A RETROSPECTIVE THAI NATIONWIDE STUDY OF THE INCIDENCE OF ACUTE HEPATITIS A INFECTION AND THE IMPACT OF CHRONIC LIVER DISEASE COMORBIDITY ON SURVIVAL

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Abstract. Hepatitis A virus (HAV) infection is common in developing countries. An accurate incidence of HAV infection and the effect of HAV infection on patients with chronic liver disease (CLD) are not well defined in Thailand. We aimed to determine the incidence of HAV infection in Thailand and the impact of CLD comorbidity on clinical outcomes among hospitalized patients. This was a nationwide, retrospective observational study conducted using hospital admission data during 2008 to 2013 from Nationwide Hospital Admission Data, National Health Security Office. All patients with a primary diagnosis of HAV infection were included in this study. Data regarding baseline characteristics, comorbidities, hospital course and survival were collected. Overall, 1,481 patients from 347 hospitals across Thailand were included in the study. Fifty-four point eight percent of patients (n=812) were from northeastern Thailand. Seventy-four point six percent of patients (n=1,105) contracted the infection during the rainy season (June to November) which was significantly more often (p<0.001) than the other seasons. The 30-day mortality after hospitalization with HAV infection was significantly higher among patients with CLD than among those without CLD (18.9% *vs* 1.6%; p<0.001). Age >60 years, history of liver cirrhosis and history of chronic hepatitis B or C infection were significantly positively associated with 30-day mortality. CLD was associated with a greater risk of mortality among study subjects. People in the study population with CLD, and those aged > 60 years should consider hepatitis A vaccination to reduce mortality risk associated with HAV infection.

Keywords: hepatitis A infection, chronic liver disease, epidemiology, mortality, Thailand

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INTRODUCTION

Hepatitis A is an acute liver infection caused by the hepatitis A virus (HAV). The HAV is a non-enveloped, single-stranded, linear RNA virus, classified as a hepatovirus in the Picornaviridae family (WHO, 2012). It is estimated to cause 126 million cases of acute hepatitis worldwide and 35,000 deaths annually (Aggarwal and Goel, 2015).

Thailand is transitioning from having a low to an extremely low HAV endemicity based on the increase in the age at which 50% of the population was positive for anti-HAV IgG antibody from 6 years in 1976 to 42 years in 2014 (Sa-nguanmoo *et al*, 2016). Despite global improvement in sanitation and hygiene, various community outbreaks of HAV have been reported in many countries (Hutin *et al*, 1999; Kim *et al*, 2017; Scavia *et al*, 2017). In addition, several outbreaks have been reported from Thailand (Theamboonlers *et al*, 2009; Poovorawan *et al*, 2013; Ruchusatsawat *et al*, 2017).

HAV infection often causes acute hepatitis in adults in contrast to asymptomatic or subclinical infection in children (Nelson and Murphy, 2013). Infection in adults is typically symptomatic, with jaundice occuring in 50%–70% of infected individuals (Van Effelterre *et al*, 2016). In Thailand, the hospital admission rate of symptomatic hepatitis A infected patients during outbreaks is 30.6% (Poovorawan *et al*, 2013).

HAV infection is generally self-limited; is effectively controlled by the host immune response and does not progress to chronic infection (Shin *et al*, 2016). Although self-limited disease is seen in most cases, fulminant hepatic failure caused by HAV infection can occasionally occur (Ajmera *et al*, 2011). HAV infection is one of the leading causes of acute liver failure among pediatric patients in South America (Uribe *et al*, 2010).

Chronic hepatitis B and C infections are common worldwide and are estimated to be a leading cause of death and disability worldwide (Stanaway *et al*, 2016). Chronic hepatitis B and C infections have been reported to be risk factors for fulminant hepatic failure during HAV infection (Vento *et al*, 1998; Pramoolsinsap *et al*, 1999; Pramoolsinsap, 2000;). Underlying chronic liver disease (CLD) is a major factor affecting the outcome among patients with acute HAV infection (Kyrlagkitsis *et al*, 2002). HAV infection is a risk factor for acute-on-chronic liver failure among CLD patients in India (Shalimar *et al*, 2016). Age has also been found to be a factor affecting outcomes among patients with HAV infection (Kyrlagkitsis *et al*, 2002; Ly *et al*, 2014). HAV super infection has been reported to be a cause of acute hepatic decompensation among a patient with Wilson's disease (Ozcay *et al*, 2007).

Despite the availability of a HAV vaccine, only some countries have introduced the vaccine in routine childhood immunizations (Nelson and Murphy, 2013). Most countries recommend the vaccine for persons at an increased risk for contracting HAV infection, such as those with CLD (WHO, 2012). However, vaccination rates among patients with CLD remain relatively low (Koenig *et al*, 2016).

An accurate incidence of HAV infection and the effect of HAV infection on patients with CLD are not well defined in Thailand. This study aimed to determine the incidence of hepatitis A infection in Thailand and the impact of CLD on the outcomes among patients hospitalized with HAV infection.

MATERIALS AND METHODS

Study design

We conducted a nationwide retrospective observational study in Thailand among patients admitted to the hospital with HAV infection during 2008-2013 using data obtained from national hospital admissions obtained from the National Health Security Office (NHSO) for Thailand. The data was obtained from 144 private hospitals and 905 government hospitals registered with the National Health Security Office. All diseases were classified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10): those with ICD10 codes B150 and B159 for acute hepatitis A were included in the study. Epidemiological data, baseline characteristics, hospital course and outcomes of each subject were recorded and all-cause mortality data were retrieved from the national death registry.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 13 (SPSS, Chicago, IL). Means ± standard deviations (SD) were used to describe continuous variables, and percentages were used to describe categorical data. Continuous variables were compared between groups using an independent *t*-test or one-way ANOVA. Categorical variables were compared between groups using the chi-square or Fisher's exact test. For survival analysis, Kaplan-Meier survival curves were compared between different groups using the log-rank test. Cox regression models were used to identify risk factors associated with 30-day mortality caused by acute hepatitis A.

Ethical considerations

This study was approved by The Gastroenterological Association of Thailand in collaboration with The National Health Security Office, Thailand. All data used in this study were de-identified and released for research purposes. The research protocol was approved by the Institutional Review Board, Faculty of Tropical Medicine, Mahidol University (MUTM-EXMPT 2015-003).

RESULTS

A total of 1,481 subjects (comprised of 1,515 admissions) from 347 hospitals were included in the study. The mean (±SD) age of study subjects was 29(±18) years; 53.6% of patients were male. Fifty-eight patients (3.9%) had CLD: alcoholic liver disease, chronic hepatitis B or C and/or liver cirrhosis. The median length of hospitalization was 3 days (interquartile range: 2-4 days) and the mean (±SD) cost of hospitalization was USD215 (±398). The mean (±SD) length and cost of hospitalization were both significantly higher among patients with CLD than without CLD [5.7(±6.1) *vs* 3.5(±3.2 days] and USD503(±906) *vs* USD202(±356), respectively; $p<0.01$) (Table 1).

The geographic distribution of cases is shown in Fig 1. The areas with the greatest densities of cases were the northeastern and western border provinces.

HAV infections occurred throughout the year. The average (±SD) number of admissions monthly ranged from 11(±3) in December to 94(±163) in July. The highest incidence of HAV infections occurred in the rainy season (June to November; 1,105/1,481; $p<0.001$). Most cases occurred during a large outbreak from June to September 2012 (Fig 2).

Table 1
Evaluation of various selected factors by presence or absence of CLD.

Factor	Total (N = 1,481)	Without CLD (n = 1,423)	With CLD (n = 58)	p-value
Mean(±SD) age in years	29.3 (±18.2)	28.6 (±18.0)	44.6 (±16.3)	<0.01
Male sex, *n* (%)	794 (53.6)	765 (53.8)	29 (50)	0.59
Mean(±SD) length of hospital stay in days	3.6 (±3.4)	3.5 (±3.2)	5.7 (±6.1)	<0.01
Mean(±SD) cost of hospitalization in USD	215 (±398)	202 (±356)	503 (±906)	<0.01
In-hospital mortality, *n* (%)	11 (0.7)	5 (0.3)	6 (1.0)	<0.01
All-cause mortality after hospitalization with hepatitis A infection				
30 days, *n* (%)	33 (2.2)	22 (1.5)	11 (18.9)	<0.01
90 days, *n* (%)	57 (3.8)	41 (2.9)	16 (27.6)	<0.01

SD, standard deviation; USD, US dollars; CLD, chronic liver disease.

The estimated annual incidence of HAV infections was calculated based on the admission rate of approximately 30.6% for acute symptomatic HAV infection, coverage of admission data and modelling data for HAV infection in Thailand, where symptomatic infection was estimated to have occurred in approximately 70% of patients during the study period (Poovorawan *et al*, 2013; Van Effelterre *et al*, 2016). The total estimated number of HAV infection cases was 7,682, and the annual incidence was estimated to be 3.2 cases per 100,000 population during the study period.

Long-term all-cause mortality after hospitalization for HAV infection increased over time. The 30- and 90-day mortality rates after hospitalization for HAV infection were significantly higher among patients with CLD than those without CLD (18.9% *vs*. 1.5% and 27.6% *vs* 2.9%, respectively; p<0.001) (Fig 3).

Using the multivariable Cox regression method, age >60 years, history of liver cirrhosis and history of chronic hepatitis B or C infection were significantly independently associated with 30-day mortality. Chronic hepatitis C infection was the risk factor with the greatest association with increased 30-day mortality (hazard ratio = 21.11; 95% confidence interval: 2.80–159.17; p = 0.003). However, alcoholic liver diseases were not significantly associated with increased 30-day mortality (Table 2).

DISCUSSION

From 2008 to 2013, 1,481 patients were hospitalized with a primary diagnosis of acute hepatitis A in Thailand. Despite the low overall incidence of hepatitis A infection, it remained epidemic along the western and northeastern borders of Thailand. Symptomatic infection occurred mostly in young adults and with no gender specificity.

The estimated annual incidence of

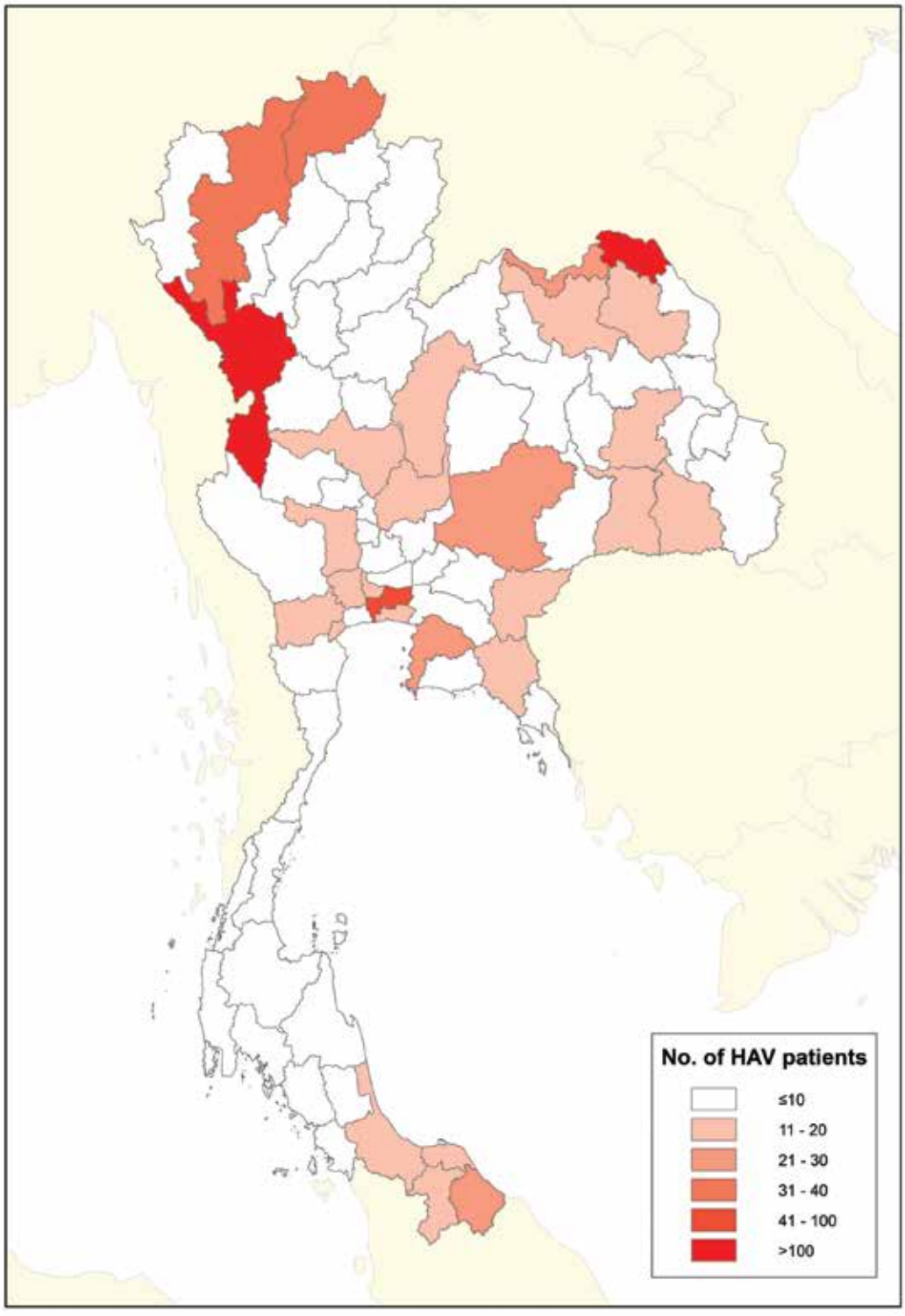

Fig 1–Geographic distribution of study subjects with HAV infection during the study period.

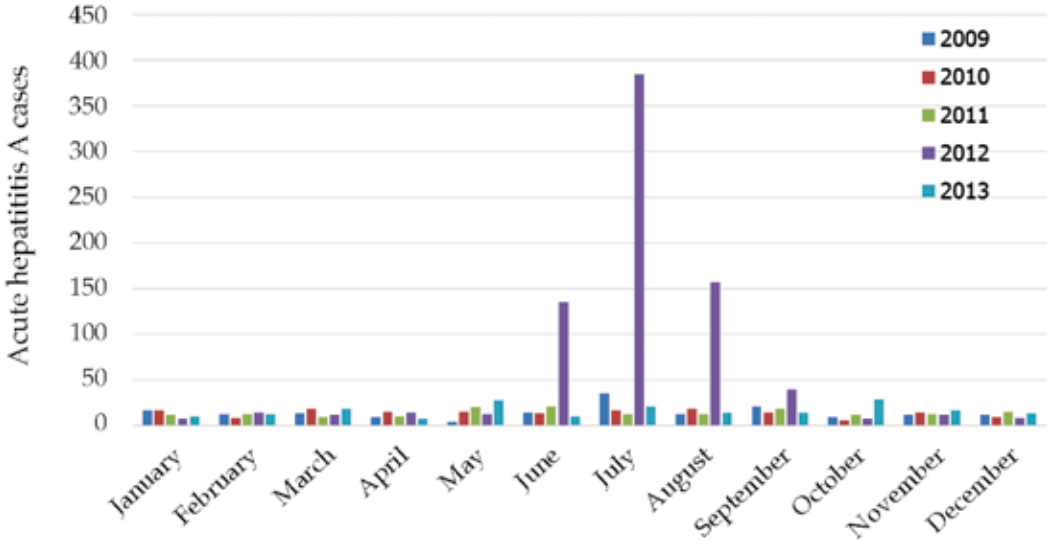

Fig 2–Monthly incidence of hepatitis A by study year.

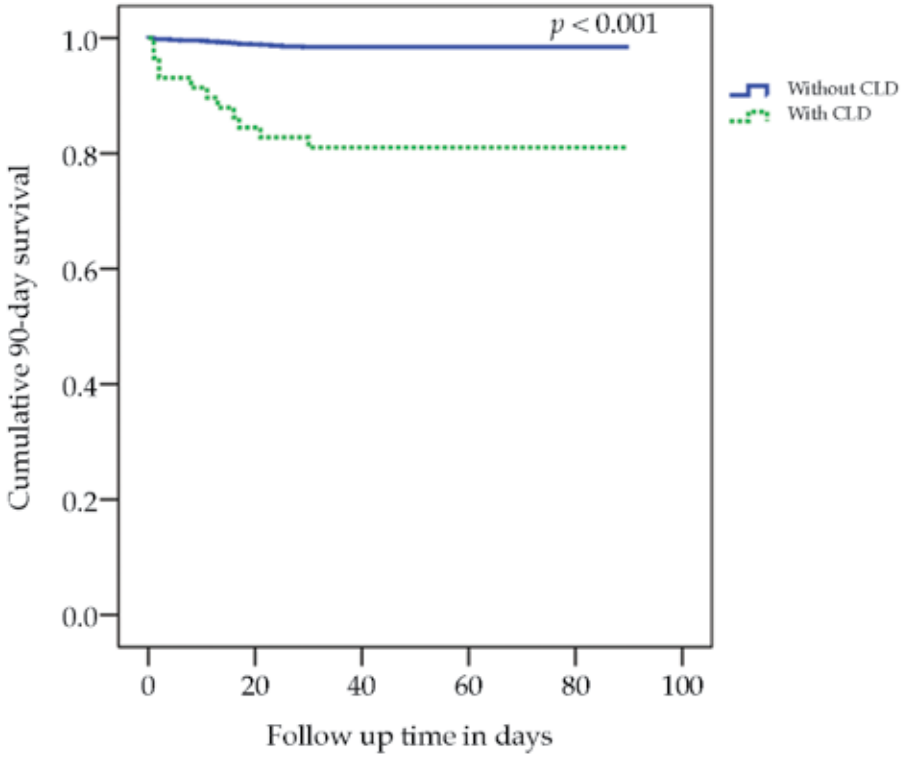

Fig 3–90-day mortality rates among study subjects with and without CLD. CLD, chronic liver disease.

Table 2
Association between various selected independent factors and 30-day mortality among study subjects.

Factor	30-day mortality (%)	Adjusted hazard ratio	95% Confidence interval	*p*-value
Overall (*N* = 1,481)	2.2	-	-	-
Age ≥ 60 years (*n* = 136)	10.3	6.36	3.10-13.06	<0.001
Cirrhosis (*n* = 29)	24.1	8.12	3.01-21.91	<0.001
Alcoholic liver disease(*n* = 17)	17.6	1.46	0.36-5.87	0.593
Chronic hepatitis B (*n* = 17)	11.7	5.83	1.37-24.75	0.017
Chronic hepatitis C (*n* = 5)	20	21.11	2.80-159.17	0.003

HAV infections in Thailand was 3.2 cases per 100,000 population, within the range for the United States in1995 and 2007 (12.0 and 1.0 cases per 100,000 individuals, respectively) (Daniels *et al*, 2009). Under-reporting of cases during non-outbreak periods might have led to underestimation of the incidence of HAV infection.

The morbidity and mortality rates were significantly higher among patients with CLD in our study. In-hospital mortality was 1%, but the 90-day all-cause mortality was much higher (up to 27.6%). These data confirm the findings of a previous study of the severity of HAV infection among CLD patients (Vento *et al*, 1998; Pramoolsinsap *et al*, 1999; Pramoolsinsap, 2000). Chronic hepatitis B, chronic hepatitis C and liver cirrhosis independently affected the mortality rates; this might be because HAV infection can cause acute-on-chronic liver failure (Shalimar *et al*, 2016).

In general, the hepatitis A vaccine is recommended for children aged ≥1 year. A recent study found continuing protective anti-HAV levels for at least 25-30 years among adult subjects who were vaccinated as children (Plumb *et al*, 2017). Although the incidence of HAV infection in developed countries is low, the increase in international travel has led to a great number of HAV infections among travellers (Wu and Guo, 2013). National immunization campaigns for hepatitis A have been adopted in some countries, including the United States, but most developing countries have not adopted this generalized recommendation (Nelson and Murphy, 2013).

Adult vaccination is recommended for individuals at an increased risk for HAV infection and among those at an increased risk of serious clinical outcomes after acquiring infection (*eg*, travellers and CLD patients) (WHO, 2012). Despite this recommendation, the HAV vaccination rates in patients with CLD remain relatively low (Koenig *et al*, 2016).

Many factors, including the seroprevalence of HAV antibodies, anticipated hepatitis A incidence, private sector costs and cost-effectiveness criteria, have an impact on the decision for vaccination among CLD patients (Joshi *et al*, 2007; Chapko *et al*, 2010). Further analysis of the cost effectiveness for each region in Thailand is needed to assess the expenditure involved in targeted vaccination to prevent HAV-related morbidity and mortality and expected benefits (Shouval, 2012).

In summary, despite the decrease in incidence of HAV infection worldwide, the mortality rate from HAV infection in Thailand remains high,particularly among patients with CLD. A hepatitis A vaccination program for CLD patients should be considered and incorporated into the national program to prevent further hepatitis A-related mortality.

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