

Clinical Characteristics and Outcomes of Acute Hepatitis A in Korea: A Nationwide Multicenter Study

So Young Kwon,¹ Sang Hoon Park,²
Jong Eun Yeon,³ Sook Hyang Jeong,⁴
Oh Sang Kwon,⁵ Jin Woo Lee,⁶
Hong Soo Kim,⁷ Yeon Seok Seo,⁸
Young Seok Kim,⁹ Joo Hyun Sohn,¹⁰
Hyung Joon Yim,¹¹ Jong Young Choi,¹²
Myung Seok Lee,² Young Oh Kweon,¹³
Jae Youn Cheong,¹⁴ Haak Cheoul Kim,¹⁵
Heon Ju Lee,¹⁶ Soon Koo Baik,¹⁷
Hyongjin An,¹⁸ and Kwan Soo Byun³

¹Department of Internal Medicine, Konkuk University School of Medicine, Seoul; ²Department of Internal Medicine, Hallym University College of Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul; ³Department of Internal Medicine, Korea University College of Medicine, Korea University Guro Hospital, Seoul; ⁴Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam; ⁵Department of Internal Medicine, Gachon University Graduate School of Medicine, Gachon University Gil Medical Center, Incheon; ⁶Department of Internal Medicine, Inha University School of Medicine, Inha University Hospital, Incheon; ⁷Department of Internal Medicine, Soonchunhyang University College of Medicine, Soonchunhyang University Cheonan Hospital, Cheona; ⁸Department of Internal Medicine, Korea University College of Medicine, Korea University Anam Hospital, Seoul; ⁹Department of Internal Medicine, Soonchunhyang University College of Medicine, Soonchunhyang University Bucheon Hospital, Bucheon; ¹⁰Department of Internal Medicine, Hanyang University College of Medicine, Hanyang University Guri Hospital, Guri; ¹¹Department of Internal Medicine, Korea University College of Medicine, Korea University Ansan Hospital, Ansan; ¹²Department of Internal Medicine, The Catholic University of Korea School of Medicine, The Catholic University of Korea St. Mary's Hospital, Seoul; ¹³Department of Internal Medicine, Kyungpook National University College of Medicine, Kyungpook National University Hospital, Daegu; ¹⁴Department of Internal Medicine, Aju University School of Medicine, Aju University Hospital, Suwon; ¹⁵Department of Internal Medicine, Wonkwang University School of Medicine, Wonkwang University Hospital, Iksan; ¹⁶Department of Internal Medicine, Yeungnam University College of Medicine, Yeungnam University Medical Center, Daegu; ¹⁷Department of Internal Medicine, Yonsei University Wonju College of Medicine, Yonsei University Wonju Christian Hospital, Wonju; ¹⁸Department of Biostatistics, Korea University College of Medicine, Seoul, Korea

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Address for Correspondence:

Kwan Soo Byun, MD

Department of Internal Medicine, Liver Center, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 152-703, Korea

Tel: +82.2-2030-5027, Fax: +82.2-2030-5029

E-mail: kwsbyun@unitel.co.kr

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The aim of this study was to investigate the clinical characteristics of acute hepatitis A during a recent outbreak in Korea. Data of patients diagnosed with acute hepatitis A from 2007 to 2009 were collected from 21 tertiary hospitals retrospectively. Their demographic, clinical, and serological characteristics and their clinical outcomes were analyzed. A total of 4,218 patients (mean age 33.3 yr) were included. The median duration of admission was 9 days. The mean of the highest ALT level was 2,963 IU/L, total bilirubin was 7.3 mg/dL, prothrombin time INR was 1.3. HBsAg was positive in 3.7%, and anti-HCV positive in 0.7%. Renal insufficiency occurred in 2.7%, hepatic failure in 0.9%, relapsing hepatitis in 0.7%, and cholestatic hepatitis in 1.9% of the patients. Nineteen patients (0.45%) died or were transplanted. Complications of renal failure or prolonged cholestasis were more frequent in patients older than 30 yr. In conclusion, most patients with acute hepatitis A recover uneventfully, however, complication rates are higher in patients older than 30 yr than younger patients. Preventive strategies including universal vaccination in infants and active immunization of hepatitis A to adult population should be considered for prevention of community-wide outbreaks of hepatitis A in Korea.

Keywords: Hepatitis A; Morbidity; Mortality

INTRODUCTION

The seroprevalence of hepatitis A differs by region according to urbanization and environmental hygiene. Hepatitis A was endemic in Korea, and most people were infected asymptotically in early childhood with lifelong immunity (1, 2). However, the seroprevalence of hepatitis A has been decreasing over the last thirty years with the improvement in the socio-economic status and general public health (3-5). The decrease in hepatitis A virus (HAV) infection in young adults has resulted in the reduction of individuals who have been naturally immunized and has thus resulted in an increase in the adult population at-risk for acquiring the disease. Sporadic cases and regional outbreaks of hepatitis A have been reported during the last 15 yr (6-10). The majority of patients develop self-limiting acute illness following HAV infection; however, the disease in adults can lead to serious complications. Recent studies showed increasing tendency in mean age and severity of the disease in symptomatic hepatitis A (11, 12). Complications of hepatitis A, such as cholestatic hepatitis, relapsing hepatitis or prolonged course, and acute renal failure are not uncommon during the course of hepatitis A (13-15). Symptomatic hepatitis A is increasing recently in Korea. The surveillance data from Korea Centers for Disease Control (KCDC) demonstrated that the number of hepatitis A patients was rapidly increasing, as a large number of patients developed hepatitis from 2007 to 2009 (16).

The aims of this study were to investigate the clinical characteristics and complications of acute hepatitis A during the recent outbreak in Korea.

MATERIALS AND METHODS

Patients

Consecutive patients with acute hepatitis A, who visited hospitals during the period between June 2007 and May 2009, were included in this study. From medical records of the institutions, the patients with hepatitis A-related disease categorization codes were collected. A disease categorization codes include the International Classification of Diseases 10 classification system, B15 (acute hepatitis A), B15.0 (hepatitis A with hepatic coma), and B15.9 (hepatitis A without hepatic coma). There were 21 tertiary hospitals from which the data was obtained and these hospitals are distributed throughout Korea. The patients' medical records were reviewed retrospectively. Acute hepatitis A was diagnosed by typical symptoms of acute hepatitis, by the presence of serum IgM anti-HAV, and by the exclusion of other etiologies of acute hepatitis including acute hepatitis B virus infection, drug, ischemia, autoimmune hepatitis, or vascular disorders.

Study design

Demographic, clinical, and laboratory data of liver function and viral markers were collected during the initial visit and at all follow ups. In addition, we studied the incidences of complications such as acute renal failure, cholestatic hepatitis, relapsing hepatitis, fulminant hepatitis, death, or transplantation. Acute renal failure was defined as an increase in serum creatinine of 0.5 mg/dL over the base-line value or an increase of more than 50% over the base-line value in patients with no history of renal dysfunction (17). Fulminant hepatic failure was defined as the presence of coagulopathy (prolongation of prothrombin time, international normalized ratio [INR] ≥ 1.5) and clinical evidence of hepatic encephalopathy within 26 weeks of symptom onset in the absence of pre-existing liver disease (18). Cholestatic hepatitis was defined as persistence of cholestatic features (bilirubin > 2.5 mg/dL) for more than 8 weeks (19). Relapsing hepati-

tis was defined as recurrence of symptoms and liver function abnormalities (ALT $> \times 2$ nadir) after an apparent recovery (14).

Statistical analysis

Continuous variables were expressed as mean and standard deviations, and the Student's t-test was employed to compare parametric data. Nonparametric data were analyzed with Mann-Whitney U-test. Categorical variables were expressed as frequency distributions, and Chi-square or Fisher's exact tests were performed. All *P* values were two-tailed, and *P* values < 0.05 were considered statistically significant.

Ethics statement

This study's protocol was approved by the institutional review board of Konkuk University Hospital (IRB No. KUH 1010092) and each institute. Informed consent was waived by the board. The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Demographic data of hepatitis A patients

A total of 4,218 patients with acute hepatitis A were included. Male gender was predominant (62.4%). Mean age of the patients was 33.3 yr (standard deviation [SD] 7.7 yr, range 4 to 76 yr). Hepatitis A frequently occurred in their thirties (52.8%), and 17.6% of the patients was over forty years old (Fig. 1). Among the 4,218 patients, 3,555 (59.1%) were admitted via emergency room for severe symptoms. The median duration of admission was 9 days (SD 5.1 days, range 2 to 59 days). During one year, the occurrence of hepatitis A peaked during the months April to August (Fig. 2).

Clinical manifestations

The frequent symptoms of hepatitis A are summarized in Table

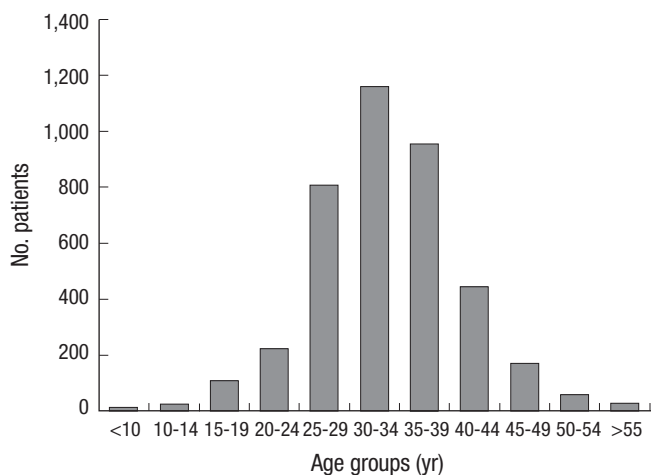


Fig. 1. Age distribution of hepatitis A patients (n = 4,218).

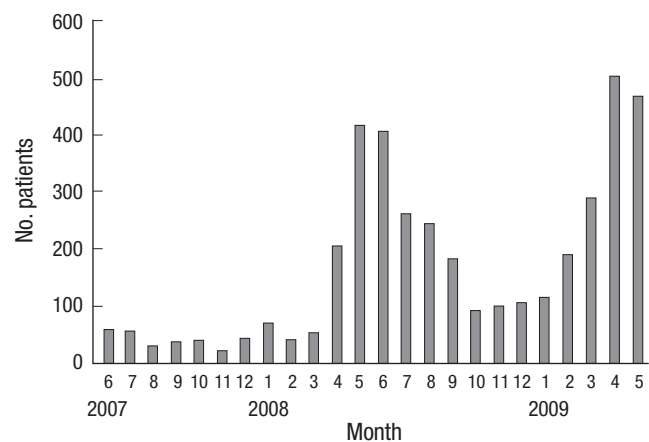


Fig. 2. Distribution of hepatitis A patients (n = 4,218) by month.

Table 1. Symptoms and signs of hepatitis A (n = 4,218)

Symptoms and signs	Frequency (%)
Nausea, vomiting	77.2
Fatigue	74
Fever	71.5
Loss of appetite	66.2
Jaundice	49
Arthralgia	17.8
Diarrhea	13.4
Skin rash	4.4

Table 2. Laboratory findings of hepatitis A patients (n = 4,218)

Laboratory items	Results
AST (IU/L)	2,676 ± 3,347
ALT (IU/L)	2,963 ± 2,412
Alkaline phosphatase (IU/L)	272 ± 179
GGTP (IU/L)	378 ± 238
Albumin (g/dL)	3.6 ± 0.5
Total bilirubin (mg/dL)	7.3 ± 5.3
Prothrombin time (INR)	1.3 ± 0.5
Creatinine (mg/dL)	1.1 ± 1.5
WBC (μL)	5,101 ± 2,509
Platelet (× 1,000/μL)	177 ± 84

Data represents mean ± S.D. of the peak (highest or lowest) level during the follow-ups. AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGTP, gamma glutamyl transpeptidase; WBC, white blood cell.

Table 3. Mortality and morbidity rates of hepatitis A

Outcomes	Frequency (case/total)
Death or transplantation	0.47 (19/4,024)
Acute renal failure	2.73 (108/3,949)
Hepatic failure	0.91 (36/3,949)
Cholestatic hepatitis	1.92 (74/3,855)
Relapsing hepatitis	0.65 (25/3,860)

1. Gastrointestinal symptoms and fever were most frequent, and jaundice was observed in approximately 50% of the patients. Laboratory findings showed severe hepatic dysfunction (Table 2). Mean peak ALT was 2,963 IU/L (SD 2,412) with a mean peak bilirubin of 7.3 mg/dL (SD 5.3).

Serologic data showed HBsAg was positive in 3.7% (153/4,049), anti-HBs in 63.7% (2,628/3,936), and anti-HCV was positive in 0.7% (29/3,937), respectively.

Outcomes of hepatitis A

Fulminant hepatic failure developed in 0.91% of hepatitis A patients. Table 3 demonstrates mortality and morbidity of the hepatitis A patients. Nineteen of 4024 (0.47%) patients died or required liver transplantation. Ten patients died due to fulminant hepatic failure and 9 patients received liver transplants, and 5 of the transplanted patients survived. The incidence of renal failure without combined fulminant hepatitis was 2.73%. The mean age of the 19 cases with mortality or transplantation was not different compared to that of total hepatitis A patients. Severe

Table 4. Clinical characteristics of cases including death or liver transplantation (n = 19)

Clinical characteristics	Results
Mean age (yr)	33 ± 12.2
Male/Female	10/9
Admission duration (day)	17.5 ± 11.9
HBsAg positive	3 cases
Anti-HCV positive	0 case
AST (IU/L)	4,059 ± 5,757
ALT (IU/L)	2,893 ± 3,419
Total bilirubin (mg/dL)	20.3 ± 13.7
Albumin (g/dL)	2.9 ± 0.6
Prothrombin time (INR)	3.3 ± 1.6
Creatinine (mg/dL)	3.8 ± 5.2

Data represents mean ± S.D. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 5. Clinical and laboratory characteristics by age groups in acute hepatitis A

Characteristics	Age < 30 (n = 1,183)	Age ≥ 30 (n = 2,824)	P value
Male/Female	667/516	1,838/986	< 0.001
Death or LT	0.61% (7/1,147)	0.44% (12/2,748)	0.644
Renal failure	1.33% (15/1,132)	3.15% (85/2,614)	0.001
Hepatic failure	0.88% (10/1,132)	0.96% (26/2,699)	0.815
Cholestatic hepatitis	0.9% (10/1,107)	2.35% (62/2,636)	0.007
Relapsing hepatitis	0.18% (2/1,107)	0.83% (22/2,647)	0.025
ALT (IU/L)	2,815 ± 2,869	3,023 ± 2,203	0.029
Total bilirubin (mg/dL)	6.5 ± 4.3	7.7 ± 5.6	< 0.001
Albumin (g/dL)	3.7 ± 0.4	3.6 ± 0.4	< 0.001
Creatinine (mg/dL)	0.9 ± 0.9	1.2 ± 1.6	< 0.001
Prothrombin time (INR)	1.3 ± 0.46	1.34 ± 0.64	< 0.001
WBC (μL)	4,900 ± 2,364	5,166 ± 2,566	0.003
Platelet (× 1,000/μL)	177 ± 81	177 ± 858	0.691

Laboratory data shows mean ± SD. LT, liver transplantation; ALT, alanine aminotransferase.

hepatic dysfunction and impairment of renal function was observed in the mortality cases including death or liver transplantation (Table 4). HBV carrier rate was high in the mortality cases (3/19 patients, 15.8%), however, statistical analysis was not available due to great difference in a number of patients.

Comparison of clinical findings by age group

The severity of hepatitis A was compared between patients younger and older than 30 yr (Table 5). There was no significant difference in mortality. However, complication rates such as renal failure and cholestasis were significantly higher in the group older than 30 yr. Laboratory data revealed that levels of transaminases, total bilirubin, and creatinine were significantly higher in the group older than 30 yr, and showed more prolonged prothrombin time and lower albumin in the group (Table 5). Those results represented greater severity in hepatic and renal dysfunction in the group older than 30 yr. Interestingly, male/female ratio was significantly different between the two groups. Proportion of male patients was higher in the group older than 30 yr.

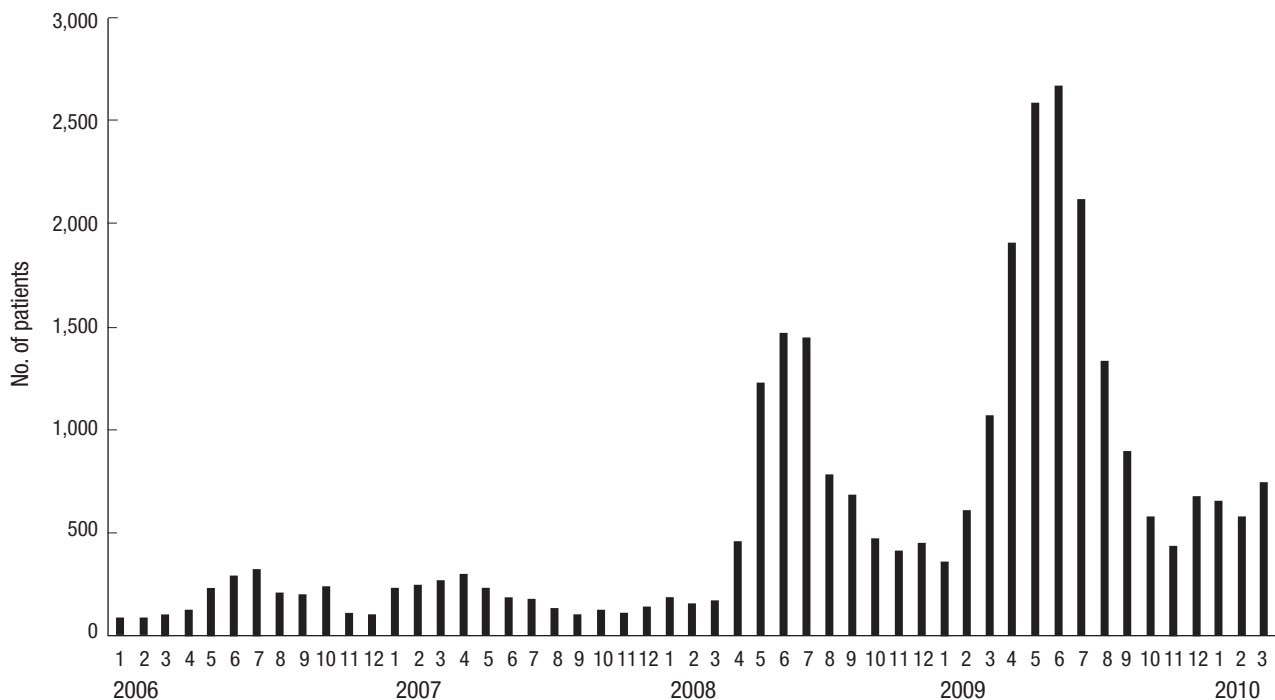


Fig. 3. Number of acute hepatitis A from data of national surveillance in 2006-2010 in Korea [Reference 16].

DISCUSSION

This study demonstrated that symptomatic hepatitis A occurred primarily in adult populations, the mortality rate including death or liver transplantation was 0.47%, and a significant number of patients experienced complication of renal impairment or prolonged cholestasis. HAV infection used to be endemic in Korea and often occurred asymptotically in early childhood with lifelong immunity. However, improvement in the economic status and general public health over the last 30 yr has led to a change in seroprevalence of hepatitis A (3-6). Recent studies have demonstrated that the positivity of anti-HAV decreased to less than 10% in the children and adolescents, 20%-30% in young adults and the seropositivity is over 90% in adults over 40 yr of age not only in Korea but also in many countries (4, 20-22). The decrease in HAV infection in young adults has resulted in an increase in the adult population that is susceptible to the infection. In Korea, symptomatic hepatitis A has been increasing from mid 1990s; in 1998, a countrywide outbreak of the disease occurred. A nationwide study of hepatitis A from 1996 to 1998 including 1391 patients showed that their mean age was 26.5 yr, and most cases recovered uneventfully (23). Lee et al. (23) reported that two cases (0.14%) with HAV superinfection among the chronic hepatitis B patients died of fulminant hepatitis. At present, the most common etiology of acute viral hepatitis is hepatitis A virus (50%-90%) (24, 25). In addition, hepatitis A is becoming a common etiology of fulminant hepatitis and an increasing need for liver transplantation (26). Surveillance data

from KCDC showed that the incidence of hepatitis A was gradually increasing after 2000, and large number of patients developed hepatitis from 2007 to 2009 (Fig. 3) (16). This study included 4,218 hepatitis A cases from the 21 participating institutions during the 2 yr of this study. The incidence of hepatitis A was highest in persons over age 30 yr. This result may suggest that the age of the population susceptible to hepatitis A is getting older and it may result in worse outcomes of the disease.

Hepatitis A is a self-limited acute disease in most cases. Most children younger than 6 yr of age are asymptomatic or develop a mild self-limiting illness (27). However, adults with HAV infection can develop more severe symptoms, which can lead to serious complications (11, 28). Therefore, the increasing incidence of HAV infection due to changing seroepidemiology in adults might have an impact on morbidity and mortality. In this study, most patients had severe clinical manifestation of gastrointestinal symptoms and jaundice, and more than a half of the patients visited emergency room for the severe illness. Laboratory data also showed severe hepatitis in terms of abnormal liver function test, the mean levels of peak ALT (2,963 IU/L) and total bilirubin (7.3 mg/dL). Also, unusual pattern of hepatitis A, such as cholestatic hepatitis, relapsing hepatitis or prolonged course, occurs in a considerable number of patients. In this study, most patients with hepatitis A recover uneventfully. However, fulminant hepatic failure occurred in 0.91% of the patients, and mortality rate including death or liver transplantation was 0.47%. This represents that hepatitis A is no longer a mild disease in the current situation as it presents in Korea. Unusual complica-

tions of hepatitis A were not rare. Acute renal failure occurred in 2.73% of the patients, and some patients were treated with renal replacement therapy. Acute renal failure without fulminant hepatitis is not uncommon during the course of hepatitis A. The patients with the acute renal failure have more severe hepatitis than those without renal failure, however, most cases have a good prognosis. Cholestatic hepatitis with prolonged cholestasis and pruritus was observed during the disease course in 1.92% of the patients. The prolonged cholestasis and itching in hepatitis A usually has a benign course, however, they results in decrease in the patients' quality of life, prolonged duration of admission, and increase in the medical costs (13, 19). The incidences of the complications were different between our study and previously published data in 1998 from Korea. They reported the complication rate of prolonged cholestasis was 4.7% and acute kidney injury was 1.5% (23). This discrepancy could be in part due to different criteria of the complication and characteristics of patients enrolled. The 19 mortality cases had similar characteristics of age and gender to the included patients. Hepatitis A may lead to a serious morbidity or mortality in those patients with chronic liver disease (29). The seroprevalence of HAV infection in patients with chronic liver diseases is similar to that in general population by age (30, 31). It has been reported that the clinical features of hepatitis A are severe in patients with chronic HBV infection (32, 33). However, the clinical impact of chronic hepatitis B on the prognosis of hepatitis A is still controversial. Kim et al. (33) reported that acute hepatitis A superimposed on chronic HBV infection is associated with serious morbidity and mortality including acute liver failure compared with acute hepatitis alone. Our data revealed that the prevalence of HBsAg in the study population was 3.7%, which is a similar rate in young Korean adults. The HBV carrier rate was high in the mortality cases (15.8%), though statistical significance could not be analyzed due to small number the mortality cases as compared with the study population. Seroprevalence of HAV was low in young and middle-aged adults, therefore, catch-up vaccination of HAV should be recommended particularly in chronic HBV carriers and cases with chronic liver diseases.

Acute renal failure associated with non-fulminant hepatitis A is not uncommon in acute hepatitis A patients. The incidence of renal failure is reported as 1%-5% and has increasing tendency by age (13, 15). The prognosis of renal failure acute hepatitis A is generally benign, although the patients with acute renal failure experience severe hepatitis in terms of clinical outcome and laboratory findings (15). Some patients need renal replacement therapy and prolonged admission, however, permanent renal complication does not occur. In this large scale study, the incidence of acute renal failure in non-fulminant cases was 2.73% (108/3949) and there was no mortality in the patients with renal failure. In addition to the renal complication, hepatic failure, cholestatic hepatitis, or relapsing hepatitis were not rare in the hep-

atitis A patients. These complications lead to mortality or prolonged course of recovery and much more medical and social costs.

The prognosis of hepatitis A is dependent on the age of patient. Young children less than 5 yr are usually asymptomatic, while most elder children and adults develop symptoms with jaundice and high levels of serum aminotransferase (11, 27, 28). Recent studies revealed the seroprevalence of anti-HAV is less than 50% in adult population of 20 yr to 40 yr (3-5, 20). In this study, the median age of the patients was 33.3 yr, and substantial numbers of patients were over 40 yr. We compared the severity of hepatitis between the groups of the patients younger and older than 30 yr. The clinical manifestations including complications and laboratory data showed that the clinical course in terms of hepatic dysfunction and renal complication was worse in the group of the patients older than 30 yr than in younger patients. These epidemiologic and clinical results suggest that the change of epidemiologic pattern of hepatitis A in our country may lead to increase the disease burden and increase in healthcare cost. Recently, most pediatricians recommend HAV vaccination during childhood, although it is not included in universal immunization program in Korea. Catch-up vaccination of HAV should be considered in the adult population to reduce community-wide outbreak of symptomatic hepatitis A and its morbidity.

This study was a large-scale, nationwide study of symptomatic hepatitis A, however, it had some limitations. First, only patients from tertiary referral centers were included. This is likely to largely influence the complication rates seen with acute hepatitis A. We included the patients visiting outpatient clinic as well as patients with admission. However, the morbidity and mortality rates might be overestimated by the patients' characteristics enrolled. Second, this data did not show the genotype distribution, which could be associated with the different severity of the disease. This demonstrated the clinical manifestations of the acute hepatitis A in a large number of cases. The genotypic differences of genotypes in recent outbreak and potential confounding factors should be investigated for the prediction of outcomes and prevention of hepatitis A.

In conclusion, symptomatic hepatitis A in adulthood occurs frequently in Korea, and the changing epidemiologic pattern of the disease may increase disease severity and incidence of complications. Strategies of vaccination against HAV in adult population, as well as children, should be established for the prevention of potential outbreaks of hepatitis A and decrease the disease burden.

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DISCLOSURE

All authors have no conflicts of interest to disclose.

ORCID

So Young Kwon <http://orcid.org/0000-0003-4290-1950>

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