Original Article

Hypoxic Hepatitis: Prevalence, Biochemical Markers, and Risk Factor of Mortality in a Large Tertiary Hospital

Wutthiphat Amornmongkhol MD[1], Tawesak Tanwandee MD[2]

[1] Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[2] Division of Gastroenterology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Hypoxic hepatitis (HH) is an acute severe liver injury usually associated with several types of hemodynamic instability. The mortality rate is about 50% to 70%.

Objective: To evaluate the prevalence of HH and to study the clinical course and outcomes of these patients.

Materials and Methods: The present study was a retrospective study conducted at Siriraj Hospital. Data were retrieved from the hospital admissions between 2008 and 2018. HH was defined by serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels of more than or equal to 20 times the upper limit of normal in the absence of other causes. Baseline patients' condition, laboratory, and clinical course were collected.

Results: Of the 4,000 admissions, 29 (0.73%) met the criteria for HH. Mean age was 68.2 years old and the median serum AST and ALT levels at the time of diagnosis were 2,065 and 815 IU/L, respectively. Underlying diseases in these patients included hypertension (69%), diabetes mellitus (48.3%), and chronic kidney disease (37.9%). Comorbidities included acute kidney injury (93.1%), sepsis (79.3%), hypotension (75.9%), requirement of vasopressors (65.5%), and acute respiratory failure (55.2%). The mortality rate at day 28 was 72.4%, none were liver related. The only significant risk factor for mortality was lower bicarbonate levels at the time of diagnosis (p=0.012).

Conclusion: HH is uncommon, at 0.73%, and most patients had episodes of hypotension and multi-organ failure. Monitoring of liver function test is advised in this group of patients. The twenty-eight-day mortality rate was 72.4% but none from liver failure. The most common cause of mortality was related to comorbidity of the patients and the only predictor of high mortality was the lower bicarbonate level.

Keywords: Hypoxic hepatitis; Ischemic hepatitis; Shock liver; Mortality; Multi-organ failure

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Hypoxic hepatitis (HH) is an acute severe liver injury usually associated with various causes of hemodynamic instability. Previously, it was called 'ischemic hepatitis' or 'shock liver' that can be misleading since only around half of these cases had no history of obvious circulatory shock[1]. The pathophysiology of HH is often multifactorial, but passive congestion of the liver related to right-sided heart failure is the most frequent mechanisms, as high as 96% of the cases[2,3].

HH is characterized by transient towering of liver transaminases, which are associated with jaundice or liver failure. Diagnosis is usually made clinically by exclusion of other conditions, such as drug-induced liver injury or acute viral hepatitis, together with a clinical setting that is compatible with HH[1]. Liver biopsy can demonstrate centrilobular necrosis but is not performed in HH patients because of multiple co-morbidities, especially with coagulopathy, and has no impact on treatment decisions.

Prior studies reported the incidence of HH in the range of 0.9% to 4.0% depending on population of patients studied. The patients in intensive care unit (ICU) showed a much higher incidence[4,5]. However, another systematic review with meta-analysis done in 2015 included 24 studies with 1,782 cases and found the incidence from all ward and ICU patients was about 2 in 1,000 admission[4]. Although HH is an uncommon condition, it has a high mortality rate of about 50% to 70%[4]. Currently, treatment of HH is just restoration of hemodynamic and treatment of

Correspondence to:

Tanwandee T.

Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.

Phone: +66-2-4197282

Email: tawesak@gmail.com

ORCID: 0000-0001-7634-0843

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underlying condition. There is no specific treatment for HH[6]. However, data on the Asian population from prior studies are scarce. The present study aimed to evaluate the prevalence of HH and to study the clinical course and outcomes of these patients.

Materials and Methods

The present study was a retrospective cohort study aimed to evaluate the prevalence of HH and to study the clinical course of these patients the present study was conducted at Siriraj Hospital, Mahidol University, Thailand between October 30, 2019 and January 25, 2021. The study was approved by the Siriraj Ethical Committee (COA No. Si740/2019) and registered in the Thai Clinical Trials Registry (TCTR20200925005).

Study population

Data were retrieved from the hospital admission chart of patients admitted at Siriraj Hospital between January 1, 2008 and December 31, 2018. This database contained demographic data, vital signs charts, laboratory and radiographic reports, discharge summaries, and death certificates with the International Classification of Diseases, Tenth edition (ICD-10).

Based on a previous study, the incidence of HH in all admissions was approximately 2.4%[4]. The authors calculated the estimated proportion of one group with 20% error of HH incidence and 95% confidence interval, thus, the sample size in the present study was approximately 3,906 admissions. The authors included 4,000 admissions, all of whom were adult patients admitted to the Department of Medicine, including ICU at Siriraj Hospital between January1, 2008 and December 31, 2018.

Of the 4,000 admissions, ICD-10 were screened with possible ICD-10 codes for HH, including K720 as hepatic failure, K759 as inflammatory liver disease, unspecified, K763 as infarction of liver, and R578 as other shock. All admissions that matched the ICD-10 were further investigated to confirm the diagnoses of HH with the following criteria, serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels of more than or equal to 20 times the upper limit of normal (ULN) in the absence of evidence of drug, toxic, or viral hepatitis. Patients with a history of drug and toxin used known to cause drug-induced liver injury were excluded. Specifically, patients with acetaminophen use with a total dose of more than 2 g/day or detectable serum acetaminophen were also excluded. Exclusion criteria for acute viral hepatitis included patients positive for any of the following, anti-HAV IgM, anti-HBc IgM, or anti-HEV IgM, and patients with recent conversion of anti-HCV with detectable HCV RNA. Patients who had evidence of chronic viral hepatitis, such as HBsAg positive or anti-HCV positive, were included only if there was no evidence of hepatitis flare. Those without adequate data would be excluded.

The admissions that met the inclusion and exclusion criteria were recorded, and demographic data including gender, age, and ethnicity, underlying diseases, comorbidities, laboratory results, and outcomes based on APACHE as Acute Physiology and Chronic Health Evaluation II score, length of stay, and death at day 28, were collected. Acute kidney injury was defined as more than or equal to 1.5 times rising in creatinine from baseline. Hypotension was defined as a blood pressure below 90/60 mmHg or a mean arterial pressure (MAP) of below 65 mmHg. Day 0 was defined as the day on which the patient met the inclusion criteria.

Statistical analysis

Age, laboratory results, APACHE II score, and length of stay were defined as continuous variables, while gender, ethnicity, underlying diseases, comorbidities, and mortality at day twenty-eight were defined as categorical variables. Continuous variables were reported as a mean with standard deviation (SD) or a median with P_{25}-P_{75} where appropriate. Categorical variables were reported as percentages. Risk factors of mortality were identified using Fisher's exact test for categorical data, independent sample t-test, and Mann-Whitney U test for continuous data. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Prevalence

Of all 4,000 admissions, 137 admissions that matched with possible ICD-10 codes for HH, but 108 were excluded due to serum AST or ALT levels of less than 20 times ULN, including seven admissions documented in ICD-10 codes as K763: infarction of liver. There were 29 cases that met the HH criteria or the prevalence of 0.73%.

Baseline characteristics

Baseline characteristics of all 29 patients are described in Table 1. Twenty patients (69%) were

Table 1. Baseline characteristics

Baseline characteristics	n=29
Sex: male; n (%)	20 (69.0)
Age (years); mean±SD	68.2±15.6
Admitted in ICU; n (%)	12 (41.4)
Underlying diseases; n (%)	
Ischemic heart disease	3 (10.3)
Severe valvular heart disease	8 (27.6)
Atrial fibrillation	9 (31.0)
COPD or asthma	3 (10.3)
Diabetes mellitus	14 (48.3)
Hypertension	20 (69.0)
Chronic kidney disease	11 (37.9)
HBV infection	1 (3.4)
HCV infection	1 (3.4)
Cirrhosis	6 (20.7)
Hepatocellular carcinoma	3 (10.3)
Other cancers	2 (6.9)
Comorbidities; n (%)	
Acute coronary syndrome	4 (13.8)
Heart failure	12 (41.4)
Unstable arrhythmia	12 (41.4)
Ischemic stroke	2 (6.9)
Mechanical ventilation use	16 (55.2)
Acute kidney injury	27 (93.1)
RRT use	7 (24.1)
Gastrointestinal bleeding	5 (17.2)
Sepsis	23 (79.3)
Cardiac arrest	5 (17.2)
Hypotension	22 (75.9)
Vasopressor use	19 (65.5)
Major surgery	1 (3.4)
APACHE II score[1]; mean±SD	24.5±8.3
Death at day 28; n (%)	21 (72.4)
Length of stay (days); median (P25-P75)	10 (4.5 to 18.5)

SD=standard deviation; ICU=intensive care unit; COPD=chronic obstructive pulmonary disease; HBV=hepatitis B virus; HCV=hepatitis C virus; RRT=renal replacement therapy; APACHE=Acute Physiology and Chronic Health Evaluation

[1] APACHE II score is based on initial values of 12 routine physiological measurements, age, and previous health status

men. The mean age was 68.2 years old. All patients were Thais, and 12 patients (41.4%) were admitted to the ICU. Underlying diseases of these patients before admission included hypertension in 20 (69%), diabetes mellitus in 14 (48.3%), chronic kidney disease in 11 (37.9%), atrial fibrillation in nine (31%), and severe valvular heart disease in eight (27.6%), as shown in Table 1. Thirteen cases (44.8%) had pre-existing heart diseases including atrial fibrillation, severe valvular heart disease, or ischemic heart

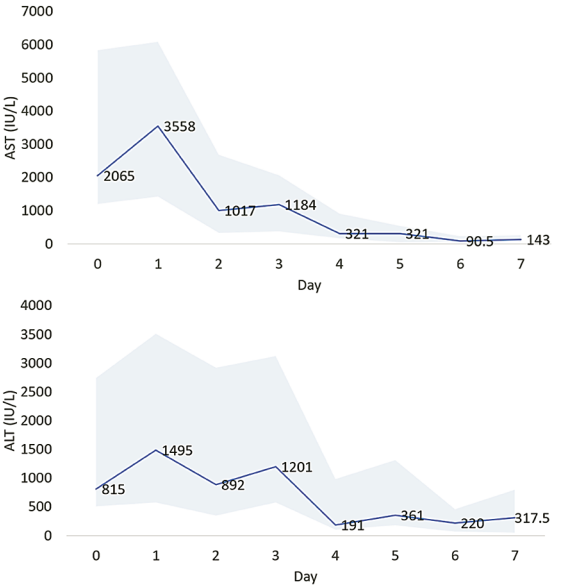

Figure 1. Change of serum AST and ALT levels.

Day 0 defined as the day of serum AST and/or ALT more than or equal to 20 times of UNL

The line and number showed median of serum AST/ALT and the area around the line showed P_{25}-P_{75} of serum AST/ALT

disease, and seven patients (24.1%) had pre-existing liver diseases such as chronic HBV or HCV infection, cirrhosis, or hepatocellular carcinoma.

Comorbidities of these patients at the time of HH were diagnosed included acute kidney injury in 27 (93.1%), sepsis in 23 (79.3%), hypotension in 22 (75.9%), requirement of vasopressor in 19 (65.5%), acute respiratory failure in 16 (55.2%), heart failure in 12 (41.4%), and unstable arrhythmia in 12 (41.4%). Acute kidney injury was the most frequent finding in 27 cases (93.1%), but there were only seven cases (24.1%) that required renal replacement therapy (RRT). Hypotension was a common finding and most of them required vasopressors, but only one was documented as cardiogenic shock. Twenty patients (68.9%) had active cardiac conditions including acute coronary syndrome, heart failure, and unstable arrhythmia. The mean APACHE II score was 24.5 and the median length of stay was 10 days.

Biochemical markers

The median serum AST and ALT levels at the time of diagnosis were 2,065 and 815 IU/L, respectively (Figure 1). Only serum AST levels showed a dramatic decreasing trend after day 1. Serum ALT levels were more discrete compared to serum AST levels. A decreasing trend was also observed in PT, aPTT, INR, serum lactate, and creatinine, while

Table 2. Risk factors for mortality at day 28 (clinical)

	Death at day 28 (21 cases)	Alive at day 28 (8 cases)	Odd ratio (95% CI)	p-value
Sex: male; n (%)	15 (71.4)	5 (62.5)	1.5 (0.27 to 8.34)	0.643
Age (years); mean±SD	69.3±16.1	65.4±14.8		0.555
Admit in ICU; n (%)	9 (42.9)	3 (37.5)	1.25 (0.23 to 6.65)	0.794
Underlying diseases; n (%)				
Ischemic heart disease	3 (14.3)	0 (0.0)	N/A	
Severe valvular heart disease	6 (28.6)	2 (25.0)	1.20 (0.19 to 7.70)	1.000
Atrial fibrillation	6 (28.6)	3 (37.5)	0.67 (0.12 to 3.71)	0.675
COPD or asthma	1 (4.8)	2 (25.0)	0.15 (0.01 to 1.96)	0.176
Diabetes mellitus	12 (57.1)	2 (25.0)	4 (0.65 to 24.66)	0.215
Hypertension	14 (66.7)	6 (75.0)	0.67 (0.11 to 4.20)	1.000
Chronic kidney disease	9 (42.9)	2 (25.0)	2.25 (0.37 to 13.87)	0.671
HBV infection	1 (4.8)	0 (0.0)	N/A	
HCV infection	1 (4.8)	0 (0.0)	N/A	
Cirrhosis	3 (14.3)	3 (37.5)	0.28 (0.04 to 1.82)	0.305
Hepatocellular carcinoma	2 (9.5)	1 (12.5)	0.74 (0.06 to 9.46)	1.000
Other cancer	0 (0.0)	2 (25.0)	N/A	
Comorbidities; n (%)				
Acute coronary syndrome	4 (19.0)	0 (0.0)	N/A	
Heart failure	9 (42.9)	3 (37.5)	1.25 (0.24 to 6.66)	1.000
Unstable arrhythmia	8 (38.1)	4 (50.0)	0.62 (0.12 to 3.18)	0.683
Ischemic stroke	2 (9.5)	0 (0.0)	N/A	
Mechanical ventilation use	13 (61.9)	3 (37.5)	2.71 (0.50 to 14.54)	0.406
Acute kidney injury	19 (90.5)	8 (100)	N/A	
RRT use	6 (28.6)	1 (12.5)	2.8 (0.28 to 27.91)	0.635
Gastrointestinal bleeding	4 (19.0)	1 (12.5)	1.65 (0.16 to 17.47)	1.000
Comorbidities; n (%)				
Sepsis	16 (76.2)	7 (87.5)	0.457 (0.05 to 4.67)	0.647
Cardiac arrest	5 (23.8)	0 (0.0)	N/A	
Hypotension	17 (81.0)	5 (62.5)	2.55 (0.42 to 15.41)	0.357
Vasopressor use	15 (71.4)	4 (50.0)	2.5 (0.47 to 13.39)	0.390
Major surgery	1 (4.8)	0 (0.0)	N/A	

CI=confidence interval; SD=standard deviation; ICU=intensive care unit; COPD=chronic obstructive pulmonary disease; HBV=hepatitis B virus; HCV=hepatitis C virus; RRT=renal replacement therapy; N/A=not applicable

The p-value was identified using Fisher's exact test for categorical data and independent sample t-test and Mann-Whitney U test for continuous data

serum total, direct bilirubin, and bicarbonate levels were increased. Other biochemical markers, including serum alkaline phosphatase, albumin, globulin, hemoglobin, white blood cell count, and platelet count, did not show significant changes.

Mortality rate and risk factor of mortality

The mortality rate at day 28 was 72.4% or 21 of 29 cases, none of which were liver-related deaths. The most common causes of death were infection-related in 11 cases and myocardial infarction with cardiogenic shock. The risk factors for 28-day mortality are described in Table 2 and 3. The only significant risk factor for mortality was lower bicarbonate level at the time of diagnosis, at 14.65 mmol/L versus 23.43 mmol/L (p=0.012). Initial INR had a trend toward higher mortality but did not reach statistically significant (5.79 versus 1.62, p=0.077).

Discussion

The present study showed the prevalence of HH was 0.73% in all medical admissions. A recent meta-analysis revealed that the incidence of HH in all admissions ranges from 0.16% to 2.5%[3]. The higher incidence in ICU admission due to older age, and patients with higher levels of serum transaminases. The present study using a cut-off for serum AST or ALT levels of more than or equal to 20 times the ULN

Table 3. Risk factors for mortality at day 28 (laboratory parameters result at day 0)

	Death at day 28 (21 cases)	Alive at day 28 (8 cases)	p-value
TB; median (P25-P75)	3.15 (1.95 to 5.06)	2.55 (1.33 to 5.9)	0.665
DB; median (P25-P75)	2.42 (1.23 to 3.28)	1.39 (0.64 to 4.92)	0.461
AST; median (P25-P75)	2,466 (1456 to 5,205)	1,422 (870 to 3,331)	0.157
ALT; median (P25-P75)	815 (480 to 2,316)	941 (540 to 2,087)	0.826
ALP; median (P25-P75)	78 (52.75 to 169.75)	97.5 (84.25 to 104.25)	0.242
Albumin; mean (95% CI)	2.74 (2.4 to 3.08)	3.08 (2.52 to 3.63)	0.269
Globulin; mean (95% CI)	3.07 (2.79 to 3.34)	2.93 (2.17 to 3.68)	0.631
PT; median (P25-P75)	27.05 (22.23 to 47.43)	22.9 (17.85 to 79.4)	0.457
aPPT; median (P25-P75)	45.5 (34.3 to 58.7)	33 (28.23 to 63.43)	0.230
INR; median (P25-P75)	5.79 (2.39 to 8.88)	1.62 (N/A)	0.077
LDH; median (P25-P75)	1,746 (N/A)	6,961 (N/A)	0.439
Lactate; median (P25-P75)	9.45 (7.15 to 14.95)	9.45 (7.08 to 15.03)	0.109
Hb; mean (95% CI)	10.09 (9.03 to 11.14)	9.84 (7.41 to 12.27)	0.811
WBC; mean (95% CI)	13.56 (9.62 to 17.49)	12.12 (6.96 to 17.28)	0.666
Platelet; median (P25-P75)	93.5 (63.2 to 117.2)	125.5 (79.7 to 192.2)	0.222
Cr; median (P25-P75)	2.37 (1.55 to 3.1)	2.25 (1.45 to 2.53)	0.479
HCO3; mean (95% CI)	14.65 (12.18 to 17.12)	23.43 (17.3 to 29.56)	0.012
APACHE II score; mean (95% CI)	25.64 (20.49 to 30.8)	21.2 (14.21 to 28.19)	0.317

CI=confidence interval; TB=total bilirubin; DB=direct bilirubin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ALP=alkaline phosphatase; PT=prothrombin time; aPTT=activated partial thromboplastin time; INR=international normalized ratio; LDH=lactate dehydrogenase; Hb=hemoglobin; WBC=white blood count; Cr=creatinine; HCO3=bicarbonate; APACHE II=Acute Physiology and Chronic Health Evaluation score II

The p-value was identified using Fisher's exact test for categorical data and independent sample t-test and Mann-Whitney U test for continuous data

or 640 U/L or more of AST or 660 U/L or more of AST, while most of the studies used cut-off values of serum AST around 400 to 1,000 U/L. Mean age in the present study was 68.2 years old, as one prospective cohort study in geriatric patients aged 65 years old or older resulted in 1% of patients developed HH[7].

The authors observed that about three-fourth of the present study cases had hypotensive episode, which was higher than in recent meta-analysis pooled result of 52.9%, defined by blood pressure below 90/60 mmHg[6]. Twenty cases (68.9%) had active cardiac conditions including acute coronary syndrome, heart failure, or unstable arrhythmia, which was similar to meta-analysis pooled result of 78.2%. The pathogenesis of HH is still not fully understood, but the proposed mechanisms are multifactorial, reduction of cardiac output together with passive congestion of the liver being one of the main mechanisms[6]. This will function as the "first hit" to the liver leading to elevated hepatic pressure that will predisposed to any "second hit" effect. These second hit can be from further hypotension from sepsis or dehydration that sometimes may be brief or transient, cardiac arrhythmia, and respiratory failure. All second hit will further compromise oxygenation, especially in pericentral area hepatocytes causing cell necrosis[7].

In terms of the biochemical profile of HH, serum AST showed a much higher rise than serum ALT at the date of diagnosis followed by dramatic fall, more than 50% within two days after diagnosis. This can be explained by the shorter half-life of AST compared to ALT and restoration of hemodynamic conditions[8-10]. Serum AST was a better laboratory marker than serum ALT in terms of rising and falling patterns.

In the present study, the authors found the all-cause mortality rate at day 28 was 72.4%, which is higher than the meta-analysis pooled result of 49%[3]. Those were infection-related and metabolic acidosis, which resulted in multiple comorbidities, especially acute kidney injury and sepsis. The only risk factor for mortality in the present study was a lower bicarbonate level at the time of diagnosis. Other risk factors of mortality found in previous studies such as INR, acute kidney injury, vasopressor use, and SAPS II score tended to be risk factors for mortality but did not reach statistically significant because of the small number of HH. A recent study had demonstrated prognostic impact of liver function test using indocyanine green plasma disappearance rate (ICG-PDR) with 28-day mortality[11], but the authors did not have that result due to the retrospective study. The most frequent cause of death was comorbidities, not liver failure.

There are limitations to the present study, firstly, this study included only adult patients admitted to the Department of Medicine; second, this was a retrospective study using the ICD-10 code screening method, which can miss the true prevalence of HH, and lastly, there were only 29 cases of HH. However, there are strength of the present study because the authors included all admission, not only patients admitted to ICU but all of the medical admission.

Conclusion

HH was uncommon with the prevalence is 0.73% in overall medical admission. Medical personnel should be mindful of HH in the patients who had episodes of hypotension, especially in the patients with heart failure and multiple organ failure. Liver function test should be part of laboratory investigation. Mortality rate was 72.4% but it was not related to HH. Mortality was usually related to comorbidity such as acute kidney injury, sepsis, hypotension, acute respiratory failure, and heart failure. The only predictor of high mortality was a lower bicarbonate level and most common causes of mortality was related to comorbidities, not the liver failure.

What is already known on this topic?

HH is an uncommon condition that can be found mostly in intensive care patients and most common associated finding was right-sided heart failure and septic shock with high mortality rate. There was no report from Asia Pacific countries.

What this study adds?

The incidence of HH in Thailand was comparable to the previous report from western countries in both general medical admission and ICU admission. However, evidence of heart failure was less than the previous studies, but shock was more commonly found followed by typical towering of liver enzymes. Mortality rate was high, but mostly not related to liver failure.

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Conflicts of interest

The authors declare no conflict of interest

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