Evolutionary relationship between antimitochondrial antibody positivity and primary biliary cholangitis in Taiwan: a 16-year hospital cohort study

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Abstract

Background: How antimitochondrial antibody (AMA)-positive patients evolve to have primary biliary cholangitis (PBC) in viral hepatitis–endemic areas is unknown.

Objectives: We aimed to investigate this evolution in Taiwan.

Design/methods: A 16-year medical center-based cohort study of 2,095,628 subjects was conducted in Taiwan, an Asian country endemic to viral hepatitis. AMA-positive subjects were those with positive AMA with alkaline phosphatase (ALP) ⩽1.5 times the upper limit of normal (ULN), and PBC was defined as positive AMA with ALP >1.5 × ULN.

Results: AMA-positive subjects had a lower average age- and sex-adjusted prevalence than PBC patients (4.68/10^5 *versus* 11.61/10^5, $p = 0.0002$), but their incidence was comparable (0.99/10^5 *versus* 1.12/10^5, $p = 0.36$). The former group had a borderline significantly lower mean age (56.59 years *versus* 58.10 years, $p = 0.06$) and a lower female-to-male ratio (2.85:1 *versus* 5.44:1, $p < 0.0001$). Both AMA-positive subjects (prevalence change: 20.0%, $p < 0.01$; incidence change: −9.2%, $p < 0.01$) and PBC patients (prevalence change: 14.6%, $p < 0.01$; incidence change: −4.7%, $p < 0.01$) prevalence rate increased but the incidence rate decreased. Among the 423 AMA-positive subjects, 77 (18.2%) developed PBC, for a mean duration of 1.757 years. Compared with AMA-positive subjects, PBC patients had similar concurrent chronic hepatitis B (CHB) rates (2.7% *versus* 4.3%, $p = 0.197$) but lower chronic hepatitis C (CHC) rates (3.69% *versus* 15.60%, $p < 0.01$).

Conclusion: PBC was more prevalent than AMA-positive subjects, and PBC patients had a higher female-to-male ratio than AMA-positive subjects, of whom 18.2% developed PBC (mean lag: 1.757 years). Upward trends in prevalence rates and downward trends in incidence rates were noted for both AMA-positive subjects and PBC. CHB was rare, CHC was more prevalent among PBC patients than the general population, and CHC was less prevalent among PBC than among AMA-positive subjects.

Plain language summary

Evolutionary relationship between AMA positivity and PBC in Taiwan

PBC was more prevalent than AMA-positive subjects, and PBC patients had a higher female-to-male ratio than AMA-positive subjects, of whom 18.2% developed PBC (mean lag: 1.757 years). Upward trends in prevalence rates and downward trends in incidence rates were noted for both AMA-positive subjects and PBC. CHB was rare, CHC was more prevalent among PBC patients than the general population, and CHC was less prevalent among PBC than among AMA-positive subjects.

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Introduction

Primary biliary cholangitis (PBC), formerly called primary biliary cirrhosis,[1] is a chronic progressive cholestatic liver disease. PBC is characterized by the presence of serum antimitochondrial antibodies (AMAs) and autoimmune-mediated destruction of the intrahepatic bile ducts of small or medium sizes,[2] and it predominantly affects middle-aged women.[3] Without adequate treatment, most PBC patients eventually develop hepatic fibrosis and may require liver transplantation in the late stage.[4] Currently, only ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are approved therapies for PBC.[5] Only approximately 70% of PBC patients treated with UDCA show optimal responses,[6] and up to 60% of UDCA suboptimal responders do not respond to OCA.[6] Early diagnosis and treatment of PBC would thus save the majority of PBC patients from preventable complications.

AMAs are highly specific for PBC in patients with abnormal alkaline phosphatase (ALP) levels. In more than 95% of cases, a diagnosis of PBC can be made in patients with unexplained ALP elevation and the presence of AMAs without biopsy verification.[7] Of AMA-positive subjects with normal ALP, over 80% of them have histological classic PBC. The above findings highlight the importance of AMA positivity, even in patients with a normal ALP level, for the diagnosis of PBC.[8] Although only one in six AMA-positive subjects with normal ALP levels might develop PBC within 5 years according to a French study,[9] how AMA positivity with normal ALP evolves into PBC in Asians remains unknown. In addition, previous studies[10,11] have shown that concurrent viral hepatitis is far less prevalent among patients with PBC in Taiwan, an Asian country hyperendemic for chronic hepatitis B (CHB)[12] and endemic for chronic hepatitis C (CHC),[13] than in the general population. This phenomenon has not been verified in other independent large cohorts.

Accordingly, we conducted a study based on a database from hospitals covering approximately 1/10 of the Taiwanese disease population[14] to quantify the differences between AMA-positive subjects with ALP ⩽1.5 times the upper limit of the normal (ULN) range[15] and PBC patients. In addition, the associations between viral hepatitis and PBC were surveyed and analyzed.

Materials and methods

Patients and study design

Hospital-wide medical records were assessed for the time between 2001 and 2016 from four branches, namely, the Keelung, Linkou, Chiayi, and Kaohsiung branches of Chang Gung Memorial Hospital of Taiwan, a medical center with 3700 beds and 4 million outpatients and 100,000 inpatients annually. Subjects who had been examined for AMA, ALP, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody (HCV Ab) at Chang Gung Memorial Hospital were recruited. Information on patient sex, age at diagnosis, and biochemical data was obtained from the medical records. AMA was assessed using indirect immunofluorescence assays in rat kidneys and stomachs for detecting immunoglobulin G as described previously.[16] The diagnoses of various diseases were defined as follows:

(1) AMA-positive subjects: AMA titer ⩾1:40 and ALP ⩽1.5 × ULN (98 IU/L), namely, ⩽147 IU/L.
(2) PBC: AMA positivity and ALP >1.5 × ULN (i.e. >147 IU/L).
(3) CHB: HBsAg positivity for ⩾6 months.
(4) CHC: HCV RNA positivity for ⩾6 months.

Patients with cholestatic liver biochemistry with causes other than PBC[17] were excluded based on the diagnosis in the medical records.

A schematic flowchart of the enrolled patients is shown in Figure 1.

Statistics

The statistical analyses were performed using Statistical Analysis System (SAS version 9.4; SAS

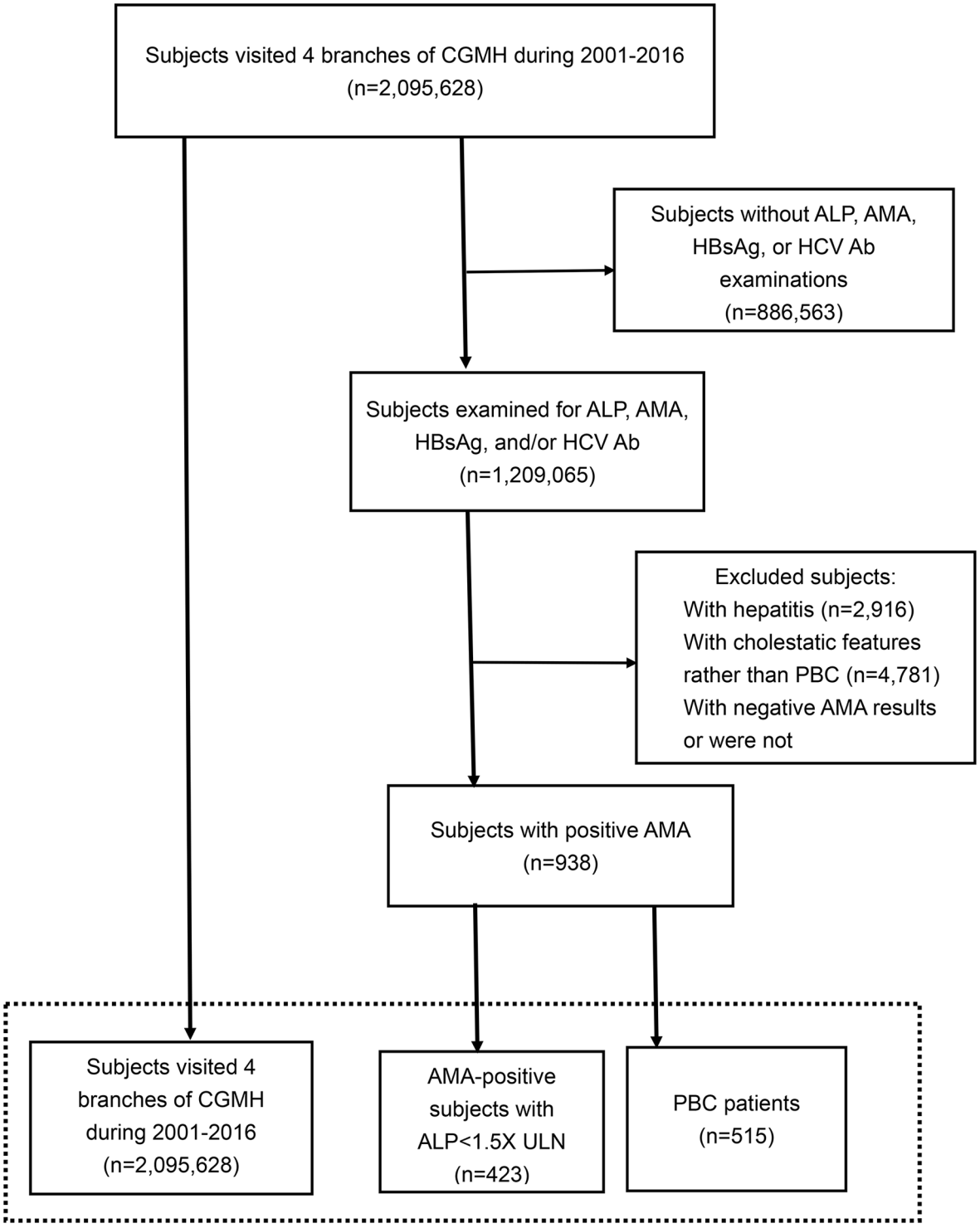

Figure 1. A schematic flowchart of the enrolled patients.
ALP, alkaline phosphatase; AMA, antimitochondrial antibody; CGMH, Chang Gung Memorial Hospital; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; PBC, primary biliary cholangitis.

Table 1. Baseline characteristics of the enrolled subjects.

	All, *n* = 2,095,628	Male, *n* = 1,058,042	Female, *n* = 1,037,586	*p* Values
Age (years)	38.53 ± 25.08	38.29 ± 27.48	38.77 ± 22.37	<0.01
AMA-positive patients with ALP ⩽1.5 × ULN				
Case number	423	110	313	<0.01
Age (years, mean ± standard deviation)	56.59 ± 12.93	57.45 ± 12.13	54.15 ± 14.76	0.04
CHB case number (% of AMA-positive patients)	18 (4.26)	9 (8.18)	9 (2.88)	0.03
CHC case number (% of AMA-positive patients)	66 (15.60)	30 (27.27)	36 (11.5)	<0.01
PBC patients				
Case number	515	80	435	<0.01
Age (years, mean ± standard deviation)	58.10 ± 11.90	62.85 ± 12.55	57.22 ± 11.58	<0.01
CHB case number (% of PBC patients)	14 (2.7)	1 (1.25)	13 (2.98)	0.70
CHC case number (% of PBC patients)	19 (3.68)	5 (6.25)	14 (3.2)	0.19

ALP, alkaline phosphatase; AMA, antimitochondrial antibody; CHB, chronic hepatitis B; CHC, chronic hepatitis C; PBC, primary biliary cholangitis; ULN, upper normal limit.

Institute, Inc., Cary, NC, USA) software. To determine the prevalence of PBC, the proportion of PBC patients was calculated out of the enrolled subjects who visited the four branches of the hospital from 2001 to 2016, adjusted for the annual mortality rate.[18] A washout period (2001–2004) of 4 years[19] was used to calculate the annual incidence of PBC from 2005 to 2016 to avoid prevalent cases because the data recording started in 2001. For the standard population, the inhabitant population served by the hospital at the end of 2010 was used because national health insurance covered more than 99% of the population of Taiwanese inhabitants. The annual incidence of PBC was calculated as the number of new PBC cases per 100,000 people per year. The data were then categorized into AMA-positive subjects and PBC patients. Student's *t*-test, nonparametric test, chi-squared test, or Fisher's exact test was used, as appropriate.

Strengthening the Reporting of Observational Studies in Epidemiology statement

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20]

Results

Baseline characteristics

As shown in Table 1, of the 2,095,628 enrolled subjects, 423 were AMA positive and had ALP ⩽1.5 × ULN, with a mean age of 56.59 years, 313 of these subjects were female (74.0%). Another 515 were diagnosed with PBC, with a mean age of 58.1 years, and 435 were female (84.5%). Subjects with PBC were 1.51 years older than AMA-positive subjects (58.10 ± 11.9 years *versus* 56.59 ± 12.93 years, $p = 0.06$). The female-to-male ratio was greater among the PBC patients than among the AMA-positive subjects (3.81:1 *versus* 2.85:1, $p < 0.01$).

Prevalence rates of AMA-positive subjects with ALP ⩽1.5 × ULN and PBC

As shown in Figure 2(a), the average annual age- and sex-adjusted prevalence rate of AMA-positive subjects with ALP ⩽1.5 × ULN in 2001–2016 was $4.68/10^5$. The average age-adjusted prevalence rate of AMA-positive subjects with ALP ⩽1.5 × ULN was $6.73/10^5$ for females and $2.64/10^5$ for males. There were upward trends in the annual prevalence rates of AMA-positive subjects with

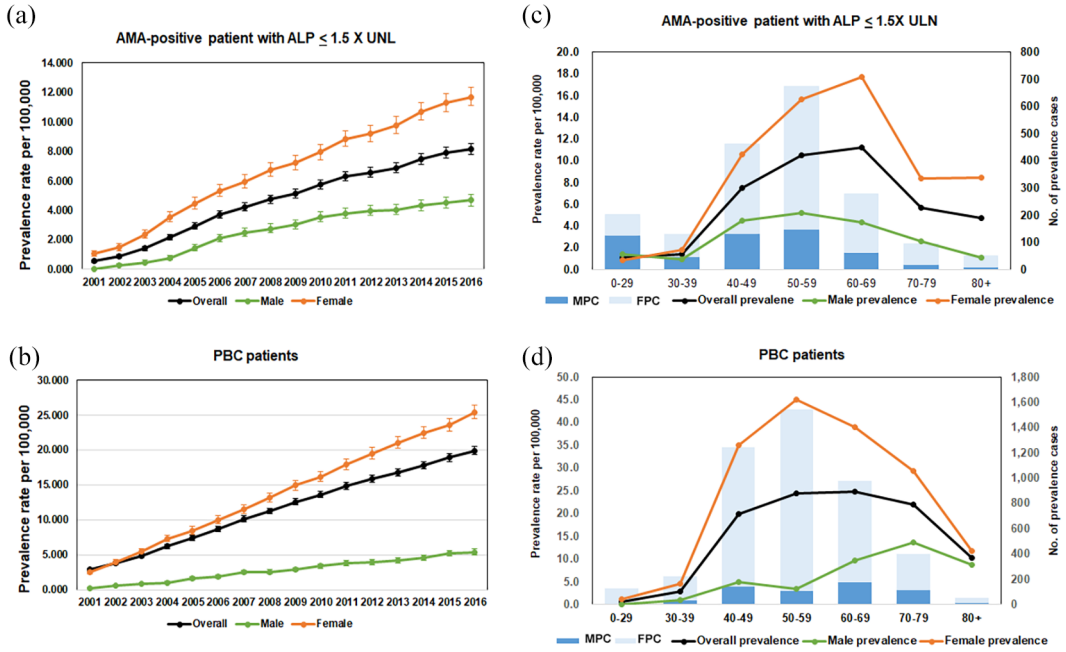

Figure 2. (a) Age-adjusted prevalence trend chart of AMA-positive patients with ALP ⩽1.5 times the ULN (prevalence rate per 10^5 individuals). Female AMA-positive patient prevalence rate: orange line; male AMA-positive patient prevalence rate: green line; and overall AMA-positive patient prevalence rate: black line. (b) Age-adjusted prevalence trend chart of PBC patients (prevalence rate per 10^5). Female PBC patient prevalence rate: orange line; male PBC patient prevalence rate: green line; and overall PBC patient prevalence rate: black line. (c) The average annual prevalence rate of AMA-positive patients per 10^5 people and prevalent case numbers of AMA-positive patients stratified by age. The bars indicate the average number of total AMA-positive cases per year, and the line indicates the prevalence rate per 10^5 people. Female AMA-positive patient prevalence rate: orange line; male AMA-positive patient prevalence rate: green line; and overall AMA-positive patient prevalence rate: black line. (d) The average annual prevalence rate of PBC patients per 10^5 people and prevalent case numbers of PBC patients by age. The bars indicate the average number of total cases with PBC per year, and the line indicates the prevalence rate per 10^5 individuals. Female PBC patient prevalence rate: orange line; male PBC patient prevalence rate: green line; and overall PBC patient prevalence rate: black line.
ALP, alkaline phosphatase; AMA, antimitochondrial antibody; FPC, female prevalent case; MPC, male prevalent case; PBC, primary biliary cholangitis; ULN, upper limit of normal.

ALP ⩽1.5 × ULN. The overall annual percentage change in prevalence was 20% ($p < 0.01$), and the annual percentage change was 17.9% ($p < 0.01$) for females and 34.4% ($p < 0.01$) for males. The average annual age- and sex-adjusted prevalence rate of PBC in 2001–2016 was $11.61/10^5$. As shown in Figure 2(b), the average age-adjusted prevalence rate of PBC was $13.98/10^5$ for females and $2.79/10^5$ for males. There were increasing trends in the annual prevalence rates of PBC. The overall annual percentage change in prevalence was 14.6% ($p < 0.01$), and the annual percentage change was 17.5% ($p < 0.01$) for females and 25.5% ($p < 0.01$) for males.

Regarding age, for AMA-positive subjects with ALP ⩽1.5 × ULN [Figure 2(c)], the prevalent cases peaked at 50–59 years among both women and men. The peak average annual sex-adjusted prevalence rate was highest in the population aged 60–69 years ($11.26/10^5$). For females and males, the prevalence rate was highest in the age bracket of 60–69 years ($17.75/10^5$) and 50–59 years ($5.24/10^5$), respectively. For PBC [Figure 2(d)], the prevalent cases peaked at 50–59 years for women and at 60–69 years for men. The peak average annual sex-adjusted prevalence rate was highest in the age bracket of 60–69 years ($24.87/10^5$). For females and males, the prevalence rate was highest in populations aged 50–59 years ($45.05/10^5$) and 70–79 years ($13.68/10^5$), respectively.

The prevalence rates of AMA positivity with ALP ⩽1.5 × ULN and of PBC were $4.68/10^5$ and $11.61/10^5$, respectively ($p = 0.0002$) [mean

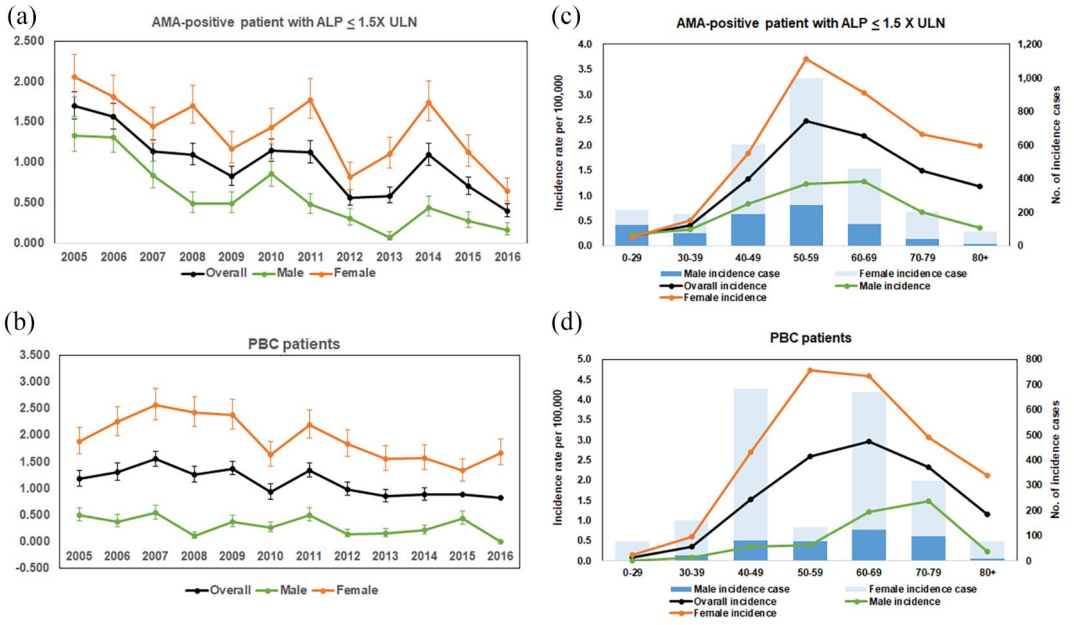

Figure 3. (a) Age-adjusted incidence trend chart of AMA-positive patients with ALP ⩽1.5 × ULN (incidence rate per 10^5). Female AMA-positive patient incidence rate: orange line; male AMA-positive patient incidence rate: green line; and overall AMA-positive patient incidence rate: black line. (b) Age-adjusted incidence trend chart of PBC patients (incidence rate per 10^5). Female PBC patient incidence rate: orange line; male PBC patient incidence rate: green line; and overall PBC patient incidence rate: black line. (c) The average annual incidence rate per 10^5 people and number of incident cases of AMA-positive patients with ALP ⩽1.5 × ULN by age. The bars indicate the number of newly diagnosed AMA-positive patients per year, and the line indicates the incidence rate per 10^5 people. Female AMA-positive patient incidence rate: orange line; male AMA-positive patient incidence rate: green line; and overall AMA-positive patient incidence rate: black line. (d) The average annual incidence rate per 10^5 people and number of incident cases of PBC by age. The bars indicate the number of newly diagnosed PBC cases per year, and the line indicates the incidence rate per 10^5. Female PBC patient incidence rate: orange line; male PBC patient incidence rate: green line; and overall PBC patient incidence rate: black line.
ALP, alkaline phosphatase; AMA, antimitochondrial antibody; PBC, primary biliary cholangitis; ULN, upper limit of normal.

difference in annual incidence: $-6.93/10^5$, standard deviation (SD) = $2.95/10^5$].

Annual incidence rates of subjects with positive AMA and ALP ⩽1.5 × ULN and PBC

As shown in Figure 3(a), from 2005 to 2016, for AMA-positive subjects with ALP ⩽1.5 × ULN, the average annual age- and sex-adjusted incidence rate from 2006 to 2015 was $0.99/10^5$. The average age-adjusted incidence rate was $1.40/10^5$ for females and $0.59/10^5$ for males. There were decreasing trends for overall annual incidence rates (average percentage change: −9.2%, $p < 0.01$); the trends decreased significantly for both the female and male patients (females: average percentage change: −6.3%, $p = 0.02$; males average percentage change: −17.1%, $p < 0.01$). For PBC [Figure 3(b)], the average annual age- and sex-adjusted incidence rate was $1.12/10^5$. The average age-adjusted incidence rate was $1.94/10^5$ for females and $0.30/10^5$ for males. There were decreasing trends for overall annual incidence rates (average percentage change: −4.7%, $p < 0.01$). However, the downward trends became nonsignificant in the male and female subgroup analyses (males: average percentage change: −5.1%, $p = 0.35$; females: average percentage change: −4.2%, $p = 0.52$).

Regarding age, for AMA-positive subjects with ALP ⩽1.5 × ULN [Figure 3(c)], most incident cases were diagnosed in the population aged 50–59 years among women and men. The average age-specific incidence rate was highest among populations aged 50–59 years ($2.48/10^5$), aged 50–59 years for females ($3.71/10^5$), and aged 60–69 years for males ($1.27/10^5$). For PBC [Figure 3(d)], most incident cases were diagnosed in the population aged 40–49 years for women and 60–69 years for men. The average age-specific incidence rates were highest among populations aged

60–69 years (2.70/10^5), aged 50–59 years for females (4.74/10^5), and aged 60–69 years for males (1.22/10^5).

The incidence rates (0.99/10^5 *versus* 1.118/10^5, $p = 0.36$) were similar among AMA-positive subjects with ALP $\leq 1.5 \times$ ULN than among PBC patients (mean difference in annual incidence: $-0.13/10^5$, SD = $0.32/10^5$).

Evolution of AMA-positive subjects with ALP $\leq 1.5 \times$ ULN

Most of the enrolled subjects were followed up every 3–6 months. Over 15 years (2001–2016), of the 423 AMA-positive subjects with ALP $\leq 1.5 \times$ ULN, 119 (28.1%) were lost to follow-up, and 77 (18.2%) developed PBC, with a mean duration of 1.757 years (range: 0.51–10.58 years). The 15-year cumulative incidence of new PBC patients was 33.15%.

Concurrent viral hepatitis

Among 423 AMA-positive subjects with ALP $\leq 1.5 \times$ ULN, 18 (4.26%) and 66 (15.6%) had concurrent CHB and CHC, respectively. Among the 515 PBC patients, 14 (2.7%) and 19 (3.68%) had concurrent CHB and CHC, respectively (Table 1). CHC was less prevalent among PBC patients than among AMA-positive subjects with ALP $\leq 1.5 \times$ ULN (3.68% *versus* 15.6%, $p < 0.01$), while CHB rates were similar among PBC patients and AMA-positive subjects (2.7% *versus* 4.26%, $p = 0.197$). No significant differences between CHB and CHC rates were demonstrated among AMA-positive subjects with ALP $\leq 1.5 \times$ ULN (4.26% *versus* 15.60%, $p = 0.33$) or among PBC patients (2.7% *versus* 3.68%, $p = 1.000$).

Discussion

The most compelling results of the current study are as follows: (1) The PBC patients had a higher female-to-male ratio (5.44:1 *versus* 2.85:1) and a borderline-older mean age (58.1 years *versus* 56.59 years) than the AMA-positive subjects with ALP $\leq 1.5 \times$ ULN. (2) The average annual age- and sex-adjusted prevalence rates for AMA-positive subjects with ALP $\leq 1.5 \times$ ULN and PBC were 4.68/10^5 and 11.61/10^5, respectively, and both showed upward trends. The average annual age- and sex-adjusted incidence rates for AMA-positive subjects with ALP $\leq 1.5 \times$ ULN and PBC were 0.99/10^5 and 1.12/10^5, respectively, and both showed downward trends. (3) CHC was less prevalent among PBC patients than among AMA-positive subjects with ALP $\leq 1.5 \times$ ULN.

Although recombinant autoantigen-enzyme-linked immunosorbent assay might be more sensitive than immunofluorescence for measuring AMAs,[21] the most common technique used in clinical practice for detecting AMAs is classical immunofluorescence. The sensitivity, specificity, and positive predictive value of indirect immunofluorescence detection of AMAs in rat tissue were 71.6%, 97.4%, and 0.94, respectively.[22] We are thus confident about the diagnoses of AMA-positive subjects and PBC patients based on AMA indirect immunofluorescence assays. The mean ages of 56.59 and 58.1 years for our Taiwanese AMA-positive subjects with ALP $\leq 1.5 \times$ ULN and PBC patients were within the reported age range of 44–66 years.[23] However, the female-to-male ratio of 2.85–5.44:1 was less than the 10:1 that has been reported for PBC.[4,23] Several population-based studies have suggested an increasing male prevalence of PBC,[18,23–26] and the percentage of male PBC patients in most case series might be underestimated, probably due to a low awareness of the possibility that males can develop PBC.[19] Notably, compared with AMA-positive patients with ALP $\leq 1.5 \times$ ULN, PBC patients were approximately 1.51 years older and had a higher female-to-male ratio; 18.2% of the AMA-positive patients with ALP $\leq 1.5 \times$ ULN developed PBC after a mean of 1.757 years, potentially reflecting a delay between autoimmunity induction and the biliary injury in patients with PBC and the characteristic female dominance of PBC.[2] Although some AMA-positive subjects with ALP $\leq 1.5 \times$ ULN might never develop PBC afterward,[9] special caution is indicated during the next 1.51–1.757 years for those first diagnosed with AMA positivity. This time coincides with the concept that overt symptoms usually develop within 2–4 years in untreated and asymptomatic PBC patients.[4] Consistent with these findings, a recent European study also reported that AMA-positive subjects without evidence of PBC were slightly younger and had a lower sex ratio imbalance than those newly diagnosed with PBC.[9] Moreover, 18.2% of

AMA-positive subjects with ALP $\leq 1.5 \times$ ULN eventually developed PBC, which was in line with the reported finding that one in six (16.6%) AMA-positive subjects with a normal ALP will develop PBC.[9] The differences noted between AMA-positive subjects with ALP $\leq 1.5 \times$ ULN and PBC patients thus support the universal trend of the course of PBC development. The estimated prevalence rate of both AMA-positive subjects with ALP $\leq 1.5 \times$ ULN ($4.68/10^5$) and PBC ($11.61/10^5$) was within the reported range of $1.9/10^5$ to $40.2/10^5$.[2] In particular, the prevalence rate of $11.61/10^5$ for PBC was close to that ($9.42/10^5$) reported for the nationwide PBC cohort in Taiwan,[26] suggesting that the prevalence rate estimated from hospital data reflects the nationwide PBC prevalence rate well. The PBC prevalence rates have increased with time,[26–31] which reflects the fact that most UDCA-treated PBC patients have a similar expected survival as the general population.[1] The average annual age- and sex-adjusted incidence rates for AMA-positive subjects with ALP $\leq 1.5 \times$ ULN and PBC patients were $0.99/10^5$ and $1.12/10^5$, respectively, both within the reported range ($0.33–5.8/10^5$).[24,32] However, in contrast to the increased or steady PBC incidence rates in most areas,[27–33] our study clearly demonstrated a decreasing trend in PBC incidence rates. As the risk of PBC increases in areas with high socioeconomic deprivation,[33] these decreasing trends in PBC incidence might suggest profound socioeconomic improvement or decreasing birth rates,[34] which decrease new cases of PBC in Taiwanese individuals. Future prospective analysis of the exact trends in the annual incidence rate of PBC nationwide is needed to verify these findings. On the other hand, the peak average annual sex-adjusted prevalence rates of both AMA positivity with ALP $\leq 1.5 \times$ ULN and PBC were highest in those aged 60–69 years. Compared with males, in females, the most prevalent age for AMA with ALP $\leq 1.5 \times$ ULN and for PBC was 10 years older and 20 years younger, respectively. A longer time might be needed for AMA-positive males than for AMA-positive females to develop PBC. Interestingly, both the most prevalent and incident ages were 10–20 years older for men than for women with PBC. Similar data were reported in the Korean PBC cohort.[35] Clinicians' alertness, patients' awareness, and sex dimorphism in the onset of autoimmune diseases[36] might all account for the age lag for male and female PBC patients. Moreover, in terms of the aged populations for most prevalent and incident rates, the PBC patients were approximately 10 years younger than Korean PBC patients.[35] Future studies are needed to elucidate the exact cause of the age lag of PBC patients between Taiwanese and Korean patients.

Interestingly, the fact that the prevalence rates of CHB among both AMA-positive subjects with ALP $\leq 1.5 \times$ ULN (4.26%) and PBC (2.7%) patients were lower than those in the general population (15–20%) of Taiwan[12] coincides with previous observations[10,11] and echoes the proposal that autoimmunity associated with PBC might aid in expelling HBV.[25] On the other hand, the prevalence rates of CHC among both AMA-positive subjects with ALP $\leq 1.5 \times$ ULN (15.6%) and PBC patients (3.68%) were higher than those in the general population (2.7%) in Taiwan,[37] suggesting that susceptibility to CHC might be linked to susceptibility to PBC, as HCV infection is also frequently associated with rheumatic and autoimmune disorders.[38–40] However, the prevalence rate of concurrent CHC was lower among PBC patients than among AMA-positive subjects with ALP $\leq 1.5 \times$ ULN, suggesting that although HCV-related lymphotropism dysregulates the host immune system,[41] it may elicit autoimmune reactions to generate AMAs, while only some CHC patients ultimately experience a cascade to PBC.

The current study has some limitations. First, liver biopsy data for diagnosing AMA-negative PBC, which accounts for $<5\%$ of all PBC cases,[42] are lacking. The prevalence and incidence of PBC might be higher if AMA-negative PBC patients were enrolled in our cohorts. Second, some PBC-specific antinuclear antibodies (ANAs), including sp100 and glycoprotein 210, could act as surrogate diagnostic markers allowing the diagnosis of PBC, even without a liver biopsy.[43] However, these specific ANAs were not assessed in hospitals. Third, due to the retrospective nature of this study, detailed symptoms such as fatigue and/or pruritus,[44] virological parameters and therapeutic regimens for PBC, and concurrent viral hepatitis were not considered or analyzed. Moreover, most patients with normal ALP levels underwent AMA tests because of abnormal liver function results. AMAs were not surveyed in all patients, and the emergence of AMAs might indicate acute liver failure[45] but not subsequent PBC and lead to potential bias. Fourth, both genetic and

environmental factors contribute to PBC, while neither genetic nor environmental factors were surveyed in the present study. Fifth, due to the nature of the patients seeking medical care and the case–control study design, selection bias, particularly Berkson's bias,[46] is an inherent problem. Future prospective multicenter studies, as well as symptom surveys and therapeutic regimens with comprehensive immunological, histological, virological, and genetic factors in both hospital-based and nonhospital-based populations, could be conducted to elucidate the intricate interactions among concurrent viral hepatitis and environmental and genetic factors among PBC patients in Taiwan.

Conclusion

Taken together, the hospital-based data showed that in Taiwan, the average annual age- and sex-adjusted prevalence rates of AMA-positive subjects with ALP $\leqslant 1.5 \times$ ULN and PBC were $4.68/10^5$ and $11.61/10^5$, respectively, and both showed upward trends. The former had a lower female-to-male ratio and a borderline younger mean age than did the latter. The average annual age- and sex-adjusted incidence rates for AMA-positive subjects with ALP $\leqslant 1.5 \times$ ULN and PBC patients were $0.99/10^5$ and $1.12/10^5$, respectively, both showing decreasing trends. Among AMA-positive subjects with ALP $\leqslant 1.5 \times$ ULN and PBC patients, concurrent CHB and CHC were less and more prevalent than in the general population. Moreover, concurrent CHC was less prevalent among PBC patients than among AMA-positive subjects with ALP $\leqslant 1.5 \times$ ULN.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with good clinical practice and all applicable regulations, including the Declaration of Helsinki and local regulatory requirements and was approved by the ethics committee of Chang Gung Memorial Hospital (IRB number: 201601323B0). The need for consent was waived because the hospital-level data used in this study were deidentified by encrypting personal identification information.

Consent for publication

Not applicable.

Author contributions

Ming-Ling Chang: Conceptualization; Supervision.

Jur-Shan Cheng: Formal analysis.

Puo-Hsien Le: Resources.

Wei-Ting Chen: Resources.

Hsin-Ping Ku: Formal analysis.

Rong-Nan Chien: Conceptualization.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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