

**Recent changes and clinical  
characteristics of acute hepatitis A  
complicated by acute kidney injury**

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**Recent changes and clinical  
characteristics of acute hepatitis A  
complicated by acute kidney injury**

Directed by Professor Kwan Sik Lee

The Master's Thesis submitted to the Department of  
Medicine, the Graduate School of Yonsei University  
in partial fulfillment of the requirements for the degree  
of Master of Medical Science

Jung Hwan Yu

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This certifies that the Master's Thesis of  
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ABSTRACT

**Recent changes and clinical characteristics of acute hepatitis A complicated by acute kidney injury**

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(Directed by Professor Kwan Sik Lee)

The incidence of acute viral hepatitis A (AHA) in Korea is increasing quickly. In addition, we are encountering more cases with acute kidney injury (AKI), which was once regarded as a rare complication of AHA. Therefore, we investigated recent aspects of the incidence and clinical characteristics of AHA complicated by AKI. Patients diagnosed with acute hepatitis A at Severance Hospital and Gangnam Severance Hospital from January 2006 to December 2009 were enrolled. Of 1025 patients, 71 (6.9%) had AKI. The incidence of AKI was 3.1%, 6.0%, 8.9%, and 6.9% in 2006 to 2009, respectively. Patients with AKI were predominantly male, heavy alcohol drinkers and smokers and had more underlying hypertension than patients without AKI. The patients with AKI had significantly higher white blood cell counts, more prolonged prothrombin times, and elevated liver enzymes, total bilirubin, direct bilirubin, gamma-glutamyltransferase, C-reactive protein, and higher peak of total bilirubin levels, whereas the serum albumin level was lower compared to patients without AKI. Most patients with AHA complicated by AKI recover with conservative treatment, however, we should

pay attention to the patients who have risk factors for AKI because of their possible poor clinical course.

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Key words : acute kidney injury, acute hepatitis A

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## **I. INTRODUCTION**

Acute hepatitis A (AHA) occurs worldwide and is an important public health problem. Recently, its incidence has gradually decreased due to hepatitis A vaccinations and improved public hygiene<sup>1,2</sup>. Conversely, in Korea, the number of AHA patients has increased gradually and the number of cases accompanied by acute kidney injury (AKI), a rare complication of hepatitis A, has also increased<sup>3-6</sup>. After its first report by Wilkinson *et al.* in 1978<sup>7</sup>, AHA accompanied by AKI has been reported regularly, and the frequency reaches 3~7.2%<sup>4,8</sup>. If AHA is accompanied by AKI, the patient often experiences more severe disease with longer hospital stay and recovery is slower. Therefore, more attention should be paid to such cases. In this study, AHA patients were divided

into those with and without accompanying AKI to examine differences in their clinical characteristics.

## **II. MATERIALS AND METHODS**

### **1. Patient selection**

Patients diagnosed with AHA at Severance Hospital and Gangnam Severance Hospital from January 2006 to December 2009 were enrolled. The diagnosis was based on the clinical symptoms and signs and confirmed by the presence of anti-HAV-IgM antibodies. Demographic and serologic data, urinalysis, history including alcohol consumption, and days in hospital were analyzed retrospectively. Exclusion criteria were chronic renal failure, liver cirrhosis, and other renal disease. AKI was defined as an increase in the serum creatinine concentration of  $>0.5$  mg/dl or 50% compared with the baseline value<sup>9</sup>. In AKI group, hepatorenal syndrome was ruled out through urine test (Hepatorenal syndrome shows urine red cell excretion of less than 50 cells per high power field and protein excretion less than 500mg/day). The definition of a heavy alcoholic was an alcohol consumption  $>45$  g/day. Smoking was defined as current smokers who smoke at least 10 cigarettes a day.

### **2. Statistical analysis**

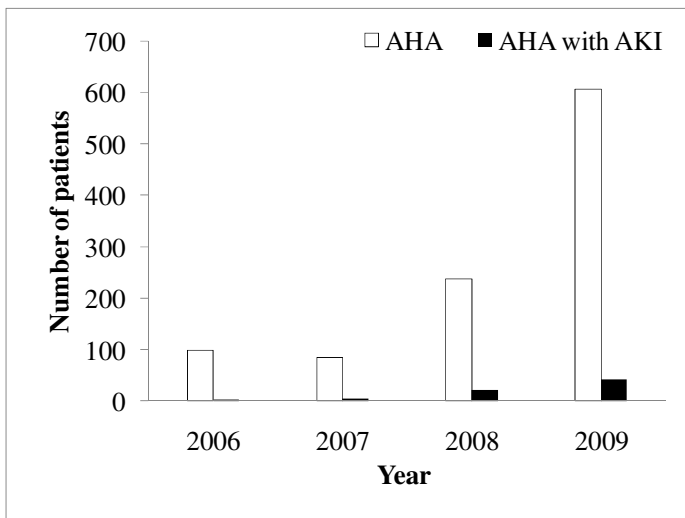
To compare numerical variables, the Student's *t*-test was applied, and for categorical variables, the chi-square test was used. To identify the risk factors for AKI in AHA, we used multivariate logistic regression analyses. All data

were analyzed using SPSS version 16.0 (SPSS, Chicago, IL, USA). The level of statistical significance was  $p < 0.05$ .

### III. RESULTS

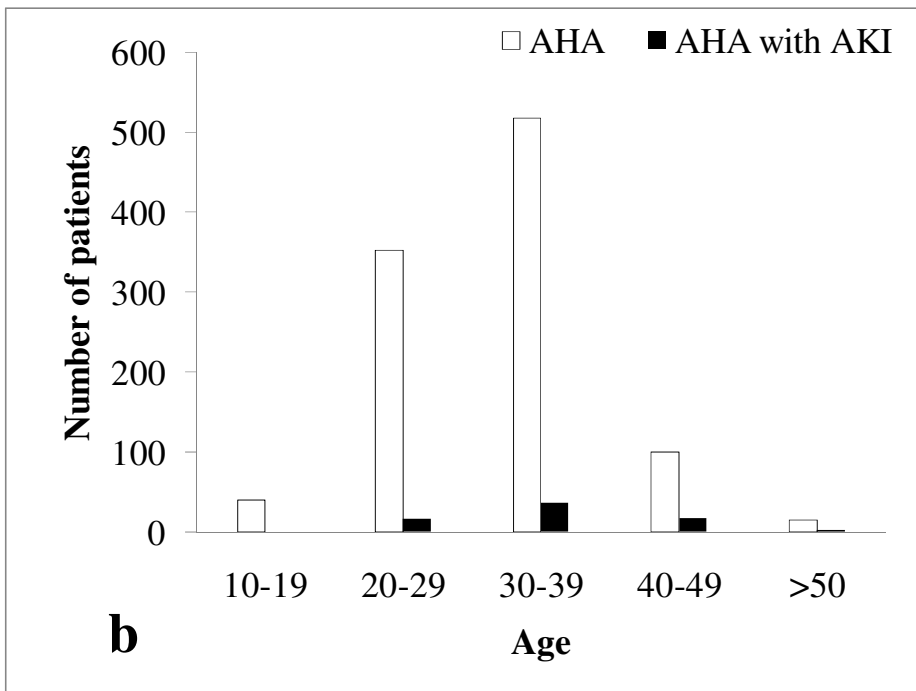
The number of AHA patients increased markedly in 2009 compared to 2006 to 2008 at both Severance Hospital and Gangnam Severance Hospital. Of the 1025 patients, 71 (6.9%) had accompanying AKI. The proportion tended to increase over the 4 years, and was 3.1% (3/98), 6.0% (5/84), 8.9% (21/237), and 6.9% (42/606) in 2006 to 2009, respectively (Figure 1a).

**Figure 1. a)** Number of patients with AHA and AKI in each year studied.



When the distribution of AHA was reviewed by age range, AHA was most frequent in patients in their 20s and 30s. The number of cases accompanied by AKI was greatest in patients in their 30s (n=36) followed by those in their 40s (n=17) (Figure 1b).

**Figure 1. b)** Distribution of AHA and AKI according to patient age.



The average age of the AHA patients in the group with accompanying AKI was 35.2 years, and it was not significantly different compared with that for the group without AKI, which was 31.6 years. The proportion of males was greater in the group with AKI. Regarding underlying diseases, the group with AKI had a statistically greater proportion of patients with hypertension, and significantly more patients who reported high alcohol intake and who were smokers. The average hospitalization was 6.9 days in the group without AKI versus 12.9 days with AKI, and this difference was significant ( $P<0.001$ ) (Table 1).

Regarding the laboratory findings, the leukocyte count, prothrombin time (INR), and aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein, total bilirubin, peak total bilirubin, and gamma-glutamyltransferase levels were significantly higher in the group with AKI, as was the urine protein level (Table 2).

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**Table 1.** Baseline characteristics of the patients with AHA

	Non-AKI group (n = 954)	AKI group (n = 71)	<i>p</i> -value
Age, years	31.6 ± 7.5	35.2 ± 7.0	0.843
Male, n (%)	581 (60.9%)	59 (83.1%)	<0.001
Underlying disease, n (%)			
Hypertension	19 (2.0%)	6 (9.2%)	0.006
Diabetes mellitus	16 (1.7%)	1 (1.4%)	0.668
Hepatitis B	32 (3.4%)	3 (4.2%)	0.442
Hepatitis C	1 (0.1%)	0 (0%)	0.941
Excessive alcohol History, n (%)*	164 (17.2%)	24 (33.8%)	0.001
Alcohol amount, g/day	18.7 ± 37.3	48.1 ± 82.5	0.004
Smoking, n (%)	284 (29.8%)	35 (49.3%)	0.001
Duration of hospital day	6.9 ± 3.2	12.9 ± 7.9	<0.001
ICU treatment	2(0.2%)	21(29.6%)	<0.001

All results are presented as n (%) or the mean ± SD

\* Excessive alcohol consumption is defined as alcohol consumption >45 g/day.

AKI, acute kidney injury; ICU, Intensive Care Unit

**Table 2.** Laboratory findings of the patients at presentation

	Reference levels	Non-AKI group (n = 954)	AKI group (n = 71)	<i>p</i> -value
White blood cells, $\times 10^9/L$	4.0-10.8	5.20 $\pm$ 2.44	9.89 $\pm$ 7.06	<0.001
Platelets, $\times 10^9/L$	150-400	184 $\pm$ 72	174 $\pm$ 84	0.265
Prothrombin time (INR)	0.96-1.16	1.25 $\pm$ 0.40	1.77 $\pm$ 0.82	<0.001
AST, IU/L	13-36	2585 $\pm$ 2628	5372 $\pm$ 5466	<0.001
ALT, IU/L	1-46	2840 $\pm$ 2017	4434 $\pm$ 3051	<0.001
ALT/AST ratio		1.81	1.99	0.499
Gamma-GT, IU/L	8-46	313 $\pm$ 187	366 $\pm$ 189	0.034
Total bilirubin, mg/dl	0.2-1.3	4.31 $\pm$ 3.65	7.72 $\pm$ 6.72	<0.001
Albumin, mg/dl	3.4-5.3	4.18 $\pm$ 1.42	3.65 $\pm$ 0.52	0.003
C- reactive protein, mg/L	0.2-6.0	20.0 $\pm$ 22.5	39.2 $\pm$ 35.9	<0.001
Serum creatinine, mg/dl	0.8-1.3	0.88 $\pm$ 0.26	4.36 $\pm$ 3.59	<0.001
U/A protein*				<0.001
Trace		236(25.6%)	10(14.1%)	
+1		197(21.4%)	13(18.3%)	
+2		362(39.3%)	28(39.4%)	
> +3		127(13.8%)	20(28.2%)	

All results are presented as n (%) or the mean  $\pm$  SD

\*Dipstick urinalysis

Gamma-GT, gamma-glutamyltransferase; INR, international normalization ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase

To identify the risk factors for AKI in AHA, we used multivariate logistic regression analysis. Multivariate analysis revealed that smoking, higher WBC count, ALT, and total bilirubin, prolonged prothrombin time, and lower albumin level were independent predictors of AKI (Table 3).

We assessed the severity of AKI with the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) classification in the 60 patients who survived. The patient distribution according to RIFLE classification were 9, 16, 26, 8, and 1 patient, respectively. The patient with failure, defined as a serum creatinine  $\times$  3 or serum creatinine  $\geq$ 4 mg/dl with an acute rise  $>$ 0.5 mg/dl were most frequent, but most of them recovered to normal renal function within 1 month. Nine patients had prolonged renal dysfunction for up to 1 month. Only one patient had continued for more than 3 months (Table 4).

In our series, 11 of 1025 patients (1.1%) died due to complications of AHA. Most of them were male, and they had high total bilirubin and creatinine levels on admission. Eight patients underwent hemodialysis, and three had liver transplants (Table 5).

**Table 3.** The independent risk factors for the development of AKI in AHA.

Covariate	Odds ratio	95% CI	<i>p</i> -value
Gender, male/female	1.887	0.170-1.651	0.273
Excessive alcohol consumption	1.169	0.447-3.056	0.750
Smoking	3.576	1.317-9.710	0.012
Hypertension	1.017	0.165-6.258	0.986
WBC (for each $1 \times 10^{12}/L$ )	1.235	1.107-1.376	0.001
Prothrombin time (INR)	2.301	1.288-4.108	0.005
AST (for each 100 IU/L)	1.020	1.001-1.038	0.038
ALT (for each 100 IU/L)	0.996	0.967-1.026	0.811
Total bilirubin, mg/dl	1.124	1.039-1.216	0.004
Gamma-GT (for each 100 IU/L)	0.842	0.661-1.072	0.163
Albumin, mg/dl	0.338	0.129-0.885	0.027
C-reactive protein, mg/l	1.013	0.999-1.026	0.060

WBC, White blood count; Gamma-GT, gamma-glutamyltransferase; INR, international normalization ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AKI, acute kidney injury

**Table 4.** Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) classification of hepatitis A patients with acute renal failure

RIFLE class	Glomerular filtration rate criteria	Patient numbers (%)
Risk	Serum creatinine $\times 1.5$	9 (15%)
Injury	Serum creatinine $\times 2$	16 (26.6%)
Failure	Serum creatinine $\times 3$ or serum creatinine $\geq 4$ mg/dl with an acute rise $>0.5$ mg/dl	26 (43.3%)
Loss	Persistent acute renal failure = complete loss of kidney function $>4$ weeks	8 (13.3%)
End-stage kidney disease	End-stage kidney disease $>3$ months	1 (1.7%)

Table 5. Clinical and laboratory data for the 11 patients who died from complications of AHA.

Patient	Age	Sex	Day	TB, mg/dl	AST, IU/L	ALT, IU/L	Cr, mg/dl	HD	HD days	LT	Cause
1	26	male	15	2.1	6992	2809	1.0	yes	11	no	brain hemorrhage
2	44	male	9	17.0	1036	1722	0.8	no		yes	fulminant hepatitis
3	41	male	3	5.4	1646	1990	3.6	no		no	fulminant hepatitis
4	31	male	53	38.6	69	31	3.4	yes	10	no	septic shock
5	44	fem ale	5	2.2	1268 5	4862	4.0	yes	5	no	fulminant hepatitis
6	36	male	11	6.9	2208 0	9309	7.5	yes	10	no	septic shock
7	65	male	8	17.1	269	1011	1.0	yes	4	yes	fulminant hepatitis
8	38	male	10	10.6	669	1763	2.3	yes	5	no	fulminant hepatitis
9	36	male	31	5.7	5755	6742	8.9	yes	15	no	brain hemorrhage
10	43	male	13	13.8	2782	5405	0.7	no		yes	septic shock
11	41	male	22	6.7	1063	7403	9.3	yes	5	no	brain hemorrhage

Day, duration of hospital stay; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cr, creatinine; HD, hemodialysis; HD days, duration of hemodialysis; LT, liver transplantation

## IV. DISCUSSION

Until recently, AHA accompanied by AKI was considered rare. In our series, however, the incidence was relatively high at 6.9%. AHA responds to conservative treatment in most cases, even when accompanied by AKI. Consequently, AKI might easily be overlooked in AHA unless the appropriate blood tests are performed. In our series, most (85%, 60/71) of the patients with accompanying AKI had high initial creatinine levels, so we feel that blood creatinine level should be determined for patients admitted to the hospital with AHA-related symptoms or confirmed AHA. In Korea, the frequency of AHA accompanied by AKI has recently increased gradually, as was also seen in our series. Therefore, this should be monitored in future studies.

Regarding the cause of AKI in AHA, several hypotheses have been proposed. First, dehydration due to pre-renal factors, such as vomiting and diarrhea, may cause circulatory collapse, which activates the rennin–angiotensin system and reduces renal blood flow<sup>10, 11</sup>. In our series, 67.9% (38/56) of the patients with accompanying AKI had a pre-renal fractional excretion of sodium (FENa) <1, implying that dehydration resulting from anorexia, vomiting, and diarrhea caused by AHA was a major cause of the AKI in most of these patients. Another cause is hyperbilirubinemia, which reduces peripheral blood vessels, thereby reducing the effective blood volume and inducing renal blood and structures to react sensitively to substances inducing vascular contraction<sup>12</sup>. The high total

bilirubin levels in the group with AKI in our series support this possibility. In addition, there are reports of AKI caused by immune complexes<sup>13</sup> or endotoxins<sup>14</sup>, although the mechanisms are unclear. As it is difficult to examine the histology of AHA patients with AKI so as to investigate the cause of the pathologically, some reports have implicated acute tubular necrosis<sup>15, 16</sup>, mesangium endothelialization, or immune complex deposition<sup>17</sup>. Many future studies of the cause of AKI in AHA are necessary.

Although the majority of our patients with accompanying AKI improved with conservative treatment, 25 patients needed hemodialysis. In 17 of the hemodialysis patients, renal functions recovered gradually after the hemodialysis, whereas in the remaining eight patients, the disease gradually progressed to fulminant hepatitis after hemodialysis. Ultimately, these eight patients died from complications of AHA. The patients requiring hemodialysis were typically male and heavy alcoholics. However, the number was small, so larger patient groups should be studied in the future.

Most of the AHA patients had positive urine protein tests, especially those with accompanying AKI. This reflects the excretion of large amounts of protein in the urine in AHA patients. As this is not a quantitative measure of urine proteins, but the result of testing for albumin values, this phenomenon should be studied further.

Although the predictors of AKI in AHA are not clear, old age and diabetes



mellitus have been reported to be related risk factors<sup>3, 18-21</sup>. In our series, smoking, elevated leukocyte count, higher AST and total bilirubin values, prolonged prothrombin time (INR), and lower albumin level were significant independent risk factors.

## **V. CONCLUSION**

In summary, most of AHA complicated with AKI could recover by conservative treatment, however, if they are smokers, elevated leukocyte count, higher AST and total bilirubin values, prolonged prothrombin time (INR), and lower albumin, there would be higher possibility of AKI complication. Attentive observation is required for the patients carrying such factors.

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## ABSTRACT (IN KOREAN)

급성 신부전과 동반된 급성 A형 간염의 최근 변화와 임상상

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유정환

배경/목적 : 급성 A형 간염은 최근 국내에서 급격한 증가 양상을 보이고 있으며, 이에 따라 그동안 급성 A형 간염의 드문 합병증으로 알려져 왔던 급성신부전을 동반한 환자도 점차 증가하고 있다. 본 연구에서는 급성신부전을 동반한 급성 A형 간염 환자의 빈도 증가 추이를 알아보고, 이들의 임상적 특징을 알아보하고자 하였다. 대상 및 방법 : 2006년 1월부터 2009년 12월까지 신촌세브란스 및 강남세브란스 병원에 내원하여 anti HAV IgM 항체가 확인되고, 임상양상이 합당하여 급성 A형 간염으로 진단된 1025명의 환자를 대상으로 급성신부전을 동반한 군과 동반하지 않은 두 군으로 나누어 후향적으로 분석하였다. 연령, 성별, 음주력, 기왕력, 재원 기간, 혈액검사결과, 소변검사 결과 등을 조사하였으며, 만성신부전이나 간경변을 가진 환자는 제외되었다. 결과 : 전체 환자 중 급성신부전이 동반된 환자는 71명으로 6.9%에 해당하였으며, 2006년

3.1%(3/98명), 2007년 6.0%(5/84명), 2008년 11.4%(21/237명), 2009년 6.9%(42/606) 로 최근 급격한 증가 추세를 보였다. 급성신부전이 동반된 환자군은 급성신부전이 동반되지 않은 환자군에 비해 남성의 비율이 높았으며( $p<0.001$ ), 알콜섭취량이 더 많았고( $p=0.004$ ), 흡연자가 더 많았으며( $p=0.001$ ), 고혈압을 가진 경우가 더 많았다( $p=0.006$ ). 혈액 검사상으로는 급성신부전이 동반된 군에서 백혈구수, INR, AST, ALT, CRP, 총 빌리루빈치가 유의하게 높은 결과를 보였으며, 알부민 수치는 유의하게 낮은 결과를 얻었다. 소변내 단백의 경우 급성 신부전이 동반된 군에서 평균 +2.01, 급성 신부전이 동반되지 않은 군에서 평균 +1.47로 유의한 차이를 보였으며, 재원기간 및 빌리루빈이 정상화되는 기간이 의미 있게 길었다. 결론 : 최근 급성 A형 간염의 빈도와 동반되는 급성신부전의 빈도는 증가하는 양상을 보였다. 대부분 보존적인 치료로 회복되지만, 남성, 음주력을 가진 경우, 백혈구수, INR, AST, ALT, 빌리루빈, CRP, 소변내 단백질이 높은 경우와 알부민 수치가 낮은 경우 급성신부전의 동반 빈도가 높으므로 이들 인자를 가진 환자에 대한 주의 깊은 관찰이 필요하겠다.

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핵심되는 말 : 급성 신부전, 급성 A형 간염