

Lower Incidence of Biliary Carcinoma in Patients With Primary Sclerosing Cholangitis and High Serum Levels of Immunoglobulin E

KENJI HIRANO,* MINORU TADA,* SUGURU MIZUNO,* HIROYUKI ISAYAMA,* NAMINATSU TAKAHARA,* RIE NAGANO,* TSUYOSHI HAMADA,* KOJI MIYABAYASHI,* YUKIKO ITO,* DAI MOHRI,* KAZUMICHI KAWAKUBO,* TAKASHI SASAKI,* HIROFUMI KOGURE,* NATSUYO YAMAMOTO,* NAOKI SASAHIRA,* NORIYO YAMASHIKI,† YASUHIKO SUGAWARA,‡ NORIHIRO KOKUDO,‡ NOBUO TODA,§ and KAZUHIKO KOIKE*

*Department of Gastroenterology, Graduate School of Medicine, †Artificial Organ and Transplantation Division, Department of Surgery, University of Tokyo, Tokyo; and ‡Department of Gastroenterology, Mitsui Memorial Hospital, Tokyo, Japan

This article has an accompanying continuing medical education activity on page e7. Learning Objectives—At the end of this activity, the successful learner will know about the importance of serum IgE levels in patients with primary sclerosing cholangitis.

BACKGROUND & AIMS: High serum levels of immunoglobulin (Ig)E often are detected in patients with primary sclerosing cholangitis (PSC), but the clinical significance is not known. **METHODS:** We analyzed data from 44 patients with PSC and known serum levels of IgE. They were divided into groups called high IgE (>170 IU/mL; $n = 17$) or normal IgE ($n = 27$). We compared occurrence of biliary carcinoma including cholangiocellular and gallbladder carcinoma, liver transplantation, and death between groups. **RESULTS:** The high IgE group had a later age of onset of PSC than the normal IgE group (54 ± 20 y vs 39 ± 16 y; $P = .010$); they also had a higher serum level of IgG (2078 ± 638 vs 1517 ± 475 mg/dL; $P = .002$) and IgG4 (104 ± 102 vs 38 ± 16 mg/dL; $P = .002$). Association with inflammatory bowel disease did not differ significantly between groups (5 of 17 vs 11 of 27; $P = .661$). No patient had biliary carcinoma in the high IgE group, but biliary carcinoma was observed during the follow-up period in 8 patients in the normal IgE group (0 of 17 vs 8 of 27; $P = .016$). The occurrence of biliary carcinoma, liver transplantation, or death did not differ between groups (4 of 17 vs 13 of 27; $P = .124$). **CONCLUSIONS:** High serum levels of IgE often are observed in older patients with PSC and are associated with a reduced incidence of biliary carcinoma.

Keywords: Prognosis; Ulcerative Colitis; Allergy; Malignancy.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease of unknown etiology characterized by fibrosing inflammatory destruction of intrahepatic and/or extrahepatic bile ducts. PSC is generally progressive, and usually leads to the development of cirrhosis. There is no medical therapy that can dramatically disrupt the disease progression, and liver transplantation remains the only option for patients with end-stage PSC.¹ Mean age at diagnosis is 40 years, and men are about 2 times more likely to be affected than women in Europe and the United States, whereas in Japan there are 2 age distribution peaks, in the 20s and 60s, even after immunoglobulin (Ig)G4-related sclerosing cholangitis (IgG4-SC) is strictly removed.² In this regard, we previously reported that high serum IgE was characteristic of PSC patients with onset age older than 50 years.³

The IgE level often is found to be increased in allergic diseases. Interestingly, it has been reported that an inverse

association exists between allergy and malignancy such as pancreatic cancer and glioma.⁴ As for IgE, an odds ratio of glioma risk in those with increased IgE levels compared with normal levels of 0.3 was reported by Wiemels et al.⁵ They also showed that glioblastoma patients with increased IgE levels had longer survival times than those with normal or borderline IgE levels.⁶ Thus, increased IgE levels may work in a protective manner against certain kinds of malignancies.

The most feared complication of PSC is biliary carcinoma, including cholangiocarcinoma (CCA) and gallbladder carcinoma.^{1,7–10} Various studies have tried to clarify risk factors of biliary carcinoma in PSC, but conclusive factors have yet to be found. To date, it is not known whether either high or normal IgE levels in PSC might be a predictive factor for biliary carcinoma. Thus, in the present study, we examined clinical differences between PSC patients with and without high IgE levels, focusing especially on the possible association with biliary carcinoma.

Patients and Methods

Sixty-six patients were diagnosed with PSC at our institutes (64 at the University of Tokyo and 2 at Mitsui Memorial Hospital) between January 1982 and February 2011. Among them, serum IgE level was measured in 44 patients (42 patients at the University of Tokyo and 2 patients at Mitsui Memorial Hospital). These 44 patients were followed up at our outpatient department and were enrolled in the present study. In principle, laboratory data were checked every 3 months and imaging studies such as abdominal ultrasonography was performed at least once a year even when the condition of the disease was stable. We used diagnostic criteria of the Mayo Clinic (published in 2003) for the diagnosis of PSC, but excluded IgG4-SC.^{3,11} Even if the serum IgE level was measured several times, the initial value was adopted. The duration of PSC was defined as the time elapsed since the first clinical, biochemical, or

Abbreviations used in this paper: CCA, cholangiocarcinoma; FEIA, fluorezymeimmunoassay; IBD, inflammatory bowel disease; Ig, immunoglobulin; PSC, primary sclerosing cholangitis; SC, sclerosing cholangitis.

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Table 1. Clinical Features of Patients With PSC

	High IgE group (n = 17, IgE > 170 IU/mL)	Normal IgE group (n = 27)	P value
Sex, M:F	8:9	16:11	.631
Onset age of PSC	54 ± 20 (11–79)	39 ± 16 (16–75)	.006
Follow-up period ^a	69 ± 66	71 ± 58	.888
Associated diseases			
Bronchial asthma	2	1	.386
Atopic dermatitis	1	0	.386
Drug allergy	4	5	.716
Inflammatory bowel disease	5	11	.661
Variceal bleeding	1	1	.999
Laboratory data			
IgE level ≤170 IU/mL	770 ± 486	69 ± 52	<.001
IgG level 800–1700 mg/dL	2078 ± 638	1517 ± 475	.002
IgG4 level <135 mg/dL	104 ± 102 (n = 17)	38 ± 16 (n = 21)	.020
IgM level 35–220 mg/dL	144 ± 76	141 ± 73	.875
Positive ANA, ≥×80	0/16	2/24	.508
Eosinophilia >1000 μ L	2/16	2/26	.999
Total bilirubin level	0.91 ± 0.60 (n = 17)	0.91 ± 0.36 (n = 24)	.967
Albumin level	4.0 ± 0.42 (n = 17)	3.9 ± 0.46 (n = 24)	.724
Model for end-stage liver disease score	7.5 ± 1.6 (n = 16)	7.3 ± 1.3 (n = 23)	.687

^aPeriod from the onset of PSC to the day of biliary carcinoma, liver transplant, death, or the last visit.

cholangiographic findings leading to the diagnosis of PSC. The diagnosis of biliary carcinoma was confirmed by histology except in one patient whose diagnosis was made only by imaging findings. This patient showed irregular gallbladder wall thickening with papillary nodule on computed tomography and magnetic resonance imaging. These findings became aggravated during the follow-up period, which made us suspect gallbladder cancer, although a close examination was not performed because of advanced liver failure. Medical records were reviewed to obtain information regarding demographic variables, laboratory data, and the presence of associated diseases. Serum IgE level was measured by fluorezymeimmunoassay (FEIA) at BML, Inc. (Saitama, Japan). Less than the mean $\pm$ standard deviation was defined as a normal value.¹² Concretely, the normal value was 170 IU/mL or less in the patients aged 7 years or older. Based on the IgE value (>170 IU/mL or not), we divided patients into 2 groups: the high IgE group (n = 17; IgE > 170 IU/mL) and the normal IgE group (n = 27; IgE $\leq$ 170 IU/mL). We compared the 2 groups in terms of associated diseases, laboratory data (mainly immunologic parameters), and prognosis. In the present study, associated diseases included inflammatory bowel disease (IBD) and allergic diseases such as bronchial asthma and atopic dermatitis. History of variceal bleeding also was examined. Laboratory parameters included IgG, IgG4, IgM, and the presence of antinuclear antibody ($\gamma \geq \times 80$). For prognosis, 3 analyses were performed. In the first analysis, only biliary carcinoma was regarded as an end point, and the frequency of biliary carcinoma was compared between the 2 groups. In the second analysis, biliary carcinoma and death by other causes were regarded as end points, and the frequency of these end points was compared. In the third analysis, biliary carcinoma, liver transplantation, and death by other causes were regarded as end points, and the frequency of these end points was compared.

Continuous variables were reported as the mean $\pm$ standard deviation. Differences were evaluated by the Student *t* test, the

Welch *t* test, the chi-square test with Yates' correction, or the Fisher exact test. Cumulative event occurrence rate curves were analyzed using the Kaplan–Meier technique with the log-rank test. A *P* value less than .05 was considered statistically significant. This retrospective study was approved by the review board of our institute.

Results

Forty-four patients (24 men and 20 women) were enrolled, and their mean age at onset of PSC was 45 ± 19 years. The clinical features of the high IgE group and the normal IgE group are summarized in Table 1. The mean onset age was significantly

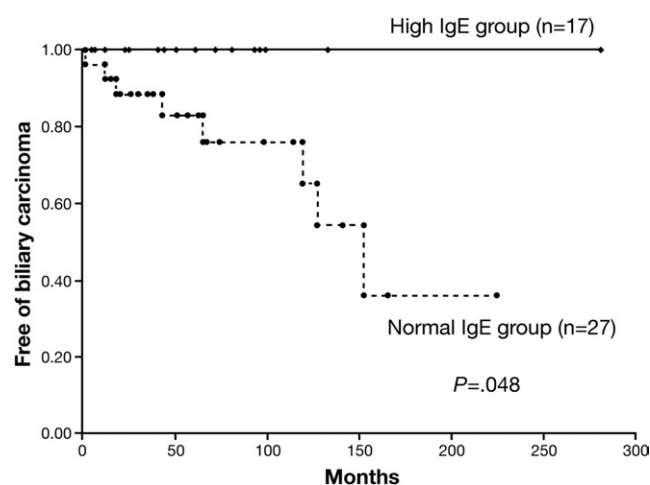


Figure 1. Kaplan–Meier curves comparing the nonoccurrence rate of biliary carcinoma between the high IgE group and the normal IgE group. Patients with liver transplantation or death from causes other than biliary carcinoma were treated as censored cases in this analysis.

Table 2. Clinical Profile of 8 Patients Associated With Biliary Carcinoma

Patient	Location of BCA	IgE level, IU/mL	IBD	Sex, M/F	Age at onset of BCA	Period from the onset of PSC to BCA, mo
1	EHBD	97	–	M	22	2
2	GB	70	+	F	48	65
3	GB	69	+	M	61	43
4	EHBD	39	–	F	52	119
5	IHBD	23	+	M	29	152
6	EHBD	22	+	F	40	12
7	IHBD	11	+	F	48	18
8	IHBD	9	+	M	39	127

BCA, biliary carcinoma; EHBD, extrahepatic bile duct; GB, gallbladder; IHBD, intrahepatic bile duct.

higher in the former group (54 ± 20 vs 39 ± 16 y; $P = .010$). Association with bronchial asthma, atopic dermatitis, drug allergy, IBD, and variceal bleeding did not differ between the 2 groups. There was no patient with allergic vasculitis or parasitic infection. The frequency of allergic rhinitis was not exactly known after reviewing medical records because allergic rhinitis caused by pollen allergy is a very common disease in Japan¹³ and many patients did not seem to report their mild allergic rhinitis if they had one. Sixteen patients were associated with IBD, and all of them had ulcerative colitis. Among them, none was associated with colorectal cancer. There was no patient with anomalous pancreatobiliary ductal union, which was confirmed by endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography. As for laboratory data, there were significant differences in IgG (2078 ± 638 vs 1517 ± 475 mg/dL; $P = .002$) and IgG4 (104 ± 102 vs 38 ± 16 mg/dL; $P = .020$) levels. Total bilirubin and albumin levels at the onset of PSC showed no significant difference. There was no difference in the model for end-stage liver disease score.

The mean disease durations (from onset to the day of biliary carcinoma, liver transplantation, death, or last visit) in the 2 groups were 69 ± 66 and 71 ± 58 months ($P = .888$). The mean follow-up periods at our institute (from the first visit to our institute to the day of biliary carcinoma, liver transplantation, death, or last visit) in the 2 groups were 50 ± 43 and 34 ± 27 months ($P = .193$). There was no occurrence of biliary carcinoma in the high IgE group, but biliary carcinoma occurred in 8 patients in the normal IgE group (0 of 17 vs 8 of 27; $P = .016$). The cumulative occurrence rate of biliary carcinoma analyzed by the Kaplan–Meier method also showed a significant difference ($P = .048$) (Figure 1). There was no occurrence of carcinoma of duodenal papilla and pancreas. Clinical profiles of the 8 patients with biliary carcinoma (6 CCA and 2 gallbladder carcinoma) are summarized in Table 2. There were 2 patients whose CCA was found within 1 year after the diagnosis of PSC. Although there is no denying that occult CCA existed at the diagnosis of PSC, their onsets were not synchronous clinically. Therefore, we also included these 2 patients in the present analyses. Biliary carcinoma was diagnosed 59 months on average after PSC onset. Surgical treatment was performed in 3 patients, and 2 showed recurrence 13 and 23 months later. Chemotherapy with or without radiation was chosen in 3 patients, and the other 2 patients were followed up only with best supportive care. Serum IgE values of these 8 patients were less than 100 IU/mL.

The comparison between patients with and without biliary carcinoma was summarized in Table 3. Besides serum IgE,

association with ulcerative colitis was related to the occurrence of biliary carcinoma.

When biliary carcinoma and death by other causes were regarded as end points, these end points were observed in 4 patients (death from liver failure) in the high IgE group, and in 10 patients (8 biliary carcinoma, 1 death from liver failure, and 1 suicide) in the normal IgE group (4 of 17 vs 10 of 27; $P = .509$). The cumulative occurrence rate of end points according to the Kaplan–Meier method showed no significant difference ($P = .766$) (Figure 2).

When biliary carcinoma, liver transplantation, and death by other causes were regarded as end points, these end points were observed in 4 patients (death from liver failure) in the high IgE group, and in 13 patients (8 biliary carcinoma, 3 liver transplantation, 1 death from liver failure, and 1 suicide) in the normal IgE group (4 of 17 vs 13 of 27; $P = .124$). The cumulative occurrence rate of end points according to the Kaplan–Meier method showed no significant difference ($P = .370$) (Figure 3).

Discussion

Biliary carcinoma including CCA and gallbladder carcinoma represents the most feared biliary complication occurring in patients with PSC. The reported prevalence of CCA in PSC varies from 3.6% to 36%, depending on the methods used to establish the diagnosis and the length of follow-up evaluation.^{2,14–18} In this study, the incidence of biliary carcinoma during the follow-up period was 18% (8 of 44), and that of CCA was 14% (6 of 44). This may not seem so high in comparison with previous reports, but the rate was much higher than that observed in a Japanese national survey of PSC in 2003 (3.6%) despite a seemingly similar

Table 3. Comparison Between Patients With and Without Biliary Carcinoma

	Biliary carcinoma (+), n = 8	Biliary carcinoma (–), n = 36	P value
Sex, M:F	4:4	20:16	.999
Age at onset of PSC	37 ± 14	47 ± 19	.198
Ulcerative colitis (+)	6/8	10/36	.019
IgG level >1700 mg/dL	2/8	15/36	.455
IgG4 level >135 mg/dL	0/7	3/36	.999
IgE level >170 IU/mL	0/8	17/36	.016
Mean IgE level	43 ± 32	405 ± 481	<.001

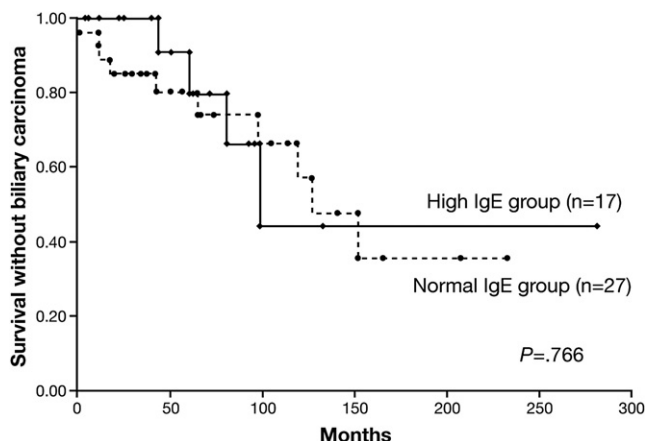


Figure 2. Kaplan–Meier curves comparing the survival rate without biliary carcinoma between the high IgE group and the normal IgE group. Patients with liver transplantation were treated as censored cases in this analysis.

follow-up period (median, about 5 y). Two PSC patients with CCA in our series were referred to our institute only after the diagnosis of CCA was made. In addition, because our institute (University of Tokyo) is a tertiary hospital in which liver transplantation is performed, our series may include patients with more severe liver dysfunction and younger age than those in the national survey. These factors may have contributed to the comparatively high rate of CCA.

In our previous study,³ it was found that a portion of the PSC patients, most of whom were elderly, showed high serum IgE levels, but the clinical significance of IgE level in PSC was still unclear. However, in addition to allergy and parasitic infections, IgE recently was shown to possess anticancer effects.⁴ It has been reported that IgE can destroy pancreatic and ovarian cancer cells through antibody-dependent cell-mediated cytotoxicity.^{19–21} The serum level of IgE was increased significantly in patients with pancreatic cancer compared with controls.²⁰ It is also known that total IgE levels may be related to natural killer cell activity, whose low level is associated with an enhanced risk of cancer at all sites.^{22,23} These findings made us suppose that IgE also might be associated with biliary carcinoma.

In the present study, there were 8 patients whose serum IgE level ranged between 100 and 170 IU/mL, and none of them had biliary carcinoma. Thus, in referring to a risk factor for biliary carcinoma in PSC, it may be more exact to use the term *lower IgE* instead of *normal IgE*. By using receiver operating characteristic curve analysis to show the ideal cut-off IgE value to predict the occurrence of biliary carcinoma in patients with PSC, the cut-off value turned out to be 100 IU/mL. Sensitivity, specificity, and accuracy were 100%, 69%, and 77%, respectively. The area under the curve was 0.84.

In one patient with PSC and CCA (patient 4 in Table 2), IgE level was measured repeatedly before and after the diagnosis of CCA, but there was no significant change in its level (20–53 IU/mL). Its variability did not seem to be related to CCA at least as far as this patient is concerned.

Increased IgE was strongly associated with old-age onset of PSC. However, in general, the serum IgE level does not change with age.²⁴ Even in patients with increased serum IgE

levels, the association with bronchial asthma or atopic dermatitis was not observed frequently. Thus, we speculate that the increase of IgE level is derived from PSC itself. However, it seems difficult to conclude that PSC with high IgE level is quite different from PSC with normal IgE level. Irrespective of the IgE levels, the association of IBD was observed, and liver dysfunction was generally progressive. Although the high IgE group showed higher IgG and IgG4 level than the normal IgE group (Table 1), we never considered that PSC with high IgE level in the present series was equal to IgG4-SC. Obvious jaundice at onset (total bilirubin level, >3 mg/dL), which often is recognized in IgG4-SC, was not observed in the present series. Even in the high IgE group, only 3 patients had IgG4 levels higher than 135 mg/dL, a commonly used cut-off value for the diagnosis of IgG4-related diseases.²⁵ Two of them had ulcerative colitis, which is infrequent in IgG4-related diseases.²⁵ Moreover, 3 patients with increased IgE level received steroid treatment, but remarkable improvement was not observed.³ Because both IgE and IgG4 productions are Th2-dependent in general, IgE-inducing antigens are also efficient IgG4 inducers.²⁶ In a sense, it may not be unusual that patients with high IgE level show a somewhat high IgG4 level. Considering these data, PSC with increased IgE should be differentiated from IgG4-SC.

Various studies have attempted to clarify the risk factors of CCA in PSC. One previous study reported that the presence of IBD was associated with an increased risk of CCA, but this was not confirmed by other studies.^{16,27} Two previous studies have identified abdominal pain as a predictor of CCA in PSC patients.^{16,28} On the other hand, absence of symptoms was a predictor of CCA according to the study of Burak et al.¹⁵ They suggested that variceal bleeding was a major risk factor for the later development of CCA, but in our study there were no patients with biliary carcinoma and a history of variceal bleeding. Among the 8 patients with biliary carcinoma in our series, one was a smoker and none was a habitual drinker, although studies have reported their association with CCA.^{28,29} Taken together, definitive factors still have to be found. The relation between IgE and biliary carcinoma has not been discussed fully. We believe our finding is very simple, but also very innovative. Because ulcerative colitis seemed to be related to biliary carcinoma in our study

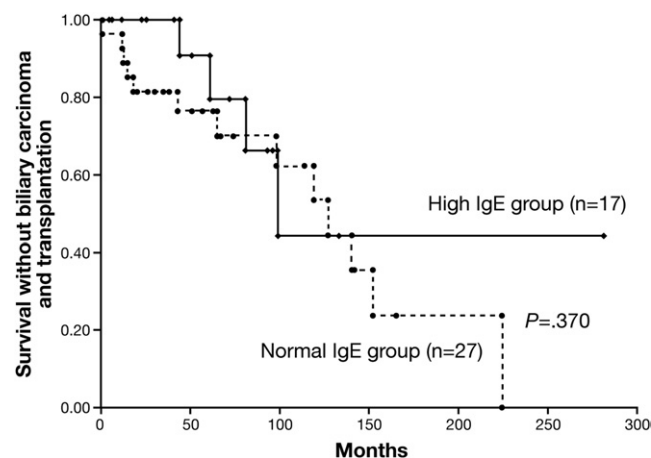


Figure 3. Kaplan–Meier curves comparing the survival rate without biliary carcinoma and liver transplantation between the high IgE group and the normal IgE group.

(Table 3), it was desirable to perform a multivariate analysis to clarify whether both IgE and ulcerative colitis were independent factors for the development of biliary carcinoma. This analysis was impossible because there was no occurrence of biliary carcinoma in the high IgE group, which meant that the odds ratio or hazard ratio could not be calculated. However, considering no significant relation between high IgE level and ulcerative colitis ($P = .661$, χ^2 test with Yates' correction) (Table 1), IgE and ulcerative colitis seemed to be independent factors.

Despite the significantly different prevalence of biliary carcinoma between patients with and without increased IgE levels, there was no significant difference in the prevalence of end points including biliary carcinoma, liver transplantation, and death by other causes. This is because PSC with increased IgE level is still a progressive disease and may lead to eventual liver dysfunction. However, considering the different occurrence rates of biliary carcinoma, a significant difference might be found if our study populations were larger.

In summary, increased IgE level was related closely to older age at onset of PSC and reduced occurrence of biliary carcinoma. It has not yet been determined whether IgE is related directly to the pathogenesis of PSC or whether it increased reactively. In any event, it is certain that grouping PSC in terms of IgE should be attempted on a larger scale to validate our finding. Adequate grouping may contribute to the clarification of the pathogenesis of PSC, which remains poorly understood.

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Reprint requests

Address requests for reprints to: Kenji Hirano, MD, PhD, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. e-mail: khirano-tky@umin.ac.jp; fax: (81) 3-3814-0021.

Conflicts of interest

The authors disclose no conflicts.

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