of DS. Statistical significance was set at $p < 0.05$.

Consent

Written, informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. The study was approved by the local ethics committee of Heidelberg University (S-043/2011; approval granted 19.04.2011).

Results

Clinical and laboratory characteristics and first diagnosis of PSC

A cohort of 215 patients with PSC was analysed in this study. Of these, 150 (69.8%) patients were male and 65 (30.2%) were female; 145 (67.4%) patients had concomitant IBD, of which 129 (60.0%) were UC,

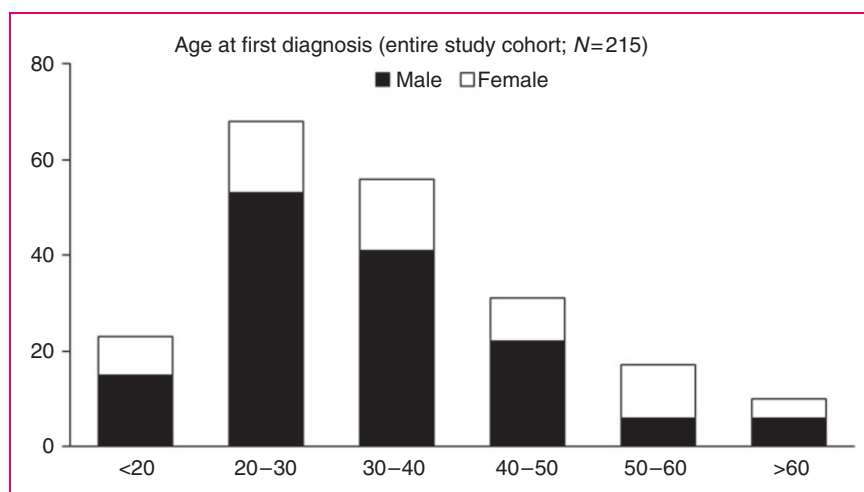


Figure 1. Distribution of age at first diagnosis of PSC.

Distribution of age at first diagnosis of PSC differentiate into decades for the whole study cohort ($N=215$) The number of patients is plotted on the y-axis. The sex ratio in patients with diagnosis after the age of 50 is significantly different compared with patients with earlier onset.

13 (6.0%) were Crohn's disease, and three (1.4%) were Colitis indeterminata. The median age at first diagnosis was 34.4 years. The clinical and laboratory baseline characteristics are depicted in Table 1. The age at PSC diagnosis was analysed and is shown in Figure 1 (a–c). Patients with first diagnosis of PSC above the age of 50 were considered as the late-onset group. The late-onset group comprised 32 patients with a median onset of PSC of 58.3 (range: 50–68) years, compared with 30.0 (range: 13–49) years in the early-onset group.

Clinical characterisation of patients with diagnosis of PSC after the age of 50

The two groups of PSC patients with earlier or later diagnosis of PSC were compared with regard to their clinical and laboratory parameters at entry into the study. We found marginally lower alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in the late-onset group ($p=0.03$ and $p=0.05$, respectively), whereas the other cholestatic and liver parameters, including INR and serum albumin, showed no statistically significant difference. The prevalence of DS did not differ significantly between the two groups (112/183 (61.2%) vs. 19/32 (59.4%)), nor did we find a statistically significant difference in prevalence of DS at first diagnosis (60/183 (32.8%) vs. 11/32 (34.4%)). However, patients from the late-onset group more often developed re-stenosis, requiring repeated endoscopic dilatation (56/112 (50.0%) vs. 15/19 (78.9%); $p=0.02$). In 52/215 patients, episodes of recurrent cholangitis requiring hospitalisation and/or

antibiotic treatment were reported. Fourteen of 32 (43.8%) belonged to the late-onset group and 38/183 (20.8%) to the earlier-onset group ($p=0.002$). Numbers of collected bile samples were comparable between both groups. Furthermore, the proportion of females was significantly higher in the late-onset group compared with the earlier-onset group (50/183 (27.3%) vs. 15/32 (46.9%); $p=0.02$).

Immunological serum markers

The amount of total serum immunoglobulin was not significantly different between both groups. Analysis of serum immunoglobulin subclasses revealed a marginal increase of IgA in the late-onset group (4.1 ± 0.6 years vs. 2.6 ± 0.2 years; $p=0.45$), whereas IgG and IgM levels did not significantly differ between the groups. Furthermore, we analysed serum levels of soluble CD30 and found decreased levels in the late-onset group (34.0 ± 13.9 years vs. 58 ± 20.7 years; $p=0.044$). Levels of serum bile acids showed no significant difference between the groups (Table 2).

Cytokines secreted into bile fluid

Cytokines secreted into bile fluid were analysed using a CBA Kit. Levels of interleukin (IL)-2 (0.78 ± 1.0 years vs. 0.03 ± 0.09 years), IL-10 (0.9 ± 0.2 years vs. 0.04 ± 0.1 years), interferon gamma (6.7 ± 11.5 years vs. 0.0 ± 0.0 years), and IL-17 (14.1 ± 14.9 years vs. 1.7 ± 4.8 years) were markedly reduced in bile fluid of patients with late-onset disease, whereas IL-4 and tumour necrosis factor showed marginal differences.

Table 2. Immunological serum markers in patients with younger and late-onset primary sclerosing cholangitis.

	means \pm SD		<i>p</i> -value
	Early onset	Late onset	
Serum bile acid [μ mol/l]	9.0 \pm 10.5	37.0 \pm 43.5	0.07
Immunoglobulin [g/l]	19.5 \pm 0.7	20.9 \pm 2.1	0.2
IgG [g/l]	17.6 \pm 0.7	21.2 \pm 2.6	0.8
IgA [g/l]	2.6 \pm 0.2	4.1 \pm 0.6	0.045
IgM [g/l]	1.7 \pm 0.2	1.6 \pm 0.2	0.6
sCD30 [U/ml]	58.0 \pm 20.7	34.0 \pm 13.9	0.044

Table 3. Cytokine profile secreted into bile fluid.

	mean \pm SD		<i>p</i> -value
	Early onset	Late onset	
IL-2	0.78 \pm 1.0	0.03 \pm 0.09	0.045
IL-4	0.52 \pm 0.8	0.01 \pm 0.02	0.06
IL-6	28.2 \pm 94.7	25.5 \pm 68.8	0.3
IL-10	0.9 \pm 0.2	0.04 \pm 0.1	0.009
TNF	1.1 \pm 1.5	0.0 \pm 0.0	0.06
IFN gamma	6.7 \pm 11.5	0.0 \pm 0.0	0.034
IL-17	14.1 \pm 14.9	1.7 \pm 4.8	0.022

IL, interleukin; TNF, tumour necrosis factor; IFN, interferon

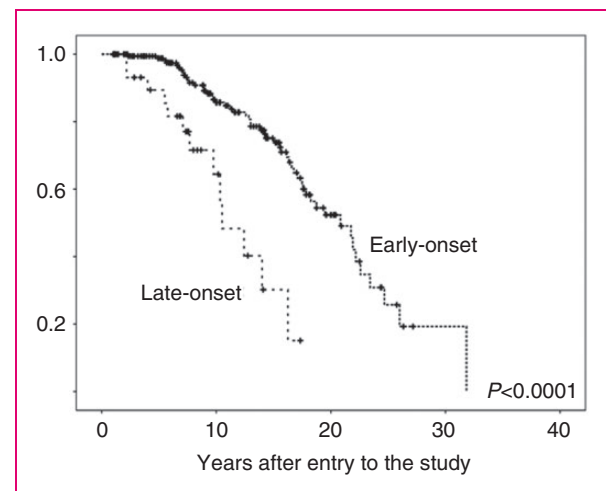
Levels of IL-6 were almost similar between both groups (Table 3). We found no correlation between biliary cytokine levels with AP level or MRS at first diagnosis.

Disease progression and survival analysis

During the observation period, 51 patients (six of whom were in the late-onset group) underwent liver transplantation. Seven of 32 (21.9%) patients in the late-onset group died, compared with 7/183 (3.8%) patients in the earlier-onset group. Causes of death among the patients with younger onset were CC (3/183 (1.6%)), progressive liver failure (1/183 (0.5%)), and colon carcinoma (2/183 (1.1%)). One patient died of non-hepatic disease. Causes of death for the patients in the late-onset group were CC (4/32 (12.5%)) and progredient liver failure (3/32 (9.4%)) (Table 4). Six of 183 (3.3%) patients with earlier onset of the disease developed CC as compared with 4/32 (12.5%) patients in the late-onset group ($p=0.02$). Development of colon carcinoma was almost equal between the two groups (11/183 (6.0%) vs. 2/32 (6.3%)). After a follow-up period of 24 years, the actuarial survival free of liver transplantation was 20.8 years in patients with earlier onset and 10.5 years in the late-onset group

Table 4. Clinical end points among patients with early- and late-onset primary sclerosing cholangitis.

	Early onset	Late onset
Orthotopic liver transplantation	45 (24.6)	6 (18.8)
Cause of death		
Progredient liver failure	1 (0.5)	4 (12.5)
Cholangiocarcinoma	3 (1.6)	3 (9.4)
Colon carcinoma	2 (1.1)	0 (0.0)
Others	1 (0.5)	0 (0.0)

**Figure 2.** Transplantation-free survival in patients with early- and late-onset PSC.

Actuarial transplantation-free survival (Kaplan-Meier estimate) of patients with early- or late-onset of PSC. Time is given in years from the time of first diagnosis (x-axis). The percentage of patients surviving without liver transplantation is plotted on the y-axis. Patients with late-onset PSC showed significantly lower transplantation-free survival.

($p < 0.0001$) (Figure 2). The median age at death or liver transplantation was 41.6 ± 0.8 years in the young-onset group and 64.4 ± 1.5 years in the late-onset group.

Prognosis factors in late-onset PSC

We performed further stratification analyses to analyse the influence of gender, presence of DS, and IBD among the late-onset cohort. In both male and female patients, late onset of the disease was associated with reduced transplantation-free survival (18.7 ± 2.1 years vs. 10.3 ± 1.6 years, $p < 0.001$; and 21.8 ± 1.6 years vs. 14.0 ± 1.2 years, $p = 0.001$, respectively). In patients with and without DS, late-onset disease was associated with reduced transplantation-free survival (17.8 ± 1.6 years vs. 10.5 ± 2.2 years, $p < 0.001$; and 23.5 ± 1.3

Table 5. Cox regression analysis.

Risk factor	Univariate			Multivariate		
	HR	HR (95% CI)	<i>p</i> -value	HR	HR (95% CI)	<i>p</i> -value
Sex	0.9	0.5–1.5	0.6	1.2	0.6–2.2	0.6
Presence of IBD	0.9	0.5–1.5	0.6	0.7	0.3–1.3	0.2
Presence of DS	0.4	0.2–0.8	0.005	0.5	0.3–1.1	0.09
MRS	1.6	1.3–2.0	<0.001	1.7	1.3–2.2	<0.001
Late onset	0.2	0.1–0.4	<0.001	0.3	0.1–0.5	<0.001

HR: hazard ratio; CI: confidence interval; IBD: inflammatory bowel disease; DS: dominant stenosis; MRS: Mayo risk score

Data show prospective factors for longer survival until liver transplantation or death. In univariate analysis presence of dominant stenosis, MRS and late-onset disease were associated with reduced actuarial survival. In multivariate analysis only MRS and late-onset disease reached significance ($p < 0.05$).

years vs. 11.3 ± 1.2 years; $p < 0.001$, respectively). In patients without IBD, late-onset disease was not associated with reduced transplantation-free survival (19.5 ± 1.6 years vs. 14.0 ± 1.4 years; $p = 0.4$) compared with a significantly reduced survival in patients with concomitant IBD (21.8 ± 2.2 years vs. 9.8 ± 2.7 years; $p < 0.001$). We performed single and multiple Cox proportional hazard regression models with adjustment for potential confounders, including gender, presence of DS, presence of IBD, MRS at baseline, and late-onset disease. Multivariate analysis revealed MRS at baseline and late-onset of disease as independent risk factors for reduced transplantation-free survival (Table 5). To analyse the influence of disease duration we further run a multiple regression analysis including disease duration from first diagnosis (HR 0.8 (HR 95%CI 0.8–0.9); $p < 0.0001$), MRS at first diagnosis (HR 1.3 (HR 95%CI 1.0–1.8); $p = 0.014$) and age at first diagnosis (HR 1.0 (HR 95%CI 1.0–1.1); $p = 0.041$) showing all risk factors independently associated with reduced transplantation-free survival.

Discussion

In this large cohort study, we describe the clinical features of patients first diagnosed with PSC after the age of 50. We found these patients to be at increased risk of developing cholangiocarcinoma and suffer from progressive liver failure. Although these patients are reaching clinical end points at older age, compared with patients with earlier diagnosis of PSC, transplantation-free survival from first diagnosis is markedly reduced. Interestingly, the sex ratio was significantly different in the late-onset group, with a higher rate of female patients. Frequency and manifestation of IBD were not different between groups. Frequency of DS was equal between earlier and late-onset patients. However, late-onset patients developed re-stenosis requiring

repeated endoscopic therapy more often, and suffered more often from recurrent episodes of cholangitis.

Worse prognosis in the late-onset cohort may be in part explained by an increased frequency of infectious complications that could aggravate disease progression.²⁰ This may be explained by mechanisms of immunosenescence and a subsequently impaired immune response.²¹ Although an immunological basis of PSC is obvious²² and, in many immunological diseases, a late onset is associated with slower disease progression, in late-onset PSC, the course of the disease may be driven more rapidly by repeated or chronic biliary infections. The increased frequency of episodes of cholangitis in the late-onset group may support this hypothesis. Notably, the number of bile samples were not different between patients with earlier or later diagnosis, as routinely bile samples were collected during endoscopic intervention. One possible explanation for the increased frequency of infectious complications in the late-onset group might be a reduced immune competence. To test this hypothesis, we analysed serum levels of immunoglobulins, showing a marginal elevation of serum IgA in the late-onset group. Elevated IgA has been linked to increased risk for infections in patients with liver cirrhosis, which may reflect a sustained exposure to bacterial pathogens derived from the gut.²³ Furthermore, elevated IgA seems to be associated with progressive liver fibrosis²⁴ as well as immunological diseases like coeliac disease.²⁵ In addition, we analysed serum levels of soluble CD30, a well-established marker of T-cell immunity, in our cohort. Increased serum levels of soluble CD30 are associated with disease activity in IBD.²⁶ Furthermore, soluble CD30 participates in the immune response against viral infectious diseases²⁷ and is a reliable marker for immune monitoring after solid organ transplantation.²⁸ CD30 knockout mice display increased susceptibility to bacterial infections due to an impaired innate function of memory phenotype CD44+, CD4+, and T cells.²⁹ An age-dependent

decrease of soluble CD30 has already been demonstrated in paediatric patients.³⁰ In line with this, we found a marked decrease in soluble CD30 in the late-onset cohort. Furthermore, we found an altered biliary cytokine composition in the late-onset cohort. However, as differences in biliary cytokines were only marginal in a small subset of patients these findings need confirmation by larger studies.

The increased frequency of CC among patients with later diagnosis of PSC accounts for a higher percentage of deaths. It is worth noting that most CC developed within the first 5 years after diagnosis of PSC in these patients. We have to emphasise that patients developing malignancies within the first 3 months after the first diagnosis were excluded according to the study protocol. Of the 10 patients excluded due to development of CC, six were older than 50 years. PSC had not been previously diagnosed in any of these patients, further supporting that late-onset disease in PSC is not an innocent diagnosis. A large multicentre cohort study also found significantly higher incidence of CC in PSC patients with advanced age at first diagnosis.³¹

Poorer outcome in late-onset patients may be explained by the later detection of a lengthy, pre-existing disease with a subclinical course.¹² The short timeframe between the first diagnosis of PSC followed by CC may point towards this explanation. To rule out this possibility, we performed extensive comparisons of laboratory and clinical parameters at first diagnosis. There were no significant differences in baseline laboratory parameters. Liver function, expressed by INR and serum albumin level, were comparable between both groups at the time of first diagnosis.

The reliability of the date of first diagnosis is a limitation of this study. A subclinical course of the disease without significant symptoms may differ between patients and hamper interpretation of the results. However, our well-characterised cohort of PSC patients with a standardised diagnostic, screening and therapy protocol, including UDCA and endoscopic treatment, should prevent this concern. Comparable baseline characteristics between both groups at entry into the study argue against a systematically missed onset of the disease.³² Importantly, there were no patients with biliary cirrhosis at first diagnosis, arguing against delayed diagnosed end-stage patients with later PSC diagnosis. Finally, age at first diagnosis is a continuous variable and the age discriminator at the age of 50 seems arbitrary. Nevertheless, we decided for this age because it has been used in other immunological diseases, and previously in a PSC cohort from Japan. Furthermore, we found the age of 50 to be the best discriminator between both groups, although the basic results (transplantation-free survival, frequency

of CC) remains equal if the discrimination is varied between the ages of 45 to 55 years.

In conclusion, we found an altered sex ratio and an increased frequency of biliary infectious complications in line with an altered immune status in late-onset PSC patients, subsequently leading to reduced transplantation-free survival with CC and progressive liver failure as leading causes of death. Patients with late-onset PSC display a different clinical phenotype, requiring adapted screening and surveillance strategies. As treatment options are often limited in elderly patients due to comorbidities and increased risk for general anaesthesia, PSC patients have to be evaluated carefully and well in advance for liver transplantation.

Acknowledgements

The authors would like to thank Petra Klötters-Plachky and Yvonne Schäfer for technical assistance.

Conflict of interest

The authors declare that they have no competing interests.

Financial support

DNG and PSa were supported by “Stiftung Elementarteilchen”, Hamburg, Germany. CR was supported by Deutsche Forschungsgemeinschaft (DFG).

Ethics approval

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. The study was approved by the local ethics committee of Heidelberg University (S-043/2011; approval granted 19.04.2011).

Informed consent

Written, informed consent was obtained from each patient included in the study.

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