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Epidemiological changes in hepatitis A in Korea: increasing age and its effect on clinical outcomes

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SUMMARY

Korea has recently experienced an increasing number of acute hepatitis A cases. We investigated the dynamics of hepatitis A and changes in the mean age of patients in a hospital in Seoul, Korea. Mean age increased consistently from 19 years in 1996 to 30 years in 2009 ($P<0{\cdot}0001$). Between two acute hepatitis A outbreaks in 1998–1999 and in 2008–2009, mean age increased from 23 to 30 years ($P<0{\cdot}001$). However, the hepatitis A clinical outcomes were similar between the outbreaks. Duration of hospital stay, creatinine level and prothrombin time did not differ. Throughout the study period, individuals born in the 1970s and 1980s comprised the largest proportion (84%) of patients. As this susceptible generation ages, the mean age of hepatitis A patients in Korea will increase consistently. However, at present, the impact of increasing age on clinical outcomes is not apparent.

Key words: Age, epidemiology, hepatitis A, Korea.

INTRODUCTION

The severity of hepatitis A is strongly related to the age of the infected patient [1]. Although most young children with hepatitis A are asymptomatic, the majority of older children and young adults suffer from symptomatic infections that frequently require hospital admission and inevitably increase a country's overall medical costs [2]. Although rare, some patients can develop complications of severe or atypical hepatitis A, such as fulminant hepatic failure, severe cholestasis and acute kidney injury [3–6]. Among the host and viral factors influencing the severity of hepatitis A, older age has been suggested to be an important demographic parameter. Some reports have found that the likelihood of hospitalization and fatal complications was higher in patients aged >40 years [7, 8].

Hepatitis A viral infection has become a health problem in recent decades in many countries. Latin America, Asia and Eastern Europe showed a hepatitis A virus (HAV) epidemiological shift from high to intermediate endemicity following many outbreaks, especially in older individuals with more severe disease [9]. Recent reports from Argentina, Brazil, Chile, India, Thailand, the Russian Federation, Saudi Arabia and China describe an increased number of people at risk of severe clinical courses [9–13]. This seems to be due to an epidemiological shift in HAV [14]. Due to the increasing availability of clean water supplies, adequate sanitation and improved socio-economic status, asymptomatic and incidental HAV infection in children has decreased markedly. The seroprevalence of anti-hepatitis A antibody has also

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decreased markedly in young children [15]. Paradoxically, decreased HAV infection in children has increased the risk of symptomatic infection. As the seroprevalence curve moves towards an older age group, repeated outbreaks of symptomatic and more severe forms of hepatitis A occur in this susceptible population over time [10].

Meanwhile, the incidence of hepatitis A has increased markedly in Korea during recent decades [16, 17]. The epidemiological change seems to be a major cause of the exponential increase in symptomatic hepatitis A cases in young adults in Korea. According to recent age-specific seroprevalence surveys, $<20\%$ of individuals in their teens and twenties had anti-HAV immunoglobulin G (IgG) [10, 18].

As the average age of patients with HAV infection increases, the utilization of medical resources and the direct and indirect burdens of this disease may become substantial [19]. However, few studies have examined epidemiological changes in the age of patients with hepatitis A. In this study, we investigated changes in the age of Korean patients with hepatitis A and the effect of age on clinical outcome.

PATIENTS AND METHODS

This study enrolled 647 patients with symptomatic acute hepatitis A who presented at Kyung Hee University Hospital, Seoul, Korea, between January 1996 and December 2010. This hospital is located in north-east Seoul and treats mostly patients referred from primary clinics. The Department of Internal Medicine admits about 7800 persons annually. Data from a single hospital can not fully represent the national disease trend. However, atypical or severe cases presenting to a large hospital may to some extent reflect national or regional epidemiological status because most such cases are referred to a local large hospital.

The diagnosis of hepatitis A was made by a positive result for anti-HAV IgM antibodies. If the initial result was negative but the clinical manifestation suggested hepatitis A, we repeated anti-HAV IgM testing within 7 days to confirm the diagnosis. Commercially available enzyme immunoassay kits were used to detect serum anti-HAV IgM (anti-HAV IgM; Roche Diagnostics, USA).

Patients' medical records were retrospectively reviewed to collect and analyse demographic, clinical and laboratory data, including age, sex, year of onset, duration of hospital stay, peak levels of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (Cr) and prothrombin time (international normal ratio, INR). Severe hepatitis was defined when the INR of prothrombin time exceeded 1·5 [4]. Acute kidney injury was defined as elevated serum Cr ($>2{\cdot}0$ mg/dl) in patients with no history of chronic renal disease [3]. Fulminant hepatitis was defined as the development of hepatic encephalopathy within 8 weeks of disease onset. Marked cholestasis was defined as when the peak level of serum bilirubin exceeded 12 mg/dl.

Quantitative variables are expressed as medians, ranges and means with standard deviations (S.D.). These variables were compared using Student's t test. A simple linear regression analysis was performed to determine the statistical significance of changes in the mean age of patients with acute hepatitis A. Values of $P<0{\cdot}05$ were considered to indicate statistical significance. All analyses were conducted using SPSS for Windows v. 15.5 (SPSS Inc., USA).

RESULTS

Change in annual number of patients with hepatitis A

The annual number of patients with hepatitis A before 1998 was fewer than three. The first hepatitis A outbreak occurred between 1998 and 1999. About 10 times the normal number of patients ($n=64$) were hospitalized during this time. The annual number of patients has increased since the early 2000s and has risen markedly since 2006 (Fig. 1*a*). We investigated the proportion of patients hospitalized with HAV. If both the number of hepatitis A cases and the total number of annual admissions to the hospital (the denominator for the rate) increased significantly from 1996 to 2010, then the increase in the number of admissions may not reflect an increase in the incidence rate. However, if the annual rate of hepatitis A admissions has increased, it would be strong evidence for an increase in the incidence of HAV infection. While the number of patients hospitalized increased from 7161 in 1996 to 9060 in 2010, the proportion of patients with HAV infection increased from 0·3/1000 admissions in 1996 to 23·1/1000 admissions in 2009. The pattern was very similar to the trend in the annual number of patients, which indicates that the incidence of symptomatic HAV infection truly increased. Moreover, this trend was similar to that indicated by cases reported in a sentinel surveillance system operated

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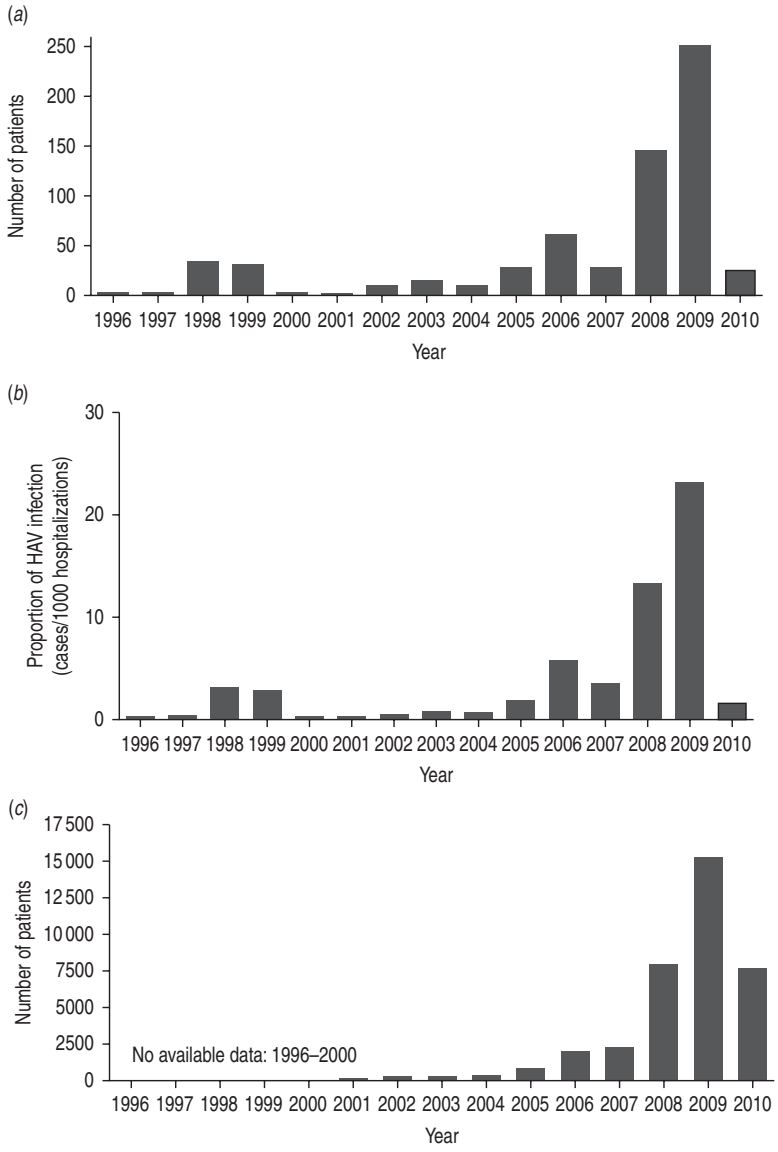

Fig. 1. (*a*) The annual number of acute hepatitis A cases in a single tertiary hospital in Seoul, Korea (1996–2010). (*b*) The proportion with hepatitis A virus (HAV) infection of the total hospitalized over 15 years in the same hospital. (*c*) The annual number of cases reported to the national sentinel surveillance system of the Korean Centers for Disease Control and Prevention (2001–2010).

by the Korea Centers for Disease Control and Prevention from 2001 to 2010 (pre-2001 data were not available) (Fig. 1*c*).

Clinical characteristics and change in age of patients with hepatitis A

The baseline characteristics and clinical outcomes of the 647 study patients are summarized in Table 1. The mean age ($\pm$S.D.) was 29 ± 8 years (range 3–60 years) and most were in their twenties (44%, $n=287$) or thirties (36%, $n=235$). A simple linear regression analysis indicated that the mean age of patients increased gradually but significantly ($R^2=0{\cdot}754$, $P<0{\cdot}0001$; Fig. 2).

We divided the patients into three groups according to the date of disease onset. During the early period (1996–2001), the mean age of the 76 patients was 23 ± 8 years. The middle period (2002–2006) included 122 patients with a mean age of 27 ± 7 years. During the late period (2007–2010, $n=449$), the mean age was 30 ± 7 years. Analysis of variance (ANOVA) indicated that this increase in mean age over time was significant ($P<0{\cdot}001$).

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Table 1. *Clinical characteristics of patients with hepatitis A*

Parameter	Total patients ($n=647$)
Age, years (median, range)	28·6 ± 7·7 (28, 1–60)
Male, *n* (%)	366 (56·6)
Total bilirubin (mg/dl), peak level	6·4 ± 3·5
AST (IU/l), peak level	2150 ± 2082
ALT (IU/l), peak level	2534 ± 1752
Creatinine (mg/dl), peak level	0·90 ± 1·18
Prothrombin time (INR)	1·26 ± 0·51
Clinical outcome, *n* (%)	
Fulminant hepatitis	2 (0·2)
Severe hepatitis*	96 (15·0)
Acute kidney injury†	14 (2·2)
Marked cholestasis	45 (7·0)
Duration of hospital stay, days	8 ± 3

All results are reported as mean ± standard deviation or number (%).
AST, Aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.
* Prothrombin time was missing in nine patients.
† Serum creatinine was missing in eight patients.

Distribution of patients according to age and year of birth

The proportion of patients in their thirties and forties also increased over time. The proportion of patients in their thirties increased from 17% (13/76) in the early period (1996–2001) to 41% (185/449) in the late period (2007–2010). The proportion of patients in their forties increased from ∼1% (1/76) in the early period to 10% (44/449) in the late period ($P=0·001$; Fig. 3).

This incremental increase in mean age implies that the generation susceptible to HAV infection aged during the study period. We thus investigated the distribution of patients according to the year they were born. As shown in Figure 4, patients born in the 1970s and 1980s comprised the largest proportion of the study population (84%, 541/647), accounting for the largest proportion of the total during the early (80%, 61/76), middle (86%, 105/122) and late (84%, 375/449) periods.

Clinical outcomes and differences in patients between the first (1998–1999) and second (2008–2009) outbreaks

We compared clinical outcomes of 65 patients in the first outbreak (1998–1999) [20, 21] and those of 397 patients in the second (2008–2009) outbreak [22–24]. Mean age of patients during the first outbreak was 23 years and that in the second was 30 years ($P<0·001$). No fulminant hepatitis was reported during the first outbreak, and one case occurred in the second ($P=0·671$). The prevalence of severe hepatitis and acute kidney injury between the outbreaks did not differ. Severe hepatitis occurred in 10 (16·1%) of 62 patients in the first outbreak and 68 (17·2%) of 396 in the second ($P=0·839$). Acute kidney injury was complicated in no patients during the first outbreak and in 11 (2·8%) of 397 patients during the second ($P=0·192$). The peak serum total bilirubin level was higher in the first outbreak than in the second (7·6 ± 4·2 *vs.* 6·1 ± 3·1 mg/dl; $P=0·007$). The peak serum ALT level was lower in the first outbreak than in the second (1459 ± 1015 *vs.* 2873 ± 1798 IU/l; $P<0·001$).

Clinical outcomes and differences between young and middle-aged patients

To investigate the effect of increasing age on the clinical characteristics of hepatitis A, we divided the patients into four age groups: 10–19, 20–29, 30–39 and 40–49 years. Only five and three patients were aged <10 or >50 years, respectively, and they were excluded from the analysis. The laboratory results and clinical outcomes of patients are presented by age group in Table 2. No difference was observed in groups in terms of the incidence of severe hepatitis, acute kidney injury, marked cholestasis or fulminant hepatitis. The mean duration of hospital stay, peak level of serum total bilirubin, Cr level and prothrombin time did not differ in the groups. However, peak aminotransferase levels were higher in young adults (aged 20–39 years) (Table 2).

Overall clinical outcomes

The laboratory results and clinical outcomes of all study patients are shown in Table 1. The ratio of male to female patients was 6:4. The mean duration of hospitalization was 8 ± 3 days. Patients' clinical courses were favourable. Most (99·8%, $n=645$) patients recovered without complications, and fulminant hepatic failure occurred in only two patients, each of whom recovered spontaneously with supportive care. No liver transplantation was performed. Severe hepatitis and elevated prothrombin time (INR >1·5) occurred in 96 (15·0%) of 638 patients for

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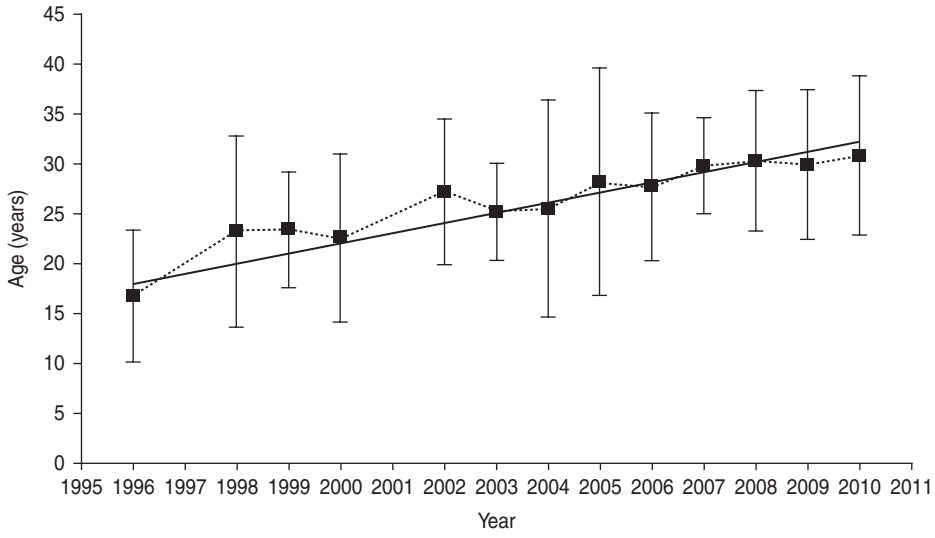

Fig. 2. Change in mean age of patients with acute hepatitis A from 1996 to 2010 ($R^2 = 0{\cdot}754$, $P < 0{\cdot}0001$).

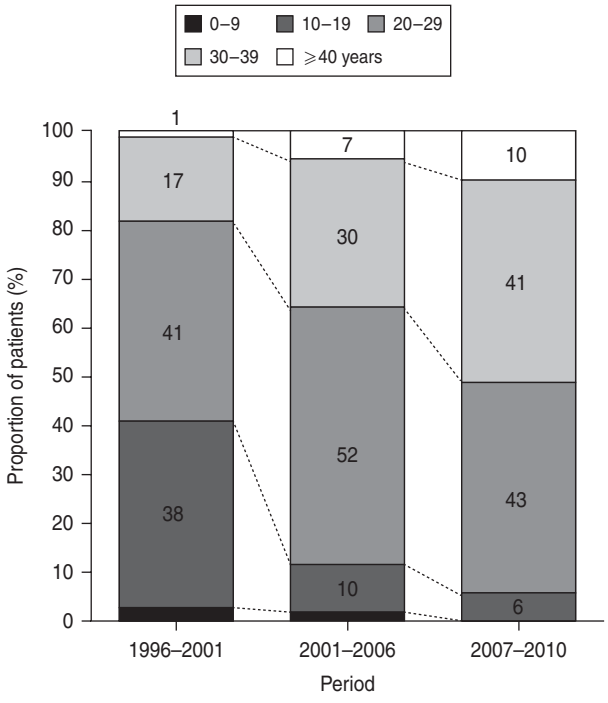

Fig. 3. Proportion of patients with hepatitis A by age group in three time periods. The proportion of patients in their thirties and forties increased while that of teenagers decreased ($P = 0{\cdot}001$).

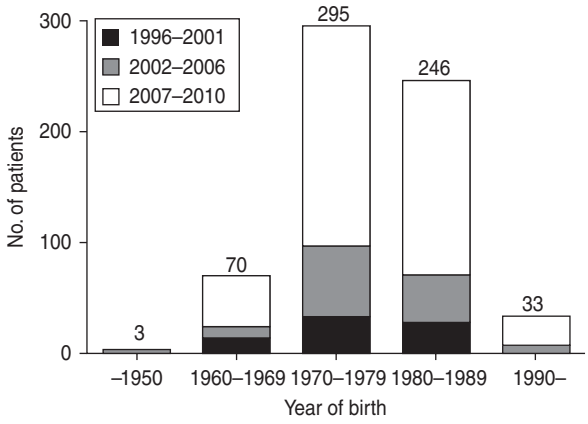

Fig. 4. Distribution of patients with acute hepatitis A according to year of birth. Patients born in the 1970s and 1980s made up the largest proportion of patients in all time periods.

whom laboratory results were available. Patients with severe hepatitis had higher ALT levels (4678 ± 1774 *vs.* 2161 ± 1449 U/l; $P < 0{\cdot}001$), higher peak bilirubin ($7{\cdot}2 \pm 3{\cdot}1$ *vs.* $6{\cdot}3 \pm 3{\cdot}6$ mg/dl; $P = 0{\cdot}013$), a longer mean duration of hospital stay (9 ± 3 *vs.* 7 ± 3 days; $P = 0{\cdot}001$) and higher risk of acute kidney injury (6·3% *vs.* 1·5%; odds ratio 4·26, 95% confidence interval 1·4–12·6; $P = 0{\cdot}014$) than patients without severe hepatitis. However, the mean age of patients with severe hepatitis A did not differ from that of patients without a severe form of HAV (29 ± 8 *vs.* 28 ± 7 years; $P = 0{\cdot}470$). Acute kidney injury (Cr > 2 mg/dl) was noted in 14 (2·2%) patients. Their median age was 31 years (range 21–42 years), which did not differ from that of patients without acute kidney injury (29 years; $P = 0{\cdot}227$). The median serum Cr level was 7·3 mg/dl (range 2·7–18·7 mg/dl). Five patients were treated with intermittent haemodialysis; the others received supportive care. No patient required kidney transplantation. The mean admission period of patients with acute kidney injury was 9 days (range 3–18 days).

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Table 2. *Comparison of clinical characteristics of hepatitis A according to age*

Parameter	Age				*P* value
	10–19 years ($n=66$)	20–29 years ($n=287$)	30–39 years ($n=235$)	40–49 years ($n=51$)	
Male, *n* (%)	29 (43·9)	165 (57·5)	135 (57·4)	33 (64·7)	0·120
Bilirubin (mg/dl), peak level	6·3 ± 3·4	6·4 ± 3·4	6·2 ± 3·4	7·1 ± 4·2	0·503
AST (IU/l), peak level	1369 ± 1591	2214 ± 2090	2341 ± 2180	1972 ± 1836	0·008
ALT (IU/l), peak level	1835 ± 1420	2620 ± 1771	2690 ± 1821	2317 ± 1375	0·003
Creatinine (mg/dl), peak level	0·7 ± 0·2	0·9 ± 0·7	1·0 ± 1·5	1·2 ± 2·1	0·145
Prothrombin time (INR)	1·3 ± 0·5	1·3 ± 0·4	1·3 ± 0·4	1·3 ± 1·2	0·794
Clinical outcome, *n* (%)					
Fulminant hepatitis	0 (0)	2 (0·6)	0 (0)	0 (0)	0·746
Severe hepatitis	9 (14·3)	46 (16·3)	35 (14·9)	5 (9·8)	0·693
Acute kidney injury	0 (0)	6 (2·1)	6 (2·6)	2 (3·9)	0·524
Marked cholestasis	6 (9·1)	13 (4·5)	17 (7·2)	7 (13·7)	0·076
Duration of hospital stay, days	7 ± 2	8 ± 3	8 ± 3	8 ± 3	0·642

All results were reported as mean ± standard deviation or number (%).
AST, Aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

DISCUSSION

In this study, we identified two major epidemiological changes in patients with hepatitis A. The number of hepatitis A cases has increased markedly since 2005 and patient age has gradually increased over time. A similar marked rise in acute hepatitis A cases has been reported in other countries that have achieved high socio-economic development [25]. This can be explained by a parallel shift in the susceptible age group. Several seroprevalence studies conducted in Korea have indicated that the majority of young people have no immunity against HAV infection. The seroprevalence rate of anti-HAV was <20% in the 10–29 years age group, while it was >90% in adults aged >40 years [10, 17, 18, 26]. The marked decrease in subclinical infection during childhood paradoxically increased symptomatic infection in young adults. Because most adults aged >40 years have natural immunity against HAV infection, few study patients (8·3%) were aged >40 years. Moreover, genotype studies showed that during the late 1990s, genotype IA was mostly isolated [27]. However, during 2005 and 2006, genotype IIIA was isolated from patients, suggesting importation of a new strain from high-endemic countries [28]. The general improvement in economic status, more frequent overseas travel, increased consumption of fresh vegetables and frequent dining out might increase the chance of viral infection in susceptible young adults and lead to a sustained community-wide hepatitis A outbreak in Korea [29].

In this study, the majority (84%) of patients belonged to the '7080' generation born between 1970 and 1989 (Fig. 4). During their childhood, Korea experienced rapid social and economic development. According to the World Bank, the gross domestic product (GDP) was about 2 billion US dollars in 1961 but reached 1049 billion US dollars in 2007 [30]. The public health index improved as a result of the increasing availability of clean water supplies and better sanitation, and HAV infection declined markedly during this period. Moreover, anti-hepatitis A vaccination programmes have been available in Korea since 1997. Thus, this '7080' generation had a very low chance of exposure to hepatitis A by natural infection or vaccination during childhood. The seroprevalence rate (10–20%) in this generation is the lowest in the Korean population [17, 26], and they are the most vulnerable Koreans to HAV infection, now and in the future. With the adoption of widespread vaccination programmes, about half of the children born after 1997 have been actively immunized against hepatitis A [31]. A seroprevalence study confirmed that 40–60% of children aged <9 years had protective antibodies in 2006 [26]. Our data revealed that a low proportion of patients born after 1990 had hepatitis A. Although younger age *per se* might be related to the low occurrence of symptomatic cases, vaccination programmes and increased

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herd immunity might also play a role in the decreased incidence of symptomatic cases in the younger generation.

Accordingly, the number of patients with hepatitis A aged >40 years will increase in the near future in Korea. This study also examined whether old age increased the risk for fatal or atypical complications of hepatitis A. According to studies conducted in developed countries, old age (>40 years) is correlated with an increased incidence of severe or fulminant hepatitis and death [7, 8, 32]. However, this association has not been confirmed in Korea. Although the severity of hepatitis A is strongly related to age in children and young adults, this relationship has not been clearly demonstrated in patients aged >40 years where studies have produced conflicting results. Because HAV is not cytopathic, the severity of symptoms and disease level seem to be related to the intensity of the host's immune response [1]. The serum HAV titre is significantly lower in patients with more severe or fulminant hepatitis than in those with milder symptoms [6, 33]. The mean age of patients in reported fulminant hepatitis A cases is 20–40 years. These findings suggest that an intense immunological response might be related to the massive destruction of infected hepatocytes and the rapid eradication of the virus [33, 34]. However, the immune reaction against pathogens seems to be lower in older patients. This may partially explain why the incidence of severe or fulminant hepatitis does not increase in older patients. This assumption is supported by the lack of a difference in the incidence of severe or fulminant hepatitis A between young and middle-aged patients in the present study. The higher serum transaminase levels of patients in their twenties and thirties detected in this study, compared to teenagers and middle-aged adults, may be an example of an intense immune response in young adults (Table 2).

On the other hand, a comorbid state including chronic liver disease may be a prognostic factor in elderly patients with hepatitis A. Chronic viral hepatitis, liver cirrhosis and other alcohol-related liver disease, and non-alcoholic steatohepatitis might affect clinical outcomes in patients with hepatitis A [7, 35]. These comorbidities may be implicated in the course of hepatitis A more commonly in elderly patients. Unfortunately, the proportion of elderly patients included in the present study was too small to fully investigate these factors. Only three (0·5%) patients in the sample were aged >50 years. However, we were able to demonstrate that outcomes in patients in their forties were not more severe than in younger patients.

In the next 10 years, Korea may be confronted with significant hepatitis A outbreaks in the elderly if no preventive strategy is established for this susceptible population. Because we do not know whether severe or fatal hepatitis A occurs more frequently in patients aged >50 years, elderly patients with or without comorbidities should be considered to be at high risk. To clarify this issue, further studies employing systematic case-collection designs are needed.

One limitation of this study is that the data were collected retrospectively from a single healthcare centre. However, we collected consistent data from a 15-year period. Despite the small number of cases, the data clearly show that the age of patients with hepatitis A has increased continuously, and that patients born in the 1970s and 1980s are the most vulnerable group.

In conclusion, the average age of Korean patients with hepatitis A is increasing. The implications of this trend are not currently clear. However, we should be alert and prepare for future outbreaks in the most susceptible people, i.e. those born in the 1970s and 1980s. The risk of severe hepatitis A may increase over time as the vulnerable population ages.

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DECLARATION OF INTEREST

None.

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