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Mortality rate of patients with asymptomatic primary biliary cirrhosis diagnosed at age 55 years or older is similar to that of the general population

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Short title;

Mortality of asymptomatic PBC patients

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PBC, primary biliary cirrhosis; AMA, anti-mitochondrial antibody; AIH, autoimmune hepatitis; HCV, hepatitis C virus; SMR, standardized mortality ratio; CI, confidence interval; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; UDCA, ursodeoxycholic acid.

Abstract

Purpose. Recent routine testing for liver function and anti-mitochondrial antibodies increased the number of newly diagnosed patients with primary biliary cirrhosis (PBC). This study investigated the prognosis of asymptomatic PBC patients, focusing on age difference, to clarify its effect on the prognosis of PBC patients.

Methods. The study is a systematic cohort analysis of 308 consecutive patients diagnosed with asymptomatic PBC. We compared prognosis between the elderly (55 years or older at the time of diagnosis) and the young patients (<55 years). The mortality rate was also compared with that of age- and gender-matched general population.

Results. The elderly patients showed higher aspartate aminotransferase to platelet ratio, and lower alanine aminotransferase than the young (P<0.01, and P=0.03, respectively). The two groups showed similar values of alkaline phosphatase and immunoglobulin M. Death of the young patients was more likely to be due to liver failure (71%), while the elderly might die from other causes before occurrence of liver failure (88%, P<0.01), especially from malignancies (35%). The mortality rate of the elderly patients was not different from that of the general population (standardized mortality ratio, 1.1; 95% confidence interval, 0.6-1.7), although this rate was significantly higher than that of the young patients (P=0.044).

Conclusions. PBC often presents more advanced disease in the elderly patients than the young. However, the mortality rate of the elderly patients is not different from that of the general population.

Key words. primary biliary cirrhosis, age difference, and mortality rate

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease characterized by progressive destruction of the small septal and interlobular bile ducts (1-3). Chronic cholestasis may result in hepatic fibrosis and portal hypertension, which may eventually progress to hepatic failure or gastrointestinal bleeding. Thirty years ago, most patients diagnosed with PBC showed liver cirrhosis and disease-related symptoms (4-6). The overall survival of PBC patients was 10-15 years, which was significantly less than that of age- and gender-matched controls from the general population (7-10).

Recent routine testing for liver function and anti-mitochondrial antibodies (AMA) has increased the number of newly diagnosed cases of asymptomatic PBC (11). There are several prognostic studies of these asymptomatic patients, suggesting that a significant proportion are in the early stage of PBC and might respond more favorably to medication without further disease progression for several years (2, 11, 12). The studies of the clinical significance of anti-nuclear antibodies (ANA) in PBC indicated that PBC-specific ANAs, such as Sp100, promyelocytic leukemia proteins, gp210, and p62 correlate with disease activity and might be a marker of poor prognosis (13). The only accepted index to estimate patient survival is the Mayo risk score, which is very useful in advanced cases, however, of limited use in patients with early disease (14).

Recent studies on age differences in patients with autoimmune hepatitis (AIH) showed more frequent presentation of elderly patients with severe disease (15, 16). However, the relationship between age at diagnosis and prognosis of PBC patients remains unclear. The present study investigated the proposal that young and elderly asymptomatic PBC patients have different prognoses. To test this, we compared clinical features including prognosis between the two age groups of patients. We also compared the mortality rates for PBC patients with those of age- and gender-matched general-population.

Patients and Methods

Patients

This study is a systematic cohort analysis of 308 consecutive patients (271 females and 37 males) diagnosed with asymptomatic PBC at Okayama University and affiliated hospitals from 1980 to 2004. A diagnosis of PBC was made based on any two of the following criteria: (1) positive test for AMA, (2) biochemical evidence of cholestasis, and (3) liver biopsy compatible with the diagnosis (12). The presence of AMA was determined by indirect immunofluorescence on murine tissue sections (cutoff value; 1:40) or enzyme-linked immunosorbent assay against beef pyruvate dehydrogenase. Pruritus, jaundice (bilirubin >2 mg/dl), bleeding varices, severe general fatigue, and ascites were defined as symptoms associated with disease progression. Patients showing serum positivity for hepatitis B surface antigen or anti-hepatitis C virus (HCV) antibodies, daily ethanol use of more than 60 grams, or other signs of liver injury, were excluded from this study. The study was in accordance with the Helsinki Declaration, and approved by the ethical committee of the institutes. All patients provided informed consent.

Histological evaluation

Histological stages were evaluated according to the criteria of Ludwig et al. (1). Briefly, stage I was defined by portal inflammation confined to the portal triads; stage II by portal and periportal inflammation without septal fibrosis or bridging necrosis; stage III by lobular fibrosis and/or bridging necrosis; and stage IV corresponded to cirrhosis.

Survival State

All patients were examined for physical status and development of disease-related symptoms. Patients who had not visited our hospitals in the previous 6 months were contacted by letter or telephone and asked to provide details of recent medications and any disease-related symptoms by using questionnaires. If they visited other hospitals, we also asked them about the results of any endoscopy or imaging studies. In cases that the patient had died, the date and cause of death were recorded. Only the patients followed for at least 1 year were included in the prognostic analysis. Survival statistics were compared between PBC patients and the general population (age- and

gender-matched), using a standardized mortality ratio (SMR). The SMR was calculated by dividing the observed number of deaths by the expected number of deaths, as calculated from gender- and age (5-year)-ranked mortality among the Japanese general population in 2003 published by the Statistics and Information Department of Japan Ministry of Health and Welfare (17). The 95% confidence intervals (CI) for the SMR values were assumed by Poisson's distribution.

Statistical Analysis

Data are expressed as mean±SD or median (range). Patient characteristics were compared among the groups by using the Chi-square, Mann-Whitney U, and Kruskal-Wallis tests. The proportional harzards model was utilized to estimate the effects of patients' characters on survival. The survival rates and disease progression to symptomatic PBC were estimated by the Kaplan-Meier method, and compared with the log rank test. A *P* value of less than 0.05 was considered significant.

Results

Patient Characteristics

Table 1 lists the clinical characteristics of the patients recruited in this study. The age of patients in this study showed a single peak in the fifties, with a median age at diagnosis of 56 years, which is agreement with several previous studies (11, 18, 19). Based on these results, the patients were divided into two groups: the young group (<55 years old) and the elderly group (≥55 years). Most patients were female (88.3%). Interestingly, the male patients had a peak age distribution in the sixties (63 ± 11 years), which was significantly higher than that of the female patients (55 ± 11 years, $P < 0.01$, Mann-Whitney U test). The frequencies of positive AMA or ANA showed no significant difference between the groups. The two groups showed similar values of alkaline phosphatase (ALP), but the young had higher alanine aminotransferase (ALT) than the elderly ($P = 0.03$, Mann-Whitney U test). The elderly group had significantly higher aspartate aminotransferase (AST) to platelet ratio and lower platelet count than the young group ($P < 0.01$, Mann-Whitney U test).

Survival of PBC patients

The survival of PBC patients was evaluated with 282 patients who were followed for at least 1 year. The mean period of follow up was 81 ± 50 months (86 ± 53 months in the young group and 77 ± 47 months in the elderly group respectively). This period was defined as the time between diagnosis and either death or the latest confirmation of survival. The accumulated observation was 1904 person-year accounting for 92.6% of the total potential follow-up. The rate of disease progression to symptomatic PBC was significantly higher in the elderly group than the young group (P = 0.023, log rank test, Figure 1). At 10 years follow up, 19% of the young and 35% of the elderly patients would progress to symptomatic PBC. Causes of death are summarized in Table 2. Liver transplantation was considered a liver-related death when calculating the SMR. Twenty-four patients died or had a liver transplant. Liver failure and malignancies were the leading causes of death in the both groups. Death of the young patients was more likely to be due to liver failure (71%), while the elderly patients might die from other causes before occurrence of liver failure (88%, $P<0.01$, Fisher exact probability test), especially from malignancies other than Hepatocellular carcinoma (HCC; 35%). Two of the three patients who died of HCC were likely to have advanced liver diseases, because they were in histological stage 3 at the time

of diagnosis and the tumors were detected in longer observation than 10 years. The incidence rate of HCC was 0.13% annually. Figure 2 shows that overall survival rate was significantly lower in the elderly group than the young group (P = 0.044, log rank test). At 10 years follow up, 4.3% of the young and 16% of the elderly patients would be dead. The results indicated that the elderly patients died from other causes before occurrence of liver failure, and their survival rate was significantly lower than that of the young patients. We evaluated the effects of patients' characters on prognosis with the proportional hazards model (Table 3). Old age, male gender, high AST to platelet ratio, and high ALP might predict short survival in the univariate analysis. The multivariate analysis, adjusting with logistic likelihood ratio test, indicated that high AST to platelet ratio, but not old age was a significant predictive factor.

Comparison of mortality with age- and gender-matched general population

Table 4 showed the overall mortality and the mortality for liver-related deaths, liver-unrelated deaths, and malignancies. The overall mortality rate of PBC patients was slightly higher than that of the general population (SMR, 1.6; 95%CI, 1.0-2.4). Importantly, the overall mortality rate of the elderly group was not different from that of the general population (SMR, 1.1; 95%CI, 0.6-1.7). Liver-related mortality was significantly higher among PBC patients (SMR, 47; 95%CI, 23-86), especially the young patients (SMR, 218; 95%CI, 71-509) than in the general population, while liver-unrelated mortality among PBC patients was not different from that in the general population (SMR, 1.0; 95%CI, 0.5-1.6). The mortality for malignancies among PBC patients was twice as high as expected (SMR, 2.3; 95%CI, 1.2-4.2), as shown in previous reports (20, 21). These results indicated that the young patients were more likely to die from liver-related causes during the course of PBC, and that the elderly patients were just as likely to die from liver-unrelated causes with survival expectancies similar to the age- and gender-matched general population.

Discussion

Routine testing for liver function and AMA increased the number of newly diagnosed cases of asymptomatic PBC, and several recent studies attempted to clarify the prognosis of those asymptomatic patients, which has not been fully understood. The relationship between age at diagnosis and prognosis remains unclear in PBC patients. We hypothesized that age difference might have an important role in prognosis of PBC patients, because age difference on disease progression has been reported in other chronic liver diseases such as chronic hepatitis C (22) and AIH (15). The present study is a systematic cohort analysis of a large group of asymptomatic PBC patients, and the first to investigate the prognosis of PBC patients more precisely by dividing the patients according to their age at diagnosis.

Considering the possibility of lead time bias that some of the elderly patients had delayed diagnosis in advanced stage, we analyzed the correlations between age at diagnosis and AST to platelet ratio, in order to estimate the effect of age difference on liver damage, and those were not significant (R = 0.11; *P* = 0.065, canonical correlation analysis). There was no significant difference between the two groups in histological stage of liver biopsy specimens obtained at the time of diagnosis, with approximately half of them defined as stage 1. The age distribution of patients of this study is similar to those of other multicenter studies (11, 18, 19). These findings do not indicate that the elderly group might involve the patients who had delayed diagnosis of PBC.

In terms of the mortality of asymptomatic PBC patients, there have been several conflicting reports. Prince et al. suggested that asymptomatic PBC patients have reduced survival compared with the general population, with an SMR >2.5-fold higher than expected deaths (12). Springer et al. reported that asymptomatic PBC patients had shortened survival, and only the patients who remained asymptomatic survived as well as a matched control population (11). Uddenfeldt et al. showed similar survival of asymptomatic patients to the general population (23). In the present study, the mortality of PBC patients was slightly higher than that of the general population (SMR, 1.6; 95%CI, 1.0-2.4). Our analysis, by dividing the patients in the two groups according to their age at diagnosis, clarified that the elderly patients had similar SMR to the general population (SMR, 1.1; 95%CI, 0.6-1.7), while the mortality rate of the young patients was seven times as high as expected. The influence of age difference on mortality occurred partly because the mortality rate of the young general population was

as low as 0.15% annually, which was one twelfth of that of the elderly general population. The mortality rate of the young patients was much higher than that of the young general population, although it was significantly lower than that of the elderly patients or the elderly general population.

The young patients might die from liver failure or receive liver transplant, while the deaths of the elderly patients were more likely to be due to liver-unrelated causes such as malignancies. The elderly patients would develop disease-related symptoms if they lived long enough, but their survival might not be affected by the subsequent development of disease-related symptoms, since a considerable number of them died of liver-unrelated causes before occurrence of liver failure. These results indicated that the young patients might die from liver-related causes during the course of PBC, and that the elderly patients were just as likely to die from liver-unrelated causes with survival expectancies similar to the age- and gender-matched general population. The reports on cancer risk of PBC patients suggested that there is a small increase in overall cancer incidence and mortality in PBC patients (20, 21). Our results are consistent with those reports, showing that overall mortality for malignancies was higher than the general population (SMR, 2.3; 95%CI, 1.2-4.2). The mortality for malignancies was slightly higher both in the young and the elderly groups than the general population, although this increase was not statistically significant. Except for hepatocellular carcinoma, it is unlikely that there is a high excess incidence for PBC patients from any cancer at a particular site. Periodical check-up for malignancies should be necessary for good management of PBC patients.

Many different drugs have been used to slow disease progression in PBC patients, with variable results. Ursodeoxycholic acid (UDCA) delays histological progression (24-29), and prolongs survival without liver transplantation (30, 31). However, these findings were challenged in two independent meta-analyses (32, 33), showing that UDCA did not affect survival. Most patients in the present study (276 patients, 89%) were treated with UDCA over the course of the disease. There was no significant difference in use of drugs between the young and elderly groups (Table 1). UDCA might be adequate as the initial treatment for the elderly patients, because they do not reduce survival at least. On the other hand, the young patients need active management to prevent from liver failure, because our results indicated that they may develop disease-related symptoms at relatively young age, and may not survive as well as the general population. Bezafibrate and immunosuppressants were additionally prescribed for 43 and 51 patients, respectively in the present study. Our data were not sufficient to assess the survival benefits of these drugs.

In conclusion, age difference should be one of the important factors to predict the prognosis of PBC patients, since the mortality rate of PBC patients aged ≥55 years diagnosed at asymptomatic stage are not different from those of the general population. The elderly patients may have more advanced diseases than the young patients. Death of the young patients was more likely to be due to liver failure, while the elderly patients died from liver-unrelated causes such as malignancies. Active management of liver disease might lead better prognosis of young PBC patients.

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Table 1: Clinical characteristics of the patients at the time of diagnosis.

	All patients (N = 308)	Young group (n = 133)	Elderly group (n = 175)	p
Age (years)	56 (24 - 83)†	48 (24 - 54)†	63 (55 – 83)†	
Gender (female/male)	272/36	123/10	149/26	0.04
Liver histology (I/II/III/IV)*	120/67/19/3	59/33/5/1	61/34/14/2	0.28
Treatment (UDCA/Others/none)	273/10/25	119/5/10	154/5/15	0.86
Laboratory Data at diagnosis				
AMA (% positive)	78.9	80.5	77.7	0.65
ANA (% positive)	58.1	57.9	58.3	1
AST (IU/L)	58 ± 70‡	57 ± 60‡	59 ± 78‡	0.73
ALT (IU/L)	62 ± 71‡	72 ± 92‡	54 ± 49‡	0.034
ALP (ratio)**	1.9 ± 1.3‡	1.8 ± 1.3‡	2.0 ± 1.3‡	0.39
Total bilirubin (mg/dl)	0.7 ± 0.3‡	0.7 ± 0.4‡	0.8 ± 0.3‡	0.02
Platelet count ($x10^4/mm^3$)	21.1 ± 6.7‡	23.3 ± 6.6‡	19.5 ± 6.3‡	< 0.01
Total cholesterol (mg/dl)	209 ± 46‡	207 ± 44‡	211 ± 47‡	0.099
Immunoglobulin G (mg/dl)	1852 ± 560‡	1817 ± 500‡	1878 ± 602‡	0.68
Immunoglobulin M (mg/dl)	473 ± 332‡	449 ± 263‡	492 ± 376‡	0.71
AST to Platelet ratio	3.3 ± 5.6‡	2.5 ± 2.2‡	4.0 ± 7.0‡	< 0.01

335 * Histological stage classified by Ludwig et al. (1); ** Expressed relative to the upper limit of normal.

†: Median (range); ‡: Mean ± SD.

UDCA, ursodeoxycholic acid; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Table 2: Causes of death.

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Cause of death	All patients	Young group	Elderly group
Liver-related	10	5	5
Liver transplantation	1	1	0
Hepatocellular carcinoma	3	0	3
Liver failure	6	4	2
Liver-unrelated	14	2	12
Malignancies*	8	2	6
Heart failure	1	0	1
Cerebrovascular disease	2	0	2
Pneumonia	3	0	3
Total deaths or Liver transplantation	24	7	17

*, Malignancies other than hepatocellular carcinoma.

Table 3: Analysis of predictive factors on survival with the proportional hazards model.

	Univariate analysis		Multivariate analysis	
Factors	Odds ratio (Range[†])	p	Odds ratio (Range[†])	p
Age (55 years or older)	2.35 (0.96-5.73)	0.061	2.90 (0.78-10.7)	0.11
Gender (male)	2.94 (1.15-7.53)	0.025	1.71 (0.57-5.17)	0.34
Liver histology (II/III/IV)	0.748 (0.29-1.90)	0.54		
ALT (higher than 2 fold of ULN)	1.58 (0.66-3.80)	0.30		
ALP (higher than 2 fold of ULN)	2.59 (1.12-6.02)	0.027	1.25 (0.42-3.69)	0.69
Platelet count (< ULN)	1.43 (0.55-3.73)	0.46		
Total cholesterol (> ULN)	1.00 (0.42-2.39)	0.99		
Immunoglobulin G (> ULN)	1.76 (0.65-4.77)	0.27		
Immunoglobulin M (> ULN)	1.23 (0.51-2.98)	0.64		
AST to Platelet ratio (> 3.0)	4.89 (1.72-13.9)	< 0.01	3.42 (1.04-11.2)	0.042

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[†]: 95% confidence interval.

ULN, the upper limit of normal; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase

350 Table 4: Standardized mortality ratio (SMR) of the patients.

	All patients (N = 282)	Young group (n = 128)	Elderly group (n = 154)
Overall deaths			
Observed/Expected	24/15	7/1	17/16
SMR (range)†	1.6 (1.0-2.4)	7.4 (3.0-15.2)	1.1 (0.6-1.7)
Liver-related deaths			
Observed/Expected	10/0.2	5/0.0	5/0.2
SMR (range)†	47 (23-86)	218 (71-509)	23 (7.3-53)
Liver-unrelated deaths			
Observed/Expected	14/14	2/0.9	12/16
SMR (range)†	1.0 (0.5-1.6)	2.2 (0.3-7.8)	0.8 (0.4-1.3)
Malignancies			
Observed/Expected	11/4.7	2/0.6	9/6.1
SMR (range)†	2.3 (1.2-4.2)	3.3 (0.4 -12)	1.5 (0.7-2.8)

†: 95% confidence interval.

Figure legends

Figure 1: Disease progression rate to symptomatic PBC, stratified by age at diagnosis.
The rates of disease progression to symptomatic PBC were estimated for both the young and elderly groups by the Kaplan-Meier method. The log rank test was used to compare the two rates. The rate of disease progression to symptomatic state was significantly higher in the elderly group than the young group (P = 0.023, log rank test). At 10 years follow up, 19% of the young and 35% of the elderly patients would progress to symptomatic state.

Figure 2: Overall survival rate of PBC patients, stratified by age at diagnosis.
Survival rates of the young and elderly groups were compared by using the Kaplan-Meier method. The survival curves showed significantly lower mortality in the elderly group than the young group (*P* = 0.044, log rank test). At 10 years follow up, 4.3% of the young and 16% of the elderly patients would be dead.