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Original Article

Estimated numbers of patients with liver disease related to hepatitis B or C virus infection based on the database reconstructed from medical claims from 2008 to 2010 in Japan

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Aim: To estimate the number of patients with liver-related diseases classified by hepatitis viruses (HBV, HCV) based on the information from re-coded medical claims including several diagnosed diseases.

Methods: We analyzed reimbursement data provided by health insurance societies for 2.1 million individuals during 2008–2010. Database information of employees and their families aged under 65 years employees with hepatitis-related disease was extracted, the 1-year period prevalence was calculated, and then number of patients with liver disease related to HBV and HCV by sex and age groups, respectively, was estimated.

Results: The estimated number of patients were almost equivalent during 2008–2010. As for HBV and HCV, the estimated numbers of patients with chronic hepatitis (CH) in a year ranged 192 641–226 601 and 282 438–306 877, respectively.

Conclusion: In the 2008 Patient Survey in Japan, the number of patients was estimated by the main disease in one patient, even though the patient was diagnosed with several diseases. Based on the database with hepatitis-related diseases after evaluating several diagnosed diseases from medical claims, the estimation method and protocol may minimize the disadvantage of medical claim analysis, and is useful for patients, especially asymptomatic carriers and those with CH which had been underestimated in the 2008 Patient Survey.

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC), from which more than 30 000 individuals die annually, has become the fourth leading cause of death due to cancers in Japan.[1] The main etiology of HCC is persistent infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). Natural courses of hepatitis virus carriers consist of asymptomatic carrier state (AC), chronic hepatitis (CH), liver cirrhosis (LC) and HCC. Thus, it is necessary to estimate the number of patients in each stage from the view of refining public health and improving the medical economy through cost-effectiveness analysis.

Some attempts have been made for estimating the numbers of patients with liver disease. Tanaka *et al.*[2] estimated the numbers of HBV and HCV carriers who were not aware of their infection to be 903 000 and 808 000, respectively, in Japan as of 2005. On the other hand, the 2008 Patient Survey[3] estimated the number of emergency patients with hepatic disease (HBV, HCV, neoplasms of liver and intrahepatic bile duct, CH [alcoholic disease excluded], and LC [alcoholic disease excluded]) to be 511 000.

"Patient survey" is one of the methods used in Japan to estimate the number of patients for all diseases. However, the number of patients by patient survey may be considered to be underestimated. Even though patients may be diagnosed with several diseases, by patient survey the estimation is calculated by one main disease in each patient Moreover, the number of patients with chronic liver-related diseases may be underestimated because in patient

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surveys the number of patients estimated are those whose interval visit is under 30 days,

In Japan, the National Health Insurance Act was launched in 1958, and the National Health Service was started in 1961. Thus, practically all Japanese participate in some sort of insurance system and part of their medical payment is refunded if and when they get sick or injured. The examination for remuneration is executed by the committee's medical experts, based on the Health Insurance Act, ordinance for medical treatment, a list of medical treatment fees and various other notifications. Therefore, the medical claims from insurance policies are regarded as a powerful tool with sufficient reliability for estimating the number of patients with any specific disease, in case the tentative diagnosis only for the clinical laboratory examination was excluded completely or the discrepancy between diagnosed disease on medical claim and International Classification of Diseases (ICD) classification were adjusted properly.

In the case of estimating patients with liver disease, it is necessary to look upon both disease categories (e.g. acute hepatitis, CH, LC) and etiologies of hepatitis viruses (i.e. HBV and HCV). However, one liver disease does not always correspond to one specific disease name in the medical claims. Therefore, it is difficult to estimate the numbers of patient with hepatic disease using medical claims alone.

In this study, we estimated the number of patients with liver-related diseases based on the information of re-coded medical claims including several diagnosed diseases.

METHODS

STUDY SUBJECTS WERE medical claims from employees, as well as their family members, who belonged to 20 business institutions with nationwide branches throughout Japan and subscribed to occupational health insurance societies. In this study, the data was obtained from a database company (The Japan Medical Data Center: JMDC) and already consolidated anonymously. The target period was 3 years, from January 2008 to December 2010, and the numbers of individuals were 582 922 in 2008, 757 051 in 2009 and 787 075 in 2010. The ages of the individuals surveyed ranged 0–99 years (before March 2008) and 0–74 years as of April 2008 when the medical insurance system for the elderly aged 75 or over was started. Age distributions of study subjects and Japanese population are shown in Figure 1.

The number of patients was estimated as follows:

1 In one medical claim for one patient per 1 month in each hospital/clinic, several diagnosed diseases are described. We extracted all medical claims in which hepatitis-related diseases (listed in Table 1) are described among several diagnosed diseases and we set the database with ID codes without personal identification.
2 We extract all medical claims from those aged under 65 years.
3 We excluded all medical claims with suspect diagnoses, including those cases diagnosed by laboratory examination on the basis of documented information of the treatment and the prescribed medicine.
4 All medical claims were sorted by consulting date in each patient for 3 years.
5 We re-coded only liver-related disease of listed diseases (Table 2) for every year in each patient considering the transition of disease, treatment and prescription of medicine.
6 We calculated 1-year prevalence classified by liver-related diseases, sex and age group.

The flowchart for estimating the number of patients is showed in Figure 2.

We also excluded cases of fatty liver, primary biliary cirrhosis, drug-induced hepatitis and liver injury, alcoholic

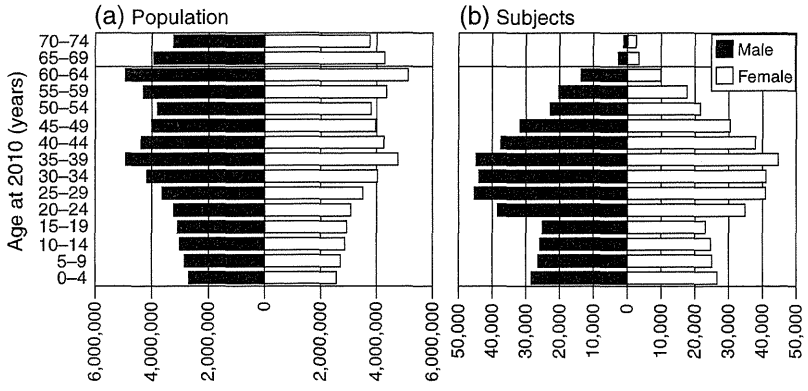

Figure 1 Age distributions of the Japanese population and study subjects. Sex-specific age distributions of the Japanese population and study subjects at 2010 are shown. (a) Japanese population. (b) Subjects.

Table 1 International Classification of Diseases (ICD)-10 classification that target extracts in this study

ICD-10 code	Disease
B15	Acute hepatitis A
B16	Acute hepatitis B
B17	Other acute viral hepatitis
B18	Chronic viral hepatitis
B19	Unspecified viral hepatitis
C22	Malignant neoplasm of liver and intrahepatic bile ducts
K70	Alcoholic liver disease
K71	Toxic liver disease
K72	Hepatic failure, not classified elsewhere
K73	Chronic hepatitis, not classified elsewhere
K74	Fibrosis and cirrhosis of liver
K75	Other inflammatory liver diseases
K76	Other diseases of liver
K77	Liver disorders in diseases classified elsewhere
Z22.5	Carrier of infectious disease

hepatitis and liver injury, autoimmune hepatitis and cirrhosis, and liver cancer aside from HCC.

We tallied patient numbers of each disease listed in Table 2, and calculated sex- and age-specific 1-year period prevalence using the number of the patients divided by the number of subscribers under 65 years as follows: let X_{ij} be a number of patients and N_{ij} be a sample size of population in (i, j)-th group, where i is index of age group ($i = 1$ for 0–9 years, $i = 2$ for 10–19 years, ..., $i = 7$ for 60–64), j is index of sex ($j = 1$ for male and $j = 2$ for female); then, estimated prevalence becomes:

$$r_{ij} = \frac{X_{ij}}{N_{ij}}$$

If $X_{ij} = 0$, the 95% confidence interval can be obtained as follows:

$$\left[0, \frac{\chi_2^2(0.025)}{2N_{ij}}\right]$$

where $\chi_2^2(0.025)$ is upper 2.5% point of χ^2-test distribution with degrees of freedom 2. Otherwise, the 95% confidence interval can be obtained as:

$$r_{ij} \pm 1.96\sqrt{\frac{r_{ij}(1 - r_{ij})}{N_{ij}}}$$

Then, we estimated the numbers of patients in Japan by means of multiplying the 1-year period prevalence estimated based on the information of re-coded medical claims by corresponding sex and age in the Japanese population, with the formula:

$$\sum_{j=1}^{2}\sum_{i=1}^{7} r_{ij} \times p_{ij}$$

where r_{ij} is 1-year prevalence of AC, CH, LC and HCC, and p_{ij} is population. Let $[l_{ij}, u_{ij}]$ be each 95% confidence interval of prevalence of (i, j)-th group. We simply calculated the 95% confidence interval of number of patients by sum product of upper or lower confidence limit and population, that is:

$$\left[\sum_{j=1}^{2}\sum_{i=1}^{7} l_{ij} \times p_{ij}, \sum_{j=1}^{2}\sum_{i=1}^{7} u_{ij} \times p_{ij}\right]$$

Table 2 Reclassified disease

	Reclassified disease
Subjects in this study	HBV-related asymptomatic carrier state
	HCV-related symptomatic carrier state
	HBV- and HCV-related asymptomatic carrier state
	Other asymptomatic carrier states
	HBV-related chronic hepatitis
	HCV-related chronic hepatitis
	HBV- and HCV-related chronic hepatitis
	Other chronic hepatitis
	HBV-related liver cirrhosis
	HCV-related liver cirrhosis
	HBV- and HCV-related liver cirrhosis
	Other liver cirrhosis
	HBV-related hepatocellular carcinoma
	HCV-related hepatocellular carcinoma
	HBV- and HCV-related hepatocellular carcinoma
	Other related hepatocellular carcinoma
	HBV-related acute hepatitis
	HCV-related acute hepatitis
	HBV- and HCV-related acute hepatitis
	HAV-related acute hepatitis
	HEV-related acute hepatitis
	Other acute hepatitis
Excluded diseases	Fatty liver
	Primary biliary cirrhosis
	Drug-induced hepatitis and liver injury
	Alcoholic hepatitis and liver injury
	Autoimmune hepatitis and liver cirrhosis
	Liver cancer other than HCC

HAV, hepatitis A virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HEV, hepatitis E virus.

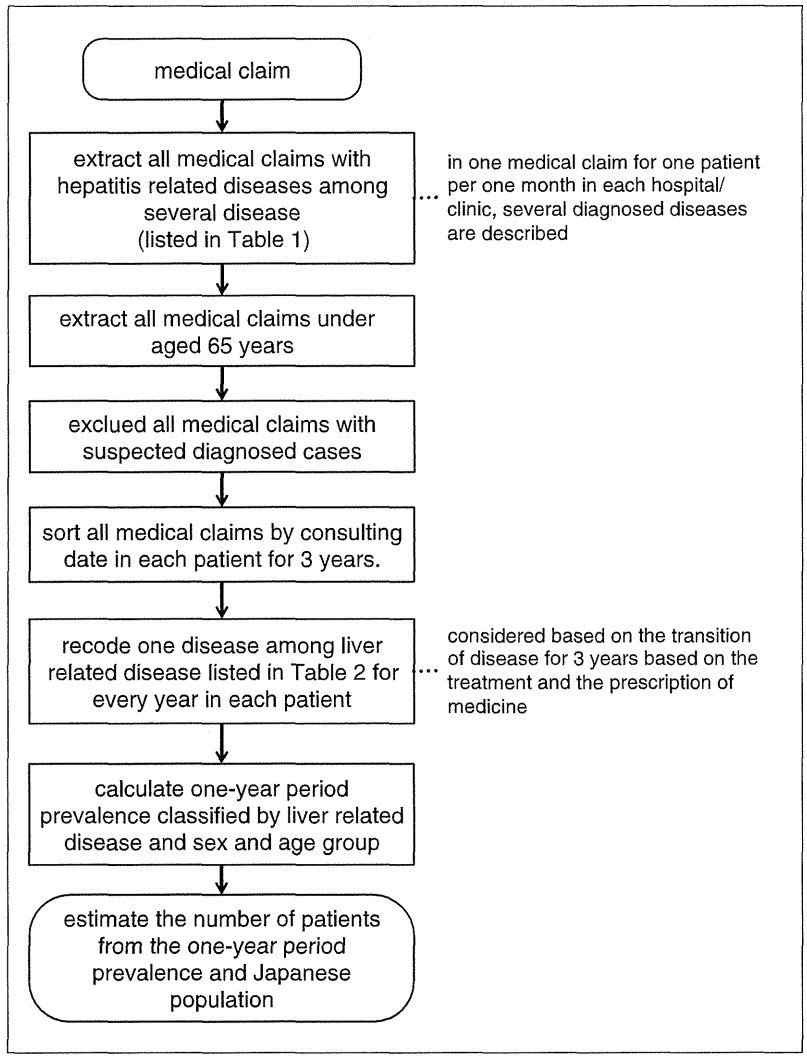

Figure 2 Flowchart of outline to estimate the number of patients.

In this study, the data is obtained from a database company (JMDC) with consolidated anonymity. This study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Medical claims for patients with liver disease

OF STUDY SUBJECTS, there were 34 998 medical claims for 10 277 patients with liver disease among 4 126 951 medical claims for 575 658 patients in total (aged 0–64 years) from January to December 2008; 55 144 medical claims for 15 605 patients with liver disease among 5 982 748 medical claims for 756 494 patients in total (aged 0–64 years) from January to December 2009; and 56 848 medical claims for 16 336 patients with liver disease among 6 174 598 medical claims for 777 417 patients in total (aged 0–64 years) from January to December 2010 (Table 3). The numbers of medical claims excepting suspected diagnosis were 27 602 medical claims for 5190 patients from January to December 2008; 43 770 medical claims for 8016 patients from January to December 2009; and 44 260 medical claims for 7930 patients from January to December 2010. The numbers of target patients in 2008, 2009 and 2010 were 4206, 6514 and 6255 by

Table 3 Medical records for estimating number of patients with liver disease

	2008		2009		2010		2008–2010	
	No. of patients	No. of receipts	No. of patients	No. of receipts	No. of patients	No. of receipts	Total no. of patients	Total no. of receipts
Subscriber	582 922	4 282 666	757 051	6 175 319	787 075	6 370 144	2 127 048	16 828 129
Subscriber aged under 65 years	575 658	4 126 951	756 494	5 982 748	777 417	6 174 598	2 109 569	16 284 297
With liver disease[†]	10 277	34 998	15 605	55 144	16 336	56 848	42 218	146 990
Except for suspected diagnosis	5190	27 602	8016	43 770	7930	44 260	21 136	115 632
Reclassified[‡]	4206		6514		6255		16 975	

[†]With International Classification of Diseases (ICD) codes listed in Table 1.
[‡]Patients with reclassified disease.

reclassification on 27 602, 43 770 and 44 260 medical claims, respectively.

One-year period prevalence

The age-specific 1-year period prevalence (in cases/100 000) of AC, patients with CH, LC and HCC were calculated for patients infected with HBV or HCV (Figs 3,4). Additionally, the age-specific 1-year period prevalence of AH was estimated for patients infected with hepatitis A virus (HAV), HBV or HCV (Fig. 5).

HBV

In comparison, no significant difference was observed in the 1-year period prevalence of each clinical entity among all age groups across 3 years, except for women aged 20–29 years with HBV-related CH (Fig. 3). In comparing the age groups in males, we found that the 1-year period prevalence of CH, LC and HCC increased with age. Likewise, for females, the 1-year period prevalence of CH and LC also increased in parallel with age. In both men and women, the 1-year period prevalence of AC among those aged 0–9 years was higher than those aged 10–19 years and 20– 29 years; they ranged 7.5–16.3/100 000 persons in males and 7.8–22.3/100 000 persons in females during the 3 years of survey.

HCV

In comparison of the 1-year period prevalence of each disease entity across 3 years, no significant difference was observed among all age groups, except for patients with HCV-related CH in men aged 40–49 years. The 1-year period prevalence of AC among each age group was low at 0–11.8/100 000 persons. In contrast, the 1-year period prevalence of CH, LC and HCC increased with age.

Acute hepatitis

In comparing the 1-year period prevalence of acute hepatitis, there was no difference in HAV, HBV and HCV patients across the age groups and throughout the 3 years. Particularly, the 1-year period prevalence of acute hepatitis C was low at 0–2.1/100 000 persons.

Estimated number of patients

Based on the age- and sex-specific 1-year prevalence of liver disease and the Japanese population during the 3 years from 2008 to 2010, the numbers of persons aged under 65 years with AC, patients with CH, LC, HCC as well as AH were estimated (Fig. 6, Table 4).

Persistent HBV infection

The estimated number of patients with persistent HBV infection was 248 229–287 350. Of these, 29 086–29 950 were AC; 192 641–226,601 had CH, 9498–12 485 had LC and 14 569–19 155 had HCC. Among patients with persistent HBV infections, those with CH accounted for 77.6–79.1%. Stratified by sex and age, the estimated numbers of patients aged 30–39 years and over, both in males and females, were greater than 10 000 (Fig. 5). Particularly, the estimated numbers of patients with HCC remained constant at zero in both men and women aged under 29 years; and over 4000 among males aged above 50 years.

Persistent HCV infection

The estimated number of patients with persistent HCV infection ranged 318 900–343 798 over the 3 years. Of those, 2006–2635 were AC, 282 438–306 877 had CH, 14 830–17,511 had LC and 14 775–19,528 had HCC. Among patients with persistent HCV infections, chronic hepatitis accounted for 88.6–90.3%. Stratified by sex and age, the

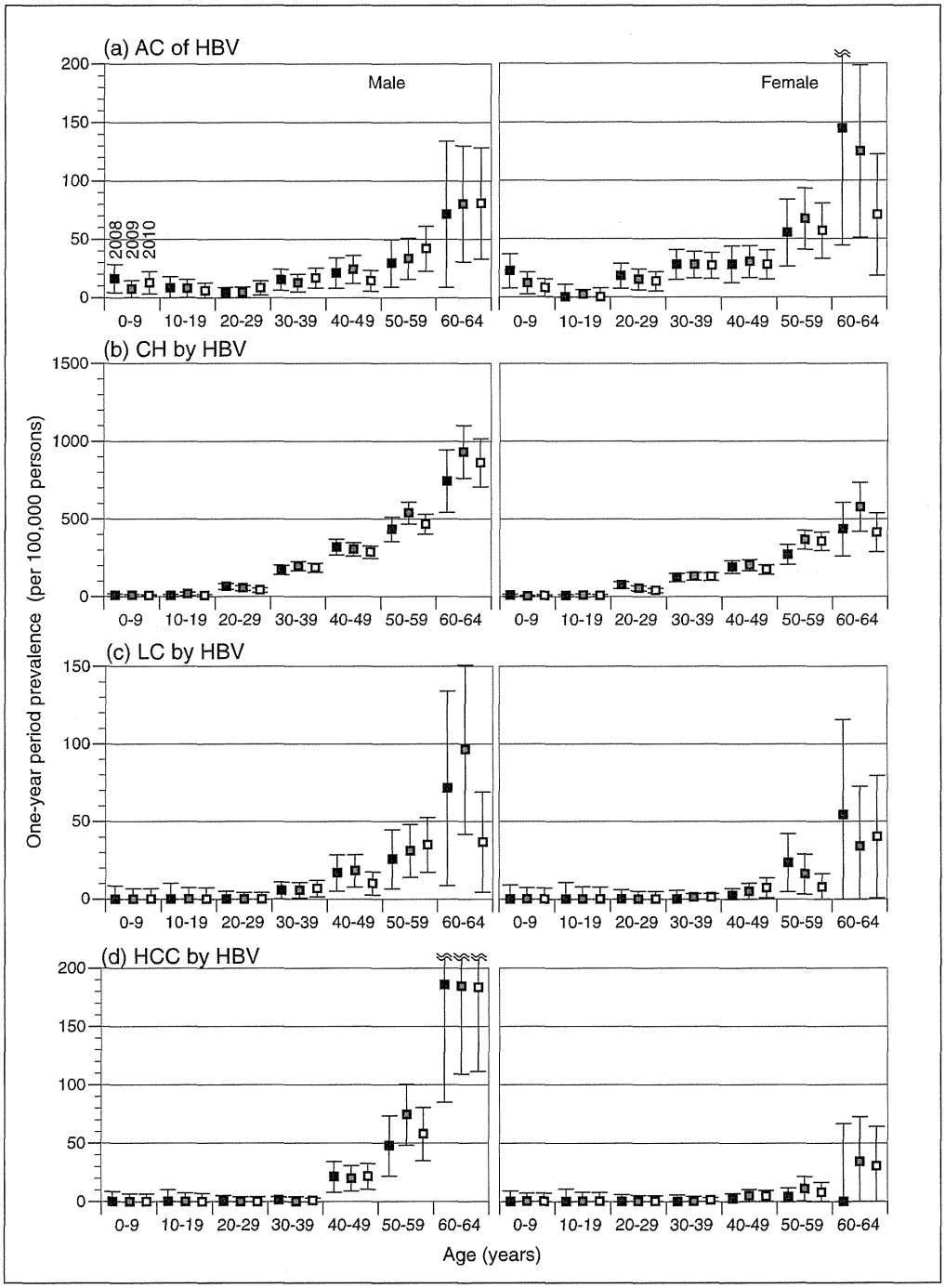

Figure 3 Prevalence of liver diseases associated with hepatitis B virus (HBV) infection. Sex- and age-specific prevalence (per 100 000 persons) of liver diseases at 2008, 2009 and 2010 are shown. Each square and bar represent an estimator of prevalence and its 95% confidence interval. (a) Asymptomatic carriers (AC). (b) Chronic hepatitis (CH). (c) Liver cirrhosis (LC). (d) Hepatocellular carcinoma (HCC).

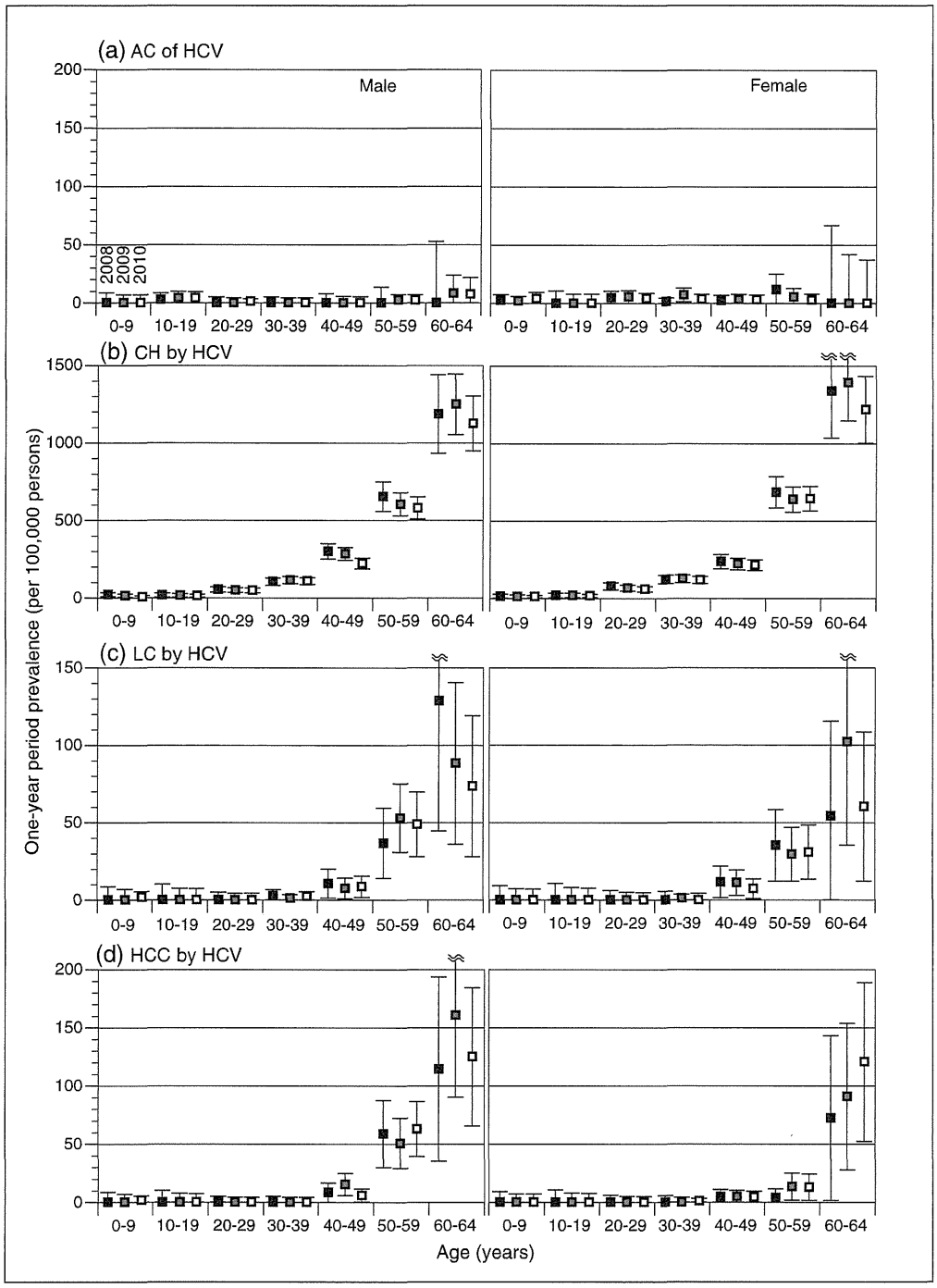

Figure 4 Prevalence of liver diseases associated with HCV infection. Sex- and age-specific prevalence of liver diseases at 2008, 2009 and 2010 are shown. Each square and bar represent an estimator of prevalence and its 95% confidence interval. (a) Asymptomatic carriers (AC). (b) Chronic hepatitis (CH). (c) Liver cirrhosis (LC). (d) Hepatocellular carcinoma (HCC).

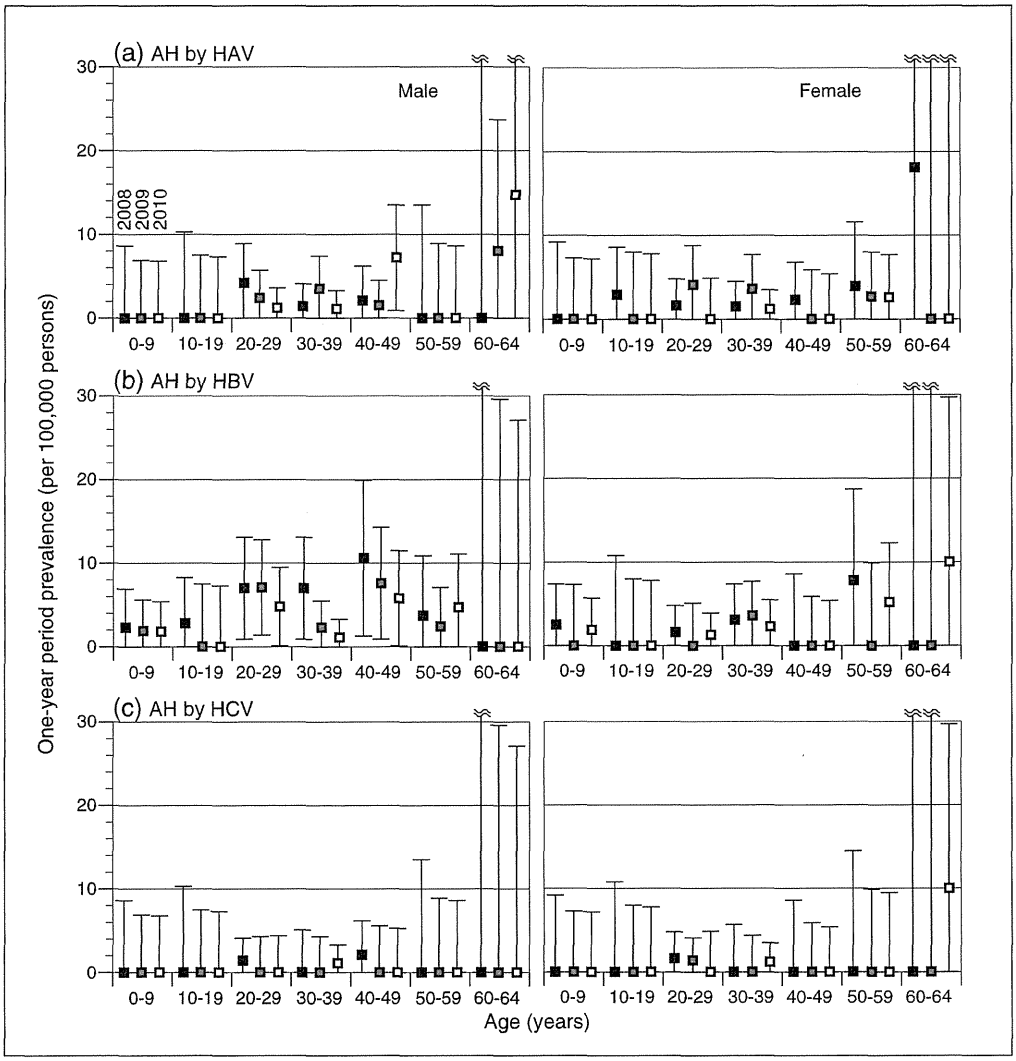

Figure 5 Prevalence of acute hepatitis. Sex- and age-specific prevalence of acute hepatitis at 2008, 2009 and 2010 are shown. Each square and bar represent an estimator of prevalence and its 95% confidence interval. (a) Acute hepatitis by HAV. (b) Acute hepatitis by HBV. (c) Acute hepatitis by HCV.

estimated number of patients aged 30–39 years and over, both in males and females, was more than 10 000 (Fig. 6). Particularly, the estimated numbers of patients with HCC stayed constant at zero in both men and women among those aged under 29 years, and over 2000 among males aged above 50 years.

Persistent HBV or HCV infections, or other etiologies

The estimated total number of patients with persistent HBV or HCV infection, as well as those of unknown etiologies, was 1 123 846–1,262,022 (Table 4). Of them, 27 966–31 635 were AC, 997 442–1 117 944 had CH, 52 659–60 815 had LC and 37 773–51 610 had HCC. Among persistent HBV or HCV infections, CH accounted for 88.6–89.0%.

Patients with AH

The estimated number of acute hepatitis A, acute hepatitis B and acute hepatitis C cases was 1800–2397, 1961–3837 and 93–720, respectively (Table 4).

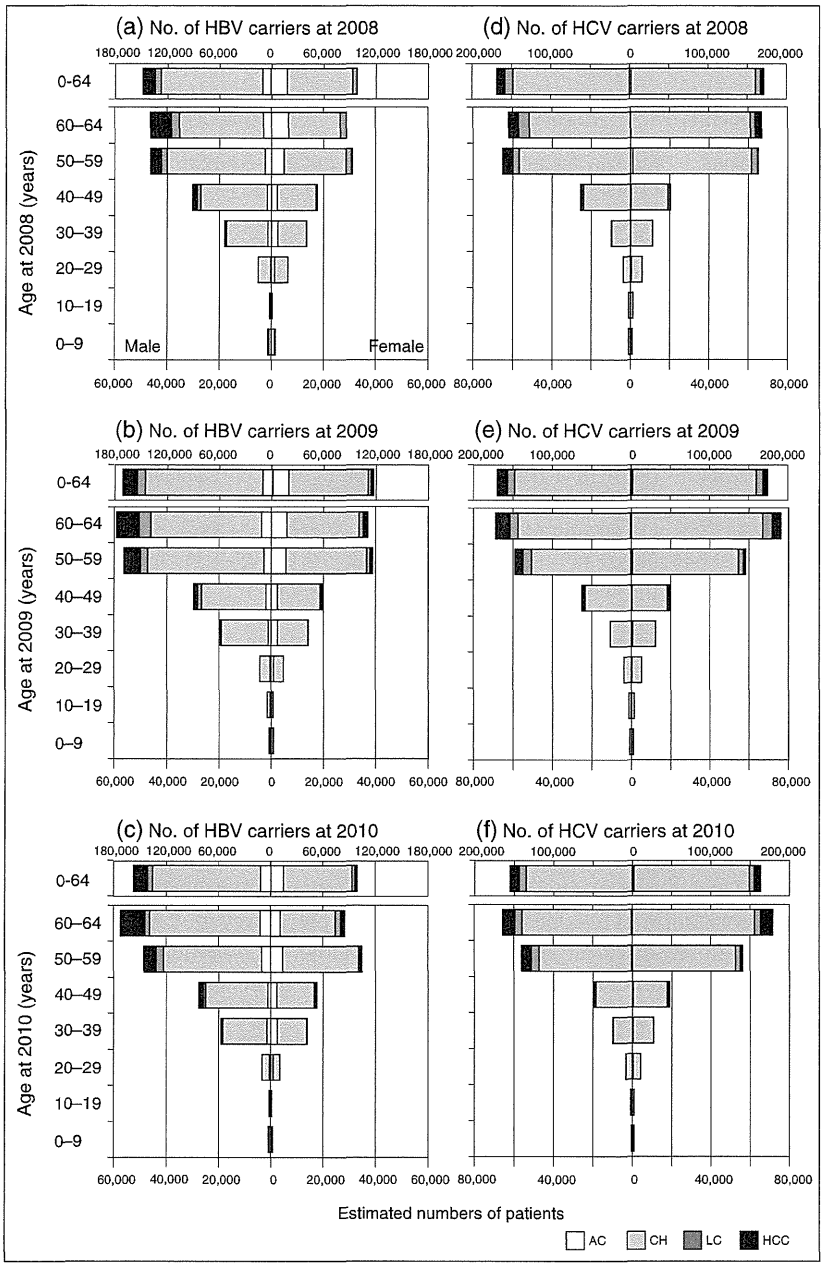

Figure 6 Number of persons who carried hepatitis B virus (HBV) or hepatitis C virus (HCV). Sex- and age-specific distributions of HBV or HCV are shown. (a) Number of HBV carriers at 2008. (b) Number of HBV carriers at 2009. (c) Number of HBV carriers at 2010. (d) Number of HCV carriers at 2008. (e) Number of HCV carriers at 2009. (f) Number of HCV carriers at 2010. (a) AC, asymptomatic carriers; CH, chronic hepatitis; HCC, hepatocellular carcinoma; LC, liver cirrhosis.

DISCUSSION

BECAUSE OF THE paucity of subjective symptoms, persons persistently infected with HBV and HCV are either undiagnosed or diagnosed. Tanaka *et al.* previously estimated that 903 000 asymptomatic carriers were persistently infected with HBV and 808 000 asymptomatic carriers were persistently infected with HCV. They all were

Table 4 Estimated number of patients under 65 years

		2008		2009		2010	
		Patients	(95% CI)	Patients	(95% CI)	Patients	(95% CI)
HBV-related chronic liver disease†	AC	29 086	(10 186–61 435)	29 109	(13 354–53 427)	25 950	(11 579–48 925)
	CH	192 641	(139 823–250 594)	226 601	(177 234–277 366)	203 278	(158 453–249 952)
	LC	11 933	(1420–38 051)	12 485	(3501–31 265)	9498	(1520–27 593)
	HCC	14 569	(5879–42 267)	19 155	(9090–39 895)	18 340	(8599–37 368)
	Total	248 229	(194 727–301 864)	287 350	(240 013–334 686)	257 065	(213 777–300 402)
HCV-related chronic liver disease†	AC	2006	(0–27 012)	2635	(127–18 621)	2104	(0–17 023)
	CH	306 877	(239 614–378 855)	305 028	(247 709–363 663)	282 438	(229 413–337 131)
	LC	16 376	(3 637–44 398)	17 511	(6 734–37 971)	14 830	(5 003–34 774)
	HCC	14 755	(3 958–41 904)	18 624	(7 818–39 892)	19 528	(8 639–39 470)
	Total	340 014	(276 789–403 239)	343 798	(291 539–396 058)	318 900	(270 065–367 735)
HBV-related or HCV-related or other chronic liver disease†	AC	31 092	(11 542–50 914)	31 653	(15 244–48 158)	27 966	(12 946–43 103)
	CH	997 442	(890 019–1 104 865)	1 117 944	(1 024 775–1 211 113)	1 046 460	(958 453–1 134 468)
	LC	57 538	(32 137–83 372)	60 815	(39 327–82 600)	52 659	(33 138–72 413)
	HCC	37 773	(19 692–59 197)	51 610	(34 066–71 334)	48 762	(31 764–67 355)
	Total	1 123 846	(1 009 469–1 238 222)	1 262 022	(1 162 905–1 361 138)	1 175 847	(1 082 365–1 269 330)
Acute hepatitis A		2379	(0–11 875)	1800	(0–9379)	1830	(75–9352)
Acute hepatitis B		3837	(247–15 275)	1961	(178–10 471)	2726	(16–9374)
Acute hepatitis C		385	(0–12 831)	93	(0–8917)	720	(0–8108)

†Including patients co-infected with HBV and HCV.
AC, asymptomatic carriers; CH, chronic hepatitis; CI, confidence interval; HCC, hepatocellular carcinoma; LC, liver cirrhosis.

identified as first-time blood donors during 2005 in Japan, and were unaware of their infections.

In this study, we estimated the number of patients who have already been diagnosed with hepatitis virus infections by analysis based on the information of re-coded medical claims including several diagnosed diseases. The medical claim is a claim from health-care facilities sent to insurance companies or the government upon payment for medical treatment which the patient has actually received. On a medical claim, for each insured patient, there is information about the patient including name, sex and date of birth, and health insurance details, together with monthly basic information of the health-care facility in which the original medical claim was made, including the name of the institution, department, disease name, number of prescriptions every month, and treatment received such as injections, medication, surgery, medical examination, imaging diagnosis and rehabilitation.

The JMDC is commissioned by the Health Insurance Society, an insurance society in Japan including approximately 25% of the entire Japan population. The JMDC has a database of health insurance medical claims, and the anonymous data are available to third parties which have a contract with the Health Insurance Society.[4] An advantage of the analysis using medical claims is that all medical information of patients belonging to the Health Insurance Society, including even their family members, is available. Because Japan has universal health insurance, practically all Japanese have joined the public health insurance scheme. Another advantage is that this study was not a sample survey but a complete enumeration of data. Therefore, the time-dependent changes in classified disease were able to be identified and dealt with accordingly.

However, generally, the results of laboratory tests and treatments were described in the medical claim, while various expressions of the name of disease might have been problematic. Also, because of the limitation of classification of diseases and the standards of insurance coverage, various expressions of the disease might have been used to indicate the same pathological condition. Thus, the number of patients could not be estimated by using the medical claim database itself.

However, in this study, based on the information of drugs and treatments retrieved from each patient's medical claim, and the natural course of their disease, a decision on the disease reclassification was made on discussions with specialists including two hepatologists. On the basis of these data, the numbers of patients with liver disease were subsequently estimated. As a result, the estimated numbers of patients under 65 years with persistent hepatitis virus infections including those with unidentified viruses were 1 123 846–1 262 022. These figures were twice that

of the estimated numbers of patients infected with hepatitis viruses. We could not recognize the transition of patients because of our short study period, but we could still distinguish between AC and CH during a follow-up period of several months to 1 year.

So far, there have been several reports analyzing medical payment records (medical claims).[5–11] Many studies of medical claims estimated the health-care costs.[12–18] There were a few reports using the medical claim database with small sample sizes for estimating the numbers of patients with other diseases such as measles,[6] acute hepatitis morbidity,[7] diabetes[8] and arthritis.[9]

On the other hand, "patient surveys", which are held every 3 years, are only to estimate the number of patients in Japan. In patient surveys, the number of patients is estimated based on the number of inpatient and outpatient visits to clinics or hospitals in 1 day out of 3 days in October, which are randomly selected from hospitals all over Japan. In case of estimation of hepatic disease, results from patient surveys may be an underestimation caused by two factors. First, a primary disease is only counted for one patient. Second, a patient whose interval between visits to clinics and hospitals is 31 days or over is excluded from the survey. The number of patients in the 2008 Patient Survey is shown in Table 5. The numbers of patients with HBV-related chronic liver disease and HCV-related chronic liver disease in this study were 192 641 and 306 877, respectively. The numbers of patients with HBV-related chronic liver disease and HCV-related chronic liver disease in the 2008 Patient Survey was 52 000 and 260 000, respectively. These results indicate that the number of patients in our study with AC or CH is estimated to be higher even under 65 years than in the 2008 Patient Survey in all ages.

Moreover, in this study we also estimated the number of patients with acute hepatitis. According to the Infectious Disease Surveillance Center (IDSC) in Japan during each year from 2008 to 2010, numbers of patients with acute hepatitis A, acute hepatitis B and acute hepatitis C were reported by medical doctors as 115–347, 174–178 and 39–52, respectively. It is regrettably said that the reported number from mandatory surveillance system could only account for 10% of cases of acute hepatitis. Estimates in this study counted 10–30 times of the reported number from the IDSC. On the other hand, along with the incidence rate of HCV infection among blood donors during the 10 years between 1994 and 2004 in Hiroshima, Japan, calculated as 1.86/100 000 person-years,[19] approximately 3335 (95% confidence interval, 483–20 866) of persons newly infected with HCV without symptoms could be estimated in a year. Thus, to prevent the outbreak of infectious diseases, it seems necessary to be aware of the fact that physicians are obligated to notify the IDSC whenever they diagnose AH according to the Law of Infectious Disease in Japan.

There are limitations in this study. First, we only estimated the number of patients aged under 65 years. However, because the onset of HCC and LC occur more frequently in persons aged over 65 years, considering the number of patients with HCC and LC of all ages, the estimated numbers of HCC and LC in our study may appear to be small. On the other hand, the number of patients with LC and HCC from patient survey may be supplemented in the estimation over 65 years, because patients with LC and HCC are consulted mostly. Second, there are some issues on the validity of the disease on the medical claims; that is, sometimes medical claims are only for clinical laboratory examination fee remuneration from insurance, and there are discrepancies between diagnosed disease on medical claims and ICD classification.

Table 5 Number of patients in the 2008 Patient Survey and infection surveillance in the Infectious Disease Surveillance Center (IDSC)

		No. of patients		
Survey	Disease (ICD)	2008	2009	2010
2008 Patient Survey	Malignant neoplasm of liver and intrahepatic bile ducts (C22)	66 000	–	–
	Liver cirrhosis (K74.3–K74.6)	59 000	–	–
	Chronic hepatitis (K73)	74 000	–	–
	Disease of liver† (K70-K77)	247 000	–	–
	Hepatitis B virus (B16–B17.0 B18.0–B18.1)	52 000	–	–
	Hepatitis C virus (B17.1 B18.2)	260 000	–	–
Infection surveillance in IDSC	Acute hepatitis A	169	115	347
	Acute hepatitis B	178	178	174
	Acute hepatitis C	52	40	39

†"Disease of liver" contains "liver cirrhosis" and "chronic hepatitis".

However, the medical claims from insurance policies are regarded as a powerful tool with sufficient reliability for estimating the number of patients with any specific disease, in cases where the tentative diagnosis from only clinical laboratory examination were excluded completely or the discrepancy between diagnosed disease on medical claim and ICD classification were adjusted properly. We determined the specific disease by constructing a theoretical flowchart for calculation and evaluating time series medical claims sorted by case ID for 3 years. This estimation method and protocol minimized the disadvantage of medical claim analysis. Thus, it should be noted that the estimates calculated in this study are possible to estimate the number of patients aged 64 years or younger precisely. Furthermore, because the number of subjects aged 60–64 years is small, the 95% confidence interval of estimated number of patients in this population ranged widely. Finally, there is a limitation of healthy worker bias. Because the estimation in this study was based on the information of re-coded medical claim of employees and their families in only 20 health insurance associations, the estimated number may be underestimated.

According to our analysis, the estimated numbers of patients aged under 65 years who have already been diagnosed with liver disease caused by HBV or HCV excluding duplicated cases were 563 688–617 421, and those caused by HBV, HCV or other chronic liver disease were 1 123 846–1 262 022. On the other hand, the estimated number of patients with undiagnosed HBV or HCV infection among first-time blood donors aged 15–69 years in 2005 was 905 397. In addition, there may be many carriers who have never been consulted or who have not been continuously treated in spite of awareness of their infection. Taken together, it is supposed that the total number of patients with liver disease is much higher than the estimated number in patients under 65 years of age. In patient survey in Japan, the number of patients is estimated by the main disease in one patient even though the patient has been diagnosed with several diseases. Based on the database with hepatitis-related diseases after evaluating several diagnosed diseases from medical claims, the estimation method and protocol may minimize the disadvantage of medical claim analysis, and are useful for patients especially with AC and CH which had been underestimated by patient survey.

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Hepatology Research

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Original Article

Hepatitis B virus infection in hemodialysis patients in Japan: Prevalence, incidence and occult hepatitis B virus infection

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Aim: A survey of hepatitis B virus (HBV) infection in hemodialysis (HD) patients was conducted to determine the burden and risk of infection and to suggest preventive measures against HBV infection among HD patients at nine hospitals in Hiroshima, Japan, from 1999 to 2003.

Methods: HBV markers were investigated for 1860 HD patients. The prevalence, incidence of HBV and prevalence of occult HBV were calculated.

Results: The prevalence of hepatitis B surface antigen (HBsAg) was 2.6%, the positive rate of anti-hepatitis B core (HBc) was 20.6% and that of anti-hepatitis B surface (HBs) was 11.7%. Among 1372 patients who started HD after the approval of erythropoietin in Japan in 1991, the prevalence of HBsAg was 2.1%. The incidence rate of HBsAg positivity was 0/1000 person-years and the incidence of anti-HBc was 0.3/1000 person-years. Among 1812 HBsAg negative patients HBV DNA was detected in two: one case was negative for anti-HBc and anti-HBs, and the other was only positive for anti-HBc. Prevalence of occult HBV was 0.11%.

Conclusion: The incidence rate of HBV was much lower than that of hepatitis C virus (HCV) in the same cohort. We supposed that the discrepancy between incidence rate of HBV and that of HCV was caused by the difference of their carrier rates and of their characteristics for persistent infection. So, we concluded that it is prerequisite to grasp the burden of HBV carriers in the group to prevent new HBV infections in HD patients.

Key words: hemodialysis, hepatitis B virus, incidence rate, occult hepatitis B virus, prevalence

INTRODUCTION

HEPATITIS B VIRUS (HBV) is highly associated with chronic liver disease in Japan. The prevalence of hepatitis B surface antigen (HBsAg) in younger Japanese has markedly improved under national measures to prevent infection of newborn babies from HBV-infected mothers since 1986.[1] Problems remain to be solved in high-risk groups such as homosexual individuals, i.v. drug abusers, medical workers and patients who require invasive treatment, particularly hemodialysis (HD)[2] who have a low acquisition rate of protective antibody with HB vaccination.[3]

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During 1999–2003, we conducted a prospective study among HD patients for hepatitis C virus (HCV) infection and revealed the prevalence and incidence of HCV infection among HD patients in Hiroshima, Japan.[4]

In this study, we aimed to determine the prevalence of HBsAg and the incidence rate of HBV infection in patients on HD who are presumed to be at higher risk for HBV infection, to determine the current status of HBV infection, and to recommend prophylactic measures against HBV infection in patients on HD.

Furthermore, we calculated the positive rate of occult HBV among the HD patients.

METHODS

Study design and serum samples from patients

A PROSPECTIVE COHORT study for hepatitis viral infections among the HD patients was conducted from

1999 to 2003 in nine dialysis centers in Hiroshima Prefecture, Japan. The cohort of the present study includes the 1860 patients who were registered during the 6 months from November 1999 to May 2000, and the survey lasted for 3 years and 3 months, from November 1999 to February 2003 (Fig. 1a). Serum samples from registered patients were gathered from nine hospitals every 3 months through routine blood tests for cell counts and biochemistry. HD patients who provided informed consent took part in this survey.

This study was approved by the ethics committee for epidemiological research of Hiroshima University in Japan.

Incidence of HBV

Among 1860 patients, 1354 were all negative for HBsAg, anti-hepatitis B core (HBc) and anti-hepatitis B surface (HBs) at the start of the survey. Among them, the blood of 1285 patients was taken more than twice (Fig. 1). The patients who became HBsAg positive or anti-HBc positive at the end of the survey were defined as "incidence cases

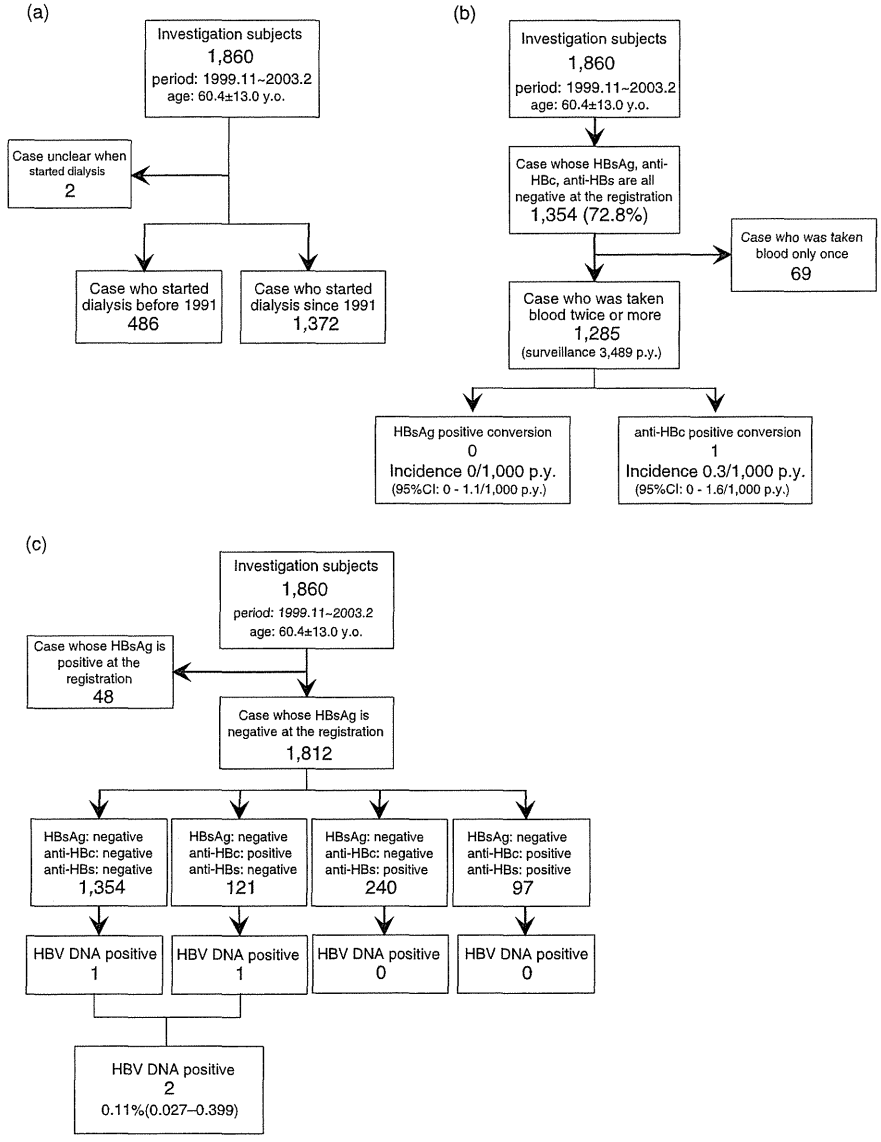

Figure 1 Study designs. (a) Classified by dialysis introduction date. (b) Study for the incidence of hepatitis B virus (HBV) infection. (c) Study for the prevalence of occult HBV infection. CI, confidence interval; HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen.

of HBV". Then, the incidence rate was calculated in person-years. In addition, the sera of all the patients who became anti-HBc positive were tested with simultaneous assays for HBsAg, anti-HBc, anti-HBs and HBV DNA.

Prevalence of occult HBV

In the total of 1860 patients, sera of 1812 patients who were negative for HBsAg at the registration were tested for HBV DNA. The sera were pooled into samples, each of which consisted of 20 patients, and were tested for HBV DNA using real-time polymerase chain reaction (PCR). For samples positive for HBV DNA, real-time PCR was then performed on each of the 20 individual serum samples included in the pooled sample, and the samples positive for HBV DNA were identified. When HBV DNA was detected, nucleic acid testing (NAT) via real-time PCR was performed at each point of the survey.

Serological tests

Hepatitis B surface antigen, anti-HBs and anti-HBc were determined using the hemagglutination method. HBsAg was determined by reversed-passive hemagglutination (R-PHA), anti-HBs by passive hemagglutination (PHA) and anti-HBc by inhibition of hemagglutination (HI) using assay kits provided by the Japanese Red Cross Blood Center (JRC).

Sera were diluted twofold serially on a microtiter plate, and the results were assessed by the highest twofold (2^N) dilution of sera that induced or inhibited hemagglutination. The threshold for positive hemagglutination results was 2^2 or more for HBsAg by R-PHA, 2^4 or more for anti-HBs by PHA and 2^5 or more for anti-HBc by HI.

Qualitative assays of HBV DNA were carried out using PCR with nested primers deduced from the S gene sequence. Quantitative assays of HBV DNA were conducted using real-time PCR with Applied Biosystems Step One Real Time PCR System (Life Technologies Japan, Tokyo, Japan) with primers and probe from the S gene. Primers were HBSF2 and HBSR2, and the probe was HBSP2.[5]

Statistical analysis

Prevalence of HBV markers and their 95% confidence interval (CI) were calculated. Differences in the prevalence among groups classified by sex and age were evaluated by the χ^2-test or Fisher's exact test. Risk factors associated with prevalence of HBV markers were determined by multivariate logistic regression analyses. *P*-values of less than 0.05 were considered statistically significant. Statistical analyses were performed with JMP version 9 (SAS Institute, Cary, NC, USA).

RESULTS

Prevalence of HBV infection

IN THIS STUDY, 1860 HD patients were registered, 1108 of whom were men and 752 women, with an average age at registration of 60.4 ± 13.0 years (range, 20–94).

The prevalence of HBsAg among the 1860 patients at registration was 2.6% (95% CI, 1.86–3.30%), anti-HBc positive rate 20.6% (95% CI, 18.81–22.48%) and anti-HBs positive rate 11.7% (95% CI, 10.26–13.18%) (Table 1a). Regarding age distribution, the HBsAg positive rate of 4.2% was highest in the patients in their 50s. Regarding sex, the HBsAg positive rate was 2.8% in men and 2.3% in women, showing the highest rate in patients in their 50s, and the second highest rate in those in their 40s in both men and women. The prevalence of anti-HBc was 20.6% (95% CI, 18.8–22.5%), and the prevalence of anti-HBc was higher in men than women with no significant difference. The prevalence of anti-HBs was 11.7% (95% CI, 10.3–13.2%) and the prevalence of anti-HBs was higher in women than men with no significant difference.

To compare HBV infection with the time of introduction of HD, the patients were divided into two groups: 1372 patients (829 men and 543 women, aged 61.89 ± 13.38 years; range, 20–94) who had started HD since 1991; and 486 patients (279 men and 207 women, aged 56.24 ± 10.64 years; range, 25–93) who started before 1991 (unclear for two patients) (when erythropoietin was approved by the health insurance policy in Japan and transfusions have rarely been used to treat anemia since then) (Figs 1,2, Tables 2,3). The prevalence of HBsAg among the 1372 patients who had started HD since 1991 was 2.1% (95% CI, 1.4–2.9%) and that of HBsAg among 486 patients who started before 1991 was 3.9% (95% CI, 2.2–5.6%). Prevalence of anti-HBc was higher among the patients who started before 1991 than the patients who started since 1991 (25.5%; 95% CI, 21.6–29.3% vs 18.9%; 95% CI, 16.8–21.0%) with significant difference ($P < 0.01$).

Prevalence of anti-HBs among the patients who started before 1991 was higher than among the patients who started since 1991 ($P = 0.0429$) (16.4%; 95% CI, 12.8–19.3% vs 10.2%; 95% CI, 8.6–11.8%).

Among the 1372 patients who started since 1991, the results of HBV infection were compared by duration on HD. The prevalence of HBsAg was the highest in patients who were on HD for over 7 years (4.7%). Likewise, anti-HBc and anti-HBs were the highest among the patients who were on HD for 7 years or more. With respect to sex, in men, the prevalence of HBsAg and anti-HBc positive rates

Table 1 Prevalence of HBsAg, anti-HBc, and anti-HBs stratified by age and sex in 1860 registered patients

Age at registration (years)	Total			Male			Female		
	n	Positive (%)	95% CI	*n*	Positive (%)	95% CI	*n*	Positive (%)	95% CI
					HBsAg				
≤39	105	2 (1.9)	0–4.52	76	1 (1.3)	0–3.88	29	1 (3.4)	0–10.09
40–49	255	9 (3.5)	1.26–5.80	162	6 (3.7)	0.80–6.61	93	3 (3.2)	0–6.82
50–59	528	22 (4.2)	2.46–5.87	330	15 (4.5)	2.30–6.80	198	7 (3.5)	0.96–6.11
60–69	491	11 (2.2)	0.93–3.55	270	7 (2.6)	0.70–4.49	221	4 (1.8)	0.05–3.57
≥70	481	4 (0.8)	0.02–1.64	270	2 (0.7)	0–1.76	211	2 (0.9)	0–2.15
Total	1,860	48 (2.6)	1.86–3.30	1,108	31 (2.8)	1.83–3.77	752	17 (2.3)	1.20–3.32
					Anti-HBc				
≤39	105	12 (11.4)	5.34–17.51	76	9 (11.8)	4.58–19.10	29	3 (10.3)	0–21.43
40–49	255	47 (18.4)	13.67–23.19	162	33 (20.4)	14.17–26.57	93	14 (15.1)	7.79–22.32
50–59	528	128 (24.2)	20.59–27.90	330	93 (28.2)	23.33–33.04	198	35 (17.7)	12.36–23.00
60–69	491	91 (18.5)	15.10–21.97	270	50 (18.5)	13.89–23.15	221	41 (18.6)	13.43–23.68
≥70	481	106 (22.0)	18.33–25.74	270	57 (21.1)	16.24–25.98	211	49 (23.2)	17.52–28.92
Total	1,860	384 (20.6)	18.81–22.48	1,108	242 (21.8)	19.40–24.27	752	142 (18.9)	16.09–21.68
					Anti-HBs				
≤39	105	6 (5.7)	1.27–10.15	76	2 (2.6)	0–6.23	29	4 (13.8)	1.24–26.34
40–49	255	32 (12.5)	8.48–16.62	162	22 (13.6)	8.30–18.86	93	10 (10.8)	4.46–17.05
50–59	528	64 (12.1)	9.33–14.91	330	35 (10.6)	7.28–13.93	198	29 (14.6)	9.72–19.57
60–69	491	57 (11.6)	8.78–14.44	270	32 (11.9)	8.00–15.71	221	25 (11.3)	7.14–15.49
≥70	481	59 (12.3)	9.33–15.20	270	36 (13.3)	9.28–17.39	211	23 (10.9)	6.70–15.11
Total	1,860	218 (11.7)	10.26–13.18	1,108	127 (11.5)	9.59–13.33	752	91 (12.1)	9.78–14.43

CI, confidence interval; HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen.

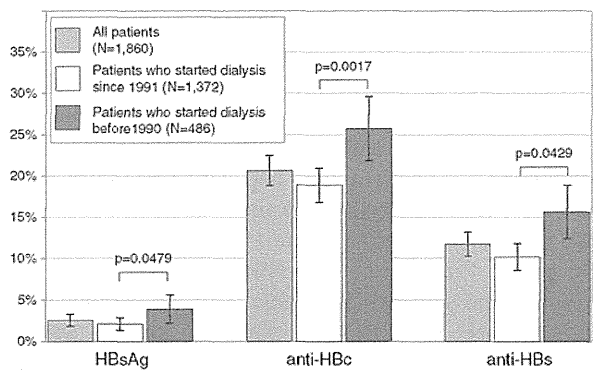

Figure 2 Prevalence of hepatitis B virus (HBV) markers classified by dialysis introduction date. HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen.

were the highest in those who had been on HD for 7 years or more, at 7.2% and 24.6%, respectively, and the anti-HBs positive rate was the highest (14%) in men who had been on HD for 5–6 years. In women, the prevalence of HBsAg was the highest (3.8%) among the patients who had been on HD for 3–4 years. Anti-HBc positive rate and anti-HBs positive rate were the highest in women who had been on HD for 7 years or more, at 25.9% and 22.4%, respectively.

Among the 1372 patients, risk factors associated with prevalence of HBV markers were determined by multivariate logistic regression analyses (Table 4). The prevalence of HBsAg in patients aged 70 years or more old is significantly lower than that in patients aged 49 years or less. There were no significant differences with respect to sex and duration of HD. Anti-HBc positive rate was significantly higher than that of patients aged 49 years or less, and the prevalence of anti-HBs in patients who had been on HD for 5 years or more was significantly higher than that of patients on HD for less than 1 year.

Among the 1860 patients, risk factors associated with prevalence of HBV markers were determined by multivariate logistic regression analyses (Table 5). Risk of anti-HBs and anti-HBc are higher significantly in the group who started HD before 1991 than in the group since 1991, but as for the risk of HBsAg, there is no significant difference between groups.

Incidence rate of HBV infection

The subjects were 1285 patients whose samples were taken more than twice and who were negative for HBsAg,

Table 2 Prevalence of HBsAg, anti-HBc, and anti-HBs stratified by age and sex in 1372 patients who started hemodialysis since 1991

Age at registration (years)	Total			Male			Female		
	n	Positive (%)	95% CI	*n*	Positive (%)	95% CI	*n*	Positive (%)	95% CI
					HBsAg				
≤39	77	1 (1.3)	0–3.83	55	1 (1.8)	0–5.35	22	0 0.0	0–16.77
40–49	156	6 (3.8)	0.83–6.86	99	5 (5.1)	0.74–9.36	57	1 (1.8)	0–5.16
50–59	340	12 (3.5)	1.57–5.49	213	8 (3.8)	1.20–6.31	127	4 (3.1)	0.11–6.19
60–69	371	7 (1.9)	0.50–3.27	214	4 (1.9)	0.06–3.68	157	3 (1.9)	0–4.05
≥70	428	3 (0.7)	0–1.49	248	1 (0.4)	0–1.19	180	2 (1.1)	0–2.64
Total	1372	29 (2.1)	1.35–2.87	829	19 (2.3)	1.27–3.31	543	10 (1.8)	0.71–2.97
					Anti-HBc				
≤39	77	7 (9.1)	2.67–15.51	55	6 (10.9)	2.67–19.15	22	1 (4.5)	0–13.3
40–49	156	21 (13.5)	8.11–18.82	99	13 (13.1)	6.48–19.78	57	8 (14.0)	5.02–23.05
50–59	340	69 (20.3)	16.02–24.57	213	49 (23.0)	17.35–28.66	127	20 (15.7)	9.41–22.08
60–69	371	68 (18.3)	14.39–22.27	214	40 (18.7)	13.47–23.92	157	28 (17.8)	11.85–23.82
≥70	428	94 (22.0)	18.04–25.89	248	52 (21.0)	15.90–26.03	180	42 (23.3)	17.15–29.51
Total	1372	259 (18.9)	16.81–20.95	829	160 (19.3)	16.61–21.99	543	99 (18.2)	14.98–21.48
					Anti-HBs				
≤39	77	4 (5.2)	0.24–10.15	55	1 (1.8)	0–5.35	22	3 (13.6)	0–27.98
40–49	156	16 (10.3)	5.49–15.02	99	11 (11.1)	4.92–17.30	57	5 (8.8)	1.43–16.12
50–59	340	33 (9.7)	6.56–12.85	213	15 (7.0)	3.61–10.48	127	18 (14.2)	8.11–20.24
60–69	371	34 (9.2)	6.23–12.10	214	21 (9.8)	5.83–13.80	157	13 (8.3)	3.97–12.59
≥70	428	53 (12.4)	9.26–15.50	248	33 (13.3)	9.08–17.53	180	20 (11.1)	6.52–15.70
Total	1372	140 (10.2)	8.60–11.81	829	81 (9.8)	7.75–11.79	543	59 (10.9)	8.25–13.48

CI, confidence interval; HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen.

anti-HBc and anti-HBs at the start of the survey (Fig. 1b). There was no case of conversion to HBsAg positivity during the survey; hence, the incidence rate of HBV infection as determined by conversion to HBsAg positivity was 0/1000 person-years (95% CI, 0–1.1/1000 person-years). On the other hand, there was one case of positive conversion to anti-HBc; hence, the incidence rate of HBV infection as determined by conversion to anti-HBc positivity was 0.3/1000 person-years (95% CI, 0–1.6/1000 person-years).

In the patient who converted to anti-HBc positivity, anti-HBc titer increased from 2^2 to 2^7 on the third examination and peaked at 2^8 on the fourth examination. Only then, when the titer was at its peak, was HBV DNA detected. Subsequently, HBV DNA was not detected (Fig. 3). This patient was a 73-year-old man who was affected by diabetic nephropathy and was on HD for 2 months before the registration, then died in May 2001 (after the seventh survey).

Prevalence of occult HBV at the registration

Among the 1812 patients who were negative for HBsAg at the start of the survey (Fig. 1c), one occult HBV infection out of 1354 patients who were negative for HBsAg, anti-HBc and anti-HBs, and one occult HBV infection out of 121 patients who were negative for both HBsAg and anti-HBs and positive for anti-HBc were determined to be HBV DNA positive. That is, two out of 1812 patients were positive for HBV DNA, and the prevalence of occult HBV rate was 0.11% (95% CI, 0.027–0.399%). Of two occult HBV infections, one was a 67-year-old woman who was affected by diabetic mellitus and on HD for 7 months before the registration. She died after taking blood samples at the start of the survey, and the status of her HBV markers is unclear. The quantity of HBV DNA was 9.87×10^4 copies/mL. The other patient was a 68-year-old woman who was affected by diabetic nephropathy and on HD for 6 years before the registration. During the survey, neither HBsAg nor anti-HBs was detected, and only anti-HBc remained positive from the start of the survey. The quantity of HBV DNA fluctuated between 6.00×10^1 copies/mL and 3.00×10^3 copies/mL.

DISCUSSION

THE RISKS OF exposure to hepatitis viruses are high in HD patients, including errors made by staff during

Table 3 Prevalence of HBsAg, anti-HBc and anti-HBs stratified by age and sex in 486 patients who started hemodialysis before 1991

Age at registration (years)	Total			Male			Female		
	n	Positive (%)	95% CI	*n*	Positive (%)	95% CI	*n*	Positive (%)	95% CI
					HBsAg				
≤39	28	1 (3.6)	0–10.45	21	0 (0.0)	0–17.57	7	1 (14.3)	0–40.21
40–49	99	3 (3.0)	0–6.41	63	1 (1.6)	0–4.67	36	2 (5.6)	0–13.04
50–59	188	10 (5.3)	2.11–8.53	117	7 (6.0)	1.69–10.28	71	3 (4.2)	0–8.90
60–69	120	4 (3.3)	0.12–6.55	56	3 (5.4)	0–11.25	64	1 (1.6)	0–4.60
≥70	51	1 (2.0)	0–5.77	22	1 (4.5)	0–13.25	29	0 (0.0)	0–12.72
Total	486	19 (3.9)	2.19–5.63	279	12 (4.3)	1.92–6.68	207	7 (3.4)	0.92–5.84
					Anti-HBc				
≤39	28	5 (17.9)	3.67–32.04	21	3 (14.3)	0–29.25	7	2 (28.6)	0–62.04
40–49	99	26 (26.3)	17.59–34.93	63	20 (31.7)	20.25–43.24	36	6 (16.7)	4.49–28.84
50–59	188	59 (31.4)	24.75–38.02	117	44 (37.6)	28.83–46.38	71	15 (21.1)	11.63–30.62
60–69	120	23 (19.2)	12.12–26.21	56	10 (17.9)	7.83–27.89	64	13 (20.3)	10.46–30.17
≥70	51	12 (23.5)	11.89–35.17	22	5 (22.7)	5.22–40.24	29	7 (24.1)	8.56–39.71
Total	486	125 (25.7)	21.89–29.61	279	82 (29.4)	24.05–34.74	207	43 (20.8)	15.25–26.30
					Anti-HBs				
≤39	28	2 (7.1)	0–16.68	21	1 (4.8)	0–13.87	7	1 (14.3)	0–40.21
40–49	99	16 (16.2)	8.91–23.41	63	11 (17.5)	8.09–26.83	36	5 (13.9)	2.59–25.19
50–59	188	31 (16.5)	11.18–21.79	117	20 (17.1)	10.27–23.92	71	11 (15.5)	7.08–23.91
60–69	120	23 (19.2)	12.12–26.21	56	11 (19.6)	9.24–30.05	64	12 (18.8)	9.19–28.31
≥70	51	4 (7.8)	0.46–15.22	22	3 (13.6)	0–27.98	29	1 (3.4)	0–10.09
Total	486	76 (15.6)	12.41–18.87	279	46 (16.5)	12.13–20.84	207	30 (14.5)	9.70–19.29

CI, confidence interval; HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen.

Table 4 4aOutput of logistic regression analyses (at registration) ($n = 1372$)

		HBsAg			Anti-HBc			Anti-HBs		
		OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Sex	*n*									
Female (Ref.)	543	1.00			1.00			1.00		
Male	829	1.23	(0.57–2.78)	0.609	1.11	(0.84–1.47)	0.474	0.92	(0.64–1.31)	0.631
Age (years)	*n*									
≤49 (Ref.)	233	1.00			1.00			1.00		
50-69	711	0.89	(0.38–2.30)	0.789	1.74	(1.14–2.74)	0.013	1.08	(0.65–1.88)	0.762
≥70	428	0.23	(0.05–0.85)	0.037	2.07	(1.33–3.33)	0.001	1.53	(0.90–2.68)	0.127
Dialysis period	*n*									
<1 (Ref.)	383	1.00			1.00			1.00		
1–4	684	1.06	(0.44–2.84)	0.895	0.94	(0.68–1.30)	0.707	1.24	(0.80–1.94)	0.345
5–8	305	1.34	(0.47–3.88)	0.578	1.09	(0.74–1.60)	0.646	1.71	(1.04–2.82)	0.033

CI, confidence interval; HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; OR, odds ratio; Ref., reference.

medical procedures, exposure to blood via dialysis instruments and contamination of equipment.[6] Transfusion therapy was one of the major infection routes of hepatitis viruses before screening tests for hepatitis viruses were established at blood centers.[7] This was especially true for HD patients[8,9] who had to receive frequent transfusion therapy to treat nephrogenic anemia, a complication of kidney disturbance. Since 1991, when erythropoietin was approved by the health insurance policy in Japan, transfusions have rarely been used to treat anemia. Therefore, the risk of HBV and HCV infection due to transfusion has decreased substantially.