けでなく，その家族や地域の医療担当者が協力して精神的活動性を保つための包括的なサポート体制を構築する必要性が考えられた。

QOL関連要因のうち，悪化した者の割合が「精神的不安定の増加」「身体の痛みの増加」に次いで多かった「食事量の減少」に関して，食事量の減少や低栄養状態がうつ状態[9)10)]や脳機能の低下[11)]と関連すること，さらに低栄養状態および食欲の低下がQOLの低下[12)]と有意に関連することが報告されている。すなわち，食事量の減少は栄養状態の悪化だけでなく，精神的不安定さの増加を介し，QOL低下度と関連する可能性が考えられる。さらに，食欲の低下は食事量の低下につながることから，家族や医療スタッフはALS患者の食欲を維持・確保する必要性が認められた。

さらに，過去の報告と同様，人工呼吸器非装着者は装着者に比べQOLが有意に低下していた。こうした低下についてLyallら[5)]は，人工呼吸器を装着することにより，睡眠時無呼吸障害の恐怖の減少に伴い，夜間の睡眠障害が改善されるためであると説明している。結果として示していないが，本調査でも人工呼吸器非装着者は装着者に比べ夜間睡眠状況が悪化した者の割合が有意に高く，この結果はLyallらの仮説を支持するものである。

今回，ALS患者のQOLの実態とその関連要因を検討した結果，QOL低下は身体的状況よりもむしろ精神的状況と関連することが認められた。さらに，QOL低下を抑止するためには精神的活動性と食事量を維持・確保する必要性が認められた。今後，ALS患者のQOLの維持・安定のために，患者家族，地域の医療担当者，心理の専門家を含めた包括的な精神的安定および精神的活動性の維持のためのサポート体制の構築，食事量の維持・確保や摂取量の評価と摂取方法の検討の必要性が認められた。

本研究は，QOLの変化の程度とその関連要因を横断的に検討したものであるため，今後，ALS患者のQOLの維持・安定のための有用な情報を提供するためにも，関連要因に関する縦断的な調査を行う必要性が考えられた。

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Original Article

Antimitochondrial Antibody Negative Primary Biliary Cirrhosis in Japan: Utilization of Clinical Data When Patients Applied to Receive Public Financial Aid

Fumio Sakauchi,[1] Mitsuru Mori,[1] Mikio Zeniya,[2] and Gotaro Toda.[3]

BACKGROUND: We examined patients who showed laboratory and histological evidence of primary biliary cirrhosis (PBC) in the absence of antimitochondrial antibody (AMA) to elucidate the characteristics of AMA negative PBC.
METHODS: From a total of 5,805 patients with symptomatic PBC, 2,419 cases (41.7%) were selected in the present study, who were diagnosed using the following criterion; chronic non-suppurative destructive cholangitis was histologically observed and laboratory data did not contradict PBC. The information collected from records included sex, age, symptoms, physical findings, and complicated autoimmune diseases. We then evaluated these data according to the positivity of AMA.
RESULTS: Of the total subjects, 470 cases (19.4%) were found to be negative for AMA. The proportion of female patients was higher among the AMA negative group than among the AMA positive one. Pruritus was found less frequently among patients with AMA negative PBC than among those with AMA positive PBC. Levels of alkaline phosphatase, γ-glutamyl transpeptidase, and IgM were significantly lower among patients with AMA negative PBC than among those with AMA positive PBC. Complications such as Sjögren's syndrome, rheumatoid arthritis, and scleroderma, including CREST syndrome, were found with significantly higher frequency among patients with AMA negative PBC than among those with AMA positive PBC.
CONCLUSION: Considering serum level of IgM and frequencies of complicated autoimmune diseases, it is possible that Japanese patients with AMA negative PBC are consistent with the disease entity of autoimmune cholangitis reported in western countries.
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Key words: Liver Cirrhosis, Biliary; antimitochondrial antibody; Cross-Sectional Studies; complications.

Primary biliary cirrhosis (PBC) is a chronic cholestatic disorder characterized by progressive, nonsuppurative inflammation and destruction of small bile ducts. The presence of antimitochondrial antibody (AMA) in the sera is a very important finding for the diagnosis of PBC. However, it has been reported that some patients with laboratory and histological findings compatible with PBC do not have detectable AMA,[1,2] and most information regarding AMA negative PBC is still limited to Europe and North America.

In Japan, symptomatic PBC was specified as one of "the intractable diseases" from 1990. Patients with symptomatic PBC who want to receive public financial aid from the Ministry of Health, Labour and Welfare have to sign agreements and write applications. They are then registered and can receive public financial aid. In 1999, the Ministry permitted the use of clinical data from the patients diagnosed with symptomatic PBC. Therefore, the data was available to the research committee of intractable hepatic diseases and the research committee on the

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epidemiology of intractable diseases. Using these data, we have already shown the clinical features of 5,805 prevalent cases of symptomatic PBC,[3] whose conditions met one of the three criteria outlined by the previous reports in Japan;[4-6] (1) chronic non-suppurative destructive cholangitis is histologically observed and laboratory data do not contradict PBC; (2) AMA is positive, and chronic non-suppurative destructive cholangitis is not histologically observed but histological findings are compatible with PBC; and (3) histological examination is not performed, but AMA is positive and clinical findings and course indicate PBC.

In the present study, we tried to elucidate the characteristics of AMA negative PBC in Japan using the clinical data when they applied to receive the public financial aid.

METHODS

In the fiscal year 1999, 9,761 prevalent cases with symptomatic PBC were registered; they were about 81% of 12,000 patients estimated in Japan.[7] We used the clinical data of 6,305 patients being that not all prefectures provided the data, and chose the cases of 5,805 patients whose clinical data were written and collected between 1999 and 2000; the data from residual cases were not written during this time, for example written in 1998 or before. From these 5,805 patients, 2,419 cases (41.7%) who were diagnosed according to the above-mentioned criterion,[1] i.e. chronic non-suppurative destructive cholangitis was histologically observed and laboratory data did not contradict PBC, were selected in the present study. After then the following information of each patient was collected from the records; sex, age, symptoms and physical findings, complicated autoimmune diseases, laboratory data including serum levels of bilirubin, alkaline phosphatase (ALP), γ -glutamyl transpeptidase (γ -GTP), total cholesterol, IgM, and frequencies of positivity of AMA. We evaluated symptoms and physical findings, laboratory data, and complicated autoimmune diseases according to the positivity of AMA. In the present study, the frequencies of items in the clinical data were analyzed, excluding "unclear" or blank spaces.

Statistical analysis was performed using SPSS® version 10.0 (SPSS Inc.). The chi-square test was used for comparing the proportions of two groups, and the Mann-Whitney test was used to evaluate differences in clinical variables. $P < 0.05$ was considered significant.

RESULTS

Sex and Age

Of the total subjects, 470 of the 2,419 cases (19.4%) were found to be negative for AMA. Table 1 presents male-to-female ratios (men/women) and age distributions according to positivity of AMA. The male-to-female ratio was 0.14 among the AMA positive group, and was 0.09 among the AMA negative one, therefore, the proportion of female cases was higher among the AMA negative group than among the AMA positive one (P=0.01). The median of age was 58 years among AMA positive cases, and was 59 years among AMA negative cases with no significant difference (P=0.53).

Symptoms and Physical Findings

Pruritus was found significantly less frequent in patients with AMA negative PBC than among those with AMA positive PBC (P=0.03) (Table 2). Splenomegaly was also found less frequent in patients with AMA negative PBC, but not significant, while frequencies of jaundice, xanthomas, and esophageal varices were almost the same between AMA negative and positive patients. We also conducted Mantel-Haenszel test to control the male-to-female ratio, but significant differences between the two groups did not change.

Laboratory Data

Key laboratory data are summarized in Table 3. Levels of ALP, γ -GTP, and IgM were significantly lower among patients with AMA negative PBC than among those with AMA positive PBC.

Table 1. Frequencies of patients with primary biliary cirrhosis according to positity of antimitochondial antibody (AMA).

		All subjects	AMA (+)	AMA (−)
Male/female ratio		0.13 (278 /2,141)	0.14 (241/1,708)	0.09 (37/433)*
Age (year): Median (interquartile range)		58 (51 - 66)	58 (50 - 66)	59 (52 - 65.5)†
Age group (year)	-49	21.5% (519)	22.1% (430)	18.9% (89)
	50-59	32.1% (777)	32.0% (623)	32.8% (154)
	60-69	33.7% (815)	32.8% (640)	37.2% (175)
	70+	12.7% (308)	13.1% (256)	11.1% (52)
	Total	100% (n=2,419)	100% (n=1,949)	100% (n=470)

* : χ^2 test for AMA(+) vs. AMA(-), P=0.01

† : Mann-Whitney test for AMA(+) vs. AMA(-), P=0.53

Table 2. Symptoms and physical findings among patients with primary biliary cirrhosis according to positivity of antimitochondrial antibody (AMA).

	All subjects	AMA (+)	AMA (−)	P value*	P value†
Pruritus	53.9% (1,274/2,362)	55.1% (1,048/1,903)	49.2% (226/459)	0.03	0.03
Jaundice	10.5% (250/2,387)	10.8% (208/1,927)	9.1% (42/460)	0.34	0.37
Xanthomas	6.5% (151/2,311)	6.5% (121/1,864)	6.7% (30/447)	0.95	0.92
Splenomegaly	37.4% (876/2,344)	38.2% (722/1,899)	33.8% (154/455)	0.09	0.09
Esophageal varices	16.5% (385/2,171)	16.8% (294/1,755)	15.4% (64/416)	0.55	0.50

Denominators are not equal because frequencies of items were analyzed excluding "unclear" or blank spaces.

*: χ^2 test for AMA (+) vs. AMA (−)

†: Mantel-Haenszel test for AMA(+) vs. AMA(−) to control male/female ratio

Table 3. Laboratory findings among patients with primary biliary cirrhosis according to positivity of antimitochondrial antibody (AMA).

	All subjects		AMA(+)		AMA(−)		
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	P value*
Total bilirubin (mg/dL)	0.6 (n=2,404)	0.5 -0.9	0.6 (n=1,843)	0.5 -0.9	0.6 (n=437)	0.5 -0.9	0.06
ALP (IU/L)	355 (n=2,530)	243-566	364 (n=1,938)	249-575	326 (n=465)	221-522	0.01
γ -GTP (IU/L)	84 (n=2,521)	37-194	91 (n=1,929)	40-203	65 (n=465)	29-165	<0.001
Total cholesterol (mg/dL)	207 (n=2,417)	178-235	207 (n=1,867)	178-235	208 (n=443)	176-235	0.65
IgM (mg/dL)	343 (n=2,060)	209-552	376 (n=1,603)	230-594	239 (n=396)	154-395	<0.001

*: Mann-Whitney test for AMA(+) vs. AMA(−)

Table 4. Complicated autoimmune diseases among patients with primary biliary cirrhosis according to positivity of antimitochondrial antibody (AMA).

Autoimmune diseases	All subjects	AMA (+)	AMA (−)	P value*	P value†
Sjögren's syndrome	16.6% (356/2,141)	15.7% (271/1,726)	20.5% (85/415)	0.02	0.04
Rheumatoid arthritis	7.0% (161/2,294)	6.4% (118/1,850)	9.7% (43/444)	0.02	0.04
Chronic thyroiditis	4.3% (103/2,419)	3.8% (75/1,949)	6.0% (28/470)	0.06	0.054
Scleroderma	2.4% (59/2,419)	2.1% (40/1,949)	4.0% (19/470)	0.02	0.03

Denominators are not equal because frequencies of items were analyzed excluding "unclear" or blank spaces.

*: χ^2 test for AMA (+) vs. AMA (−)

†: Mantel-Haenszel test for AMA(+) vs. AMA(−) to control male/female ratio

Complicated Autoimmune Diseases

Complications such as Sjögren's syndrome, rheumatoid arthritis, chronic thyroiditis, and scleroderma, including CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectases) were found in 20.5%, 9.7%, 6.0%, and 4.0% of the patients with AMA negative PBC, respectively (Table 4). These complicated diseases, excluding chronic thyroiditis, were found with significantly higher frequency in patients with AMA negative PBC than among those with AMA positive PBC. We also conducted Mantel-Haenszel test to control the male-to-female ratio, but significant differences between the two groups did not change.

DISCUSSION

AMA is the serologic hallmark of PBC. However, a small number of patients with PBC lack AMA, as such these patients are often referred as AMA negative PBC. When patients who have cholestatic disorders are found, it is necessary to differentiate PBC from other diseases causing cholestasis, such as primary sclerosing cholangitis.[8] In the present study, therefore, cases that had been diagnosed by histological confirmation were selected.

Our patients with AMA negative PBC presented some revealing features; (1) The proportion of female cases was higher among the AMA negative group than among the AMA positive

one. (2) Pruritus was found less frequently among patients with AMA negative PBC than among those with AMA positive PBC. (3) Levels of ALP, γ -GTP, and IgM were lower among patients with AMA negative PBC. And (4) Complicated autoimmune diseases were found more frequently among patients with AMA negative PBC. It may be one explanation to the frequencies of pruritus and complicated autoimmune diseases in two groups that the AMA negative group included more women than the AMA positive one. It could be that hormonal differences between the sexes may exert modulating factors that predispose each sex toward a particular immune response.[9,10] However, we cannot immediately conclude that these statistical differences are truly meaningful, because we dealt a large number of cases with PBC in the present study. Fore example, difference in percentage of pruritus was 6% and not so large. Further studies of the pathophysiological mechanism of PBS will need to be conducted in order to explain these differences comprehensively.

Michieletti et al.[11] and Lacerda et al.[12] reported that the AMA negative group had significantly lower serum IgM than the AMA positive controls, but the level of ALP showed no significant difference between the AMA negative and positive groups. Regarding the level of IgM, our result was consistent with these two reports, but our AMA negative group had significantly lower levels of ALP, and γ -GTP compared with the AMA positive group. One possible explanation may be the number of cases examined; In the previous studies, 17 and 35 cases with AMA negative PBC were examined respectively, whereas we examined 470 AMA negative PBC cases. Although Michieletti et al.[11] and Lacerda et al.[12] showed that the AMA negative group had lower levels of ALP compared with the AMA positive group, these were not statistically significant. Sánchez-Pobre et al. also reported lower serum levels of ALP and IgM among AMA negative PBC patients.[13]

Ben-Ari et al. described four AMA negative patients with overlapping features of PBC and autoimmune chronic active hepatitis,[14] and it was considered that such a subgroup might be termed autoimmune cholangiopathy;[15] sometimes AMA tests by immunofluorescence technique (IFT) were negative but other autoantibodies such as antinuclear antibody were positive.[16,17] In addition, 'autoimmune cholangitis' was proposed in some reports.[11,12,18-21] Michieletti et al. believed that AMA negative patients have a form of autoimmune cholangitis distinct from that seen in AMA positive PBC and other autoimmune liver diseases.[11] Lacerda et al. presented AMA negative PBC cases having other atutoantibodies, such as antinuclear antibody and antismooth muscle antibody, despite the chronic non-suppurative destructive cholangitis in liver biopsy specimens.[12] On the other hand, the belief that PBC and autoimmune cholangitis are part of the same spectrum of immunologically mediated disease has risen recently.[22] This spectrum would include classic AMA positive PBC as well as the syndrome with the absence of AMA in the serum. Perhaps a similar pathogenetic mechanism may underlie these diseases.[22-24] It was also suggested that a part of AMA negative PBC might rapidly progress to liver cirrhosis within a short time.[13] Future research is required to clarify the relationship between AMA positive and negative PBC.

Serum from patients suspected of having PBC is usually tested by IFT or enzyme linked immunosorbent assay (ELISA) for the detection of AMA. Most patients with PBC have AMA when serum samples are tested by IFT, but it was suggested that 1-16% of PBC patients do not have AMA when tested by IFT.[11,21,22,25] Moreover, the prevalence of positivity of AMA by ELISA method is reported to be 92-93% among patients with PBC.[16] It has been suggested that patients with AMA negative results may be shown to have AMA by more sophisticated detection techniques.[25,26] For detecting AMA, more sensitive assays, such as immunoblotting, have been developed, and this method is expected to prove AMA positivity for most patients with AMA negative PBC by IFT or ELISA.[26]

The present study has several limitations. Firstly, we cannot completely deny that our AMA negative cases obtained by IFT or ELISA turn into AMA positive ones by other AMA detection methods such as immunoblotting. This is a critical problem that needs to be resolved, but it may be difficult to generalize immunoblotting methods for detecting AMA because of the complex nature of their techniques and expenditure. Secondly, other clinical findings including level of IgG, autoimmune antibodies such antinuclear antibody and antismooth muscle antibody were not available, because our patients' protocols had only the information essential for their receiving public financial aid. Additionally, we could not get adequate information about treatment and use of drugs, such as ursodeoxycholic acid. Nevertheless, to our knowledge, the present study has reported the largest number of AMA negative PBC in Japan, and we consider that we could present an outline on AMA negative PBC.

In conclusion, considering serum level of IgM and frequencies of complicated autoimmune diseases, it is possible that Japanese patients with AMA negative PBC are consistent with the disease entity of autoimmune cholangitis reported in western countries.

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臨床研究

全国疫学調査による難治性の肝疾患の日本の患者数推定

大 浦 麻 絵*

難治性の肝・胆道疾患に関する調査研究班，特定疾患の疫学に関する研究班

索引用語 ■ 疫学，原発性胆汁性肝硬変，自己免疫性肝炎，劇症肝炎

1 はじめに

原発性胆汁性肝硬変（primary biliary cirrhosis; PBC），自己免疫性肝炎（autoimmune hepatitis; AIH），劇症肝炎（fulminant hepatitis; FH）などの難治性の肝疾患について取り巻く環境は近年変化が見られ，B型肝炎ウイルス（HBV）の母子感

表1 難治性の肝疾患の全国疫学調査の実施状況

層	病院の区分	対象機関数	抽出機関数	抽出率（%）	回収機関数	回収率（%）
1	特別階層病院#)	14	14	100.0	12	85.7
	その他の大学付属病院	76	76	100.0	42	55.3
2	特別階層病院#)	4	4	100.0	4	100.0
	その他の大学付属病院	89	89	100.0	51	57.3
3	100床未満の病院	3,207	160	5.0	78	48.8
	100～199床の病院	1,327	137	10.3	60	43.8
	200～299床の病院	515	111	21.6	50	45.0
	300～399床の病院	382	160	41.9	62	38.8
	400～499床の病院	210	169	80.5	47	27.8
	500床以上の病院	233	233	100.0	73	31.3
4	大学付属病院	126	126	100.0	108	85.7
	100床未満の病院	1,111	59	5.3	33	55.9
	100～199床の病院	690	72	10.4	46	63.9
	200～299床の病院	395	81	20.5	63	77.8
	300～399床の病院	341	138	40.5	105	76.1
	400～499床の病院	195	157	80.5	123	78.3
	500床以上の病院	220	220	100.0	164	74.5
	合計	9,135	2,006	22.0	1,121	55.9

#：難治性の肝・胆道疾患に関する研究班が指定した大学付属病院，または，その他の病院；層1：消化器専門内科で消化器疾患を診療する特別階層病院，その他の大学附属病院；層2：一般内科の中で消化器疾患を診療する特別階層病院，その他の大学附属病院;層3:特別階層病院，その他の大学附属病院を除いた病院の内科；層4：小児科

Asae OURA et al: An estimate of a number of Japanese patients on primary biliary cirrhosis, autoimmune hepatitis, and fulminant hepatitis by nationwide epidemiological survey

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表2　PBCの全国疫学調査による患者数の推計

層	病院の区分	全体 実数	全体 全国推計患者数（標準偏差）	男性 実数	男性 全国推計患者数（標準偏差）	女性 実数	女性 全国推計患者数（標準偏差）
1	特別階層病院#)	350	408.3（35.1）	27	31.5（2.2）	323	376.8（33.9）
	その他の大学付属病院	824	1,491.0（219.6）	98	177.3（33.2）	712	1,288.4（190.4）
2	特別階層病院#)	137	137（0）	11	11（0）	102	102（0）
	その他の大学付属病院	366	638.7（98.5）	50	87.3（16.1）	316	551.5（85.5）
3	100床未満の病院	38	1,562.4（941.7）	5	205.6（132.7）	33	1,356.8（819.5）
	100～199床の病院	37	818.3（181.1）	6	132.7（58.8）	31	685.6（171.6）
	200～299床の病院	101	1,040.3（219.3）	12	123.6（40.5）	86	885.8（198.4）
	300～399床の病院	276	1,700.5（272.4）	30	184.8（42.8）	246	1,515.7（239.7）
	400～499床の病院	398	1,778.3（330.5）	48	214.5（52.8）	350	1,563.8（293.2）
	500床以上の病院	980	3,127.9（559.5）	140	446.8（93.9）	840	2,681.1（471.0）
4	大学付属病院	0	0（0）	0	0（0）	0	0（0）
	100床未満の病院	1	33.7（32.7）	0	0（0）	1	33.7（32.7）
	100～199床の病院	0	0（0）	0	0（0）	0	0（0）
	200～299床の病院	2	12.5（8.0）	1	6.3（5.7）	1	6.3（5.7）
	300～399床の病院	0	0（0）	0	0（0）	0	0（0）
	400～499床の病院	0	0（0）	0	0（0）	0	0（0）
	500床以上の病院	4	5.4（1.6）	3	4.0（1.2）	1	1.3（0.7）
合計		3,514	12,754.4	431	1,625.4	3,042	11,048.8
（95%信頼区間）			（10334.4,15174.4）		（1245.5,2005.3）		（8945.6, 13151.9）

#：難治性の肝・胆道疾患に関する研究班が指定した大学付属病院，または，その他の病院
層1：消化器専門内科で消化器疾患を診療する特別階層病院やその他の大学附属病院の消化器専門内科
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層4：小児科

染予防対策の確立[1]や，C型肝炎ウイルスの抗体検査を含めた輸血後肝炎感染防止対策の充実[2,3]などが与える影響は少なくない．厚生労働省特定疾患の全国疫学調査は，20年以上にわたり行われてきた．難治性の肝・胆道疾患に関する調査研究班（大西三朗・主任研究者）と特定疾患の疫学に関する研究班（永井正規・主任研究者）とが共同でPBC，AIH，および，FHに関する全国疫学調査を2005年に行った．今回は一次調査からPBC，AIH，FHの全国患者数の推計を行ったので，報告をする．

2 対象と方法

層化無作為抽出法によって，2005年1月から9月までの間に，一次調査と二次調査からなる難治性の肝疾患（PBC，AIH，FH）の全国疫学調査を行った．層化無作為抽出法では，消化器専門内科で消化器疾患を診療する特別階層病院やその他の大学附属病院，一般内科の中で消化器疾患を診療する特別階層病院やその他の大学附属病院，その他の病院の内科，小児科の4層に分けて，さらに病床数区分で細分化して，あらかじめ定めた抽出率で無作為抽出をした．特別階層病院とは，難治性の肝疾患に関する調査研究班（平成11年度～16年度，戸田剛太郎・主任研究者）が，分担研究者の所属する病院を中心に選定した病院（18施設）である．特別階層病院と大学付属病院の抽出率は100%であった．

一次調査では，郵送法によって2004年1月1

表3 AIHの全国疫学調査における患者数の推計

層	病院の区分	全体 実数	全体 全国推計患者数（標準偏差）	男性 実数	男性 全国推計患者数（標準偏差）	女性 実数	女性 全国推計患者数（標準偏差）
1	特別階層病院#)	242	282.3 (25.6)	30	35.0 (3.4)	212	247.3 (23.3)
	その他の大学付属病院	450	814.3 (109.9)	43	77.8 (13.3)	396	716.6 (97.8)
2	特別階層病院#)	84	84 (0)	14	14 (0)	62	62 (0)
	その他の大学付属病院	266	464.2 (62.8)	26	45.4 (8.2)	240	418.8 (57.1)
3	100床未満の病院	30	1,233.5 (605.8)	6	246.7 (170.1)	24	986.8 (449.8)
	100～199床の病院	28	619.3 (138.3)	5	110.6 (55.5)	23	508.7 (122.6)
	200～299床の病院	79	813.7 (176.4)	8	82.4 (34.9)	69	710.7 (151.7)
	300～399床の病院	268	1,651.2 (241.8)	31	191.0 (38.1)	237	1,460.2 (224.4)
	400～499床の病院	237	1,058.9 (206.0)	20	89.4 (19.9)	217	969.6 (197.7)
	500床以上の病院	770	2,457.7 (444.2)	114	363.9 (88.1)	656	2,093.8 (361.0)
4	大学付属病院	17	19.8 (2.4)	7	8.2 (1.3)	10	19.8 (1.8)
	100床未満の病院	0	0 (0)	0	0 (0)	0	0 (0)
	100～199床の病院	0	0 (0)	0	0 (0)	0	0 (0)
	200～299床の病院	1	6.3 (5.7)	0	0 (0)	1	6.3 (5.7)
	300～399床の病院	1	3.2 (2.7)	0	0 (0)	1	3.2 (2.7)
	400～499床の病院	3	4.8 (1.7)	1	1.6 (1.0)	2	4.8 (1.4)
	500床以上の病院	15	20.1 (6.4)	6	8.0 (2.5)	9	20.1 (4.2)
合計 (95%信頼区間)		2,491	9,533.3 (7856.0,11210.6)	311	1,273.9 (867.0,1680.8)	2,159	8,228.7 (6880.0,9577.5)

#：難治性の肝・胆道疾患に関する研究班が指定した大学付属病院，または，その他の病院
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層4：小児科

日から12月31日までの間に受診した患者数を調査した．全国患者数の推計は，橋本らの報告[4]に基づく超幾何分布を仮定する計算式で行った．本調査研究は札幌医科大学倫理審査委員会の承認を得て行った．

3 結　果

表1に，難治性の肝疾患の全国疫学調査の実施状況を示した．抽出機関2006機関中1,121機関（55.9%）より回答を得た．表2にPBC，表3にAIH，表4にFHの全国疫学調査による患者数の推計結果を示した．難治性肝疾患の全国疫学調査による2004年1年間の推計患者数は，PBCが12,754人（95%信頼区間＝（10334.4,15174.4）），AIHは9,533人（7856.0,11210.6），FHは429人（326.8,531.3）と推定された．表5に，過去2回実施された1989年[5]と1996年[6]の全国患者数の推計値を参照して，難治性の肝疾患（PBC，AIH，FH）の全国疫学調査による患者数推計値の経年的変化を示した．図1に，PBCとFHの特定疾患医療受給者証交付件数の年次推移を示した（難病情報センター：http://www.nanbyou.or.jp/what/nan_kouhu1.htm）．表6には，全国疫学調査による難治性の肝疾患（PBC，AIH，FH）の男女比を示した．

4 考　察

PBCに関しては，無症候性PBCを中心にその

表4　FHの全国疫学調査における患者数の推計

層	病院の区分	全体 実数	全体 全国推計患者数(標準偏差)	男性 実数	男性 全国推計患者数(標準偏差)	女性 実数	女性 全国推計患者数(標準偏差)
1	特別階層病院#)	13	15.2 (2.3)	7	8.2 (1.5)	6	7.0 (1.0)
	その他の大学付属病院	39	70.6 (11.6)	22	39.8 (6.9)	17	30.8 (6.0)
2	特別階層病院#)	2	2 (0)	1	1 (0)	1	1 (0)
	その他の大学付属病院	30	52.4 (10.4)	13	22.7 (5.6)	17	29.7 (6.4)
3	100床未満の病院	0	0 (0)	0	0 (0)	0	0 (0)
	100～199床の病院	2	44.2 (30.1)	1	22.1 (21.4)	1	22.1 (21.4)
	200～299床の病院	4	41.2 (23.3)	2	20.6 (13.6)	2	20.6 (13.6)
	300～399床の病院	11	67.8 (18.8)	4	24.6 (10.9)	7	43.1 (14.1)
	400～499床の病院	7	31.3 (9.6)	4	17.9 (7.5)	3	13.4 (6.6)
	500床以上の病院	22	70.2 (19.0)	12	38.3 (12.4)	10	31.9 (9.4)
4	大学付属病院	11	12.8 (1.5)	5	5.8 (1.0)	6	7.0 (1.0)
	100床未満の病院	0	0 (0)	0	0 (0)	0	0 (0)
	100～199床の病院	1	15.0 (14.3)	0	0 (0)	1	15.0 (14.3)
	200～299床の病院	0	0 (0)	0	0 (0)	0	0 (0)
	300～399床の病院	1	3.2 (2.7)	1	3.2 (2.7)	0	0 (0)
	400～499床の病院	2	3.2 (1.4)	1	1.6 (1.0)	1	1.6 (1.0)
	500床以上の病院	0	0 (0)	0	0 (0)	0	0 (0)
合計 (95%信頼区間)		145	429.0 (326.8,531.3)	73	205.9 (141.9,269.8)	72	223.2 (153.6,292.8)

#：難治性の肝・胆道疾患に関する研究班が指定した大学付属病院，または，その他の病院
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層4：小児科

表5　難治性の肝疾患（PBC, AIH, FH）の全国疫学調査による患者数推計値の経年的変化

調査対象年	1989年	1996年	2004年
PBC	2,500	12,000	12,754
AIH	1,400	6,800	9,533
FH	750	1,050	429

（注1）1989年，1996年は過去2回，実施された全国疫学調査の推計値である．
（注2）1989年における調査は，1996年や2004年と調査方法が異なる．

患者数が増加している[7]．1990年，1996年の全国疫学調査[8]や，奥秋ら[9]の報告では，無症候性PBCの増加やそれに伴うPBCの死亡率の低下が示唆されている．特定疾患治療研究による医療受給者の調査の1992年の報告[10]では診療所での患者数は151人と全体の6.1%を占め，1997年の報告[11]では患者数625人と全体の8.9%を占めていた．今回の調査では，診療所やクリニックなどは調査対象機関に含まれていないため，診療所の推計患者数を推計値に加えて考える必要がある．特定疾患医療受給者証交付件数も年々増加しており，本結果と一致した．PBCの患者数の増加と関連する要因としては，診断技術の向上と普及，治療方法の向上による死亡率の低下などが考えられるが，何らかの環境要因が関与しているかどうかについては現在のところ不明である．

FHに関しては，調査方法がほぼ同じである1996年と2004年の患者数推計値の比較から，FH患者数が減少した，という印象を受ける．厚生省特定疾患難治性の肝炎調査研究班（前；厚

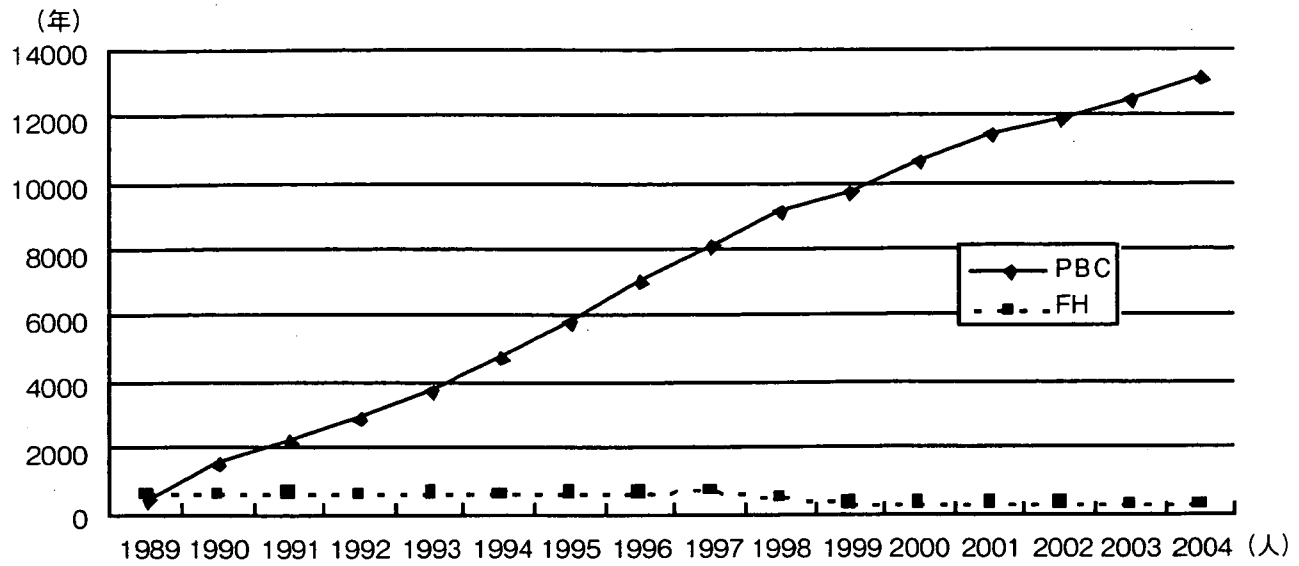

図1　PBC と FH の特定疾患医療受給者証交付件数の年次推移

表6　全国疫学調査による難治性の肝疾患（PBC，AIH，FH）の男女比

	実数				全国推計数			
	全体	男	女	男：女	全体	男	女	男：女
PBC	3,514	431	3,042	1：7.1	12,754	1,625	11,049	1：6.8
AIH	2,491	311	2,159	1：6.9	9,533	1,274	8,229	1：6.5
FH	145	73	72	1：1.0	429	206	223	1：1.1

生省特定疾患難治性の肝炎肝内胆汁うっ滞調査研究班）の報告では，FH の年間推定発症数は 1972 年では約 3,700 例であったが[12]，1989 年には約 750 例[13] に減少した．特定疾患医療受給者証交付件数は 1989 年の 644 件に対し，2004 年は 277 件と減少している．また，難治性の肝・胆道疾患に関する調査研究班の全国調査でも各年の FH 新規発症者数は 2002 年 117 例[14]，2003 年 82 例[15]，2004 年 68 例[16] と減少しており，本調査結果と同様の傾向を示していた．FH の患者数の減少と関連する要因としては，ウイルス性肝炎の患者数の減少[17]，肝疾患に対する治療技術の向上などが考えられる．

3 回の全国疫学調査の比較から，AIH の患者数は増加する傾向がみられた．AIH の患者数の増加と関連する要因としては，PBC と同様に診断技術の向上と普及や治療方法の向上による死亡率の低下などが考えられる．また，環境要因の関与については現在のところ不明である．AIH は特定疾患治療研究の対象疾患ではないので，医療受診者証の交付件数から患者数の推移を把握することはできない．したがって今後も同様の全国疫学調査を行って患者数の推移を観察することが望まれる．なお，2004 年に小児の AIH の全国調査が行われ[18]，2001 年から 2003 年までに 57 例が報告されている（回答率：60 ～ 70%）．

1996 年調査[6] における 2 次調査完了患者数は PBC の男女比が 1:7.8，AIH では 1:8.0，FH では 1:1.0 であった．今回の実数比では，PBC は 1:7.1，AIH は 1:6.9，FH は 1:1.0 であった．PBC，AIH の男女比は前回の 1996 年調査と比べて比が小さくなった印象を受けるが，FH には大きな変化は見られなかった．しかし，診断基準の変化や医療制度の変遷などが影響している可能性があるので，それらとの関連性を今後，検討する必要があると考えられた．

5 まとめ

難治性肝疾患の全国疫学調査による2004年1年間の患者数は，PBCが12,800人程度，AIHは9,500人程度，FHは430人程度と推定された．

謝　辞

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HEART FAILURE AND CARDIOMYOPATHY

Prognosis and prognostic factors in patients with hypertrophic cardiomyopathy in Japan: results from a nationwide study

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Objective: To investigate prognosis and prognostic factors in patients with hypertrophic cardiomyopathy (HCM) in Japan.
Design: A nationwide epidemiological study.
Setting: Hospitals selected randomly from among all hospitals in Japan.
Patients: Clinical and epidemiological information for 2155 patients with HCM were collected in 1999.
Main outcome measures: Patients were classified on the basis of baseline prognostic factors. Survival rates up to 5 years were calculated by Cox's proportional hazard model for 1605 patients.
Results: During the follow-up period, 241 deaths were recorded. The crude 5-year survival rate for the entire cohort was 86% (95% CI 84 to 88), and annual mortality ranged from 2.2% to 3.0%. A higher cardiothoracic ratio on chest x ray (HR 1.61; 95% CI 1.26 to 2.05, with 1 SD (6.2%) increase), a lower left ventricular ejection fraction (HR 1.42; 95% CI 1.20 to 1.69, with 1 SD (13%) decrease) and the presence of left bundle branch block (HR 3.14; 95% CI 1.28 to 7.71) were independently associated with a poorer prognosis, whereas the presence of apical hypertrophy at baseline (HR 0.58; 95%CI 0.36 to 0.92) predicted a better chance of survival.
Conclusions: The nationwide survey of patients with hypertrophic cardiomyopathy yielded important information on its prognosis and prognostic factors. These observations afford, for the first time, a measure of risk stratification in patients with HCM in Japan.

Hypertrophic cardiomyopathy (HCM) is a relatively common cardiac disease that has been the subject of intense investigation over the past few decades, especially in Western populations.[1–5] By contrast, few large-scale and prospective studies have been conducted to examine the prognosis and prognostic factors of HCM in the far-east Asian populations. Asian patients may differ considerably from Western patients in the pattern of hypertrophy distribution and clinical manifestations.[1 6] Because of marked heterogeneity in clinical expression, it is necessary to identify the prognostic factors and their association with death, within the broad disease spectrum of HCM, to obtain a realistic clinical perspective in the far-east Asians.

In 1999, the Japanese research committees on epidemiology of intractable diseases undertook a nationwide epidemiological survey of idiopathic cardiomyopathy in Japan to describe the detailed clinicoepidemiological features for appropriate health service planning. A detailed description of the clinicoepidemiological features of patient characteristics have been presented elsewhere.[7] The estimated total number of patients with HCM was 21 900 (95% confidence interval (CI) 20 600 to 23 200), with a crude prevalence rate of 17.3/100 000.[8] The purpose of this study was to evaluate the 5-year survival rate according to the presence and/or level of baseline prognostic factors from this nationwide study on patients with HCM in Japan, and to clarify factors that can predict the prognosis of this disease independently and effectively.

METHODS

The nationwide survey on cardiomyopathies, including HCM, was designed to show the prevalence and clinical features of HCM in Japan. Detailed methods have been described elsewhere.[7 8] The Japanese Research Committee on idiopathic cardiomyopathies prepared classification criteria, which were on the basis of the report of the World Health Organization/International Society and Federation of Cardiology task force on the definition and classification of cardiomyopathies.[9 10] HCM was characterised by disproportionate hypertrophy of the left ventricle and occasionally also of the right ventricle, which typically involves the septum more than the free wall, but occasionally is concentric. Specific heart muscle disease, defined as heart muscle disease of known aetiology or associated with disorders of other systems, was excluded from the survey. The hospitals included in each survey were randomly selected by stratified sampling of all departments of internal medicine, cardiovascular medicine and paediatrics throughout Japan, identified in a directory of names, department addresses and number of hospital beds obtained from the Ministry of Health and Welfare in Japan.

Data acquisition

The survey investigated patients with HCM as either inpatients or outpatients in the randomly selected departments in 1998. Firstly, the questionnaire for the survey on the number of patients with HCM was mailed directly to 2414 departments in January 1999. Of those 2414 departments, 1409 (58.4%) departments responded, reporting data on 7262 patients. The second survey was performed to collect detailed clinical data. From a total of 577 departments that reported one or more patients with HCM in the first survey, 235 departments agreed to participate in the second survey and detailed clinical data were collected from a total of 2155 patients. Patients who died before 1998 or those visiting a hospital for the first time after

Abbreviations: AF, atrial fibrillation; BMI, body mass index; HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LV, left ventricular; NYHA, New York Heart Association

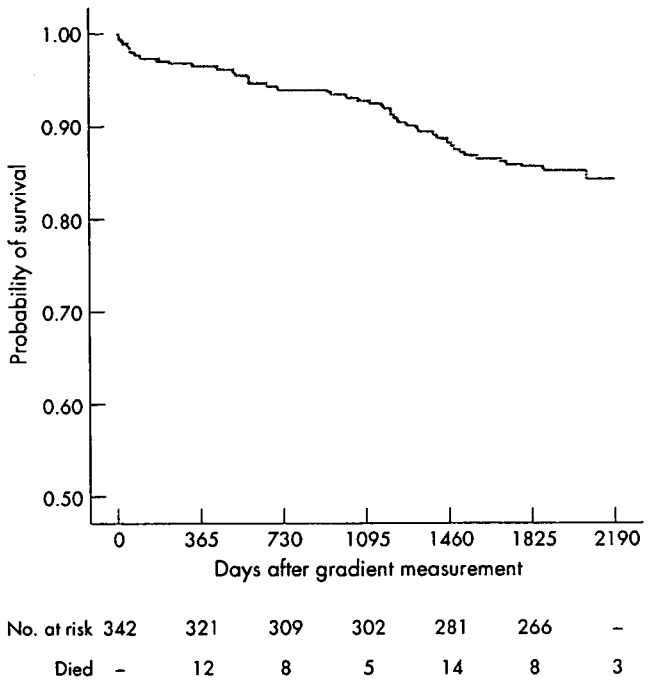

Figure 1 Kaplan–Meier survival curve of 342 patients with hypertrophic cardiomyopathy after first diagnosis in 1998.

1999 were excluded from this study as inappropriate cases, as were patients whose data were reported from more than one department (duplicate cases). The questionnaire requested detailed clinicoepidemiological information for each patient, including age, sex, symptoms and New York Heart Association (NYHA) functional class. Data from a physical examination and baseline laboratory measurements, including standard 12-lead ECG, chest *x* ray and echocardiography (for measuring left ventricular ejection fraction (LVEF), thickness of interventricular septum (IVS), and left ventricular (LV) shape), were available. LV hypertrophy by ECG was determined by left high voltage (Minnesota code: 3–1 or 3–3). M mode echocardiographic assessment for LVEF and two dimensional echocardiographic assessment for maximum IVS thickness and LV shape were conducted for nearly all patients. Apical hypertrophy was defined as LV wall thickness confined to the most distal region at the apex below the papillary muscle level. Data on blood tests and cardiac catheterisation were only obtained for a small portion of the subjects and, therefore, we did not include them in our analysis.

Medication

Patients were generally given medical treatment as reported previously from this study.[7] Medical treatment was directed toward control of symptoms, arrhythmias, coexisting hypertension and prevention of embolisation.

Follow-up

Of 235 departments reporting 2155 patients, 182 departments (reporting 1693 patients) agreed to participate in the 5-year follow-up survey. Patients' vital status was reported by doctors, with vital status for 607 withdrawn cases obtained from the residence-based register of the local government for each patient. However, follow-up was not possible for 88 patients, so these patients were excluded. Therefore, the 5-year follow-up was completed for 1605 (74.5%) patients. With regard to follow-up bias, we found no significant difference for sex, age, body mass index (BMI) and NYHA functional class distribution between those who participated and those who did not participate in the follow-up. The ethical committees of the Kanazawa Medical University and the Kyoto University Graduate School of Medicine approved the study protocol.

Statistical analysis

Survival estimates were calculated using the Kaplan–Meier method, and the 5-year survival probability was calculated for the overall cohort. Patients were classified on the basis of baseline prognostic factors. The significant differences in survival rates among classifications were tested by the log rank test for trends. Hazard ratios (HRs) according to baseline characteristics were calculated by Cox's proportional hazard model, with 95% CI up to the longest follow-up time of 2190 days. The model includes variables with a p value <0.05 by the log rank test for the 5-year survival and some other important variables. HRs for continuous variables were reported for 1 SD change. The log minus log plotted against survival time for each covariate did not show any deviation from the proportionality assumption. The data were analysed with SPSS V.12.0J. All reported significance levels are $p<0.05$ (two tailed tests).

RESULTS

Of the 1605 patients identified at baseline, 241 (15%) died during the follow-up period. The probability of actuarial survival was calculated from the time of the baseline survey for 342 patients who were initially diagnosed in 1998 (fig 1). The crude 5-year survival rate for those diagnosed in 1998 was 86% (95% CI 82 to 90). The crude 5-year survival rate for the whole cohort was 86% (95% CI 84 to 88).

Table 1 shows the baseline characteristics of the patients. Of the 1605 patients in the study, 30.3% were women and 57.1% were aged >60 years. Most patients (94.5%) had experienced none or only mild symptoms (NYHA function classes I or II) at baseline.

Clinical, echocardiographic and standard 12-lead ECG variables were examined for an association with survival during the follow-up period (table 1). Crude 5-year survival rates significantly decreased with decreasing BMI, higher grade of NYHA classification, presence of atrial fibrillation (AF) or flutter, presence of left bundle branch block (LBBB), increasing CTR, decreasing LVEF and decreasing number of hospital beds. The presence of apical hypertrophy was associated with a better survival rate. There was no significant difference in the crude survival rate between men and women. Thickness of IVS, family history of HCM, the presence or absence of hypertension, and smoking and drinking habits were not associated with the 5-year survival rates.

Table 2 presents the results of proportional hazard analysis. The model includes nine variables, which were statistically significant in table 1 (age, BMI, diabetes mellitus, NYHA classification, rhythm, LBBB, apical hypertrophy, CTR and LVEF), and two other important variables (sex and IVS thickness). The multivariate-adjusted HR for all-cause mortality was not significantly different between men and women. The presence of LBBB was an independent predictor of death (HR = 3.14), and the presence of apical hypertrophy, seen in 41.1% of study patients, resulted in a better prognosis (HR = 0.58). The multivariate-adjusted HR for death significantly and independently increased with a 1 (6.2%) SD increase of CTR, and with a 1 (13%) SD decrease of LVEF. The Wald statistic showed that these two factors had the strongest relationship with prognosis of all the factors in the model. BMI and IVS thickness were not independently related to prognosis. A backward elimination stepwise analysis to check if there is confounding among the non-significant factors, did not find a significant difference with the results in the original model.

Table 1 Five-year survival rates for predictive variables in patients with hypertrophic cardiomyopathy in Japan

	n (%)	Deaths	5-year survival rate	p Value for log rank test
Sex				
Men	1118 (69.7)	142	0.87	
Women	487 (30.3)	85	0.84	0.151
Age (years)				
<30	157 (9.9)	14	0.90	
30–59	531 (33.1)	42	0.92	
≥60	917 (57.1)	158	0.82	<0.001
BMI (kg/m²)				
<20	182 (14.0)	40	0.77	
20–24.9	733 (56.3)	92	0.87	
≥25	387 (29.7)	39	0.90	<0.001
Family history of HCM				
Yes	207 (16.9)	27	0.87	
No	1015 (83.1)	132	0.87	0.991
Hypertension				
Yes	456 (31.2)	68	0.85	
No	1005 (68.8)	129	0.87	0.336
Diabetes mellitus				
Yes	131 (8.9)	30	0.76	
No	1332 (91.1)	178	0.86	0.002
Alcohol drinking				
Yes	475 (36.3)	71	0.85	
No	832 (63.7)	113	0.86	0.525
Smoking				
Yes	535 (39.3)	68	0.87	
No	825 (60.7)	115	0.86	0.524
NYHA classification				
I	908 (65.3)	89	0.90	
II	406 (29.2)	62	0.84	
III	62 (4.5)	28	0.53	
IV	14 (1.0)	7	0.43	<0.001
Rhythm				
Sinus rhythm	1347 (91.4)	161	0.88	
Atrial fibrillation	113 (7.7)	28	0.74	
Atrial flutter	13 (0.9)	4	0.68	<0.001
Left ventricular hypertrophy (detected by ECG)				
Yes	1021 (68.9)	132	0.86	
No	461 (31.1)	61	0.87	0.814
LBBB				
Yes	45 (3.3)	15	0.66	
No	1303 (96.7)	165	0.87	<0.001
Apical hypertrophy				
Yes	532 (41.1)	56	0.89	
No	763 (58.9)	110	0.85	0.031
CTR (%)				
<50	353 (26.7)	25	0.93	
50–54	484 (36.7)	54	0.89	
55–59	283 (21.4)	36	0.87	
≥60	200 (15.2)	59	0.70	<0.001
LVEF (%)				
<50	67 (5.9)	27	0.59	
50–59	88 (7.8)	19	0.77	
60–69	243 (21.5)	29	0.88	
70–79	439 (38.9)	49	0.89	
≥80	292 (25.9)	31	0.89	<0.001
Thickness of IVS (mm)				
<11	145 (9.8)	17	0.88	
11–15	540 (36.5)	62	0.88	
16–20	476 (32.1)	68	0.85	
21–25	208 (14.0)	37	0.83	
≥26	112 (7.6)	18	0.83	0.255
Hospital beds				
<299	140 (8.9)	27	0.79	
300–399	93 (5.9)	19	0.80	
400–499	121 (7.7)	14	0.88	
≥500	360 (22.8)	60	0.83	
University hospital	867 (54.8)	93	0.89	0.002
Time from diagnosis (years)				
<1	463 (30.6)	62	0.86	
1–1.9	116 (7.7)	16	0.85	
2–2.9	144 (9.5)	15	0.89	
3–3.9	97 (6.4)	14	0.85	
4–4.9	97 (6.4)	14	0.85	
5–9.9	312 (20.6)	35	0.89	
≥10	283 (18.7)	51	0.81	0.231

BMI, body mass index; CTR, cardiothoracic ratio; HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2 Multivariate-adjusted HRs of predictive variables for all-cause mortality in patients with hypertrophic cardiomyopathy

	Adjusted HR* (95% CI)	Wald statistic	p Value
Sex			
Men	1		
Women	0.77 (0.46 to 1.30)	1	0.324
Age			
1-year increase	1.02 (1.01 to 1.04)	8.2	0.004
Diabetes mellitus			
Yes	1.03 (0.47 to 2.28)	<0.1	0.941
No	1		
NYHA classification			
I	1		
II	1.19 (0.74 to 1.94)	0.5	0.472
III	3.41 (1.75 to 6.67)	12.9	<0.001
IV	2.85 (0.87 to 9.39)	3.0	0.084
Rhythm			
Sinus rhythm	1		
Atrial fibrillation	1.36 (0.75 to 2.46)	1.0	0.306
Atrial flutter	0.62 (0.16 to 2.30)	0.5	0.471
LBBB			
Yes	3.14 (1.28 to 7.71)	6.2	0.013
No	1		
Apical hypertrophy			
Yes	0.58 (0.36 to 0.92)	5.4	0.021
No	1		
CTR† (increase of 6.2%)	1.61 (1.26 to 2.05)	14.4	<0.001
BMI† (increase of 3.4 kg/m²)	0.80 (0.63 to 1.01)	3.7	0.056
Thickness of IVS† (increase of 5.8 mm)	1.15 (0.94 to 1.40)	1.9	0.163
LVEF (decrease of 13%)	1.42 (1.20 to 1.69)	16.4	<0.001

BMI, body mass index; CTR, cardiothoracic ratio; IVS, interventricular septum; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
*All variables are included in the same model.
†Hazard ratio for 1 SD increase or decrease; value of 1 SD given in parentheses.

DISCUSSION

In this paper, we report the crude probability of death and the HRs for all-cause mortality by baseline prognostic factors, from a nationwide study of HCM in Japan. To our knowledge, this is the first nationwide follow-up survey in Japan conducted on patients with HCM.

One methodological issue in this survey involves the diagnostic criteria used. In 1995, the World Health Organization/International Society and Federation of Cardiology task force reported a new definition and classification of cardiomyopathy in which the cardiomyopathies were defined simply as diseases of the myocardium associated with cardiac dysfunction.[11] However, we used the definition and classification provided by the earlier task force of 1980,[9 10] in which idiopathic cardiomyopathy was distinguished from other specific heart muscle diseases. Our reasons for doing this were, firstly, that nearly all cardiologists and specialists in general medicine in Japan have been applying this definition to their diagnosis of cardiomyopathies for a long time; and secondly, that numerous previous reports have also used the same definition, allowing us to compare our data with those reports.

General clinical outcome

Several previous clinical studies on the natural history and prognosis of HCM have been based on populations of selected patients from referral centres,[12–14] and therefore, on the basis of different levels of care and management, various prognoses would be expected. The clinical outcome and perception of prognostic factors in HCM is profoundly affected by a bias in patient selection.[15] However, our study is free from this referral bias since patients were recruited from all over the nation and from different diagnostic centres.

The average (SD) age at entry into study was 58.0 (17.5) years. Both the overall crude probability of 5-year survival in our study (86%) and the annual mortality (2.2–3.0%) were comparable with the results from Western studies,[14 16] which were based on selected referral centres. According to previous report,[8] the male/female ratio for HCM is 2:3 in Japan. In our study, the probability of survival did not differ between women and men, a finding which is consistent with previous data on sex comparisons of survival in patients with HCM.[16] However, in Chinese patients, HCM was found to have a worse clinical outcome in female patients.[13] The reason for this inconsistency between our data and Chinese patients is not clear, but the small number of participants in the Chinese study and the point that less female than male patients were in the stage I of the NYHA function class in their study may explain the difference with our result.

Prognostic factors

Our results suggest for the first time that a simple chest *x* ray could be a reliable prognostic predictor in HCM. Although a CTR of 55–59% (21.4% of study patients) posed a slight increase in the risk of mortality, a CTR of >60% (15.2% of study patients) was strongly associated with a poorer prognosis. LVEF at baseline was also found to be a significant predictor of all-cause mortality in our study, with an LVEF of <60% (13.7% of study patients) associated with poorer prognosis. Progression of HCM to LV dilatation and systolic dysfunction sometimes occurs, although the mechanism of this is not fully understood.[17] However, data are limited on the prognosis of different LVEF levels in patients with HCM. Our findings confirmed the result of a previous study involving 10 patients with HCM, which concluded that an LVEF of <50% was associated with poor prognosis.[18]

Apical hypertrophy has been associated with a more benign prognosis and rarely with cardiovascular mortality and morbidity in Western populations of patients with HCM.[19 20] Our data support this finding, as patients with apical hypertrophy had a better prognosis in the multivariate model. Previous studies in the Japanese population have also indicated a benign prognosis in patients with this condition.[21 22]

A direct relationship between LV wall thickness and the risk of sudden death or heart failure-related death has been reported in patients with HCM.[23–25] Our data did not support this finding, as LV wall thickness did not show a significant relationship with prognosis. Our results support previous findings that suggest LV wall thickness should not be considered as an isolated risk factor for mortality due to cardiovascular diseases in patients with HCM.[26 27] Olivotto *et al*[27] proposed that the presence of LV hypertrophy might be a potential risk factor for sudden death only in those patients diagnosed with HCM at a very young age.

In a community-based HCM study, AF was reported to be a substantial risk factor for heart failure-related mortality and severe functional disability.[28] The prevalence of AF was lower (7.7% of study patients) in our study than the 22% seen in this previous report.[28] In our study, the crude survival rate for all-cause mortality in patients with AF at baseline was significantly lower than for those patients with sinus rhythm. However, the significant relationship with AF disappeared in the multivariate model. We observed that the presence of LBBB at baseline was associated with a poorer prognosis on multivariate analysis. The infrequent occurrence of LBBB in our study (3.3%) was comparable with previous data, which showed a prevalence of 6% among 204 patients with obstructive HCM and free from obstructive coronary artery disease.[29]

Study limitations

Although the follow-up time in our study was limited to 5 years, shorter than follow-up times in previous studies,[13 20 27] our study group was an average of 10 times larger than that of those studies, thus covering a comparable number of patient-years for the subgroups of baseline prognostic factors. A limitation of this study, which is shared by other studies,[13 26] is that a single measurement of prognostic factors, although reproducible and practical for clinical purposes, does not accurately reflect the total burden of predictors in individual patients. Another limitation of this study is that we failed to differentiate HCM-related deaths including sudden deaths and deaths caused by end-stage cardiac failure from other causes of mortality, and we reported all-cause mortality as our main outcome.

CONCLUSIONS

HCM has relatively good prognosis in Japanese patients. A poorer prognosis in HCM is predicted by high cardiothoracic ratio, low LVEF and the presence of LBBB, with a better prognosis in patients with apical hypertrophy. The presence of hypertension, AF and the level of IVS thickness were not independent predictors of prognosis during the 5-year follow-up period.

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特発性大腿骨頭壊死症の疫学

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特定疾患である特発性大腿骨頭壊死症は発生がまれであるため，本邦における疫学は主として全国規模の調査により明らかにされてきた。本稿では，厚生労働省（あるいは旧厚生省）の研究班で実施されてきた調査を中心に，本疾患の臨床疫学特性および規定要因を概括する。

Epidemiology of Idiopathic Osteonecrosis of the Femoral Head in Japan.

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The Ministry of Health, Labour and Welfare (MHLW) designates idiopathic osteonecrosis of the femoral head (ION) as so-called "intractable diseases" and has been promoting research. To summarize descriptive or analytic epidemiology of the ION in Japan, we present findings obtained through nationwide studies with the support of MHLW.

はじめに

疫学は，その手法により記述疫学と分析疫学に大別される。記述疫学とは，「疾病の流行状況を把握し，その特徴と関連を示す他の現象を見出すことによって，その流行に関与する要因を"推定"する」ものである。一方，分析疫学とは「疾病の流行に関与すると推定される要因を"検証"する」手法である。

特定疾患である特発性大腿骨頭壊死症（idiopathic osteonecrosis of the femoral head：ION）は発生がまれであるため，本邦における疫学は主として全国規模の調査により明らかにされてきた。本稿では，厚生労働省（あるいは旧厚生省）の研究班で実施されてきた調査を中心に，本疾患の臨床疫学特性および規定要因を概括する。

記述疫学

記述疫学は主として，疾病の全体像を把握する

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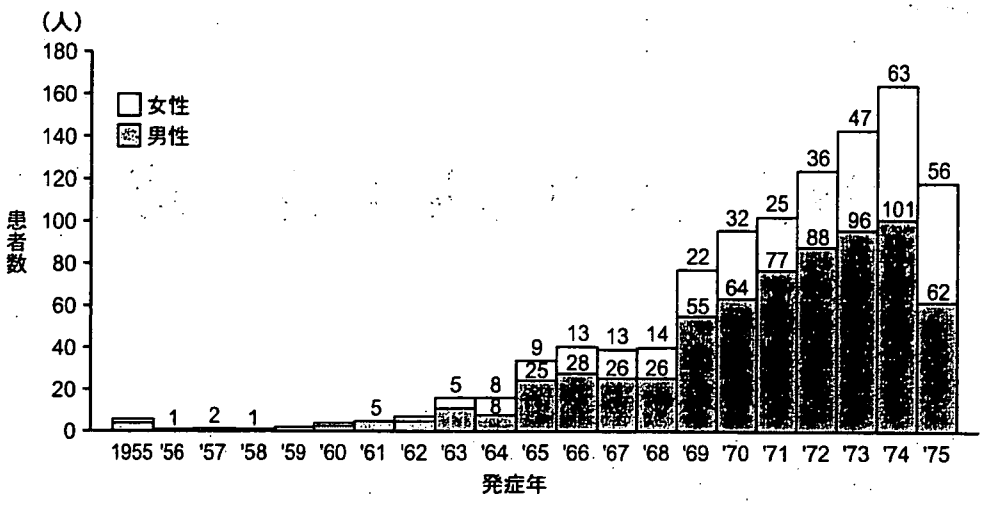

図1　ION の患者発生数の推移

1955 ～ 1976 年の新患症例 1,155 人について，発症年別に集計している。発生数は 1965 年より増加し，1969 年以降に急増を認める。なお，1975 年の患者数が減少してみえるのは，発症年で図示しているため当該年の新患の一部が 1974 年に移動したことによる。

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ための基本情報を得ることが目的である。しかし，当該疾病の病因論展開の糸口を提供するという観点からも，重要な位置づけを有する。

1．全国調査

本邦における全国調査は，厚生省「ION 調査研究班」が 1976 ～ 1977 年にかけて独自に実施したものが最初であろう[1,2]。全国 857 病院のうち「ION 症例あり」と回答した 199 病院を対象とし，報告された新患症例 1,155 人について発症年別に集計した結果，1969 年頃から患者数が急増していることが示唆された（図 1）。その後も「ION 調査研究班」独自の全国調査が 2 回実施され[2)~4)]，基本的な臨床疫学特性が明らかにされてきた。さらに，1995 年に厚生省「難病の疫学調査班」と共同で実施した全国疫学調査では，1994 年の年間受療患者数が初めて推計された[2,5]。

直近の全国疫学調査は，厚生労働省「ION に関する研究班」と「特定疾患の疫学に関する研究班」が共同で 2005 年に行っている[6]。1995 年の全国疫学調査と同じく，既に確立されたプロトコール[7]に従って実施した。全国の整形外科から，層化無作為抽出法にて選定した 999 科を対象に一次調査を実施した結果，回答が得られた 577 科（58%）から 5,612 人の患者数が報告された。これにより，2004 年 1 年間の受療患者数は 11,400 人（95%信頼区間：10,100 ～ 12,800），新患数は約 2,200 人と推定された。二次調査では 178 科より受療患者 1,502 人の情報を収集し，表 1 に示すような特性の概要を得ている。

2．定点モニタリングシステム

上述のような全国調査は，確度が高い疫学情報を得ることができる一方，多大な労力を要するため度々の実施は現実的に困難である。このような点を踏まえ，厚生労働省「ION に関する研究班」で

ION：idiopathic osteonecrosis of the femoral head（特発性大腿骨頭壊死症）

表1 2005年実施のION全国疫学調査：二次調査結果の概要

全国の整形外科から層化無作為抽出法にて選定した999科のうち，178科から報告されたION患者1,502人の臨床疫学特性を集計した。

- 現在の年齢のピーク：男女ともに50代
- 確定診断時年齢のピーク：男性は40代，女性は30代
- 誘因の分布
  - ステロイド全身投与歴あり 51%・・・対象疾患はSLEが最多（31%）
  - アルコール愛飲歴あり 31%
  - 両方あり 3%
  - 両方なし 15%
- 確定診断時の病型分類：Type C-2が最多（52%）
- 確定診断時の病期分類：Stage 2が最多（28%）
- 手術：60%に施行・・・内訳は人工骨頭・人工関節置換術65%，骨切り術25%

ION：特発性大腿骨頭壊死症，SLE：全身性エリテマトーデス （文献6より）

は「定点モニタリングシステム」を運営し，継続的な情報収集を行っている。本システムは，当該研究班の班員が所属する医療施設を定点として，新患および手術症例を所定の様式により逐一（あるいは随時）報告し，登録するものである[8]。1997年6月に開始し，1997年1月以降の症例について報告を得ている。2006年12月31日現在，データベースに新患症例1,722人，手術症例1,242人を蓄積しており，基本的臨床疫学特性を随時集計している。

本システムにより収集した情報は，全国疫学調査結果と比較して，ION確定診断時年齢が低く，骨切り術施行の頻度が多い傾向があるものの，性比や誘因等，その他の基本的特性に関しては統計学的に有意な相違点を認めないことが示されている。さらに，本システムにより全国疫学調査における報告新患症例の約40%の情報をカバーすることも試算されており，より効率的に記述疫学特性を把握できる有効な手法と考えられる[9]。

分析疫学

記述疫学により得られた「ION患者の31%にアルコール愛飲歴あり」という知見は，IONとアルコールの関連を強く示唆するが，本質的に「ION患者の31%に朝夕毎日歯磨きをする習慣あり」という情報と変わりない。記述疫学を通じて設定された仮説は，分析疫学による検証を経ることによって，はじめて関連の程度や因果性が明らかになる。

分析疫学の研究デザインとしては，介入研究，コホート研究，症例・対照研究が該当する。このうち，IONのように発生がまれな疾病に関しては，実行可能性および費用の面から，症例・対照研究デザインを選択するのが最も合理的である。

1．飲酒との関連

本邦における症例・対照研究結果は，これまでに2編報告されている[10][11]。Matsuoらの研究は西日本の4医療施設をベースに実施し，Hirotaらの研究は厚生省「ION調査研究班」と「難病の疫学調査研究班」が共同で全国20施設をベースに実施したものである。いずれも非ステロイド性（ステロイド全身投与歴を有さない）ION患者を症例とし，対照は症例ごとに医療機関，初診日，性，年齢をマッチさせて選択している。飲酒歴については，Matsuoらは電話インタビューにより，Hirotaらは自記式質問表票により情報を得ている。

両研究ともに，IONに対する飲酒のオッズ比