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Clinical outcomes and healthcare utilization of acute hepatitis A virus infection with acute kidney injury in hospitalized patients

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Background Patients with acute hepatitis A virus (HAV) infection are at risk of developing acute kidney injury (AKI) which may result in increased healthcare resource utilization and worse clinical outcomes. We investigated the impact of AKI on healthcare utilization and clinical outcomes in patients hospitalized with acute HAV infection utilizing a large database.
Methods We queried the National Inpatient Sample (NIS) 2007–2014 to identify acute HAV infection-related hospitalizations with and without AKI. Primary outcomes were prevalence of AKI and its predictors with secondary outcomes included the mean length of stay (LOS), hospitalization cost and mortality in both groups.
Results Out of 68 364 acute HAV infection-related hospitalizations, 47 620 met our study criteria and 7458 (15.7%) had concurrent AKI. HAV patients with AKI were older (62.5 vs. 53.7 years; *P* value <0.001). A higher mean LOS (10.03 vs. 5.6 days; *P* value <0.001) and mean total hospitalization cost ($27 171.35 vs. $12 790.26; *P* value <0.001) were observed in HAV patients with the AKI group. A total of 1032 patients (13.8%) in the AKI group died during the same hospitalization as compared to 681 patients (1.5%) in the non-AKI group, *P* value <0.001. AKI in HAV was also found to be an independent predictor of mortality [adjusted odds ratio (aOR), 3.28; 95% confidence interval, 2.23–4.84; *P* value <0.001) after adjusting for the confounding factors.
Conclusion We found that 15.67% of patients hospitalized with acute HAV had AKI which contributed to increased healthcare utilization and higher mortality which is preventable. Eur J Gastroenterol Hepatol XXX: 00–00

Introduction

Acute hepatitis A virus (HAV) infection is a communicable yet preventable infectious disease that is more prevalent in under-developed countries. According to the WHO, almost 1.4 million cases are reported each year worldwide [1]. In the USA, there have been recent outbreaks of acute HAV infections, and more than 34 347 cases with 21 104 (61%) hospitalizations and 333 deaths have been reported since 2016 [2]. In another study, the incidence of HAV infections has been reported with an increase of 294% between 2016 and 2018 [3]. Most of the time, it is a self-limiting disease, and clinical presentations vary from mild to severe disease with progression to the fulminant hepatic failure in less than 1% of cases [4]. Acute kidney injury (AKI) is one of the most common extrahepatic manifestations of acute HAV infection resulting from oral intake intolerance resulting into prerenal azotemia or due to the development of immune complex-mediated glomerulonephritis. Although AKI is more prone to develop in fulminant HAV cases, few small studies have reported an increased incidence of AKI in nonfulminant cases with an overall incidence ranging between 5 and 7% [5]. Existing studies have shown that patients with HAV infection who develop AKI are at an increased risk of higher morbidity and mortality with major economic implications. However, the majority of these studies are limited by small sample size and lack of generalizability; furthermore, the prevalence of AKI with its impact on in-hospital mortality, length of stay (LOS) and costs in patients hospitalized with HAV infection at a large scale is not well described. We aimed to estimate the prevalence of AKI, its effect on healthcare utilization and clinical outcomes in patients hospitalized with acute HAV infection through this study utilizing the largest US national inpatient database.

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Keywords: Charlson Comorbidity Index, Healthcare Cost and Utilization Project, hepatitis A, HCUP, hospitalization cost, national inpatient sample, predicters of acute kidney injury

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Methods

Data source

We queried the National Inpatient Sample (NIS) database from 2007 to 2014 to identify HAV-related hospitalizations, with and without concomitant AKI. The description of NIS is described elsewhere [6]. Briefly, it is a large publicly available all-payer nationwide database, an initiative of the Healthcare Cost and Utilization Project (HCUP), that contains information on more than 7 million (unweighted) and 35 million (weighted) hospitalizations each year. This database provides national estimates of in-hospital mortality and resource utilization associated with various conditions and provides data for the policymakers and healthcare organizations to improve the quality and outcomes related to the in-hospital care. The structure of the NIS database follows the complex survey design methodology, and each year data contained a 20-percent stratified sample from all the acute care hospitals from the states participating in the HCUP. In 2012, the sampling method was changed to a 20-percent stratified sample from all the discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals. The stratification is based on the US census region, division, hospital control, location, teaching status and hospital bed size based on the American Hospital Association criteria. The unit of observation in the database is a single hospitalization identified through a principal discharge diagnosis with up to 29 secondary discharge diagnoses. These discharge diagnoses are based on the International Classification of Diseases, Ninth Revision or Tenth Revision, Clinical Modification Codes (ICD-9-CM) system depending upon the year.

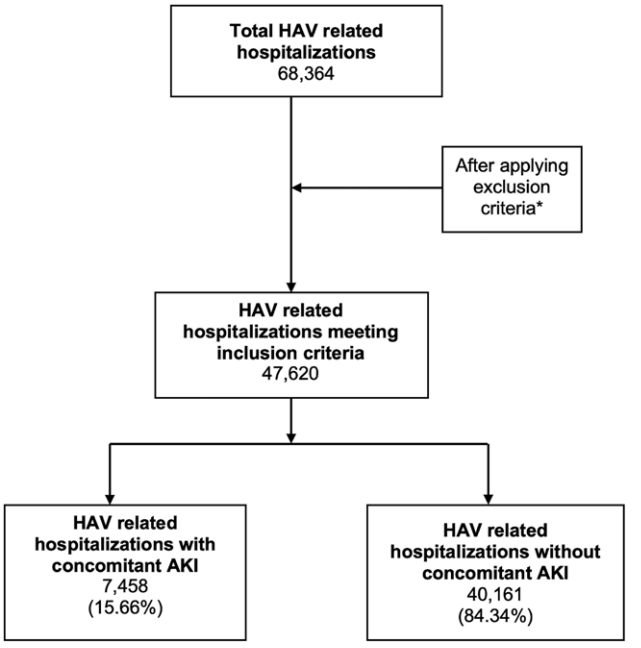

Fig. 1. Patient selection flow diagram.AKI, acute kidney injury; HAV, hepatitis A virus; *, nonadult patients, elective admissions, end-stage renal disease patients and those with missing data related to outcomes.

Cohort selection and study variables

Each hospitalization was considered to be HAV infection-related if it included the ICD-9 codes 070.0 (hepatitis A with hepatic coma) and 070.1 (viral hepatitis A without mention of hepatic coma) as a primary or secondary discharge diagnosis code. Similarly, AKI was defined by the ICD codes 584.9, 584.6, 584.7, 584.5 and 584.8. We divided the patients into two groups, that is, (1) HAV infection with AKI and (2) HAV infection without AKI.

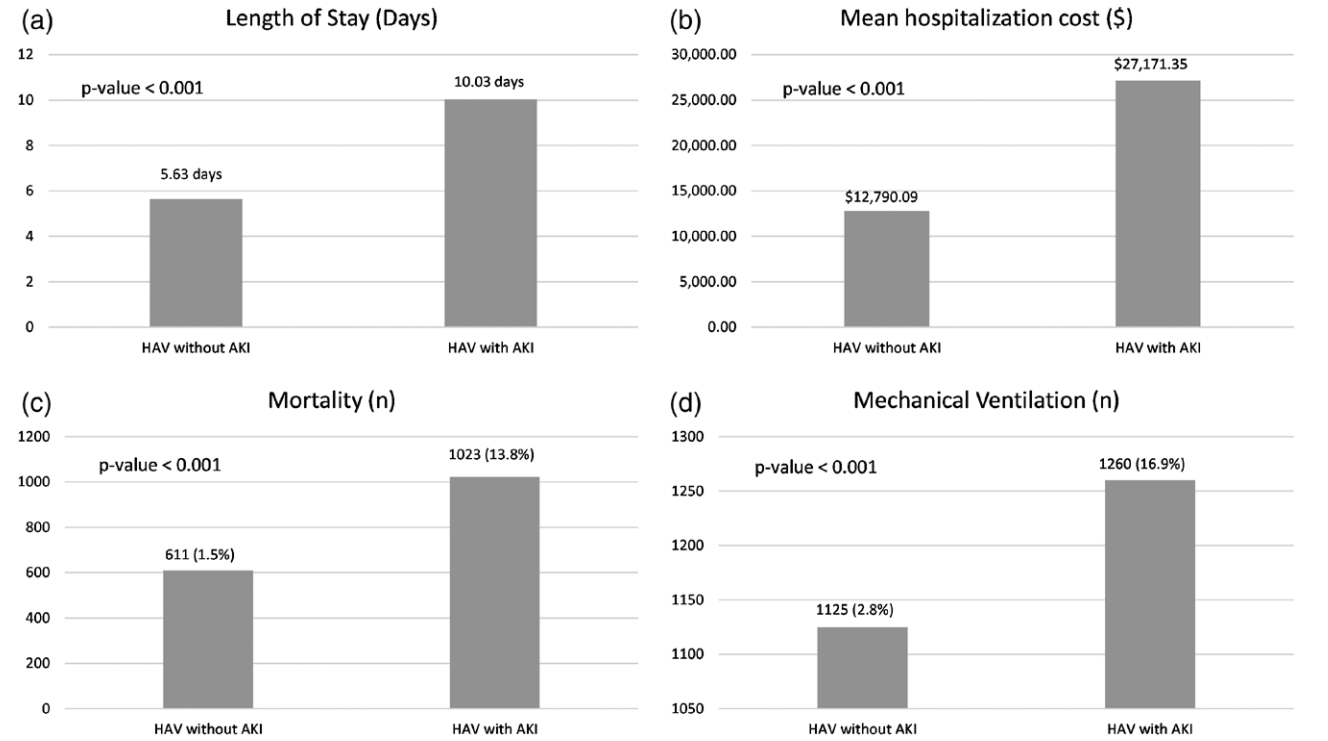

Fig. 2. Primary and secondary outcomes in patients with acute hepatitis A with and without acute kidney injury (AKI); (a) length of stay (b) hospitalization cost (c) inpatient mortality (d) mechanical ventilation. HAV, hepatitis A virus.

Table 1. Baseline patient and hospital characteristics for hospitalized cases of acute hepatitis A virus infection with and without acute kidney injury

Variable	HAV without AKI *N* (%)	HAV with AKI *N* (%)	*P* value
No. of patients	40161 (84.34%)	7458 (15.66%)	
Patient Characteristics			
Male	21004 (52.3%)	4452 (59.7%)	<0.001
Age (years)			
Mean age	53.74	62.52	<0.001
18–34	6586 (16.4%)	410 (5.5%)	
35–44	5301 (13.2%)	492 (6.6%)	
45–64	17912 (44.6%)	3229 (43.3%)	
≥65	10362 (25.8%)	3319 (44.5%)	
Race			<0.001
White	23815 (59.3%)	4631 (62.1%)	
Black	5502 (13.7%)	1313 (17.6%)	
Hispanic	7028 (17.5%)	962 (12.9%)	
Other	3815 (9.5%)	552 (7.4%)	
Median income based on the zip code			0.95
$1–$38 999	12972 (32.3%)	2439 (32.7%)	
$39 000–$47 999	10241 (25.5%)	1939 (26%)	
$48 000–$62 999	9277 (23.1%)	1693 (22.7%)	
>$63 000	7671 (19.1%)	1380 (18.5%)	
Insurance provider			<0.001
Medicare	14739 (36.7%)	4065 (54.5%)	
Medicaid	9719 (24.2%)	1387 (18.6%)	
Private	11165 (27.8%)	1402 (18.8%)	
Uninsured	4538 (11.3%)	604 (8.1%)	
Charlson comorbidity index			<0.001
0	16105 (40.1%)	1193 (16%)	
1	8956 (22.3%)	1029 (13.8%)	
2	4900 (12.2%)	1052 (14.1%)	
3 or more	10201 (25.4%)	4184 (56.1%)	
Comorbidities			
Hypertension	16386 (40.8%)	4236 (56.8%)	<0.001
Diabetes mellitus	7992 (19.9%)	2334 (31.3%)	<0.001
Chronic kidney disease			<0.001
Stage 3	683 (1.7%)	731 (9.8%)	
Stage 4	120 (0.3%)	321 (4.3%)	
Stage 5	40 (0.1%)	60 (0.8%)	
Liver cirrhosis	3896 (9.7%)	1178 (15.8%)	<0.001
Complications			
Electrolyte imbalance	12450 (31%)	5280 (70.8%)	<0.001
Acute liver failure	683 (1.7%)	701 (9.4%)	<0.001
Hemodialysis	40 (0.1%)	619 (8.3%)	<0.001
Mechanical ventilation	1125 (2.8%)	1260 (16.9%)	<0.001
Discharge disposition			<0.001
Home	29197 (72.7%)	3416 (45.8%)	
Home with home health	3574 (8.9%)	895 (12%)	
Skilled nursing facility	4659 (11.6%)	1686 (22.6%)	
Against medical advice	924 (2.3%)	97 (1.3%)	
Hospital characteristics			
Teaching status			0.28
Nonteaching hospital	17229 (42.9%)	3334 (44.7%)	
Teaching hospital	22932 (57.1%)	4124 (55.3%)	
Hospital location			0.02
Rural hospital	3655 (9.1%)	500 (6.7%)	
Urban hospital	36506 (90.9%)	6958 (93.3%)	
Hospital size			<0.001
Small	4739 (11.8%)	679 (9.1%)	
Medium	10321 (25.7%)	1805 (24.2%)	
Large	25101 (62.5%)	4982 (66.8%)	
Hospital region			<0.001
Northeast	9317 (23.2%)	1350 (18.1%)	
Midwest	6707 (16.7%)	1320 (17.7%)	
South	16225 (40.4%)	3229 (43.3%)	
West	7912 (19.7%)	1559 (20.9%)	

AKI, acute kidney injury; HAV, hepatitis A virus.

We excluded patients with age less than 18 years, elective admissions and cases with preexisting end-stage renal disease to correctly identify the need for hemodialysis in patients with HAV who develop or present with AKI. Each observation in the NIS contains patient, treatment and hospital-level information, including age, gender, race, median income by zip code, number and type of procedures, LOS, hospitalization charges, hospital region, hospital teaching status, hospital size based on the number of beds available and its geographical location. We utilized the Charlson Comorbidity Index (CCI) to assess the burden of comorbidities of patients in both groups. The CCI score predicts 1-year survival in patients based on the presence or absence of multiple comorbidities in studies utilizing the administrative databases [7].

Primary and secondary outcomes

The primary outcomes of our study were the prevalence and predictors of AKI in patients hospitalized with acute HAV infection. Secondary outcomes included estimation of healthcare utilization including LOS, inflation-adjusted total hospitalization costs, requirement of mechanical ventilation, need for the hemodialysis and all-cause in-hospital mortality.

Statistical analysis

We used STATA, version 16.0 (StataCorp, College Station, Texas, USA), to conduct all statistical analyses. Descriptive statistics for patients and hospital characteristics were analyzed using Pearson's chi-square test for categorical and Student's *t*-test for the continuous variables. Categorical variables are reported as proportions or percentages, whereas continuous variables are described as means with standard deviations (SD). We treated the missing data with case-wise deletion, and only less than 5% of the data for LOS, hospitalization cost and mortality were missing. We chose an a-priori alpha value of less than 0.05 as a level of significance. We used bivariate linear and logistic regression analysis followed by multivariate regression models to adjust for the confounding factors to assess the effect of AKI on secondary outcomes. We selected the variables to construct the multivariate models, which showed a significance level of 0.2 in the bivariate analysis. The total hospitalization cost variable is not available in the NIS as a default; hence we used the HCUP cost-to-charge ratio Supplementary files, Supplemental digital content 1, *http://links.lww.com/EJGH/A706* to calculate the hospital cost [8]. We adjusted the hospitalization cost to the year 2018 for inflation utilizing the Medical Expenditure Panel Survey factors [9].

Results

Baseline characteristics

A total of 68 364 HAV-related adult hospitalizations were identified between 2007 and 2014; however, a total of 47 620 met our study inclusion criteria and of these, 7458 (15.7%) had a concomitant diagnosis of AKI as shown in Fig. 1. Patients in the AKI cohort were significantly older with the mean age of 62.5 vs. 53.7 years in non-AKI patients (*P* value <0.001), with approximately 88% older than 45 years. The majority of patients were males (59.7% in AKI and 52.3% in the non-AKI group; *P* value <0.001) and majority belonged to white race (62.1 % in AKI and 59.3% in the non-AKI group; *P* value <0.001). More than half of the patients in the AKI group

Table 2. Bivariate and multivariate logistic regression showing predictors for acute kidney injury in patients hospitalized with acute hepatitis A virus infection.

	Bivariate logistic regression			Multivariate logistic regression		
	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Female	0.72	(0.64–0.82)	<0.001	0.76	(0.65–0.9)	<0.001
Race						
White			Reference			
Black	1.25	(1.05–1.48)	0.01	1.45	(1.16–1.8)	<0.001
Hispanic	0.69	(0.56–0.84)	<0.001	0.82	(0.64–1.05)	0.12
Other	0.77	(0.6–1)	0.05	0.92	(0.67–1.27)	0.62
Age (mean)	1.03	(1.03–1.04)	<0.001	1.02	(1.01–1.04)	<0.001
18–34			Reference			
35–44	1.47	(1.07–2.03)	0.02	0.83	(0.54–1.29)	0.41
45–64	2.81	(2.17–3.64)	<0.001	0.95	(0.58–1.55)	0.83
≥65	5.14	(3.96–6.67)	<0.001	0.92	(0.45–1.88)	0.82
Charlson comorbidity index						
0			Reference			
1	1.59	(1.29–1.97)	<0.001	1.24	(0.95–1.62)	0.11
2	3.08	(2.5–3.78)	<0.001	1.73	(1.32–2.26)	<0.001
3 or more	5.44	(4.61–6.42)	<0.001	2.74	(2.17–3.44)	<0.001
Median income based on the zip code						
$1–$38 999			Reference			
$39 000–$47 999	1.02	(0.87–1.21)	0.78	–	–	–
$48 000–$62 999	0.99	(0.82–1.18)	0.89	–	–	–
>$63 000	1	(0.83–1.21)	0.97	–	–	–
Insurance provider						
Medicare			Reference			
Medicaid	0.52	(0.44–0.61)	<0.001	0.98	(0.77–1.26)	0.9
Private	0.47	(0.4–0.55)	<0.001	0.97	(0.77–1.22)	0.78
Uninsured	0.48	(0.38–0.59)	<0.001	1.3	(0.95–1.76)	0.1
Comorbidities						
Diabetes mellitus	1.82	(1.59–2.07)	<0.001	1.08	(0.9–1.29)	0.42
Hypertension	1.88	(1.67–2.13)	<0.001	1.18	(1–1.41)	0.06
Chronic kidney disease						
Stage 2			Reference			
Stage 3	6.19	(4.7–8.15)	<0.001	1.69	(0.77–3.71)	0.19
Stage 4	15.57	(9.13–26.55)	<0.001	3.64	(2.56–5.17)	<0.001
Stage 5	9.29	(3.72–23.19)	<0.001	5.99	(2.72–13.18)	<0.001
Liver Cirrhosis	1.71	(1.45–2.03)	<0.001	4.8	(1.12–20.63)	0.04
Complications						
Acute liver failure	6.4	(4.97–8.26)	<0.001	4.12	(2.9–5.86)	<0.001
Mechanical ventilation	7.05	(5.77–8.61)	<0.001	3.69	(2.81–4.85)	<0.001
Electrolyte imbalance	5.42	(4.76–6.18)	<0.001	4.08	(3.49–4.78)	<0.001
Hospital location						
Rural			Reference			
Urban	1.27	(0.97–1.65)	0.08	1.43	(1.01–2.03)	0.05
Hospital teaching status						
Nonteaching			Reference			
Teaching	0.89	(0.78–1.01)	0.07	0.96	(0.81–1.14)	0.63
Hospital size						
Small			Reference			
Medium	1.21	(0.96–1.53)	0.11	1.29	(0.95–1.74)	0.11
Large	1.36	(1.1–1.67)	<0.001	1.47	(1.11–1.94)	0.01
Hospital region						
Northeast			Reference			
Midwest	1.39	(1.13–1.7)	<0.001	1.01	(0.77–1.34)	0.94
South	1.43	(1.2–1.7)	<0.001	1.03	(0.83–1.27)	0.79
West	1.38	(1.13–1.69)	<0.001	1.23	(0.96–1.59)	0.1

(54.5%) had Medicare as a primary payer compared to the non-AKI group (36.7%), *P* value <0.001. There were no significant differences in median incomes of patients based on their zip codes in two groups. Patients in the AKI group had a higher comorbidity index, with 56.1% having CCI >3 compared to 25.4% in the non-AKI group, *P* value <0.001. In terms of individual comorbidities, the proportions of hypertension, diabetes mellitus, chronic kidney disease (CKD) and liver cirrhosis were significantly higher in the AKI group relative to the non-AKI group. Almost twice as many patients in the AKI group required a skilled nursing facility on discharge compared to the non-AKI group (22.5 vs. 11.6%; *P* value <0.001). Rest of the hospital characteristics and geographical regions were similar in the two groups (Table 1).

Prevalence and predictors of acute kidney injury

We observed that prevalence of AKI in hospitalized patients with acute HAV was 15.7% (7458/47 620). A total of 619 (8.3%) patients who developed AKI required hemodialysis during their hospitalizations. Multivariate logistic regression analysis showed that advanced age [adjusted odds ratio (aOR), 1.02; 95% confidence interval (CI), 1.01–1.04; *P* value <0.001], African American race (aOR, 1.45; 95% CI, 1.16–1.8; *P* value <0.001), CCI

≥2 and higher (aOR, 1.73; 95% CI, 1.32–2.26; *P* value <0.001), CKD stages 3 and 4 (aOR, 3.64; 95% CI, 2.56–5.17; *P* value <0.001), liver cirrhosis (aOR, 4.8; 95% CI, 1.12–20.63; *P* value 0.04), fluid and electrolyte imbalance (aOR, 4.08; 95% CI, 3.49–4.78; *P* value <0.001), acute liver failure (aOR, 4.12; 95% CI, 2.9–5.86; *P* value <0.001) and the requirement for mechanical ventilation (aOR, 3.69; 95% CI, 2.81–4.85; *P* value <0.001) were independent predictors for the development of AKI as shown in Table 2.

Resource utilization

AKI contributed to an increase in the mean LOS (10.03 vs. 5.63 days; *P* value <0.001) with increased hospitalization costs ($27 171.35 vs. $12 790.09; *P* value <0.001) as shown in Table 3. On adjusted analysis, AKI was found to be an independent predictor of increased LOS (β: 2.12; 95% CI, 1.39–2.85; *P* value <0.001) and hospitalization cost (β: 5763.39; 95% CI, 3790.5–7736.28; *P* value <0.001) as depicted in Table 4. Moreover, patients in the AKI group had more electrolyte and fluid imbalance (70.80 vs. 31%; *P* value <0.001) and required more hemodialysis (8.3 vs. 0.1%; *P* value <0.001). Similarly, patients in the AKI group needed mechanical ventilation (16.9 vs. 2.8%; *P* value <0.001) when compared to the patients without AKI.

All-cause in-hospital mortality

Increased all-cause in-hospital mortality was also observed among the HAV-infected patients with AKI [1023/7458; 13.8% as compared to HAV infection without AKI (681/40 161; 1.5%), *P* value <0.001]. We found that AKI was an independent predictor of mortality (aOR, 3.29; 95% CI, 2.23–4.85; *P* value <0.001) after adjusting for confounders such as age, gender, race, comorbidities, insurance status, hospital location, hospital teaching status, hospital bed size and geographic region.

Discussion

In our study, we used the largest national inpatient database to assess the overall prevalence of AKI in patients admitted with acute HAV infection and we found that about 15.7% patients presented with or developed AKI during their course of hospitalization. Patients with advanced age, black race, higher comorbidity burden, especially with CKD and those who develop complications such as fluid and electrolyte imbalance, acute liver failure or require mechanical ventilation were at a higher risk of having AKI. These patients also stayed longer in the hospital, that is, twice as compared to patients without AKI which eventually increased the hospitalization cost substantially. Similarly, patients hospitalized with HAV who had concomitant AKI are more likely to die during the hospitalization with AKI as an independent predictor of mortality after adjusted for confounding factors.

Our study is an extension of the findings published in the previous studies from outside the USA. The prevalence of AKI in hospitalized patients with HAV in small single center retrospective studies is reported between 3 and 7.2% [5,10–12]. In a retrospective study performed by Choi *et al*., [13] authors have reported an incidence of 7.6% in patients with acute HAV infection in both fulminant and nonfulminant cases. However, after excluding the fulminant cases of acute HAV, the incidence of AKI remained as high as 5.2%. Some of the risk factors for the development of AKI reported in these studies are advanced age, diabetes, heavy alcohol intake and fulminant course of hepatitis A [10,11,13]. However, we found that 15.7% of the patients admitted with acute HAV infection had a concomitant discharge diagnosis of AKI. In our analysis, advanced age, black race, CCI ≥2 and more, preexisting CKD, fluid, and electrolyte imbalance, acute liver failure, and the requirement for mechanical ventilation are identified as independent predictors for the development of AKI. The findings in our study are more generalizable due to large sample size, which represent patients from different hospitals varying in size, academic status, rural and urban location as well as geographical region.

The precise mechanism of AKI in patients with HAV remains unknown. Prerenal causes, hyperbilirubinemia, pigment nephropathy and immune-complex-mediated nephritis have all been proposed for the pathophysiology in development of AKI in patients with acute hepatitis infection [14]. In a study of 26 patients with HAV and AKI, Kim *et al*. [10] found that only three patients had urinary sodium of <20 meq/L suggesting the majority of the cohort had AKI secondary to nonprerenal causes. Pigment nephropathy and cholemic nephrosis related to direct tubular dysfunction and acute tubular necrosis have also been well described in renal biopsies [15]. Human hepatocyte growth factor (hHGF) is a paracellular growth factor and has been implicated as one of the pathogenic mechanisms in fulminant liver failure due to acute viral hepatitis [16]. Although high levels of hHGF were found in nonsurvivors as compared to survivors, others have speculated that its ability to help in tissue regeneration and angiogenesis might help with recovery from liver and kidney failure [17].

In general, AKI is also associated with increased healthcare utilization in patients hospitalized with various conditions [18]. In a large retrospective study performed by Bedford *et al*. [19] consisting of 66 829 hospitalized

Table 3. Secondary outcomes and the impact of acute kidney injury on the length of stay, hospitalization cost and all-cause inpatient mortality, in patients hospitalized with acute hepatitis A virus infection.

	HAV without AKI	HAV with AKI	Crude odds ratio/coefficient (95% confidence interval)	Adjusted odds ratio/coefficient (95% confidence interval)	*P* value
Length of Stay	5.63 days	10.03 days	4.40 (3.78–5.03)	2.12 (1.38–2.84)	<0.001
Mean hospitalization cost	$12 790.09	$27 171.35	14 381.26 (12284.28–16478.24)	5763.39 (3790.50–7736.28)	<0.001
Mortality	611	1023	10.27 (7.98–13.23)	3.28 (2.23–4.84)	<0.001
Hemodialysis	40 (0.1%)	619 (8.3%)	–	–	<0.001
Mechanical Ventilation	1125 (2.8%)	1260 (16.9%)	–	–	<0.001

AKI, acute kidney injury; HAV, hepatitis A virus.

Table 4. Multivariate regression analysis to study the impact of acute kidney injury on secondary outcomes including length of stay, hospitalization cost and all cause in-hospital mortality

	Length of stay			Hospitalization cost			Mortality		
	Coefficient	95% confidence interval	*P* value	Coefficient	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Acute kidney injury	2.12	(1.39–2.85)	<0.001	5763.39	(3790.5–7736.28)	<0.001	3.29	(2.23–4.85)	<0.001
Female	–0.34	(–0.66 to –0.02)	0.04	–1210.75	(–2040.45 to –381.05)	<0.001	0.77	(0.54–1.1)	0.15
Race									
White					Reference				
Black	0.09	(–0.45 to 0.62)	0.76	–	–		0.56	(0.34–0.95)	0.03
Hispanic	0.28	(–0.29 to 0.85)	0.34	–	–		1.09	(0.67–1.77)	0.73
Other	0.13	(–0.44 to 0.7)	0.65	–	–		0.8	(0.36–1.78)	0.59
Age (mean)	0.03	(0.01–0.06)	0.01	72.54	(–2.8 to 147.88)	0.06	1.07	(1.04–1.1)	<0.001
18–34					Reference				
35–44	0.1	(–0.6 to 0.8)	0.78	904.73	(–783.09 to 2592.54)	0.29	1.05	(0.35–3.2)	0.93
45–64	–0.18	(–1.05 to 0.7)	0.69	606.22	(–1548.12 to 2760.55)	0.58	0.68	(0.2–2.3)	0.53
≥65	–0.84	(–2.28 to 0.61)	0.26	–415.99	(–4539.12 to 3707.15)	0.84	0.38	(0.07–1.95)	0.25
Charlson comorbidity index									
0					Reference				
1	–0.34	(–0.76 to 0.09)	0.12	937.05	(–70.14 to 1944.24)	0.07	1.11	(0.57–2.17)	0.76
2	–0.07	(–0.56 to 0.43)	0.79	5610.02	(3777.32–7442.72)	<0.001	1.56	(0.8–3.05)	0.19
3 or more	–0.12	(–0.62 to 0.38)	0.64	4135.22	(2722.1–5548.34)	<0.001	3.43	(1.9–6.18)	<0.001
Median income based on the zip code									
$1–$38 999					Reference				
$39 000–$47 999	–0.34	(–0.76 to 0.09)	0.12	1124.52	(144.59–2104.44)	0.03	0.87	(0.55–1.38)	0.56
$48 000–$62 999	–0.07	(–0.56 to 0.43)	0.79	2337.87	(1021.11–3654.62)	<0.001	0.84	(0.51–1.39)	0.51
>$63 000	–0.12	(–0.62 to 0.38)	0.64	2845.68	(1560.35–4131)	<0.001	0.71	(0.41–1.24)	0.23
Insurance provider									
Medicare					Reference				
Medicaid	0.55	(–0.04 to 1.14)	0.07	962.68	(–426.43 to 2351.8)	0.17	1.44	(0.84–2.46)	0.18
Private	–0.61	(–1.09 to –0.13)	0.01	233.46	(–1208.45 to 1675.37)	0.75	1.72	(1.05–2.8)	0.03
Uninsured	0.39	(–0.27 to 1.05)	0.25	717.32	(–967.24 to 2401.88)	0.4	2.51	(1.39–4.54)	<0.001
Comorbidities									
Diabetes mellitus	–	–	–	–	–	–	–	–	–
Hypertension	–	–	–	–	–	–	0.55	(0.38–0.8)	<0.001
Chronic kidney disease									
Stage 2		Reference						Reference	
Stage 3	–2.36	(–3.14 to –1.57)	<0.001	–6143.27	(–8345.9 to –3940.64)	<0.001	0.51	(0.23–1.13)	0.1
Stage 4	–1.11	(–2.73 to 0.5)	0.18	–5020.16	(–9414.02 to –626.3)	0.03	0.37	(0.09–1.45)	0.15
Stage 5	–0.63	(–2.4 to 1.14)	0.49	–4761.41	(–9536.85 to 14.04)	0.05	2.12	(0.31–14.49)	0.44
Liver Cirrhosis	–0.7	(–1.29 to –0.11)	0.02	–1712.31	(–3324.09 to –100.52)	0.04	1.31	(0.86–2)	0.22
Complications									
Acute liver failure	0.59	(–0.74 to 1.91)	0.39	3683.99	(–257.06 to 7625.04)	0.07	1.5	(0.83–2.72)	0.18
Mechanical ventilation	7.27	(5.76–8.78)	<0.001	34713.52	(29759.79–39667.25)	<0.001	22.62	(15.28–33.5)	<0.001
Hemodialysis	3.84	(1.78–5.9)	<0.001	14699.01	(7360.13–22037.89)	<0.001	2.31	(1.16–4.57)	0.02
Electrolyte imbalance	1.54	(1.19–1.9)	<0.001	2683.94	(1785.99–3581.88)	<0.001	1.42	(0.99–2.04)	0.06
Hospital location									
Rural					Reference				
Urban	0.78	(0.27–1.3)	<0.001	3717.26	(2706.74–4727.78)	<0.001	–	–	–
Hospital teaching status									
Nonteaching					Reference				
Teaching	0.86	(0.49–1.23)	<0.001	–207.45	(–1444.72 to 1029.82)	0.74	–	–	–
Hospital size									
Small		Reference							
Medium	–0.31	(–0.88 to 0.25)	0.28	–779.11	(–2116.11 to 557.9)	0.25	–	–	–
Large	0.54	(0.01–1.08)	0.05	1716.45	(385.51–3047.38)	0.01	–	–	–
Hospital region									
Northeast					Reference				
Midwest	–1.08	(–1.65 to –0.51)	<0.001	–2311.61	(–3853.82 to –769.4)	<0.001	0.6	(0.3–1.21)	0.15
South	–0.3	(–0.82 to 0.21)	0.25	–1250.56	(–2693.77 to 192.64)	0.09	1	(0.63–1.59)	0.99
West	–0.86	(–1.44 to –0.27)	<0.001	1927.68	(125.21–3730.15)	0.04	0.83	(0.49–1.42)	0.5

patients admitted for various reasons, the patients who developed AKI had 2.2 times higher LOS after adjusting for confounding factors. We found that HAV patients who developed AKI had a longer hospital stay (10.03 days in the AKI group vs. 5.63 days in the non-AKI group), which is also directly responsible for a higher hospitalization cost. A recent report on the hospital cost per HAV hospitalization reported an average cost of $16 232 (SD $602; 95% CI, $15 052–$17 411) [20]. However, we observed that the hospital cost is almost twice in patients who develop AKI as compared to the non-AKI group. The increase in LOS and higher hospitalization cost in the AKI group can be attributable to dialysis-related procedure expenses and nephrology consultation; however, Collister *et al*., [18] reported that even the mildest forms of AKI contributed 1.2–1.3 times higher cost of care in patients who developed AKI than those without AKI.

The overall mortality rate for HAV-infected patients have been reported less than 1% (range 0.3–1%) [21]; however, the mortality in patients who develop AKI is estimated to be significantly higher in previous studies. In a study reported by Choi *et al*., [13] the authors reported

in-hospital mortality of 16.7% for patients in the AKI group, slightly higher than our study findings (13.8%) [13]. Lin *et al*. [22] reported in their prospective study including patients with fulminant HAV infection, day one serum creatinine level of >2.0 mg/dl was found to be 54% sensitive and 88% specific for predicting nonsurvival, defined as death or need for liver transplantation. We found AKI to be an independent predictor of mortality (adj OR, 3.29; 95% CI, 2.23–4.85; P <0.001) after adjusting for confounders such as age, gender, race, comorbidities, insurance status, hospital location, teaching, bed size and geographic region. Although it is not possible to establish a causal link between AKI and mortality through this epidemiologic study but higher mortality in patients with AKI can be explained by the presence of concomitant multiple organ system failures, especially in critically ill patients.

We acknowledge several limitations to our study findings; majority of them are related to the database itself. First, we utilized the NIS database, which is subjective to coding errors due to its administrative nature and dependence on the ICD-9 coding system [23]. However, the ICD-9 codes we used in our study are very well-validated and used in several studies based on the NIS database [24,25]. Second, the lack of data availability on medications, laboratory and radiologic data has significantly limited our ability to determine the baseline assessment of kidney function, the severity of AKI, and dynamicity in the serum creatinine level and individual patient level management strategies. Nevertheless, we used CCI, which is a validated tool to determine the comorbidity burden of patients as an important prognostic factor. Third, Agency for Healthcare Research and Quality recommends against using the NIS to derive state-level estimates owing to the small representation of hospitals in the NIS from many states [26]. State-level data, if obtainable, could have been helpful to public health policymakers to help focus public health efforts in states affected more with HAV infection. However, we included the geographical regions to study the variations in the outcomes across the USA. Fifth, as noted by Hofmeister *et al*., [20] cost estimates utilizing an administrative database can significantly overestimate hospitalization costs as patients who were incidentally diagnosed with HAV infection but were admitted primarily for other more costly conditions might have skewed the cost analysis. We limited our analysis to nonelective hospitalizations which excludes admissions planned for procedures, hence minimizing the probability of overestimation in the cost analysis. Also, our data only represent the costs and outcomes of HAV-infected patients admitted to hospitals and do not capture visits to emergency rooms, primary care physician offices and urgent care; hence, it may not represent the true incidence and resource utilization of HAV infections in the USA.

To our knowledge, despite of all the limitations, this is the first study to report the impact of AKI in the hospitalized patients with acute HAV infection in the USA on a large scale. Our report suggests that AKI is an independent predictor of increased length of hospital stay, higher total hospitalization costs and inpatient mortality. Our study highlights that AKI in acute HAV patients affects the healthcare utilization, morbidity and mortality. Therefore, it is very important to identify patients who are at risk for developing AKI and timely manage them with adequate fluid resuscitation to prevent AKI which ultimately will help to reduce healthcare utilization, morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

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