Journal of Autoimmunity 46 (2013) 81–87

Contents lists available at SciVerse ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review

The limitations and hidden gems of the epidemiology of primary biliary cirrhosis

Mauro Podda [a,*], Carlo Selmi [b,c], Ana Lleo [a], Luca Moroni [a], Pietro Invernizzi [a,c]

[a] Liver Unit and Center for Autoimmune Liver Diseases, Humanitas Clinical and Research Center, Rozzano, Milan, Italy
[b] Division of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy
[c] Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis, Davis, CA, USA

ARTICLE INFO

Article history:
Received 22 June 2013
Accepted 23 June 2013

Keywords:
Clinical epidemiology
Primary biliary cirrhosis

ABSTRACT

Epidemiology is expected to provide important clues to our understanding of the enigmatic etiopathogenesis of primary biliary cirrhosis (PBC). First, a systematic review of population based studies indicated a wide range in the yearly incidence (0.33–5.8/100.000) and point prevalence (1.91–40.2/100.000) rates. Though different ethnic representations may also contribute it is likely that methodological issues, based on the retrospective survey of diagnosed cases, and time trend play a major role, also in view of the prolonged asymptomatic period of the disease. Of note, the highest prevalence rates (35–40/100.000) were found in areas characterized by high medical awareness and easier access to healthcare. Second, the search for serum AMA in unselected population sera may identify the largest possible number of patients who have or will develop the disease. Indeed, a surprisingly high AMA prevalence rate, ranging between 0.43 and 1%, appears likely in the general population despite the lack of adequate work-up in most studies. Third, the median female to male ratio for PBC is classically accepted as 9–10:1 but is significantly lower for AMA prevalence (2.5:1), death certificates for PBC (4.3:1) and liver transplantation (6:1), thus suggesting that PBC in men may be underdiagnosed in early stages or manifest a more severe progression. Lastly, studies of both PBC and serum AMA prevalence among family members and monozygotic twins strongly support the role played by genetic factors in the etiopathogenesis of the disease. In conclusion, PBC epidemiology is far from being a closed case and the numerous open issues will be solved through a collaborative effort and powerful data mining tools.

1. Introduction

The etiopathogenesis of primary biliary cirrhosis (PBC) remains largely enigmatic despite the well established role of autoimmunity and genetic factors [1–3]. In such uncertainty, epidemiology becomes pivotal in suggesting clues to etiology and to shed light on putative environmental factors which may trigger the disease process in predisposed individuals, similarly to other autoimmune conditions [4–6]. It could be argued that epidemiological data are of major importance for all complex diseases, but we are convinced that this holds particularly true in the case of PBC for its scientific implications and to establish the real burden for healthcare resources of a disease once considered very rare and now significantly more common [7–9]. Indeed, the steep increase in PBC prevalence observed in data collected over time and the wide geographical variations have been the object of discussion [8] and we are convinced that a major role is due to the improved diagnostic accuracy and more complete data collection, favored by easier access to laboratory screening and availability of digitalized medical databases. Nevertheless, in some cases similar methodology changes led to widely variable data in different geographical areas or in groups with different ethnic background in a phenomenon coined geoepidemiology [9–12], thus leaving the crucial questions unanswered and warranting this critical reappraisal of epidemiology papers.

We herein report the results of critical evaluation of the available studies with a specific attention to the recurrent biases responsible for the variability and the limited value of the data. First and foremost, nearly all studies are aimed at establishing the number of patients with a reliable diagnosis of PBC in a definite area. It is therefore clear that the denominator, i.e. the population of the catchment area, may be easily and exactly obtained at any time

* Corresponding author. Liver Unit and Center for Autoimmune Liver Diseases, Department of Gastroenterology, Humanitas Clinical and Research Center, Via Manzoni 56, 20089 Rozzano, Milan, Italy. Tel.: +39 02 82244014.
E-mail address: mauro.podda@humanitas.it (M. Podda).

0896-8411/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jaut.2013.06.015

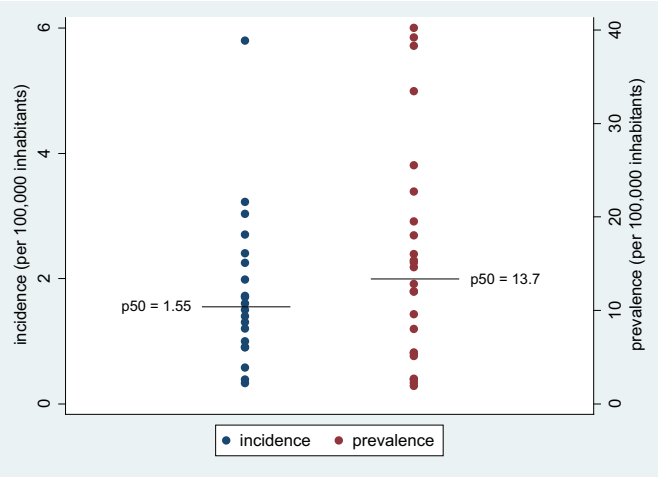

Fig. 1. PBC incidence and prevalence rates [7,15–30].

from census registries, while the numerator, i.e. the number of PBC cases, is largely dependent on a plethora of factors including the location- and time-dependent access to diagnoses in the general population. As a result, we have the ambitious goal to critically discuss the published data and to suggest directions for future research.

2. Prevalence and incidence rates in population-based studies

A comprehensive systematic review of population-based studies for PBC epidemiology was recently published [13]. It followed the checklist proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [14] to include 24 studies. The review reported PBC incidence and prevalence rates obtained from the population of well defined geographical areas with populations exceeding 100,000 inhabitants. We have updated this search over the next 23 months until December 2012 and included two additional articles fulfilling the above mentioned criteria [15,16]. All studies were case-finding studies, reporting the number of patients with an established diagnosis of PBC in a well defined geographic area, usually corresponding to the catchment area of one or a group of hospitals. Interestingly, in a single area, i.e. the Calgary Health region of Canada, cases were collected from administrative databases used for reimbursement and management purposes [17].

Values of yearly incidence and point prevalence from the 26 papers are illustrated in Fig. 1 [7,15–30]. Both the yearly incidence (0.33–5.8/100.000) and point prevalence (1.91–40.2/100.000) rates manifest a wide variability, with median values of 1.55/100.00 and 13.7/100.00, respectively. Though different ethnic representations might contribute to the high data heterogeneity, we are convinced that methodological aspects and time trend play a preponderant role. This hypothesis is supported by later studies performed with different approaches in the Australian State of Victoria [31,32] and in the Canadian States of Ontario and Alberta [17,33] showing 3- to 10-fold prevalence increases. As somehow expected, the analysis of single articles indicated that higher values of incidence and prevalence were obtained in studies that applied a more rigorous methodology to trace PBC cases. In this regard, the search strategy applied and recommended by the Newcastle group in 1997 [34] is comprehensive and has been adopted by most investigators since its publication. This strategy has its cornerstone in the survey of serum antimitochondrial antibody (AMA) detection in regional laboratories and may have well contributed to the increase over time of PBC incidence and prevalence. Furthermore, medical awareness of the higher frequency of PBC also grew with time and stimulated appropriate testing in a wider number of subjects, usually with mild elevations of serum liver enzymes, even in the absence of symptoms classically associated with PBC such as pruritus. The introduction in many settings of digitalized medical records improved data collection tools and made this approach easier and more reliable in recent years [35]. We are convinced that these factors, taken altogether, should be credited at least partially for the time trend increase of both incident and prevalent cases in more recent papers as well as in those studies spanning through an extended number of years. On the other hand, we note that the improved management of advanced liver disease, the more frequent access to liver transplantation and the widespread use of ursodeoxycholic acid [3] at appropriate doses have clearly prolonged patient survival, thus ultimately affecting PBC prevalence. The obvious fact that these factors are not evenly distributed in different geographical areas reflects the discrepancy of access and expertise in healthcare and may further account for the wide data variability. As an indirect confirmation of this observation, it is noteworthy that the three studies reporting the highest rates for PBC point prevalence (Table 1) the search methods were similar and were performed in different well defined settings that were curiously corresponding to a whole city (Newcastle, UK) [25], county (Olmsted, MN) [28], and country (Iceland) [15]. Among these settings, the city of Newcastle hosts the Academic group which pioneered PBC epidemiology and set the standard for such studies with original and stimulating results, including the most recent one, indicating a seasonal variation in PBC identification [36]. Second, Olmsted country is the site of the Mayo Clinic which has established a network with other county hospitals to create a common database favoring the collaboration for epidemiologic investigations. Third, Iceland has unique conditions for an epidemiologic survey as AMA are measured in a single laboratory that makes it feasible “to select the entire country’s population as a study cohort” [15]. As an indirect confirmation of our hypothesis, remarkably similar point prevalence rates were reported in the three studies with 39.2 cases per 100.000 people in Newcastle, 40.2 in Olmsted County, and 38.3 in Iceland. We are convinced that this homogeneity within studies performed in different settings and at different latitudes but sharing an adequate methodology by highly experienced investigators, suggests that the highest values may represent standard values that can be presently obtained in case finding studies, at least in Westernized countries. Another peculiar aspect of these three studies is the commonly overlooked stability of PBC yearly incidence rates throughout the period of data collection, somehow in contrast with the significant trend of increasing values reported by the large majority of other studies [13] and confirms that in ideal conditions consistent data are found both between and within different studies. The only study based on administrative data in the State of Alberta [17] reported a frequency of PBC that is to be considered among the highest out of individual patient identification studies. Although the use of administrative data is applicable only where healthcare delivery is not fragmented, it represents a promising approach to collect a large volume of information for epidemiology and also for natural history of chronic diseases. This methodology, however, does not overcome the limits of case finding studies which will be discussed in the next section.

3. The limits of case-finding studies

All case finding studies are subject to obvious shortcomings which may influence the resulting incidence and prevalence rates to a variable extent. As already stated in the introduction, all problems reside in the numerator, i.e. the number of diagnoses made and detected in the population of a definite area (the

Table 1
Features of the three population studies with the highest PBC prevalence.

Area	Period	Population	PBC cases	Incidence per 10^5 per yr	Prevalence per 10^5	Male (%)	Ref.
Newcastle, UK	1987–1994	285,310	160	4.30	39.2	10	[25]
Olmsted County (MN), USA	1975–1995	–	46	2.70	40.2	11	[28]
Iceland	1991–2010	317,630	168	2.25	38.3	18	[15]

denominator). Potential biases of case finding studies have been extensively discussed for rheumatic diseases elsewhere [37], but these are more crucial in PBC research, due to the elusive and asymptomatic status of most patients, especially at earlier stages. Before overt disease becomes evident with clinical symptoms and/or liver decompensation two stages are traditionally recognized as part of PBC natural history [3]. The first stage is coined preclinical PBC, characterized by positive serum AMA, early but definite histological lesions. The second stage, asymptomatic PBC, features the two previous characteristics (positive AMA and histology) along with a cholestatic biochemical profile [3]. The preclinical and asymptomatic stages may last for decades [3], or most of PBC natural history, when diagnosis can be only incidental, usually via three different pathways. First, the probability of being diagnosed with PBC is largely dependent on the chance that an affected individual will seek medical advice for any iatrotropic reason with a workup including a liver screening. In the case of PBC, an abnormal laboratory test will lead to AMA determination. Second and more rarely, hepatomegaly at clinical examination or ultrasound is found and triggers the search for liver disease. Finally, the presence of an immune-mediated disease known to be associated with PBC, such as scleroderma or Sjogren syndrome, may induce the physician to order serum AMA or cholestasis indices. It is quite obvious that the limiting steps for an early PBC diagnosis are the former two and that the large variability in medical awareness of the disease and in the access to a laboratory performing accurate AMA determination are an issue, particularly in developing countries or in rural areas of Westernized countries. Indeed, this variability in different regions and settings, even with similar healthcare quality, is based on numerous scientific, cultural, social, and economic factors. When specific environmental factors are sought in PBC such variables are of seminal importance and cannot be overlooked.

The limitations that have been discussed appear to act only in one way, that is by decreasing the number of PBC cases that are properly diagnosed or otherwise detected, thus reducing both incidence and prevalence rates. The risk of overdiagnosing PBC, on the other hand, is negligible as objective and validated criteria have been established and are universally applied in all studies [38,39]. There is no reliable estimate of the magnitude of these underestimates in PBC epidemiology as we cannot expect that all asymptomatic patients with PBC have undergone the appropriate workup while the opposite, i.e. that not all symptomatic PBC cases have been diagnosed especially in areas of low medical awareness, is significantly more likely. Independent of the magnitude, two conclusions may be drawn following the previous considerations. First, we are convinced that there is an inverse relationship between the incidence and prevalence rates and the degree of PBC underestimation of 'submersed' data. Second, the PBC incidence and prevalence increase over the years, reported in most studies, is likely to derive from the easier access and the more appropriate use of diagnostic tools (as in the case of serum AMA, among others) for PBC differential diagnosis [40,41], in analogy with other chronic liver diseases [42]. As the natural subsequent step in this dissertation, we will now discuss the data of AMA prevalence in the general population; these observations are of major importance in this context, as AMA-positive subjects may well indicate the highest hypothetical number of PBC cases in a defined population subset despite the minor underestimation of AMA-negative PBC [40,41].

4. Serum AMA prevalence

It should be now clear that case-finding studies are prone to the risk of underestimating the prevalence of rare diseases. Conversely, the search for AMA-positive subjects in unselected population samples has the potential to identify the largest number of patients who have or may develop PBC, with the minor discrepancy of the small percentage of patients with AMA-negative PBC [43,44]. The assumption that asymptomatic subjects with normal laboratory values and an isolated positivity for AMA have preclinical PBC or will develop the disease was derived from the seminal paper of the Newcastle group [45]. The authors demonstrated that 75% of 29 asymptomatic individuals with an incidental finding of serum AMA positivity at indirect immunofluorescence and normal liver function tests eventually had PBC at baseline histology or developed the disease after a median follow-up of 18 years. This proportion became 100% when the frozen baseline serum samples of 21 subjects were tested years later by ELISA using the recently developed AMA recombinant autoantigens. This breakthrough discovery allowed higher specificity and reproducibility compared to indirect immunofluorescence, and the screening of large population samples became feasible at lower costs. However, only a few studies based on this technology have been reported thus far, usually on a small number of subjects who in most cases were not submitted to adequate clinical investigations to establish if they actually had PBC (Table 2). Addressing in details the molecular and diagnostic characteristics of different antigens and laboratory techniques is beyond the aims of this article but it should be noted that this variable increases the complexity of the scenario and that AMA prevalence data should be evaluated also on this basis.

Table 2
AMA prevalence in the general population.

Reference	Year	Region	Source	Subjects			Cases			M %
				Tot	M	F	Tot	M	F	
Lazaridis [48]	2005	US	Routine health check	196	20	176	2 (1.00%)	0 (0%)	2 (1.10%)	0
Liu [44]	2006	Southern China	Routine health check	8126	4248	3878	35 (0.43%)	15 (0.35%)	20 (0.52%)	43
Mattalia [47]	1998	Northern Italy	Blood donors and healthy subjects	1530	555	975	9 (0.59%)	4 (0.72%)	5 (0.51%)	44
Turchany [46]	1997	Estonia	Unselected general population	1565	666	899	14 (0.89%)	3 (0.45%)	11 (1.22%)	21
Shibata [54]	1999	Japan	Yearly health check	1714	959	755	11 (0,64%)	3 (0.31%)	8 (1.06%)	27

When data are cumulatively considered a surprisingly high prevalence rate ranging from 0.43 to 1% is gathered from the general population. At present, the diverse nature of the studies, the limited number of subjects included, and the lack of an adequate diagnostic work-up do not allow to draw firm conclusions on the frequency and clinical significance of AMA positivity in otherwise healthy subjects. On these grounds, discussing specific studies is instrumental in explaining the limitations of the available data.

The screening of a random population of two neighboring Estonian villages identified 14 AMA positive individuals out of 1565 subjects [46]; of these, 8 were available for follow up and none agreed to undergo a liver biopsy. Over 9 years of follow up, 3 of the 8 subjects developed abnormal tests of liver biochemistry. Interestingly, a case finding study by the same group in the whole country of Estonia [24] indicated for PBC a point prevalence of 2.69/100.000 corresponding to a ratio of about 1 diagnosis of PBC to 350 AMA positive subjects.

Mattalia and Colleagues [47] investigated a large number of sera that included a majority of young blood donors and was mainly focused on the characterization of the antibody pattern in healthy subjects. In this Italian cohort 0.59% of subjects were AMA positive and 8/9 were retested after one year with the detection of a wider AMA pattern compared to baseline.

Quite surprisingly, 2 subjects tested positive for AMA in a small sample of 196 healthy subjects selected as matched controls for first degree relatives of patients with PBC [48].

The study with the largest number of cases combined an initial indirect immunofluorescence screening with subsequent ELISA and immunoblotting with PBC specific antigens [49]. Of the 8445 subjects reporting to a Southern China hospital for annual check up, 35 tested positive at indirect immunofluorescence and 22 of them confirmed their positivity with a more specific assay.

In conclusion, if adequate population studies in terms of patient selection and series, with proper diagnostic work-up and sufficient duration of follow up of positive cases will confirm the findings of the Newcastle group, PBC will no more be considered a rare disease but rather a relatively common condition. As a direct consequence, geoepidemiology, risk factors, and environmental associations need to be established on more solid grounds and an agreement between PBC and serum AMA should be expected as an indirect proof of the chosen approach.

5. Sex differences

A significant female preponderance is a widely accepted feature of PBC clinical description and the median ratio in case finding studies corresponds to approximately 9–10:1. This value, albeit not surprising, is among the highest for autoimmune diseases [12,50,51]. We note that PBC sex ratio is shared with frequently coexisting conditions such as Sjogren syndrome and autoimmune thyroid disease and the putative mechanisms influencing female preponderance have been recently reviewed for both PBC and autoimmune diseases and are outside the aims of this discussion [12,51,52]. As previously discussed, case finding studies are based on clinical recognition and the initial clues leading to the suspicion of PBC may be more easily appreciated in women than in men as suggested by the “anchoring bias” of behavioral economics. The subtle onset and long persistence of PBC at asymptomatic stages leaves wide space to mere heuristics for early diagnostic suspicion, which obviously privilege a more straightforward approach to diagnostic tests such as autoantibodies in women. The opposite bias, favoring men, has been reported in a paradigmatic condition of male-predominant disease, i.e. coronary artery disease, and one study demonstrated that general physicians tend to inquire about typical symptoms in men and women to support different evaluation processes [53]. The resulting possibility that PBC could be underdiagnosed in men is supported by different lines of evidence. First, AMA positivity in the general population reports a female preponderance reduced to approximately 2:1 (Fig. 2 [46,47,49,54]) but the small size of these studies falls short to draw solid conclusions. Second, a 4.3:1 ratio among the people deceased for PBC during a 20 year period [55] although this may also represent a more rapid progression rate or a worse response to treatment in men. Third, women outnumber men by a factor of 6 among cases of PBC undergoing liver transplantation in the UNOS dataset ([56] and Dr A.K. Singal personal communication). Taken altogether, these lines of evidence underline that, although female preponderance is confirmed in all studies, the universally accepted 9–10:1 ratio is likely an overestimate. Finally, and for more discussion, we note a recent symposium devoted entirely to gender, sex hormones, pregnancy and autoimmunity [12,57–101].

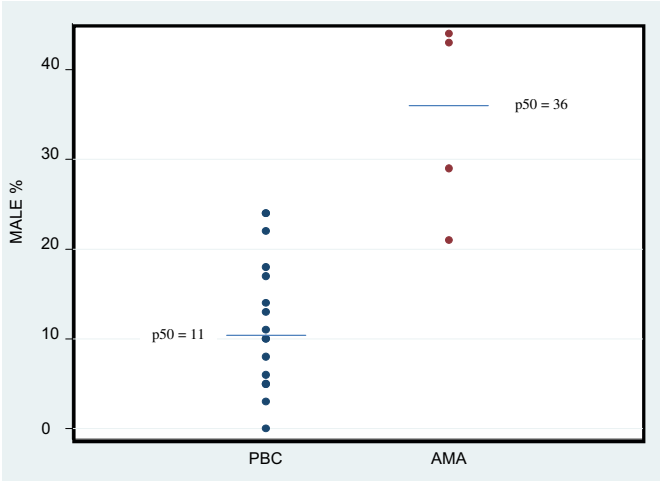

Fig. 2. PBC and serum AMA female/male ratios [46,47,49,54].

6. Familial PBC

Diagnosing multiple PBC cases within the same family has been coined familial PBC and anectodal familial PBC clusters have been reported for the first time over 40 years ago, also including female [102] and even male [48] twins. Cumulatively, based on family studies of both PBC and serum AMA prevalence and especially from concordance rates in identical twins we can confidently draw the conclusion that there is a fundamental role played by genetic factors in the etiopathogenesis of PBC. In the 1990s the prevalence of patients with PBC having a positive family history, i.e. at least one affected relative, was investigated by several groups (Table 3) [103–109]. Nevertheless almost all these studies are burdened by numerous shortcomings, since the methodology was substantially based on case-note review and the criteria for case ascertainment

Table 3
Prevalence rates of familial PBC.

Study	PBC probands (n)	Affected families	First degree relatives
Bach [12]	405	17 (4.3%)	–
Brind [58]	736	8 (1.1%)	10 (1.3%)
Floreani [59]	156	6 (3.8%)	5 (3.2%)
Jones [60]	160	10 (6.4%)	8 (5.0%)
Tsuji [61]	156	8 (5.1%)	8 (5.1%)
Corpechot [63]	221	8 (3.6%)	8 (3.6%)
Gershwin [62]	1032	57 (5.5%)	57 (5.5%)

Table 4
PBC prevalence in first degree relatives of patients (modified from Ref. [60]).

Population group	PBC prevalence (%)
All first-degree relatives	0.72
Female first-degree relatives	1.4
All siblings	0.41
Female siblings	0.82
All offspring	1.2
Daughters	2.3
Control population (Newcastle)	0.04

were not uniform or clearly illustrated. Further, no attempt was made to calculate the size of the patient pedigree, and the relative proportion of affected members and all studies were performed in tertiary referral centers with the inherent "referral bias" favoringpeculiar or interesting cases. Finally, in most studies no control group was available for comparison of the prevalence rate. Despite these limits, similar results were more recently reported by two case–control studies [108,109] in which the occurrence of familial PBC was self-reported.

Of note, the careful investigation by Jones et al. [106] was designed as a "geographically based population study" that avoided referral bias and compared prevalence rates within all family members with that of the area population [106]. Interestingly, the authors calculated a risk for a first-degree relative to have PBC as less than 1%, with higher values for female relatives (Table 4). The sibling relative risk, that is the odd ratio for PBC of a subject with a sibling affected by the disease is 10.5, surprisingly among the lowest for autoimmune diseases.

Once again, the search for serum AMA in apparently healthy first-degree relatives of patients with PBC is of major relevance, as discussed in a previous section. Furthermore, the presence of AMA in first-degree relatives is a strong indicator of the role of genetic factors in breaking tolerance towards mitochondrial antigens. Early studies based on immunofluorescence found a prevalence ranging from 4.9 to 7.4% in screened relatives [110,111], however almost half of them were children, while siblings were a minor fraction. In a more recent study, carefully selected first-degree relatives were screened for AMA by ELISA using recombinant mitochondrial autoantigens and an overall 13.1 prevalence was detected with higher rates, as expected, in siblings [48] (Table 5). Of note, a recent paper from Greece, employing the same study design and methodology, reported a prevalence rate of 18.1 [112]. These values are 15–20 times higher than those reported by Jones for clinical PBC [106], and reinforce the similar finding in the general population (Table 6).

Ultimately, we note that the reported 63% concordance rate among monozygotic twins compared to the null concordance among dizygotic pairs [113] together with growing evidences from genome wide association studies [114–117] demonstrated the importance of genetic factors for PBC [2,118].

Table 5
AMA prevalence in first degree relatives of patients with PBC, modified from Lazaridis et al. [48].

	N	Mean age (years)	AMA positive (%)
PBC probands	350	–	88.0
PBC FDRs	306	–	13.1
Mother	53	77.1 (56–91)	15.1
Father	27	76.1 (60–86)	3.7
Sister	111	60.1 (39–82)	20.7
Brother	51	58.1 (35–78)	7.8
Daughter	41	41.2 (18–58)	9.8
Son	23	40.6 (20–53)	0

Table 6
Data on coronary artery disease awareness with patients of both sexes may suggest a female bias in PBC diagnosis [53].

	Men	Women	*P* value
Questions asked (*n*)	7.0	5.7	0.011
Certainty of CHD diagnosis	57%	47%	0.003
Ordering diagnostic tests	90%	80%	0.025
Appropriate prescriptions	64%	52%	0.048
Specialist referral	27%	16%	0.025

7. Concluding remarks and auspices

As we are confident should be clear from our review of the available evidence, PBC epidemiology is far from being a closed case and several issues remain to be addressed. First, prevalence rates of "clinically recognized" PBC as high as 40 per 100.000 should be considered the standard rather than the high extreme of prevalence. This is particularly true among Caucasians and in geographical areas characterized by a high level of clinical expertise, easy access to laboratory investigations, and optimal organization to retrieve information from medical databases. Second, reported rates underestimate the whole population of subjects with PBC which includes preclinical and "lanthanic" patients. Third, the exact prevalence of a predominantly asymptomatic disease such as PBC can be established only through an appropriate screening of an adequate sample of unselected population. Unfortunately, this approach would require high costs in view of PBC relative rarity and would raise ethical questions from at least two points of view. It would allow the diagnosis of a disease at a stage in which the prognosis and treatment are largely undetermined, with unclear consequences for the patient, and in case of positive AMA and normal alkaline phosphatase a liver biopsy would be needed to establish the diagnosis of PBC. The latter point would be applicable also for a more straightforward and less expensive approach based on the screening for serum AMA and alkaline phosphatise of blood samples collected for other purposes from sufficiently large population series. In case of positive AMA and normal alkaline phosphatase levels follow up could be informative in a subgroup, without the need of a liver biopsy. A fourth open issue is the variable sex ratio among studies with different methodologies, with case finding studies favouring a larger female predominance as compared to serum AMA prevalence, death certificates and liver transplantations. We cannot overlook the possibility that this may also be caused by a more severe progression in men with shorter survival and more frequent need for transplantation. Though early retrospective study did not find differences in survival [119] further accurate investigations are warranted. Fifth, the clinical significance of "isolated" AMA and the natural history of early PBC could also be clarified by follow up of subjects detected through the screening procedure.

In conclusion, the switch from descriptive to clinical epidemiology could offer principles of major relevance to "the basic science of the clinician" as clinical epidemiology was defined [120] and we encourage a strenuous multidisciplinary effort to tackle this goal as data mining tools become more powerful and effective.

References

[1] Kaplan MM, Gershwin ME. Primary biliary cirrhosis. N Engl J Med 2005;353:1261–73.
[2] Hirschfield GM, Invernizzi P. Progress in the genetics of primary biliary cirrhosis. Semin Liver Dis 2011;31:147–56.
[3] Invernizzi P, Selmi C, Gershwin ME. Update on primary biliary cirrhosis. Dig Liver Dis 2010;42:401–8.
[4] Prince MI, James OF. The epidemiology of primary biliary cirrhosis. Clin Liver Dis 2003;7:795–819.

[5] Selmi C, Lu Q, Humble MC. Heritability versus the role of the environment in autoimmunity. J Autoimmun 2012;39:249–52.
[6] Invernizzi P. Human leukocyte antigen in primary biliary cirrhosis: an old story now reviving. Hepatology 2011;54:714–23.
[7] James OF, Bhopal R, Howel D, Gray J, Burt AD, Metcalf JV. Primary biliary cirrhosis once rare, now common in the United Kingdom? Hepatology 1999;30:390–4.
[8] Lazaridis KN, Talwalkar JA. Clinical epidemiology of primary biliary cirrhosis: incidence, prevalence, and impact of therapy. J Clin Gastroenterol 2007;41: 494–500.
[9] Invernizzi P. Geoepidemiology of autoimmune liver diseases. J Autoimmun 2010;34:J300–6.
[10] Parikh-Patel A, Gold E, Mackay IR, Gershwin ME. The geoepidemiology of primary biliary cirrhosis: contrasts and comparisons with the spectrum of autoimmune diseases. Clin Immunol 1999;91:206–18.
[11] Selmi C, Invernizzi P, Zuin M, Podda M, Gershwin ME. Genetics and geoepidemiology of primary biliary cirrhosis: following the footprints to disease etiology. Semin Liver Dis 2005;25:265–80.
[12] Moroni L, Bianchi I, Lleo A. Geoepidemiology, gender and autoimmune disease. Autoimmun Rev 2012;11:A386–92.
[13] Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol 2012;56:1181–8.
[14] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[15] Baldursdottir TR, Bergmann OM, Jonasson JG, Ludviksson BR, Axelsson TA, Bjornsson ES. The epidemiology and natural history of primary biliary cirrhosis: a nationwide population-based study. Eur J Gastroenterol Hepatol 2012;24:824–30.
[16] Delgado JS, Vodonos A, Delgado B, Jotkowitz A, Rosenthal A, Fich A, et al. Primary biliary cirrhosis in Southern Israel: a 20 year follow up study. Eur J Intern Med 2012;23:e193–8.
[17] Myers RP, Shaheen AA, Fong A, Burak KW, Wan A, Swain MG, et al. Epidemiology and natural history of primary biliary cirrhosis in a Canadian health region: a population-based study. Hepatology 2009;50:1884–92.
[18] Triger DR. Primary biliary cirrhosis: an epidemiological study. Br Med J 1980;281:772–5.
[19] Eriksson S, Lindgren S. The prevalence and clinical spectrum of primary biliary cirrhosis in a defined population. Scand J Gastroenterol 1984;19:971–6.
[20] Lofgren J, Jarnerot G, Danielsson D, Hemdal I. Incidence and prevalence of primary biliary cirrhosis in a defined population in Sweden. Scand J Gastroenterol 1985;20:647–50.
[21] Danielsson A, Boqvist L, Uddenfeldt P. Epidemiology of primary biliary cirrhosis in a defined rural population in the northern part of Sweden. Hepatology 1990;11:458–64.
[22] Myszor M, James OF. The epidemiology of primary biliary cirrhosis in northeast England: an increasingly common disease? Q J Med 1990;75:377–85.
[23] James OF, Myszor M. Epidemiology and genetics of primary biliary cirrhosis. Prog Liver Dis 1990;9:523–36.
[24] Remmel T, Remmel H, Uibo R, Salupere V. Primary biliary cirrhosis in Estonia. With special reference to incidence, prevalence, clinical features, and outcome. Scand J Gastroenterol 1995;30:367–71.
[25] Metcalf JV, Bhopal RS, Gray J, Howel D, James OF. Incidence and prevalence of primary biliary cirrhosis in the city of Newcastle upon Tyne, England. Int J Epidemiol 1997;26:830–6.
[26] Berdal JE, Ebbesen J, Rydning A. Incidence and prevalence of autoimmune liver diseases. Tidsskr Nor Laegeforen 1998;118:4517–9.
[27] Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol 1998;33:99–103.
[28] Kim WR, Lindor KD, Locke 3rd GR, Therneau TM, Homburger HA, Batts KP, et al. Epidemiology and natural history of primary biliary cirrhosis in a US community. Gastroenterology 2000;119:1631–6.
[29] Rautiainen H, Salomaa V, Niemela S, Karvonen AL, Nurmi H, Isoniemi H, et al. Prevalence and incidence of primary biliary cirrhosis are increasing in Finland. Scand J Gastroenterol 2007;42:1347–53.
[30] Pla X, Vergara M, Gil M, Dalmau B, Cistero B, Bella RM, et al. Incidence, prevalence and clinical course of primary biliary cirrhosis in a Spanish community. Eur J Gastroenterol Hepatol 2007;19:859–64.
[31] Watson RG, Angus PW, Dewar M, Goss B, Sewell RB, Smallwood RA. Low prevalence of primary biliary cirrhosis in Victoria, Australia. Melbourne Liver Group. Gut 1995;36:927–30.
[32] Sood S, Gow PJ, Christie JM, Angus PW. Epidemiology of primary biliary cirrhosis in Victoria, Australia: high prevalence in migrant populations. Gastroenterology 2004;127:470–5.
[33] Witt-Sullivan H, Heathcote J, Cauch K, Blendis L, Ghent C, Katz A, et al. The demography of primary biliary cirrhosis in Ontario, Canada. Hepatology 1990;12:98–105.
[34] Metcalf J, James O. The geoepidemiology of primary biliary cirrhosis. Semin Liver Dis 1997;17:13–22.
[35] Baron JA, Weiderpass E. An introduction to epidemiological research with medical databases. Ann Epidemiol 2000;10:200–4.
[36] McNally RJ, James PW, Ducker S, James OF. Seasonal variation in the patient diagnosis of primary biliary cirrhosis: further evidence for an environmental component to etiology. Hepatology 2011;54:2099–103.
[37] Guillemin F. Describing the epidemiology of rheumatic diseases: methodological aspects. Curr Opin Rheumatol 2012;24:187–92.
[38] EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237–67.
[39] Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. Hepatology 2009;50:291–308.
[40] Invernizzi P, Lleo A, Podda M. Interpreting serological tests in diagnosing autoimmune liver diseases. Semin Liver Dis 2007;27:161–72.
[41] Bogdanos DP, Invernizzi P, Mackay IR, Vergani D. Autoimmune liver serology: current diagnostic and clinical challenges. World J Gastroenterol 2008;14:3374–87.
[42] Feld JJ, Heathcote EJ. Epidemiology of autoimmune liver disease. J Gastroenterol Hepatol 2003;18:1118–28.
[43] Invernizzi P, Crosignani A, Battezzati PM, Covini G, De Valle G, Larghi A, et al. Comparison of the clinical features and clinical course of antimitochondrial antibody-positive and -negative primary biliary cirrhosis. Hepatology 1997;25:1090–5.
[44] Liu H, Norman GL, Shums Z, Worman HJ, Krawitt EL, Bizzaro N, et al. PBC screen: an IgG/IgA dual isotype ELISA detecting multiple mitochondrial and nuclear autoantibodies specific for primary biliary cirrhosis. J Autoimmun 2010;35:436–42.
[45] Metcalf JV, Mitchison HC, Palmer JM, Jones DE, Bassendine MF, James OF. Natural history of early primary biliary cirrhosis. Lancet 1996;348:1399–402.
[46] Turchany JM, Uibo R, Kivik T, Van de Water J, Prindiville T, Coppel RL, et al. A study of antimitochondrial antibodies in a random population in Estonia. Am J Gastroenterol 1997;92:124–6.
[47] Mattalia A, Quaranta S, Leung PS, Bauducci M, Van de Water J, Calvo PL, et al. Characterization of antimitochondrial antibodies in health adults. Hepatology 1998;27:656–61.
[48] Lazaridis KN, Juran BD, Boe GM, Slusser JP, de Andrade M, Homburger HA, et al. Increased prevalence of antimitochondrial antibodies in first-degree relatives of patients with primary biliary cirrhosis. Hepatology 2007;46: 785–92.
[49] Liu H, Liu Y, Wang L, Xu D, Lin B, Zhong R, et al. Prevalence of primary biliary cirrhosis in adults referring hospital for annual health check-up in Southern China. BMC Gastroenterol 2010;10:100.
[50] Invernizzi P, Miozzo M, Battezzati PM, Bianchi I, Grati FR, Simoni G, et al. Frequency of monosomy X in women with primary biliary cirrhosis. Lancet 2004;363:533–5.
[51] Lleo A, Battezzati PM, Selmi C, Gershwin ME, Podda M. Is autoimmunity a matter of sex? Autoimmun Rev 2008;7:626–30.
[52] Gleicher N, Barad DH. Gender as risk factor for autoimmune diseases. J Autoimmun 2007;28:1–6.
[53] Arber S, McKinlay J, Adams A, Marceau L, Link C, O'Donnell A. Patient characteristics and inequalities in doctors' diagnostic and management strategies relating to CHD: a video-simulation experiment. Soc Sci Med 2006;62:103–15.
[54] Shibata M, Onozuka Y, Morizane T, Koizumi H, Kawaguchi N, Miyakawa H, et al. Prevalence of antimitochondrial antibody in Japanese corporate workers in Kanagawa prefecture. J Gastroenterol 2004;39: 255–9.
[55] Mendes FD, Kim WR, Pedersen R, Therneau T, Lindor KD. Mortality attributable to cholestatic liver disease in the United States. Hepatology 2008;47: 1241–7.
[56] Singal AK, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. Transplantation 2013;95:755–60.
[57] Shoenfeld Y, Tincani A, Gershwin ME. J Autoimmun 2012;38:J71–3.
[58] Jorgensen KT, Pedersen BV, Nielsen NM, Jacobsen S, Frisch M. Childbirths and risk of female predominant and other autoimmune diseases in a population-based Danish cohort. J Autoimmun 2012;38:J81–7.
[59] Selmi C, Brunetta E, Raimondo MG, Meroni PL. The X chromosome and the sex ratio of autoimmunity. Autoimmun Rev 2012;11:A531–7.
[60] Lleo A, Moroni L, Caliari L, Invernizzi P. Autoimmunity and Turner's syndrome. Autoimmun Rev 2012;11:A538–43.
[61] Landek-Salgado MA, Rose NR, Caturegli P. Placenta suppresses experimental autoimmune hypophysitis through soluble TNF receptor 1. J Autoimmun 2012;38:J88–96.
[62] Pan Z, Chang C. Gender and the regulation of longevity: Implications for autoimmunity. Autoimmun Rev 2012;11:A393–403.
[63] Dillon SP, Kurien BT, Li S, Bruner GR, Kaufman KM, Harley JB, et al. Sex chromosome aneuploidies among men with systemic lupus erythematosus. J Autoimmun 2012;38:J129–34.
[64] Borchers AT, Gershwin ME. Sociological differences between women and men: implications for autoimmunity. Autoimmun Rev 2012;11:A422–9.
[65] Strickland FM, Hewagama A, Lu Q, Wu A, Hinderer R, Webb R, et al. Environmental exposure, estrogen and two X chromosomes are required for disease development in an epigenetic model of lupus. J Autoimmun 2012;38: J135–43.
[66] Menon R, Di Dario M, Cordiglieri C, Musio S, La Mantia L, Milanese C, et al. Gender-based blood transcriptomes and interactomes in multiple sclerosis:

Involvement of SP1 dependent gene transcription. J Autoimmun 2012;38:J144–55.
[67] Duarte-Rey C, Bogdanos DP, Leung PSC, Anaya J-M, Gershwin ME. IgM predominance in autoimmune disease: genetics and gender. Autoimmun Rev 2012;11:A404–12.
[68] Bogdanos DP, Smyk DS, Rigopoulou EI, Mytilinaiou G, Heneghan MA, Selmi C, et al. Twin studies in autoimmune disease: genetics, gender and environment. J Autoimmun 2012;38:J156–69.
[69] Persani L, Bonomi M, Lleo A, Pasini S, Civardi F, Bianchi I, et al. Increased loss of the Y chromosome in peripheral blood cells in male patients with autoimmune thyroiditis. J Autoimmun 2012;38:J193–6.
[70] Andreoli L, Fredi M, Nalli C, Reggia R, Lojacono A, Motta M, et al. Pregnancy implications for systemic lupus erythematosus and the antiphospholipid syndrome. J Autoimmun 2012;38:J197–208.
[71] Martinez de la Torre Y, Pregnolato F, D'Amelio F, Grossi C, Di Simone N, Pasqualini F, et al. Anti-phospholipid induced murine fetal loss: novel protective effect of a peptide targeting the β2 glycoprotein I phospholipid-binding site. Implications for human fetal loss. J Autoimmun 2012;38:J209–15.
[72] Sawalha AH, Wang L, Nadig A, Somers EC, McCune WJ, the Michigan Lupus Cohort, Hughes T, et al. Sex-specific differences in the relationship between genetic susceptibility, T cell DNA demethylation and lupus flare severity. J Autoimmun 2012;38:J216–22.
[73] Shelly S, Boaz M, Orbach H. Prolactin and autoimmunity. Autoimmun Rev 2005;11:A465–70.
[74] Petrikova J, Lazurova I. Ovarian failure and polycystic ovary syndrome. Autoimmun Rev 2012;11:A471–8.
[75] Chang C. Neonatal autoimmune diseases: a critical review. J Autoimmun 2012;38:J223–38.
[76] Westbrook RH, Yeoman AD, Kriese S, Heneghan MA. Outcomes of pregnancy in women with autoimmune hepatitis. J Autoimmun 2012;38:J239–44.
[77] Pennell LM, Galligan CL, Fish EN. Sex affects immunity. J Autoimmun 2012;38:J282–91.
[78] Nussinovitch U, Shoenfeld Y. The role of gender and organ specific autoimmunity. Autoimmun Rev 2012;11:A377–84.
[79] Gleicher N, Weghofer A, Barad DH. Cutting edge assessment of the impact of autoimmunity on female reproductive success. J Autoimmun 2012;38:J74–80.
[80] Pollard KM. Gender differences in autoimmunity associated with exposure to environmental factors. J Autoimmun 2012;38:J177–86.
[81] Lee T-P, Chiang B-L. Sex differences in spontaneous versus induced animal models of autoimmunity. Autoimmun Rev 2012;11:A422–9.
[82] Oertelt-Prigione S. The influence of sex and gender on the immune response. Autoimmun Rev 2012;11:A479–85.
[83] Quintero OL, Amador-Patarroyo MJ, Montoya-Ortiz G, Rojas-Villarraga A, Anaya J-M. Autoimmune disease and gender: plausible mechanisms for the female predominance of autoimmunity. J Autoimmun 2012;38:J109–19.
[84] Jorgensen KT, Nielsen NM, Pedersen BV, Jacobsen S, Frisch M. Hyperemesis, gestational hypertensive disorders, pregnancy losses and risk of autoimmune diseases in a Danish population-based cohort. J Autoimmun 2012;38:J120–8.
[85] Sammaritano LR. Menopause in patients with autoimmune diseases. Autoimmun Rev 2012;11:A430–6.
[86] Ostensen M, Villiger PM, Forger F. Interaction of pregnancy and autoimmune rheumatic disease. Autoimmun Rev 2012;11:A437–46.
[87] Lateef A, Petri M. Hormone replacement and contraceptive therapy in autoimmune diseases. J Autoimmun 2012;38:J170–6.
[88] Bianchi I, Lleo A, Gershwin ME, Invernizzi P. The X chromosome and immune associated genes. J Autoimmun 2012;38:J187–92.
[89] Cutolo M, Sulli A, Straub RH. Estrogen metabolism and autoimmunity. Autoimmun Rev 2012;11:A460–4.
[90] Oertelt-Prigione S. Immunology and the menstrual cycle. Autoimmun Rev 2012;11:A486–92.
[91] Carp HJA, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. J Autoimmun 2012;38:J266–74.
[92] Twig G, Shina A, Amital H, Shoenfeld Y. Pathogenesis of infertility and recurrent pregnancy loss in thyroid autoimmunity. J Autoimmun 2012;38:J275–81.
[93] Chighizola C, Meroni PL. The role of environmental estrogens and autoimmunity. Autoimmun Rev 2012;11:A493–501.
[94] Hughes GC. Progesterone and autoimmune disease. Autoimmun Rev 2012;11:A502–14.
[95] Geurs TL, Hill EB, Lippold DM, French AR. Sex differences in murine susceptibility to systemic viral infections. J Autoimmun 2012;38:J245–53.
[96] Amur S, Parekh A, Mummaneni P. Sex differences and genomics in autoimmune diseases. J Autoimmun 2012;38:J254–65.
[97] Lidar M, Langevitz P. Pregnancy issues in scleroderma. Autoimmun Rev 2012;11:A515–9.
[98] Carvalheiras G, Faria R, Braga J, Vasconcelos C. Fetal outcome in autoimmune diseases. Autoimmun Rev 2012;11:A520–30.
[99] Rogers MAM, Levine DA, Blumberg N, Fisher GG, Kabeto M, Langa KM. Antigenic challenge in the etiology of autoimmune disease in women. J Autoimmun 2012;38:J97–102.
[100] Munoz-Suano A, Kallikourdis M, Sarris M, Betz AG. Regulatory T cells protect from autoimmune arthritis during pregnancy. J Autoimmun 2012;38:J103–8.
[101] Gatto M, Iaccarino L, Canova M, Zen M, Nalotto L, Ramonda R, et al. Pregnancy and vasculitis: a systemic review of the literature. Autoimmun Rev 2012;11:A447–59.
[102] Borchers AT, Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmun Rev 2012;11:A544–54.
[103] Freeman HJ. Primary biliary cirrhosis in genetically identical twins. Gastroenterology 2004;127:1645 [author reply 1645].
[104] Bach N, Schaffner F. Familial primary biliary cirrhosis. J Hepatol 1994;20:698–701.
[105] Brind AM, Bray GP, Portmann BC, Williams R. Prevalence and pattern of familial disease in primary biliary cirrhosis. Gut 1995;36:615–7.
[106] Floreani A, Naccarato R, Chiaramonte M. Prevalence of familial disease in primary biliary cirrhosis in Italy. J Hepatol 1997;26:737–8.
[107] Jones DE, Watt FE, Metcalf JV, Bassendine MF, James OF. Familial primary biliary cirrhosis reassessed: a geographically-based population study. J Hepatol 1999;30:402–7.
[108] Tsuji K, Watanabe Y, Van De Water J, Nakanishi T, Kajiyama G, Parikh-Patel A, et al. Familial primary biliary cirrhosis in Hiroshima. J Autoimmun 1999;13:171–8.
[109] Gershwin ME, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. Hepatology 2005;42:1194–202.
[110] Corpechot C, Chretien Y, Chazouilleres O, Poupon R. Demographic, lifestyle, medical and familial factors associated with primary biliary cirrhosis. J Hepatol 2010;53:162–9.
[111] Feizi T, Naccarato R, Sherlock S, Doniach D. Mitochondrial and other tissue antibodies in relatives of patients with primary biliary cirrhosis. Clin Exp Immunol 1972;10:609–22.
[112] Galbraith RM, Smith M, Mackenzie RM, Tee DE, Doniach D, Williams R. High prevalence of seroimmunologic abnormalities in relatives of patients with active chronic hepatitis or primary biliary cirrhosis. N Engl J Med 1974;290:63–9.
[113] Zografos TA, Gatselis N, Zachou K, Liaskos C, Gabeta S, Koukoulis GK, et al. Primary biliary cirrhosis-specific autoantibodies in first degree relatives of Greek primary biliary cirrhosis patients. World J Gastroenterol 2012;18:4721–8.
[114] Selmi C, Mayo MJ, Bach N, Ishibashi H, Invernizzi P, Gish RG, et al. Primary biliary cirrhosis in monozygotic and dizygotic twins: genetics, epigenetics, and environment. Gastroenterology 2004;127:485–92.
[115] Hirschfield GM, Liu X, Xu C, Lu Y, Xie G, Gu X, et al. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. N Engl J Med 2009;360:2544–55.
[116] Liu X, Invernizzi P, Lu Y, Kosoy R, Bianchi I, Podda M, et al. Genome-wide meta-analyses identify three loci associated with primary biliary cirrhosis. Nat Genet 2010;42:658–60.
[117] Mells GF, Floyd JA, Morley KI, Cordell HJ, Franklin CS, Shin SY, et al. Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis. Nat Genet 2011;43:329–32.
[118] Nakamura M, Nishida N, Kawashima M, Aiba Y, Tanaka A, Yasunami M, et al. Genome-wide association study identifies TNFSF15 and POU2AF1 as susceptibility loci for primary biliary cirrhosis in the Japanese population. Am J Hum Genet 2012;91:721–8.
[119] Lucey MR, Neuberger JM, Williams R. Primary biliary cirrhosis in men. Gut 1986;27:1373–6.
[120] Sackett DL. Clinical epidemiology. What, who, and whither. J Clin Epidemiol 2002;55:1161–6.