在する．「基本的にすべての症例に」ではなく，それぞれの症例でガイドラインに示されたように，生命予後の改善が期待できるかどうかの判断のうえでの積極的な抗ウイルス療法が必要と考えられる．

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Clinicopathological features of liver injury in patients with type 2 diabetes mellitus and comparative study of histologically proven nonalcoholic fatty liver diseases with or without type 2 diabetes mellitus

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Abstract
Background The Japan Society of Diabetes Mellitus reported that the leading cause of death in patients with diabetes mellitus (DM) was chronic liver disease; however, there are limited studies investigating the cause of liver injury in these patients. Our study aimed to clarify the clinicopathological features of liver injury and the characteristics of nonalcoholic fatty liver disease (NAFLD) in DM patients.
Methods In total, 5,642 DM patients and 365 histologically proven NAFLD patients were enrolled. Clinical and laboratory parameters and liver biopsy results were, respectively, recorded and analyzed for the two sets of patients.
Results Positivity rates for Hepatitis B surface antigens (HBsAg) and anti-hepatitis C virus antibodies (anti-HCV Ab) were 1.7 and 5.1 %, respectively. The proportion of drinkers consuming 20–59 g and ≥60 g alcohol daily was 14.9 and 4.3 %, respectively. The percentage of DM patients with elevated serum alanine aminotransferase (ALT) levels (≥31 IU/L) was 28.6 %. Alcohol consumption had no significant effect on serum ALT levels. Seventy-two percent of HBsAg-positive patients were serum hepatitis B virus (HBV)-DNA negative, whereas 10 % exhibited high levels of the same (>4.0 log copies/ml).

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Thirty-eight percent of anti-HCV Ab-positive patients were serum HCV-RNA negative. Among the NAFLD patients, the frequencies of NASH and advanced stage NASH were significantly higher in male DM patients than in male patients without DM.

Conclusions Although HBsAg- and anti-HCV Ab-positivity rates were high in our Japanese DM patients, a majority of liver injuries could be associated with NAFLD/nonalcoholic steatohepatitis.

Keywords Nonalcoholic fatty liver disease · Nonalcoholic steatohepatitis · Diabetes mellitus · Hepatitis virus carrier · Alcoholic liver disease · Nationwide study

Abbreviations

HCC	Hepatocellular carcinoma
NAFLD	Nonalcoholic fatty liver disease
DM	Diabetes mellitus
NASH	Nonalcoholic steatohepatitis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma glutamyl transpeptidase
FPG	Fasting plasma glucose
HOMA-IR	The homeostasis model assessment of insulin resistance index
HBsAg	Hepatitis B surface antigen
anti-HBc Ab	Anti-hepatitis B core antibody
anti-HCV Ab	Anti-hepatitis C virus antibody
HBV-DNA	Hepatitis B virus-deoxyribonucleic acid
HCV-RNA	Hepatitis C virus-ribonucleic acid
OR	Odds ratio
CI	Confidence interval

Introduction

As per the International Diabetes Federation, the number of diabetes mellitus (DM) sufferers rose to 366 million in 2011, representing 8.3 % of the global adult population, which is increasing in every country [1]. Worldwide, hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer mortality [2]. HCC largely occurs in patients with chronic liver disease. Persistent hepatitis C virus (HCV) or hepatitis B virus (HBV) infections are the main causes of HCC; however, non-HCV- and non-HBV-associated HCC cases are increasing in Japan [3].

In 2007, the Japan Society of DM reported that the most frequent cause of death among 18,385 DM patients who died in hospitals during 1991–2000 was malignancy (34.1 %), followed by ischemic heart disease (10.2 %) and cerebrovascular disease (9.8 %) [4]. Among the malignancies, HCC showed the highest frequency (8.6 %), followed by lung (5.3 %), pancreatic (4.8 %), and gastric cancer (3.5 %). Furthermore, the frequency of deaths caused by liver cirrhosis was 4.7 %, and in total, 13.3 % DM patients died of liver diseases. The cancer death rate in that study was quite different from that reported in the general Japanese population, in which lung (5.7 %), gastric (4.7 %), and colon (2.5 %) cancer occur with high frequencies [5]. Moreover, the death rate from liver diseases (13.3 %) was three times higher than that in the general Japanese population (HCC 3.2 %, liver cirrhosis 1.5 %, total 4.7 %) [6]. However, the incidences of HBV and HCV infection and the details of alcohol intake were not analyzed in that report.

The Japan Nonalcoholic Steatohepatitis (NASH) Study Group was founded in 2007 to investigate the cause of death in DM patients, the genetic factors in nonalcoholic fatty liver disease (NAFLD) patients, and the background of NASH-HCC patients [7]. This study focused on clarifying the cause of liver injury in Japanese DM patients and investigating the histological distribution of NAFLD in patients with and without DM.

Patients and methods

Patients

In total, 5,642 DM patients (3,238 males, 2,404 females) who visited nine DM clinics belonging to the Japan NASH Study Group (Saiseikai Suita Hospital; Kagoshima University Graduate School of Medical and Dental Sciences; Graduate School of Medicine, The University of Tokyo; Kanazawa University Graduate School of Medical Science; Department of Medicine, Asahikawa Medical College; Yamagata University Faculty of Medicine; Kyoto Prefectural University of Medicine; Okayama Saiseikai General Hospital; Fukui-ken Saiseikai Hospital) between January 2008 and December 2009 were enrolled in this observational study.

Three hundred and sixty-five NAFLD patients (182 males, 183 females) who visited Saiseikai Suita Hospital were enrolled in the histopathological study.

The study protocol was approved by the Human Ethics Committee of each participating hospital. Informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Clinical and laboratory assessment

Demographic parameters, including age, sex, height, weight, and body mass index (BMI), and comorbidities, including alcohol consumption, hypertension, and dyslipidemia, were

recorded for all subjects in addition to the treatment administered for DM and the frequency of HCC occurrence. Clinical laboratory tests were conducted to measure aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), albumin, total cholesterol, triglyceride (TG), ferritin, uric acid, hemoglobin A1c, fasting plasma glucose (FPG), and insulin levels. The homeostasis model assessment of insulin resistance (HOMA-IR) index; platelet (PLT) count; and hyaluronic acid, type IV collagen 7S, hepatitis B surface antigen (HBsAg), anti-hepatitis B core antibody (anti-HBc Ab), anti-HCV antibody (anti-HCV Ab), HBV-DNA, and HCV-RNA levels were also measured.

Blood samples were procured in the morning after overnight fasting. HOMA-IR was only calculated for subjects with FPG <140 mg/dL. HBV-DNA levels were measured by PCR (Amplicor HBV-DNA kit, Roche Diagnostics) or real-time PCR (TaqMan HBV-DNA kit, Roche Diagnostics) for HBsAg-positive, whereas HCV-RNA levels were measured by PCR (Amplicor HCV-RNA kit, version 2.0, Roche Diagnostics) or real-time PCR (TaqMan HCV-RNA kit, Roche Diagnostics) for anti-HCV Ab-positive patients.

Histopathological examination

In total, 365 patients (177 non-DM and 188 DM) at Saiseikai Suita Hospital fulfilled the criteria for NAFLD, namely serum HBsAg and anti-HCV Ab negativity, no alcohol consumption, and the absence of autoimmune liver diseases or hereditary liver injury. These patients underwent an ultrasound-guided liver biopsy using a 16G needle.

Specimens were fixed in formalin, embedded in paraffin, and subjected to hematoxylin–eosin, Masson trichrome, and Perl's iron staining. Histological features of samples were interpreted according to a method described by Matteoni et al [8]. NASH stage was classified according to Brunt's classification [9].

Statistical analysis

All statistical analyses were performed using SPSS for Windows (SPSS Japan Inc.). Data were summarized by frequency for categorical variables and mean ± standard deviation (SD) for continuous variables. The Chi-square test was used to determine the differences between categorical variables. Student's t test was used to compare means of continuous valuables with equal variance, and the Mann–Whitney U test was used for non-normally distributed variables. The Cochran–Armitage test was used to study the trend of continuous variables. Forward stepwise logistic regression analysis was used to identify independent variables related to elevated serum ALT (≥31 IU/L) levels. A p value of <0.05, obtained by a two-tailed test, was considered statistically significant.

Since there is no official report on the HBV and HCV carrier rate in the general Japanese population, we utilized blood donor data for comparison with our patients [10].

Results

Baseline characteristics

The mean age and BMI of male and female DM patients was 62.2 and 64.8 years and 24.5 and 24.7 kg/m^2, respectively (Table 1). Hypertension and dyslipidemia occurred in 51.0 and 63.3 % of DM patients, respectively. Respective DM treatment types in DM patients were as follows: no medication, 20.5 %; oral drugs, 47.7 %; insulin, 28.9 %; and oral drugs and insulin, 2.8 % (Table 2).

Mean ALT level was significantly higher in males (30.6 IU/L) than in females (Table 1). Abnormal serum ALT levels (≥31 IU/L) were found in 28.6 % of DM patients (males 32.8 %, females 23.0 %). When the healthy upper limit of abnormal serum ALT level in females was defined as 20 IU/L according to Prati et al.'s [11] criteria, the frequency of abnormal ALT (≥21 IU/L) levels in females was 43 %. The mean PLT count was 20.8 × 10^4/μL in males and 21.9 × 10^4/μL in females. Mean values of other clinical laboratory tests are shown in Table 1.

Prevalence of HBV and HCV infection and drinking and their effects on liver function tests

HBsAg positivity was detected in 1.7 % of DM patients (M 1.8 %, F 1.6 %) (Table 2); this was significantly higher than that (total 0.9 %, M 1.0 %, F 0.7 %) detected in 1.7 million blood donors aged >40 years ($p < 0.001$). For both sexes, the HBsAg detection rate was significantly higher in DM patients than in blood donors in the 50- to 59- and 60- to 69-year age groups ($p < 0.05$) (Fig. 1). There were no significant differences in serum AST, ALT, and GGT levels between HBsAg-positive and HBsAg-negative DM patients of both sexes.

Seventy-two percent of HBsAg-positive patients (M 69 %, F 79 %) demonstrated HBV-DNA negativity (<2.6 log copies/ml) (Table 3). Of the HBsAg-positive patients, only 10 % showed high serum HBV-DNA levels (≥4.0 log copies/ml); these could be HBV infection-induced liver injury cases. Mean values of age, serum ALT level, and PLT counts in HBV-DNA-negative HBV carriers were 63.6 years, 25.3 IU/L, and 20.5 × 10^4/μL, respectively. HBV-DNA-negative HBV carriers were older and exhibited lower ALT levels and higher PLT counts; however, the differences were not significant.

Table 1 Backgrounds of diabetes mellitus patients (1)

Characteristic	Total subjects		Males		Females		
	n	M ± SD	*n*	M ± SD	*n*	M ± SD	*p*
Age (years)	5,510	63.3 ± 12.7	3,164	62.2 ± 12.5	2,346	64.8 ± 12.9	<0.001
BMI (kg/m^2)	5,173	24.6 ± 4.7	2,987	24.5 ± 4.2	2,186	24.7 ± 5.2	0.629
Aspartate aminotransferase (IU/L)	5,568	26.4 ± 17.2	3,188	27.1 ± 18.0	2,380	25.5 ± 15.9	<0.001
Alanine aminotransferase (IU/L)	5,569	28.2 ± 24.5	3,190	30.6 ± 26.9	2,379	24.9 ± 20.5	<0.001
GGT (IU/L)	5,476	48.3 ± 72.5	3,131	59.6 ± 86.7	2,345	33.1 ± 42.9	<0.001
Albumin (g/dL)	5,031	4.2 ± 0.4	2,869	4.2 ± 0.5	2,162	4.1 ± 0.4	<0.001
Platelet (×10^4/μL)	5,419	21.3 ± 6.1	3,112	20.8 ± 6.0	2,307	21.9 ± 6.1	<0.001
Fasting plasma glucose (FPG; mg/dL)	5,123	152.7 ± 61.7	2,945	156.0 ± 63.9	2,178	148.3 ± 58.2	<0.001
HbA1c (%)	5,479	7.2 ± 1.7	3,143	7.2 ± 1.7	2,336	7.2 ± 1.6	0.744
HOMA-IR (FPG <140)	1,005	2.55 ± 2.60	570	2.51 ± 2.59	435	2.61 ± 2.60	0.209
Total cholesterol (mg/dL)	5,260	195.1 ± 39.5	3,016	191.6 ± 40.0	2,244	199.6 ± 38.5	<0.001
Triglycerides (mg/dL)	5,443	136.3 ± 102.7	3,119	145.1 ± 111.9	2,324	124.5 ± 87.5	<0.001
Hyaluronic acid (ng/mL)	559	74.5 ± 98.6	319	59.3 ± 73.0	240	94.6 ± 122.1	<0.001
Type 4 collagen 7S (ng/mL)	474	4.9 ± 2.0	269	4.8 ± 2.0	205	4.9 ± 1.9	0.544
Ferritin (ng/mL)	1,838	142.0 ± 157.0	1,084	171.9 ± 174.9	754	99.1 ± 114.1	<0.001
Uric acid (mg/dL)	3,645	5.4 ± 1.5	2,043	5.7 ± 1.4	1,602	4.9 ± 1.4	<0.001

Results are shown as mean ± SD

GGT gamma glutamyl transpeptidase, *HOMA-IR* homeostasis model assessment of insulin resistance

Table 2 Backgrounds of diabetes mellitus patients (2)

Characteristic	Total subjects		Males		Females		
	n	Positive (%)	*n*	Positive (%)	*n*	Positive (%)	*p*
Hepatitis B surface antigen	4,867	83 (1.7 %)	2,796	50 (1.8 %)	2,071	33 (1.6 %)	0.604
Anti-hepatitis B core antibody	3,211	958 (29.8 %)	1,824	572 (31.4 %)	1,387	386 (27.8 %)	0.030
Anti-hepatitis C virus antibody	4,877	247 (5.1 %)	2,812	144 (5.1 %)	2,065	103 (5.0 %)	0.834
Alcohol	4,443		2,554		1,889		<0.001
<20 g/day		3589 (80.8 %)		1769 (69.3 %)		1820 (96.3 %)	
20–59 g/day		661 (14.9 %)		609 (23.8 %)		52 (2.8 %)	
≥60 g/day		193 (4.3 %)		176 (6.9 %)		17 (0.9 %)	
Hypertension	4,936	2515 (51.0 %)	2,841	1419 (49.9 %)	2,095	1096 (52.3 %)	0.100
Dyslipidemia	5,423	3434 (63.3 %)	3,091	1882 (60.9 %)	2,332	1552 (66.6 %)	<0.001
Diabetes mellitus (intervention)	5,227		3,013		2,214		0.002
None		1072 (20.5 %)		629 (20.9 %)		443 (20.0 %)	
Oral drugs		2495 (47.7 %)		1489 (49.4 %)		1006 (45.4 %)	
Insulin		1513 (28.9 %)		810 (26.9 %)		703 (31.8 %)	
Oral drugs + insulin		147 (2.8 %)		85 (2.8 %)		62 (2.8 %)	
Hepatocellular carcinoma	4.700	67 (1.4 %)	2,696	48 (1.8 %)	2,004	19 (0.9 %)	0.017

Anti-HCV Ab positivity was detected in 5.1 % (M 5.1 %, F 5.0 %) of DM patients; this rate was significantly higher than that (total 1.0 %, M 1.1 %, F 1.0 %) in blood donors of every age group of both sexes ($p < 0.001$), except for females aged 50–59 years (Table 2; Fig. 2). ALT and GGT levels were significantly higher in male anti-HCV Ab-positive patients than in their negative counterparts ($p < 0.001, p < 0.05$) (Fig. 2). For both sexes,

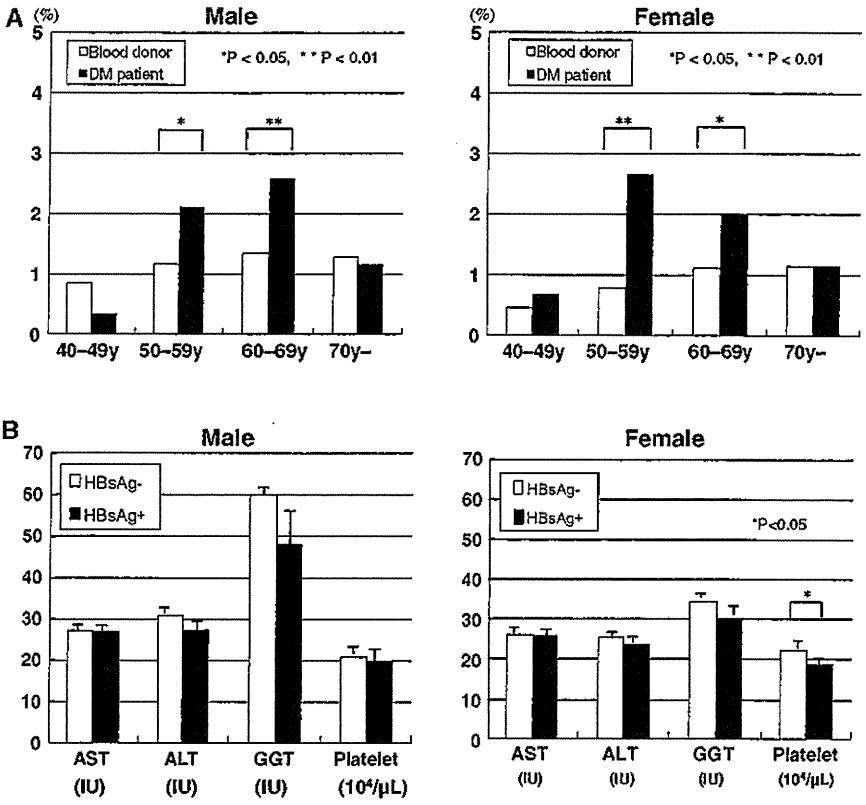

Fig. 1 Prevalence of HBV infection and the effect of HBV infection on laboratory tests in DM patients. a Prevalence of HBV infection in blood donors and DM patients. b The effect of HBV infection on laboratory tests in DM patients. There were no significant differences in serum AST, ALT, and GGT levels between HBsAg-positive and HBsAg-negative DM patients of both sexes. *Error bars* SD

Table 3 Serum HBVDNA and HCVRNA levels, age, serum ALT level, and platelet (PLT) counts in HBsAg-positive patients and anti-HCV Ab-positive patients

	% (*n*)	Mean age (years)	Mean ALT levels (IU/L)	Mean PLT count($\times 10^4$/μL)
Serum HBV-DNA[a]				
Negative (<2.6 log copy/ml)	72 (29)	63.6	25.3	20.5
Positive (=2.6 log copy/ml)	28 (11)	55.6	28.0	18.5
=2.6<4.0	18 (7)	61.9	26.6	18.9
=4.0	10 (4)	50.0	30.5	17.8
Serum HCV-RNA[b]				
Negative (<2.7 log IU/ml)	38 (57)	67.2	28.2	17.7
Positive (=2.7 log IU/ml)	62 (91)	67.4	51.7	15.3
=2.7<5.0	3 (4)	65.1	28.0	16.4
=5.0	59 (87)	67.5	52.7	15.2

[a] Results are presented as either frequency or mean in 40 HBsAg-positive patients

[b] Results are presented as either frequency or mean in 148 anti-HCV Ab-positive patients

the PLT count was significantly lower in anti-HCV Ab-positive DM patients than in their negative counterparts ($p < 0.001$).

Thirty-eight percent of anti-HCV Ab-positive patients (M 36 %, F 42 %) demonstrated HCV-RNA negativity (Table 3), and 96 % of HCV-RNA-positive patients exhibited high serum HCV-RNA levels (≥5.0 log IU/ml). Serum ALT levels in anti-HCV Ab-positive patients with HCV-RNA positivity and those with HCV-RNA negativity were 51.7 ± 39.7 and 28.2 ± 18.1 IU/L, respectively, whereas those in anti-HCV Ab-negative patients were 27.7 ± 22.8 IU/L. Serum ALT levels were significantly higher in HCV-RNA-positive patients than in HCV-RNA-negative patients ($p < 0.001$).

The proportion of DM patients consuming >60 g and 20–59 g alcohol daily was 4.3 % (M 6.9 %, F 0.9 %) and

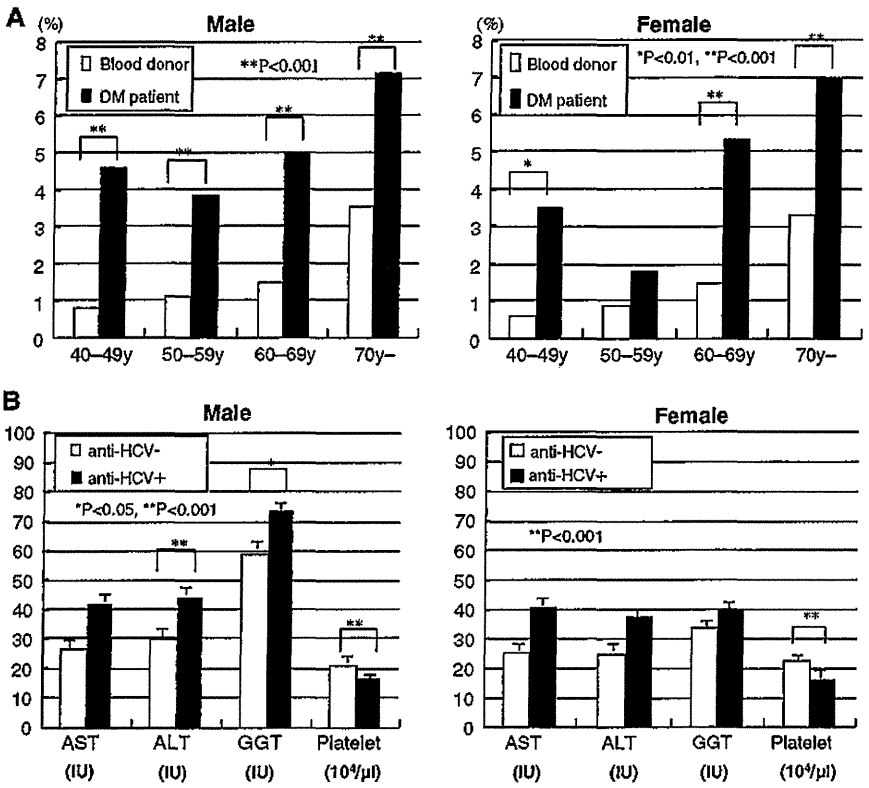

Fig. 2 Prevalence of HCV infection and the effect of HCV infection on laboratory tests in DM patients. **a** Prevalence of HCV infection in blood donors and DM patients. **b** The effect of HCV infection on laboratory tests in DM patients. *GGT* gamma glutamyl transpeptidase. ALT and GGT levels were significantly higher in male anti-HCV Ab-positive patients than in their negative counterparts. *Error bars* SD

14.9 % (M 23.8 %, F 2.8 %), respectively (Table 2). The highest percentage of drinkers were males in the 60- to 69-year age group and females in the <40-year age group. Male drinkers consuming >60 g alcohol daily had significantly higher serum AST and GGT levels compared with nondrinkers (patients consuming <20 g of daily alcohol intake) ($p < 0.001$). Serum ALT levels in drinkers consuming >60 g alcohol daily were comparable with those in nondrinkers. Drinkers of both sexes consuming 20–59 g alcohol daily had significantly higher serum GGT levels ($p < 0.001$) (Fig. 3).

Factors related to serum ALT levels

With increasing age in both sexes, the number of DM patients with elevated serum ALT levels and high BMI decreased, whereas those with decreased PLT counts increased. The number of DM patients with elevated serum ALT levels increased with increasing BMI in both sexes (Fig. 4).

A forward stepwise logistic regression model yielding odds ratios (ORs) and 95 % confidence intervals (CIs) was used to analyze the factors related to elevated serum ALT levels. The model included BMI, age, drinking status, HBsAg status, anti-HCV Ab status, PLT count, hypertension status, and dyslipidemia status as independent variables. The odds ratio shown indicates the change in odds for one SD increase in each variable.

Multivariate analysis showed that age (M: OR 0.674, CI 0.613–0.741; $p < 0.001$; F: OR 0.767, CI 0.683–0.861; $p < 0.001$), PLT count (M: OR 0.806, CI 0.732–0.886; $p < 0.001$, F: OR 0.714, CI 0.632–0.808, $p < 0.001$), anti-HCV Ab status (M: OR 1.321, CI 1.218–1.433; $p < 0.001$; F: OR 1.232, CI 1.117–1.359; $p < 0.001$), and BMI (M: OR 1.509, CI 1.374–1.657; $p < 0.001$; F: OR 1.487, CI 1.330–1.663; $p < 0.001$) were significantly associated with elevated serum ALT levels (Table 4).

For both sexes, AST and ALT levels were similar in drinkers consuming 20–59 g alcohol daily and those consuming <20 g alcohol daily (Fig. 3). After eliminating HBV-positive patients and/or HCV carriers and heavy drinkers consuming >60 g alcohol daily, the number of male, female, and total DM patients with elevated serum ALT levels were 33.4, 23.3, and 28.3 %, respectively. These values were comparable with those in all DM patients, including those with hepatitis and/or those consuming alcohol (M 32.8 %, F 23.0 %, total 28.6 %).

Liver histology in DM patients

The median age of histologically proven, DM- ($n = 87$) and non-DM-associated ($n = 95$) male NAFLD patients

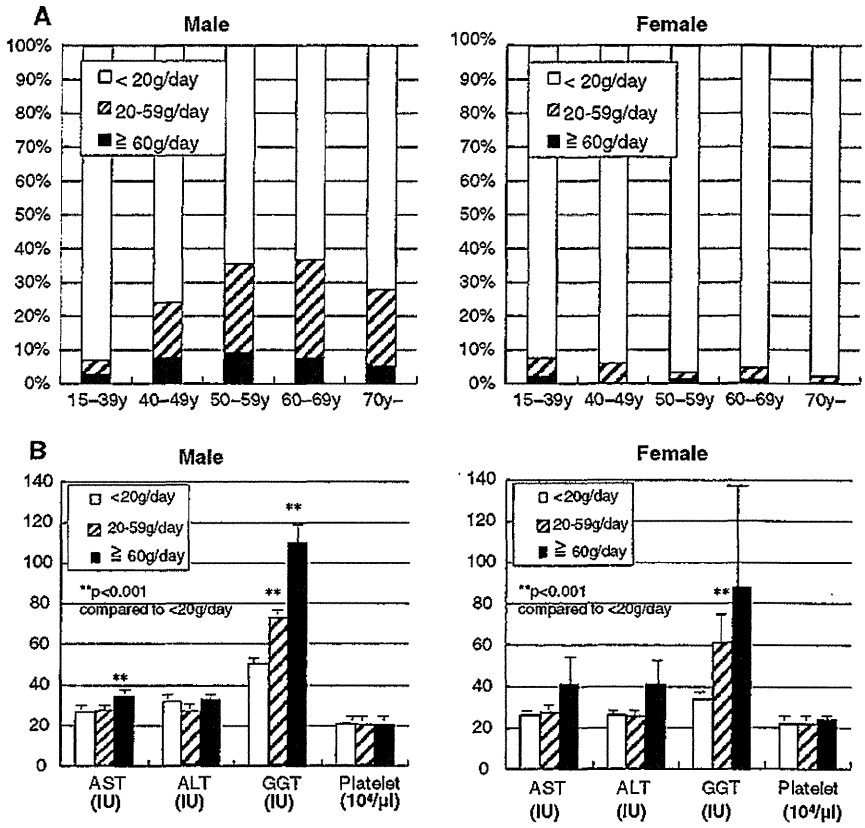

Fig. 3 Drinking habits and the effect of alcohol consumption on laboratory tests in DM patients. a Drinking habits in individual age. b The effect of alcohol consumption on laboratory tests in DM patients. *GGT* gamma glutamyl transpeptidase. Serum ALT levels in drinkers consuming >60 g alcohol daily were comparable with those in nondrinkers. *Error bars* SD

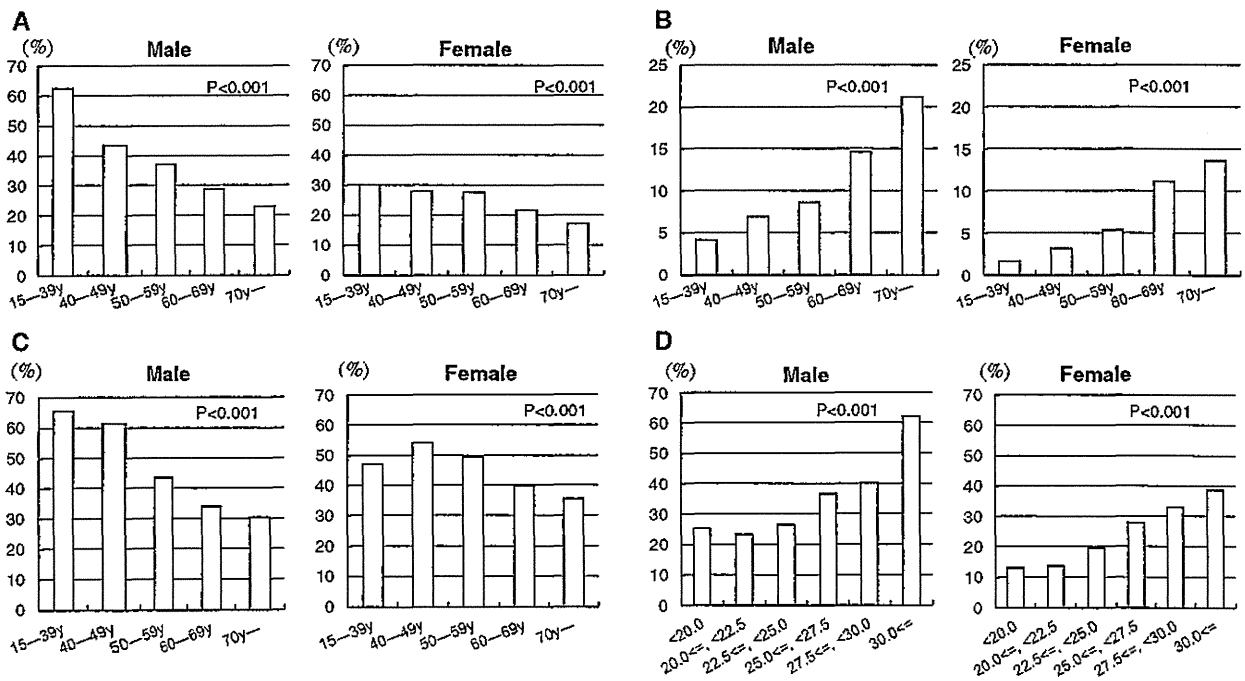

Fig. 4 Influence of age on the ratio of patients with elevated serum ALT level, decreased PLT count and abnormal BMI, and the relationship between BMI and the ratio of patients with elevated serum ALT level. a The ratio of patients with elevated serum ALT level (≥31 IU/L). b The ratio of patients with decreased PLT count (<15 × 10^4/μL). c The ratio of patients with abnormal BMI (≥25). d The relationship between BMI and the ratio of patients with elevated serum ALT level (≥31 IU/L)

Table 4 Multivariate analysis to identify independent variables related to elevated serum ALT level (≥31 *IU/L*)

	Regression coefficient	Standard error	Odds ratio	95 % confidence interval	*p*
Males					
Age	−0.394	0.048	0.674	0.613–0.741	<0.001
Platelet	−0.216	0.049	0.806	0.732–0.886	<0.001
Anti-hepatitis C virus	0.278	0.042	1.321	1.218–1.433	<0.001
Body mass index	0.411	0.048	1.509	1.374–1.657	<0.001
Females					
Age	−0.265	0.059	0.767	0.683–0.861	<0.001
Platelet	−0.336	0.063	0.714	0.632–0.808	<0.001
Anti-hepatitis C	0.208	0.050	1.232	1.117–1.359	<0.001
Body mass index	0.397	0.057	1.487	1.330–1.663	<0.001

was 60 and 45 years, respectively; in corresponding females, the median age was 66 ($n = 101$) and 61 years ($n = 82$), respectively. No significant difference was noted in BMI between DM and non-DM NAFLD patients (M 26.0 and 27.5 kg/m^2, respectively; F 26.0 and 27.0 kg/m^2, respectively). Male NAFLD patients without DM were significantly younger than those with DM ($p < 0.001$).

NAFLD patients were classified according to Matteoni's classification. Type 1, 2, 3, and 4 cases were 14 (16 %), 14 (16 %), 4 (5 %), and 55 (63 %), respectively, among male DM patients and 28 (29 %), 23 (24 %), 11 (12 %), and 33 (35 %), respectively, among male non-DM patients. Type 1, 2, 3, and 4 cases were 16 (16 %), 8 (8 %), 4 (4 %), and 73 (72 %), respectively, among female DM patients and 9 (11 %), 9 (11 %), 7 (9 %), and 57 (69 %), respectively, among female non-DM patients (Fig. 5). The frequency of Type 4 NASH was significantly higher in male DM patients than in male non-DM patients ($p < 0.001$).The rate of Type 4 NASH was high in both female DM and non-DM patients.

In total, 244 (M 103, F 141) NASH patients were classified according to Brunt's classification. The number of patients with stage 0 (Matteoni Type 3), 1, 2, 3, and 4 were 2 (3 %), 27 (46 %), 10 (17 %), 17 (29 %), and 3 (5 %), respectively, among male DM patients and 10 (23 %), 16 (36 %), 8 (18 %), 9 (21 %), and 1 (2 %), respectively, among male non-DM patients. Stage 0, 1, 2, 3, and 4 cases were 4 (5 %), 25 (33 %), 24 (31 %), 13 (17 %), and 11 (14 %), respectively, among female DM patients and 4 (6 %), 28 (44 %), 20 (31 %), 10 (16 %), and 2 (3 %), respectively, among female non-DM patients (Fig. 6). The frequency of advanced stage NASH was significantly higher in male DM patients than in male non-DM patients ($p < 0.05$).The rate of Stage 4 NASH was higher in female DM patients than in female non-DM patients; however, the difference was not significant ($p = 0.198$).

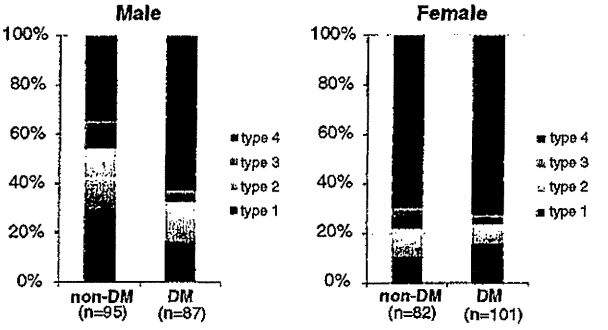

Fig. 5 Distribution of Matteoni's type classification in individual status of glucose metabolism among NAFLD patients. The frequency of type 4 NASH was significantly higher in male DM patients than in male non-DM patients ($p < 0.001$). The rate of type 4 NASH was high in both female DM and non-DM patients

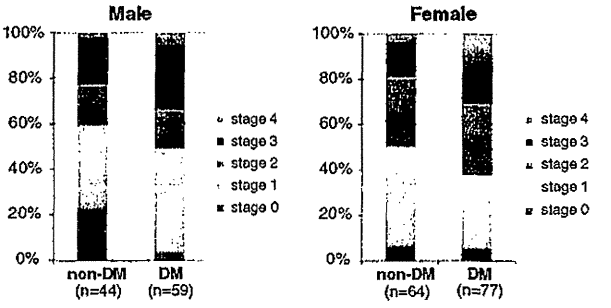

Fig. 6 Distribution of Brunt's stage in individual status of glucose metabolism among NASH patients. The frequency of advanced stage NASH was significantly higher in male DM patients than in male non-DM patients ($p < 0.05$). The rate of stage 4 NASH was higher in female DM patients than in female non-DM patients; however, the difference was not significant ($p = 0.198$)

HCC incidence in DM patients

In total, 67 (M 48, F 19) HCC cases (1.4 %) were reviewed (Table 2). HCC incidence was significantly higher in males

than in females. Five of 67 HCC patients consumed >60 g alcohol daily, and two of these five patients were anti-HCV Ab positive. HBsAg positivity, anti-HCV Ab positivity, and non-B non-C prevalence in the HCC patients was 8.6, 50.0, and 41.4 %, respectively. In a Japanese nationwide survey of 19,499 HCC patients [3], HBsAg positivity, anti-HCV Ab positivity, and non-B non-C prevalence was 15.0, 67.7, and 17.3 %, respectively. Non-B non-C prevalence was higher in our DM patients with HCC than in the nationwide HCC survey participants ($p < 0.001$). Mean PLT count in DM patients with HCC was as follows: HBsAg-positive patients, 12.4 ± 6.8; anti-HCV Ab-positive patients, 12.4 ± 5.6; and non-B non-C patients, 16.0 ± 7.0 ($\times 10^4/\mu L$); PLT count was significantly higher in the non-B non-C patients than in the anti-HCV-positive patients ($p < 0.05$). Mean BMI in these three patient groups was as follows: HBsAg-positive patients, 23.2 ± 5.1; anti-HCV Ab-positive patients, 22.8 ± 3.3; and non-B non-C patients, 27.2 ± 4.4 (kg/m^2); BMI was significantly higher in the non-B non-C patients than in the anti-HCV Ab-positive patients ($p < 0.001$).

Discussion

This is the first multicenter study, as per our knowledge, that clarifies the cause of liver injury in DM patients in Japan. Most Japanese HBV carriers are genotype C, acquired via perinatal vertical transmission or early childhood infection [12]. The HBV carrier rate in Japan is higher than that in western countries and significantly lower than that in other Asian countries [13]. In 1986, the Japanese government initiated a nationwide hepatitis B immunization program for infants born to HBV carrier mothers to prevent perinatal transmission. Consequently, the number of young serum HBsAg-positive individuals is extremely low. In our study, although the HBV carrier rate in DM patients was significantly higher than that in blood donors, 72 % of HBsAg-positive patients were serum HBV-DNA negative. Only 10 % of HBsAg-positive patients exhibited high serum HBV-DNA levels (≥4.0 log copies/ml), which is likely to induce hepatitis. These results indicate that a majority of DM patients who are HBV carriers may be asymptomatic.

Chronic hepatitis C may result in life-threatening complications, including cirrhosis and HCC. Worldwide, cirrhosis can be attributed to HBV (30 %) and HCV infection (27 %) [14]. The leading cause of cirrhosis among HBV and HCV sufferers and alcohol consumers varies with individual countries. A recent nationwide Japanese survey reported the etiology of cirrhosis in Japan as follows: HCV 60.9 %, HBV 13.9 %, alcoholism 13.6 %, primary biliary cirrhosis 2.4 %, NASH-related 2.1 %, and autoimmune hepatitis 1.9 % [15]. However, we must consider that hepatic triglycerides diminish with liver fibrosis progression in NASH patients (so-called "burned-out" NASH), resulting in difficulty in diagnosing NASH. Sixty-two percent of anti-HCV Ab-positive DM patients were HCV-RNA positive; these patients showed significantly higher serum ALT levels compared with HCV-RNA-negative patients. These results indicate that HCV infection is involved in the etiology of liver disease in DM patients.

There is no doubt that the positive rates of serum HBsAg and anti-HCV Ab in the general population are higher than in blood donors. Unfortunately, there were no data in the distribution of the rate of hepatitis virus carriers in each age group in Japan. In the present study, the positive rates of HBsAg and anti-HCV Ab in DM patients were significantly higher than that in blood donors. However, the present study demonstrated that most of HBsAg positive patients were negative for serum HBV DNA or had low serum HBV DNA levels and around one-third of anti-HCV Ab positive patients were negative for serum HCV RNA.

These results indicate the possibility that the frequency of hepatitis virus carriers in DM patients is higher than that in general population but no significant differences might be noted between DM patients and the general population.

Alcohol consumption is reportedly a significant factor associated with the risk of HCC development in patients with NASH-associated cirrhosis [16]. In our study, serum AST and ALT levels were comparable between drinkers consuming 20–59 g alcohol daily and nondrinkers. The ratio of heavy drinkers consuming >60 g alcohol daily was low (4.3 %) in our study. Moreover, drinking was not chosen as a variable related to elevated serum ALT levels. These results suggest that alcohol intake is not an important factor in the pathogenesis of liver disease in DM patients.

In our study, the frequency of anti-HCV Ab-positive DM patients was 5 %, whereas the serum HCV-RNA positivity rate in anti-HCV Ab-positive patients was 62 %. Therefore, the HCV carrier rate was calculated as 3 %. Since the proportion of HCV carriers and patients with elevated ALT levels were 3 % and up to 29 %, respectively, the influence of HCV infection is estimated to be no more than 10 % (3 % divided by 29 %) among DM patients with elevated ALT levels. There was no significant change in the number of DM patients with elevated ALT levels before and after elimination of HBV and/or HCV carriers and heavy drinkers. These results suggested that the major cause (up to 90 %) of liver injury in DM patients may be NAFLD.

In the present study, the frequency of advanced stage NASH was significantly higher in male DM patients than

in male non-DM patients. Neuschwander-Tetri et al. [17] reported that patients with advanced stage NASH were more likely to have DM. Mayaaki et al. [18] also examined the relationship between hepatic fibrosis stage and DM prevalence. In the mild fibrosis group, only 42 % were complicated with DM, whereas in the severe fibrosis group, the prevalence was as high as 71 % ($p = 0.020$). Lo et al. [19] reported that DM exacerbated diet-induced NASH fibrosis in mice. Therefore, DM may be an important factor in hepatic fibrosis development in NAFLD patients.

HCC frequency is significantly higher in obese and DM patients than in non-obese and non-DM patients [20, 21]. Recently, Tokushige et al. [22] reported on the backgrounds of Japanese HCC patients, and non-B non-C HCC accounted for 16 % of cases. A recent report has shown that NASH patients are likely to develop HCC in an earlier stage of fibrosis compared with chronic hepatitis C patients [23]. Our previous study analyzed 87 histologically proven NASH-HCC patients [24]; 37 % (20/54) of male HCC patients had a mild to moderate stage of liver fibrosis (F1 or F2); however, no female HCC patients were F1 stage, and only 15 % (5/33) were F2 stage. In the present study, DM patients with non-B non-C HCC exhibited a tendency to have higher PLT counts than those in DM patients with HCV-HCC, indicating that non-B non-C HCC is more likely to occur in DM patients with less advanced liver disease than in those with viral hepatitis.

In conclusion, HBsAg and anti-HCV Ab positivity rates were high; however, most of these patients were HBV-DNA negative or had low serum HBV-DNA levels. One-third of anti-HCV Ab-positive patients were HCV-RNA negative, and 4.3 % patients were drinkers whose ALT levels were comparable with those of nondrinkers. From these results, we conclude that up to 90 % of Japanese DM patients with liver injury may have NAFLD/NASH.

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Conflict of interest The authors declare that they have no conflicts of interest to disclose.

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Original Article

Validation and limitation of age–period–cohort model in simulating mortality due to hepatocellular carcinoma from 1940 to 2010 in Japan

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Aim: We aimed to simulate the mortality due to hepatocellular carcinoma (HCC) by the age–period–cohort (APC) model with use of sex- and age-specific mortality data, for the purpose of validating the utility and assessing the limitation of this model.

Methods: Age-specific mortality due to HCC was gleaned from people aged 20–84 years during 1940 through 2010 in Japan.

Results: The APC model had a high performance in reproducing HCC mortality (modified determination coefficient $R^2_{COR} \geq 0.99$). Risk of HCC increased with age in both sexes, while risk of period barely changed in both sexes. The birth cohort factor in the APC model in males highlighted the maximum point within birth years 1931–1935. The observed HCC mortality in 2010 in males (19 444) was lower than the predicted, and corresponded to 72.3% of the predicted 26 883.4, and in all age groups by 5-year increments (55.6–90.9%). In females, the observed mortality was lower than that predicted in those aged 64 years or less, but not in those aged 65 years or more.

Conclusion: We applied the APC model to predict HCC mortality rate, and it reproduced the observed mortality rate faithfully. However, in the recent past, the observed morality rate in males was only 72.3% that of the predicted. Such differences would be attributed to combined effects of medical interventions, such as antiviral treatments and screening for hepatitis viruses implemented in the early 1990s in Japan.

Key words: age–period–cohort model, epidemiology, hepatitis B virus, hepatitis C virus, hepatocellular carcinoma

INTRODUCTION

MALIGNANT NEOPLASM REMAINS the most common cause of death in Japan. Mortality caused by liver cancer in males started to increase in 1975, peaked at around 2000, and has been slightly decreasing in recent years. By contrast, the mortality due to liver cancer in females is still increasing slightly. At present, liver cancer remains the fourth leading cause of death among malignant neoplasms in Japan, and 32 765 people died of it in 2010.[1]

The age–period–cohort (APC) model[2] is based on epidemiological experiences in which incidence or mortality is influenced by three major factors: (i) age factor; (ii) period factor; and (iii) birth cohort factor. Age factor reflects the risk of aging, while period factor mirrors the common risk posed on constituent members during a given period, regardless of age. The birth cohort factor reflects the risk of historical background of medical policies, such as treatments, vaccinations, health insurance and screenings, as well as environment shared by the birth cohort. The APC model is used increasingly frequently for analyzing temporal age-specific incidence or mortality data in late years. For example, Pham *et al.*[3] analyzed the mortality due to chronic obstructive pulmonary disease in Japan using

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the APC model, and proposed the relation to cigarette smoking. Likewise, Ito *et al.*[4] applied the model to incidence rates and mortality of some cancers in Osaka, Japan, and discussed the factor characteristics of each cancer. Lee *et al.*[5] analyzed mortality data of hepatocellular carcinoma (HCC) in Taiwan using the APC model.

From the etiological point of view, however, persistent infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) are the primary cause of HCC in Japan.[6,7] HCC is principally caused by persistent infections with HBV and HCV that were responsible for 16% and 80% of the cases in 1995,[6] 13% and 81% in 2000,[8] and 15% and 68% in 2005 of the cases, respectively.

Because HCC accounts for the great majority (94%) of liver cancer in Japan,[9] they were deemed equivalent and will be collectively referred to as HCC in this study.

Since HCV was cloned in 1989,[10] anti-HCV screening was introduced to blood donors for the first time in the world in Japan.[11] The opportunity to undergo HCV testing has increased swiftly in hospitals and clinics, as well as in health check-ups. We analyzed the utility of the APC model, as well as the limitation, in simulating yearly deaths due to HCC in Japan. We went on to assess how countermeasures against hepatitis and HCC implemented since 1990, such as hepatitis virus screening and antiviral treatments, influenced the HCC mortality predicted by the APC model.

METHODS

Data sources

SEX- AND AGE-SPECIFIC mortality data of HCC were obtained from Vital Statistics of Japan[1] for 15 time points in 5-year increments from 1940 through 2010 (e.g. 1940, 1945, 1950). During the study period, the International Classification of Diseases (ICD) changed six times, and therefore we needed to employ the time-dependent codes listed in Table 1. Vital Statistics of Japan in 1944 and 1945 are not published, so we used Vital Statistics of Japan in 1943 to represent number of deaths and population in 1945. No ethical problem occurred in this study, because only census data were used as the data source.

Table 1 Target cause of death due to liver cancer

Year	ICD	Code
1940, 1945	ICD4	46 (一)
1950, 1955	ICD6	155, 156
1960, 1965	ICD7	155, 156
1970, 1975	ICD8	155, 197.8
1980, 1985, 1990	ICD9	155
1995, 2000, 2005, 2010	ICD10	C22

ICD, International Classification of Diseases.

Data analysis

All mortality data were tabulated into 13 5-year age groups (from 20–24 to 80–84 years) in each of 15 5-year time periods (from 1940 to 2010).

First, we estimated the sex-specific effects of age factor, time period factor and birth cohort factor on HCC mortality using the APC model:

$$y_{ij} \sim \text{Poisson}(\mu_{ij}),\ \log(\mu_{ij}) = \log(P_{ij}) + \mu + A_i + P_j + C_k,$$

where μ, A_i, P_j and C_k denote intercept, factor of i-th age group ($i = 1, 2, \ldots, 13$), factor of j-th time period ($j = 1, 2, \ldots, 15$) and factor of k-th birth cohort ($k = 1, 2, \ldots, 27$), respectively. μ_{ij}, y_{ij} and P_{ij} denote expected number of deaths, real number of deaths and population in i-th age group, and j-th time period, respectively. The APC model has methodical drawbacks, such as the "identification problem" (see Appendix I for details). We assumed that two effects of the birth cohort factor, C_9 (1896–1900) and C_{10} (1901–1905), would be the same with respect to the influence of this problem by Barrett's technique.[12] We set the baseline of each factor as 20–24 years old (age factor), year 1940 for time period (period factor) and 1896–1900 and 1901–1905 for birth year cohorts (birth cohort factor), respectively, in the calculation of 95% confidence interval (95% CI).

We estimated effects and their 95% CI of age factor, period factor and birth cohort factor by the maximum likelihood method, and estimated the mortality by the APC model using estimated effects for evaluating the validity of the model. The expanded determination coefficient R^2_{COR}[13] was used for comparison between observed and estimated mortality rates (see Appendix II for details).

Second, we estimated the effects of age, period and birth cohort factors by using data confined to 1940–1990 in the same manner, and estimated number of deaths due to HCC in 1995, 2000, 2005 and 2010 on the basis of these effects. We assumed that effects of the period factor after 1990 and those of the birth cohort factor after 1970 would have remained unchanged.

Statistical analyses were performed using JMP ver. 9 (SAS Institute, Cary, NC, USA).

RESULTS

Performance of APC model in simulating mortality due to HCC

THE 3-D PLOTS of sex- and age-specific mortality rates from 1940 through 2010 are depicted in Figure 1, for comparison of the observed mortality against that estimated by APC model in males (a vs b) and females (c vs d). Observed mortality rates are closely reproduced by predicted mortality rates in both sexes with very high expanded determination coefficients ($R^2_{COR} > 0.99$).

Risk of HCC deaths in relation to age, time period and birth cohort

The effects of age factor, time period factor and birth cohort factor on the APC model are displayed graphically in Figure 2. Age effect was based on the 20–24 year old group with 95% CI values. There was a trend for higher risk for HCC mortality with increasing ages. The effect of the period factor did not change enormously. With respect to 95% CI values based on the year 1940, there was no difference in the age-specific risk for HCC mortality. In late years, however, the risk of HCC deaths decreased gradually in males.

The birth cohort effect is exhibited based on 95% CI of the 1896–1905 birth year group. In males, it was high in birth cohorts born during 1916–1940, and culminated in the 1931–1935 birth year cohort. In females, the risk of HCC mortality was the highest in 1881–1935 birth year cohorts.

Discrepancy between HCC deaths predicted by APC from those observed since 1990

Numbers of HCC deaths were estimated by the APC model based on 1940–1990 data, and they are compared against observed numbers in Figure 3. In males, predicted numbers of deaths became higher than observed numbers since 2000. [Correction added on 11 October 2013, after first online publication: 'In males, predicted numbers of deaths became lower than observed numbers since 2000' has been corrected to '. . . higher than observed'.] Predicted HCC deaths in 2010 are 26 883.4, which correspond to 138.3% of the 19 444 observed. [Correction added on 11 October 2013, after first online publication: 'Predicted HCC deaths in 2010 are 26 883.4, which correspond to 72.3% of the 19 444 observed' has been corrected to '. . . correspond to 138.3% of the 19 444 observed'.] In females, by remarkable contrast, predicted numbers of

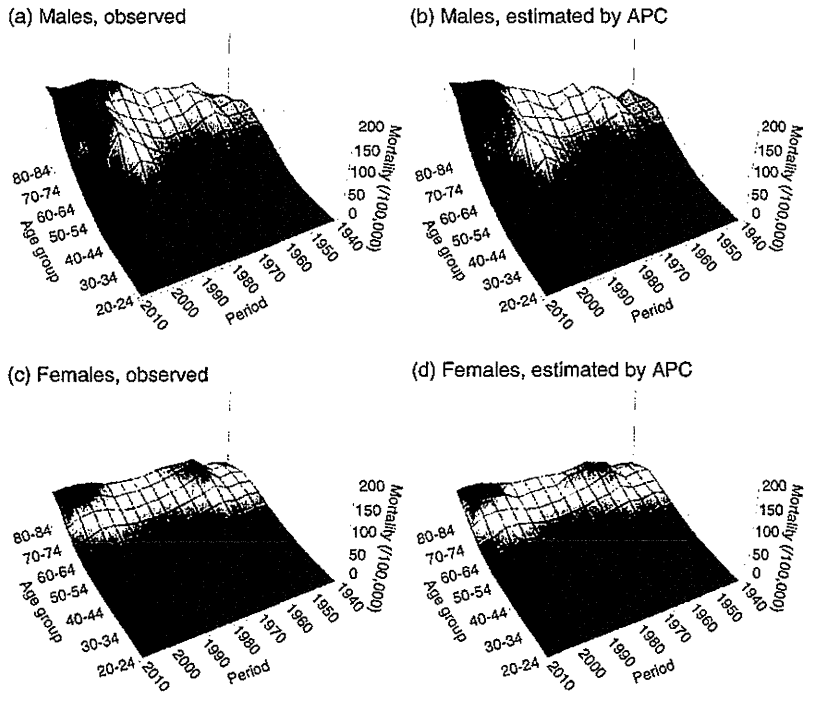

Figure 1 Trend in observed and estimated age-specific mortalities of hepatocellular carcinoma (HCC) in males and females. Observed and estimated (by the age–period–cohort [APC] model) mortalities (per 100 000 people) due to HCC during 1940 through 2010 are shown in the 3-D plot. (a) Observed mortality in males, (b) mortality estimated by the APC model in males, (c) observed mortality in females, (d) mortality estimated by the APC model in females.

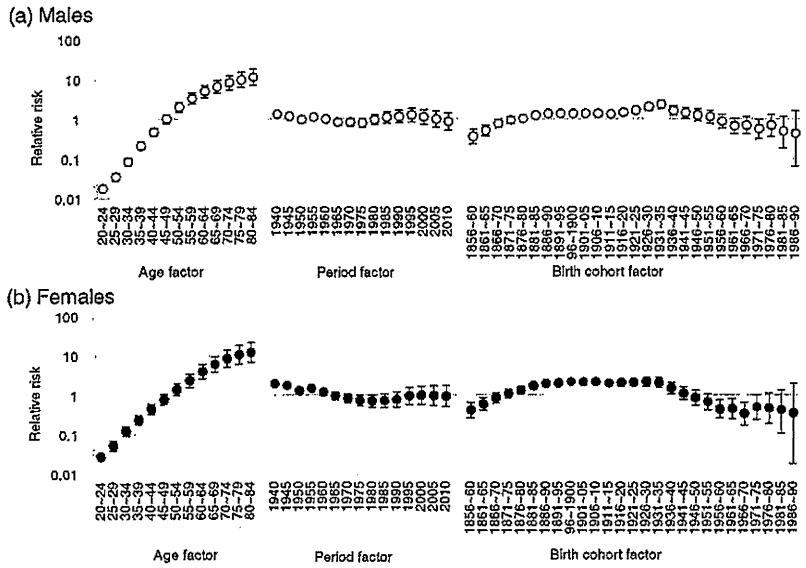

Figure 2 Effects of age, period and birth cohort factors on hepatocellular carcinoma (HCC) mortality in males and females predicted by the age-period-cohort (APC) model. The relative risk of age factor, period factor and birth cohort factor were estimated by the APC model in (a) males and (b) females. The baselines of age, period and cohort effects were 20–24 years old, the year 1940, and 1896–1900 as well as 1901–1905 birth year cohorts, respectively.

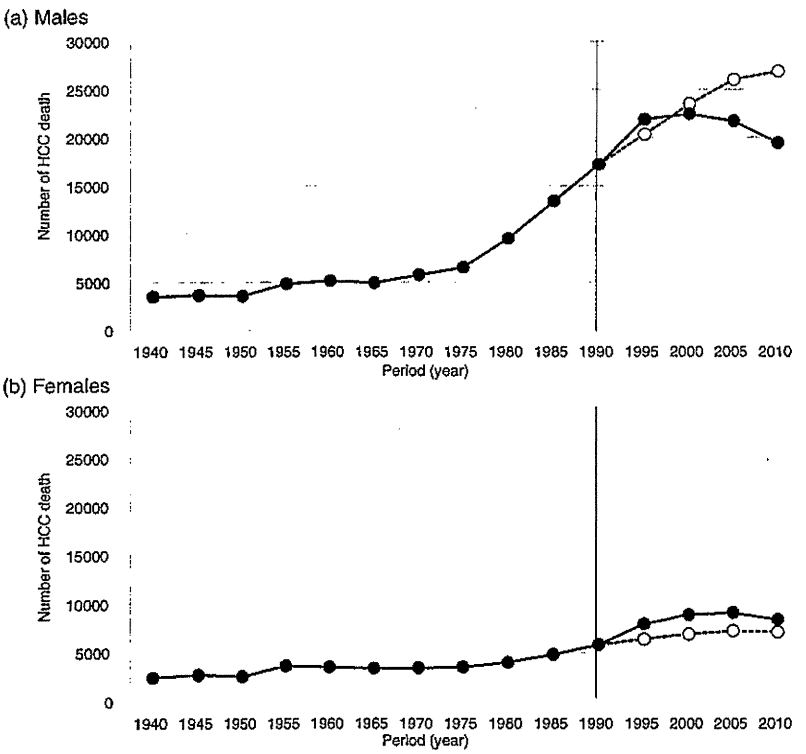

Figure 3 Comparison between observed and predicted numbers of deaths. Number of deaths during 1991 through 2010 were estimated based on mortality during 1940–1990 by the age-period-cohort (APC) model in (a) males and (b) females. ○, predicted; ●, observed.

death were a little lower than those observed. [Correction added on 11 October 2013, after first online publication: 'In females, by remarkable contrast, predicted numbers of death were a little higher than those observed' has been corrected to '. . . lower than observed'.] Thus, predicted HCC deaths in 2010 are 7093.1, corresponding to 84.7% of the 8374 observed. [Correction added on 11 October 2013, after first online publication: 'Thus, predicted HCC deaths in 2010 are 7093.1, corresponding to 118.1% of the 8374 observed' has been corrected to '. . . corresponding to 84.7% of the 8374 observed'.]

Predicted and observed numbers of sex- and age-specific HCC deaths in 2010, as well as differences between them, are given in Table 2. In males, observed HCC deaths were lower than those predicted through all age groups; observed HCC deaths accounted for 55.6–90.9% of those predicted. Likewise, in females aged 64 years or less, observed HCC deaths were lower than those predicted, and accounted for 21.1–99.4%. In females aged 65 years or more, on the contrary, observed HCC deaths were higher than those predicted, and corresponded to 115.1–132.7%.

Table 2 Comparison between predicted and observed number of deaths due to hepatocellular carcinoma in 2010

Sex and age	No. of deaths		
	Predicted	Observed	Ratio†
Male			
20–24	3.6	2	55.6%
25–29	7.5	5	66.7%
30–34	22.0	20	90.9%
35–39	64.5	40	62.0%
40–44	128.3	100	77.9%
45–49	261.4	229	87.6%
50–54	705.6	549	77.8%
55–59	1 984.4	1 258	63.4%
60–64	4 127.8	2 462	59.6%
65–69	4 266.0	2 993	70.2%
70–74	4 762.5	3 665	77.0%
75–79	6 677.7	4 752	71.2%
80–84	3 872.0	3 369	87.0%
Total	26 883.4	19 444	72.3%
Female			
20–24	2.9	1	34.5%
25–29	6.0	4	66.7%
30–34	17.8	6	33.7%
35–39	40.4	15	37.1%
40–44	71.1	15	21.1%
45–49	81.1	41	50.6%
50–54	153.8	80	52.0%
55–59	297.7	220	73.9%
60–64	599.3	596	99.4%
65–69	843.9	971	115.1%
70–74	1 312.3	1 606	122.4%
75–79	1 873.5	2 439	130.2%
80–84	1 793.4	2 380	132.7%
Total	7 093.1	8 374	118.1%

†Ratio = observed/predicted.

DISCUSSION

WE ANALYZED HCC mortality data by the APC model. Based on HCC deaths registered during 1940 through 2010 in Japan,[1] approximately 30 000 people died of HCC annually. According to hepatitis virus carrier rates among the first-time blood donors,[14] the peak frequency of hepatitis B surface antigen (HBsAg) was demonstrated by the 1941–1945 birth cohort, and the peak frequency of antibody to HCV by the 1931–1935 birth cohort. Hence, 1931–1935 birth years have the highest birth cohort effect in males with the APC model.

The national project for preventing mother-to-baby transmission of HBV was implemented in 1986 in Japan. As a result, the HBsAg positive rate among birth cohorts born after 1986 is extremely low at 0.04%.[15] In this study, birth cohorts born after 1986 were not subject to analysis and, therefore, we cannot evaluate the effect of the national immunoprophylaxis project by the APC model. However, we can reasonably expect that the birth cohort effect by the project will manifest itself in future analysis.

We applied the APC model to HCC mortality rate, and it reproduced the observed rate faithfully. However, in males, the observed mortality in 2010 is lower than the predicted mortality in 2010, which were calculated using data until 1990. This discrepancy would be a reflection of the introduction of new antiviral treatments and progress in surgical techniques since the 1990s, as well as the promotion of hepatitis virus screening and construction of clinical network between hospitals and clinics in each prefecture. On the contrary, in females, the observed number of HCC deaths in 2010 was a little higher than the predicted. The observed mortality of HCC would have increased because the female life expectancy was prolonged, and decompensated cirrhosis did not become the cause of death with progress of the treatment. In addition, it would reflect a lower response to interferon therapies

in women than men aged more than 50 years.[16] Furthermore, women may have fewer chances for receiving antiviral therapies than men. Also, we have demonstrated that the cumulative incidence of HCC increased with age of over 60 years in women, which is 10 years later than in men by the Markov model.[17] Another possibility is that effects of some factors, such as obesity, might have impacted especially women aged 65 years or more; they cannot be predicted by data before 1990 in Japan.

Comparison of HCC deaths predicted by the APC model with those observed demonstrates, for the first time, the impact of medical treatments for hepatitis and HCC in Japan and medical as well as control policies implemented by the Japanese government, including screening for HBV and HCV infections.[6,7] At the same time, the APC model is found to be limited in the application to predict HCC mortality in Japan since 2000.

The APC model examines mortality by three factors, and there are identification problems, such as "birth cohort = period – age". Thus, some methods have been invented to improve the application of the APC model to mortality data; effects of these methods are not in agreement, however. We employed the special structure in the birth cohort factor (Barrett's technique).[12] We accomplished a unique solution for each effect, but it may or may not be valid under another assumption.

Several limitations exist in this study. First, six time changes in the ICD codes might have influenced some effects, especially the period effect in the APC model. Second, we could not adjust confounding factors in applying the APC model, such as carrier rates of HBV and HCV infections; complete data on them are not available all through the studied period 1940–2010. Third, during this period, the difference of diagnostic ability might have influenced the analytic results obtained by the APC model. Finally, we must evaluate and discuss the results, keeping in mind the assumption of the birth cohort effect.

In conclusion, while the APC model is useful for reproducing observed HCC deaths, it would not be able to predict the mortality or incidence of the disease that can be influenced by medical intervention and prophylactic policies. In these regards, the present study does not only verify a high performance of the APC model in estimating HCC mortality, but also demonstrates the limitation of it in the application to disease that can be prevented by treatment or screening that keeps improving with time.

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APPENDIX I

Identification problem

THE AGE–PERIOD–COHORT (APC) model is constructed by three parts: (i) age factor; (ii) period factor; and (iii) birth cohort factor. However, three factors are not independent (birth cohort = period − age), so it has an "identification problem" in the methodology. For instance, let μ, A_i, P_j and C_k be one solution of the APC model, then

$$\mu^* = \mu,\ A_i^* = A_i - t(2i - I + 1)/2,\ P_j^* = P_j - t(2j - J + 1)/2,\ C_k^* = C_k - t(2k - K + 1)/2$$

is also the solution of the APC model for any number t. Thus, we cannot get a proper solution without some conditions.

There are several methods which overcome the identification problem. For example, Nakamura[18] proposed a Bayesian APC model, which assumes that the successive parameters should change gradually. Meanwhile, effects in each factor can have mathematically separate linear trend and curvature components. Based on this, Tango[19] suggested estimating only the calculable part that they designated "curvature components". On the other hand, Ohtaki *et al.*[20] or Kamo *et al.*[21] suggested an interaction model, which contains the age factor, period factor and interaction of the age and period factor, instead of the birth cohort factor.

APPENDIX II

Criteria of goodness of fit

USUALLY, DETERMINATION COEFFICIENT R^2 is used for simple and multivariate regression analysis because of assumption of variance. We used modified determination coefficient as below:[13]

$$R^2_{COR} = \frac{\left(\sum (r_{ij} - \bar{r})(\hat{r}_{ij} - \bar{\hat{r}})\right)^2}{\sum (r_{ij} - \bar{r})^2 \sum (\hat{r}_{ij} - \bar{\hat{r}})^2}$$

as criteria of goodness of fit, where r_{ij} means mortality, symbol "hat" means estimator and symbol "bar" means average. R^2_{COR} has a similar character with R^2 such as $0 \le R^2_{COR} \le 1$.

Special Report

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Report from a Viral Hepatitis Policy Forum on implementing the WHO framework for global action on viral hepatitis in North Asia

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Background & Aims: The World Health Organisation (WHO) Prevention & Control of Viral Hepatitis Infection: Framework for Global Action offers a global vision for the prevention and control of viral hepatitis. In October 2012, the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP) organised the North Asia Workshop on Viral Hepatitis in Taipei to discuss how to implement the WHO Framework in the North Asia region. This paper presents outcomes from this workshop.

Methods: Twenty-eight representatives from local liver associations, patient organisations, and centres of excellence in Hong Kong, Japan, Korea, and Taiwan participated in the workshop.

Findings: Priority areas for action were described along the four axes of the WHO Framework: (1) awareness, advocacy and resources; (2) evidence and data; (3) prevention of transmission; and (4) screening and treatment. Priorities included: axis 1: greater public and professional awareness, particularly among primary care physicians and local advocacy networks. Axis 2: better economic data and identifying barriers to screening and treatment uptake. Axis 3: monitoring of vaccination outcomes and targeted harm reduction strategies. Axis 4: strengthening links between hospitals and primary care providers, and secure funding of screening and treatment, including for hepatocellular carcinoma.

Conclusions: The WHO Framework provides an opportunity to develop comprehensive and cohesive policies in North Asia and the broader region. A partnership between clinical specialists, primary care physicians, policy makers, and people with or at risk of viral hepatitis is essential in shaping future policies.

Keywords: Hepatitis B; Hepatitis C; Asia; Policy.
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Introduction

In 2012, the World Health Organisation (WHO) launched the *Prevention & Control of Viral Hepatitis Infection: Framework for Global Action*. This strategy offers a global vision for the prevention and control of viral hepatitis [1]. The Framework was welcomed by hepatitis experts and advocacy groups who have been struggling for the attention of policymakers about this 'silent epidemic' for many years [2,3].

Asia is home to 75% of all chronic hepatitis B cases [4] and China alone has more cases of hepatitis C infection than all of Europe or the Americas [5]. The majority of people infected with either hepatitis B virus or hepatitis C virus do not know that they are infected, and are not aware of the precautions they need to take to avoid infecting others or to enable them to reduce the impact of the infection [6]. Uptake of screening, when available, is low, and treatment rates are 4–10% in Asia compared to rates of 20% in the United States [7].

Against this background, the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP) was established in 2010 to contribute towards an Asia Pacific region free from the significant health, social and economic burden of viral hepatitis (www.cevhap.com). CEVHAP is uniquely positioned to support and facilitate the implementation of the WHO framework in different countries across the region through its network of members who are experts in their respective fields in the Asia Pacific region and globally.

In October 2012, CEVHAP organised the North Asia Workshop on Viral Hepatitis in Taipei, with participants from Hong Kong, Japan, Korea, and Taiwan. These four jurisdictions were chosen because, to varying degrees, they have some initiatives in place