Acute Kidney Injury among Salicylate Intoxication Hospitalizations in the United States

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Abstract

Background: This study aimed to evaluate the risk factors and the association of acute kidney injury (AKI) with outcomes, and resource utilization in patients hospitalized due to salicylate intoxication in the United States. Methods: Hospitalized patients with a primary diagnosis of salicylate intoxication from 2003 to 2014 were identified in the National Inpatient Sample (NIS) database. End-stage kidney disease patients were excluded. The occurrence of AKI was identified using hospital diagnosis code. Clinical characteristics, in-hospital treatment, outcomes and resource utilization were compared between patients with and without AKI. Results: A total of 13,787 eligible hospital admissions were included in the analysis. AKI occurred in 1,279 (9.3%) admissions. Older age, male sex, more recent year of hospitalization, anemia, hypertension, congestive heart failure, chronic kidney disease, volume depletion, sepsis, and ventricular arrhythmia/cardiac arrest were significantly associated with increased risk of AKI, whereas Hispanic race was associated with decreased risk. AKI was significantly associated with increased risk of organ failure, and in-hospital mortality. In addition, the need for ventilation support, blood component transfusion, renal replacement therapy, length of hospital stay, and hospitalization cost were higher in AKI patients. Conclusion: Approximately one tenth of salicylate intoxication patients developed AKI during hospitalization. AKI was associated with higher morbidity, mortality, and resource utilizations.

What's already known about this topic?

Acute kidney injury has been reported as a complication of salicylate intoxication.

What does this article add?

- Acute kidney injury occurred in about 9% of hospitalization for salicylate intoxication.
- Several clinical characteristics were identified as risk factors for acute kidney injury.
- Acute kidney injury was associated with higher morbidity, mortality, and resource utilization.
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INTRODUCTION

Salicylate-containing products are one of the most commonly used over-the-counter pharmaceuticals in the US. Acetylsalicylate and methyl salicylate are two preparations of salicylate available on the market. For many years, acetylsalicylate (aspirin) has been used as analgesic, antipyretic, and antiplatelet agents, while methyl salicylate can be found in topical ointment, herbal oil, lotions, solutions used in hot vapor and topical analgesia.[1] Due to its widespread use and easy accesability, salicylates have been implicated in accidental and intentional overdose. Moreover, some salicylate containing topical preparations including herbal oils, lotions, and ointments are gaining popularity, and can potentially increase incidence of salicylate toxicity. Some of these products may contain 98-100% of methyl salicylate. Consequently, 1 ml of solution containing approximately 5,000 mg of methyl salicylate can potentially cause severe toxicity when ingested.[1]In 2018, approximately 27,000 toxic exposures to salicylates were reported by the American Association of Poison Control Center, with mortality rate of 0.4%.[2] Among these reported cases, approximately half was due to intentional ingestion as an attempt to commit suicide.

Salicylates are absorbed in the stomach and small intestine. Most salicylates are metabolized in the liver and then excreted by the kidneys as salicyluric acid, gentisic acid, acylglucuronides, and salicylic phenolic glucuronides, while approximately 10-30% of salicylates are excreted by kidney as free salicylic acid. Salicylate intoxication can manifest by several presentations, including hyperpnea, nausea, vomiting, dizziness, tinnitus, fever, sweating, altered mental status, coma, and organ failures.[1] Acid-base abnormality is common in a setting of salicylate intoxication. Salicylates are able to directly stimulate the respiratory center resulting in hyperventilation and subsequent respiratory alkalosis. Concurrently, by interfering with aerobic metabolism salicylates cause anion-gap metabolic acidosis due to an increase of ketone bodies, lactate, and pyruvate. In addition, normal anion-gap metabolic acidosis may concomitantly occur, and is attributed to renal bicarbonate loss and chloride retention, compensating for respiratory alkalosis.[3]

Salicylate toxicity has been reported to affect kidneys. Several mechanisms have been proposed to be responsible for acute kidney injury (AKI). Insensible fluid loss due to increase in body temperature along with gastrointestinal losses from emesis have a potential to results in severe volume depletion, up to 6 L in some cases, causing renal hypoperfusion.[4] In addition, salicylate-induced nephrotoxicity can manifest through acute tubular necrosis, acute interstitial nephritis, papillary necrosis, and proximal tubular dysfunction.[5-7] Although AKI has been reported as a complication of salicylate intoxication, the epidemiology and impact of AKI on outcomes has been limited. Therefore, we conducted this study aiming to assess the risk factors and the association of AKI with outcomes of salicylate toxicity, and resource utilization in patients hospitalized with salicylate intoxication in the US.

MATERIALS AND METHODS

Data Source

This cohort study was conducted using the NIS database, which is the largest all-payer inpatient database in the US. The NIS database contains discharge data set from a 20% stratified sample of US hospitals with patient encounter-level information. The data set includes primary and secondary diagnosis codes as well as procedure codes in form of International Classification of Diseases, Ninth Revision (ICD-9). Sample weight is used to generate national estimates for hospitalization nationwide. The approval from institutional review board was exempted as the information was obtained from a de-identified public database.

Study Population

All hospitalized patients with the primary ICD-9 diagnosis code for salicylate intoxication (965.1) were included. Patients with ICD-9 diagnosis codes for chronic kidney disease stage 5 (585.5), and end stage renal disease (585.6) were excluded.

Data Collection

AKI was identified by the presence of ICD-9 diagnosis codes of 584.5 (acute kidney failure with lesion of

tubular necrosis), 584.6 (acute kidney failure with lesion of renal cortical necrosis), 584.7 (acute kidney failure with lesion of renal medullary necrosis), 584.8 (acute kidney failure with other specified pathological lesion in kidney), or 584.9 (acute kidney failure, unspecified) in any of the listed diagnoses. The identification of AKI using ICD-9 diagnosis code has a specificity of 98% but a sensitivity of 17% and are likely to capture a more severe spectrum of AKI, compared with KDIGO serum creatinine-based criteria.[8,9]

Clinical characteristics, treatments, and outcomes during hospitalization were identified using ICD-9 codes (Table S1). Clinical characteristics included age, sex, race, year of hospitalization, alcohol consumption, certain comorbidities (obesity, anemia, diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, congestive heart failure, atrial flutter/fibrillation, chronic kidney disease, and cirrhosis), and acute conditions (sepsis, volume depletion, seizure, gastrointestinal bleeding, ventricular arrhythmia/cardiac arrest). Treatments included gastric lavage, non-invasive and invasive mechanical ventilation, blood component transfusion, and renal replacement therapy. Outcomes included end-organ failure (respiratory, circulatory, liver, neurological or hematological failures), and in-hospital mortality. Resource utilization included length of hospital stay and hospitalization cost.

Statistical Analysis

Clinical characteristics, treatments, outcomes, and resource utilization between salicylate intoxication patients with and without AKI were compared using student's t-test for continuous variables, and Chi-squared test for categorical variables. Clinical characteristics associated with AKI were identified using multivariable logistic regression with backward stepwise selection. The association of AKI with clinical outcomes was evaluated using logistic regression analysis, and the association of AKI with length of hospital stay and hospitalization cost was evaluated using linear regression analysis, with pre-specified adjustment for clinical characteristics. Statistical significance was achieved when two-tailed p-value <0.05. SPSS statistical software (version 22.0, IBM Corporation, Armonk, NY, USA) was used for all analyses.

RESULT

Incidence of and Risk Factors for development of AKI in Patients Hospitalized with Salicylate Intoxication

Between 2003 and 2014 there were 13,805 admissions with a primary diagnosis of salicylate intoxication. A total of 18 patients with end stage renal disease were excluded, a total of 13,787 admissions were included in the study. Of these, 1,279 (9.3%) had an AKI. Overall, among patients with salicylate intoxication, AKI was more commonly present in patients who were male, Caucasian, older and had associated comorbidities and acute conditions (**Table 1**). Multivariable analysis identified older age (OR 1.90 for age 20-29 years, 2.93 for age 30-39 years, 4.54 for age[?]40 years; all $p<0.001$), male sex (OR 2.59; $p<0.001$), more recent period of hospitalization (OR 2.23 for year 2007-2010, and 3.19 for year 2011-2014; all $p<0.001$), anemia (OR 2.31; $p<0.001$), hypertension (OR 1.19; $p=0.03$), congestive heart failure (OR 1.67; $p=0.002$), chronic kidney disease (OR 7.00; $p<0.001$), volume depletion (OR 3.48; $p<0.001$), sepsis (OR 5.61; $p<0.001$), and ventricular arrhythmia/cardiac arrest (OR 1.72; $p=0.04$) as clinical characteristics significantly associated with increased risk of developing AKI, and Hispanic race (OR 0.70; p-0.01) as clinical characteristics significantly associated with decreased risk of AKI (Table 2).

The Association of Acute Kidney Injury with In-Hospital Treatments, and Outcomes

Salicylate intoxication patients with AKI had higher requirment for non-invasive ventilation support (OR 3.06; $p<0.001$), invasive mechanical ventilation (OR 3.99; $p<0.001$), blood component transfusion (OR 2.70; $p<0.001$), and renal replacement therapy (OR 7.25; $p<0.001$) than patients without AKI. After adjustment for potential confounding errors, a statistically significant association between development of an AKI with risk of organ failure, including respiratory failure (OR 4.08; $p<0.001$), circulatory failure (OR 2.76; $p<0.001$), liver failure (OR 6.30; $p<0.001$), neurological failure (OR 2.05; $p<0.001$), hematological failure (OR 3.48; $p<0.001$) and in-hospital mortality (OR 4.93; $p<0.001$) (**Table 3**).

Impact of Acute Kidney Injury on Resource Utilization

The mean length of stay in patients who developed AKI was 1.7 days longer than non-AKI patients (p<0.001). The mean hospitalization cost for AKI patients was significantly higher than non-AKI with additional adjusted mean hospitalization cost of $17,013 (p<0.001) (**Table 3**).

DISCUSSION

This large cohort study demonstrated risk factors associated with developing AKI in patients with salicylate intoxication and its impact on outcomes and resource utilization. Overall, 9.3% of salicylate intoxication patients developed AKI. Factors associated with increased risk of AKI included presence of chronic kidney disease, sepsis, older age, volume depletion, more recent period of hospitalization, male sex, anemia, ventricular arrhythmia/cardiac arrest, congestive heart failure, and hypertension. Requirement of renal replacement therapy, invasive mechanical ventilation support, non-invasive ventilation support, and blood component transfusion was higher in salicylate intoxication patients with AKI. Furthermore, AKI was associated with an increased risk of organ failure and in-hospital mortality, as well as longer length of stay and higher hospitalization cost.

In our study, AKI occurred in 9.3% of patients hospitalized with salicylate toxicity, while in general the incidence of AKI range from 10 to 20% in hospitalized patients[10-16] and 30 to 50% in critically ill patients.[17,18]Development of AKI in salicylate intoxication is attributed to several factors, as described above. Our study identified independent factors associated with an increased risk of AKI. Pre-existing chronic kidney disease represented the highest risk factor predisposing to AKI in our study, with the adjusted odds ratio of 7.0. Not suprizingly, baseline chronic kidney disease has always been considered the risk factor for developing AKI.[19]Moreover, the lower eGFR was associated with the higher risk of AKI.[20] The reduction of renal reserve due to precipitating factors, such as hypotension, hypovolemia, use of nephrotoxic agents, is the probable explainion of chronic kidney disease patients being at risk for AKI.[21] Sepsis also has strong association with AKI, development of AKI in critically ill patients has been attributed to sepsis in 47.5% of cases.[22] Although sepsis-induced AKI is common, the pathogenesis has not been clearly explained. Several mechanisms may contribute to an increased risk of AKI in sepsis, including hemodynamic instability induced renal hypoperfusion, the injury of renal tubular endothelial cells by inflammatory mediators, microcirculation alteration, and mitochondrial dysfunction.[23] Other previously reported risk factors for AKI are older age, diabetes mellitus, hypertension, congestive heart failure, use of vasopress/inotropic agents, hemodynamic instability, and anemia, requiring blood transfusion.[24-26]

Our study also addressed the impact of AKI among patient with salicylate intoxication on clinical outcomes. Overall, presence of AKI in salicylate intoxication patients was associated with increased in-hospital mortality. The in-hospital mortality was 4.3%, with the odds ratio of 4.93 (p<0.001). AKI has also been reported to increase the mortality in several conditions, such as critical illness, acute coronary syndrome, solid organ/hematologic transplantation, cirrhosis, stroke, and cardiac surgery.[27-35] In addition, greater degree of resource utilization, including renal replacement therapy, invasive/non-invasive mechanical ventilation support, and blood transfusion has been correlated with AKI. As previously described, at therapeuric doses, 10-30% of salicylate is eliminated through renal exctretion as free salicilyc acid, while the remainder is metabolized by the liver.[1] In a setting of salicylate overdose, the oversaturation of hepatic metabolism, especially if accompanied by renal function impairment, results in accumulation of salicylate. This accumulation can lead to severe complications, including acidosis, acute lung injury, and central nervous system toxicity.[5] Regarding pharmacokinetic physiology, salicylates are highly bound to protein at therapeutic doses. In contrast, protein binding becomes saturated at supratherapeutic dose, increasing free salicylate serum concentration. Hemodyalysis is another option for salicylate elimination. Although used only in certain settings and mainly in severe cases, hemodialysis is very efficient in eliminating salicylate and restoring acid-base balance.[1,3]Some cases of salicylate intoxication require ventilation support. Acute encephalopathy, severe acidosis, and acute lung injury could be the contributing factors to respiratory failure requiring ventilation support in severe cases.[1] In addition to respiratory failure, development of AKI in patients with salicylate intoxication was associated with an increased risk of other organ systems failure.

Salicylic acid has a pK_a value of 3, which essentially means that alkaline pH stabilizes more than 99% of

salicylate in the ionized form. In its ionized form, the drug loses ability to easily penetrate cell membrane. On the other hand, nonionized form of salicylate in a setting of acidosis, is able to penetrate cells more readily, particularly the central nervous system, leading to neurologic toxicity.[1,3]The consequence of acidosis also manifests its effects in cardiovascular system. Previous studies demonstrate that acidosis could result in myocardial dysfunction and vascular dilatation.[36] Finally, salicylates also affect the liver and hematological system, resulting in liver injury, thrombocytopenia, and coagulopathy.[37-39] As described above, the accumulation of saliciylate due to delayed clearance precipitated by AKI, enhances the severity of disease and leads to organ failure.

Nevertheless, our study has some limitations. According to the NIS structure, hospitalized database, we could not evaluate the long term outcome of AKI, such as renal recovery or long-term mortality. Secondly, data obtained from the NIS was extracted using diagnosis codes. Therefore, we could not conclude that these complications were consequences from AKI or concomitant complications of salicylate intoxication. The effect of co-ingestion was also not evaluated in our study, which might demonstrate some degree of effects not accounted for in this study. Finally, this study did not address the variability in outcomes between acute and chronic intoxication.

CONCLUSION

In conclusion, approximately 10% of salicylate intoxication patients developed AKI during hospitalization. Development of AKI in a setting of salicylate intoxication was associated with increased in-hospital mortality and organ failure development. Additionally, development of AKI was also found to be associated with increase in resource utilization, length of stay, and hospitalization cost. Chronic kidney disease, sepsis, older age, volume depletion, more recent year of hospitalization, male sex, anemia, ventricular arrhythmia/cardiac arrest, congestive heart failure, and hypertension were found to be associated with an increased risk of developing AKI, and therefore, could be possible predisposing factors.

Disclosure

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Authors' contributions

All authors had access to the data and a role in writing the manuscript.

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Table

Table 1 Clinical characteristics, in-hospital treatments, outcomes, and resource utilization in salicylate intoxication patients with and without acute kidney injury

Table 2 Factors associated with acute kidney injury in salicylate intoxication patients

Table 3 The association of acute kidney injury with in-hospital treatment, complications, outcomes, and resource utilization in salicylate intoxication patients

Table 1 Clinical characteristics, in-hospital treatments, outcomes, and resource utilization in salicylate intoxication patients with and without acute kidney injury

	Total	Acute Kidney Injury	No Acute Kidney Injury	P-
Clinical characteristics	Clinical characteristics			
N (%)	13787	1279	12508	
Age (years)	33.9±18.7	48.0±19.5	32.5±18.0	<(
<20	3902 (28.3)	96 (7.5)	3806 (30.5)	<(
20-29	3227 (23.4)	188 (14.7)	3039 (24.3)	
30-39	1951 (14.2)	182 (14.2)	1769 (14.2)	?¿
40	4693 (34.1)	812 (63.5)	3881 (31.1)	
Male	4807 (35.0)	719 (56.2)	4088 (32.8)	<(

	Total	Acute Kidney Injury	No Acute Kidney Injury	P-
Race				
Caucasian	7721 (56.0)	796 (62.2)	6925 (55.4)	<0
African American	1386 (10.1)	156 (12.2)	1230 (9.8)	
Hispanic	1309 (9.5)	65 (5.1)	1244 (9.9)	
Asian or Pacific Islander	199 (1.4)	20 (1.6)	179 (1.4)	
Other	3172 (23.0)	242 (18.9)	2930 (23.4)	
Year of hospitalization				
2003-2006	5010 (36.3)	208 (16.3)	4802 (38.4)	<0
2007-2010	4425 (32.1)	448 (35.0)	3977 (31.8)	
2011-2014	4352 (31.6)	623 (48.7)	3729 (29.8)	
Alcohol consumption	2216 (16.1)	218 (17.0)	1998 (16.0)	0.3
Obesity	520 (3.8)	62 (4.8)	458 (3.7)	0.0
dialysis	885 (6.4)	213 (16.7)	672 (5.4)	<0
Diabetes Mellitus	794 (5.8)	155 (12.1)	639 (5.1)	<0
Hypertension	2123 (15.4)	421 (32.9)	1702 (13.6)	<0
Dyslipidemia	747 (5.4)	153 (12.0)	594 (4.7)	<0
Coronary artery disease	505 (3.7)	127 (9.9)	378 (3.0)	<0
Congestive heart failure	234 (1.7)	72 (5.6)	162 (1.3)	<0
Atrial flutter/fibrillation	169 (1.2)	46 (3.6)	123 (1.0)	<0
Chronic kidney disease	200 (1.5)	127 (9.9)	73 (0.6)	<0
Liver cirrhosis	116 (0.8)	26 (2.0)	90 (0.7)	<0
Sepsis	126 (0.9)	60 (4.7)	66 (0.5)	<0
Volume depletion	738 (5.4)	201 (15.7)	537 (4.3)	<0
Seizure	563 (4.1)	67 (5.2)	496 (4.0)	0.0
Gastrointestinal bleeding	362 (2.6)	55 (4.3)	307 (2.5)	<0
Ventricular arrhythmia/cardiac arrest	94 (0.7)	26 (2.0)	68 (0.5)	<0
Treatments	Treatments			
Gastric lavage	344 (2.5)	25 (2.0)	319 (2.6)	0.1
Non-invasive ventilation	64 (0.5)	27 (2.1)	37 (0.3)	<0
Invasive mechanical ventilation	759 (5.5)	253 (19.8)	506 (4.0)	<0
Blood component transfusion	354 (2.6)	116 (9.1)	238 (1.9)	<0
Renal replacement therapy	796 (5.8)	346 (27.1)	450 (3.6)	<0
Complication and outcomes	Complication and outcomes			
Respiratory failure	941 (6.8)	308 (24.1)	633 (5.1)	<0
Circulatory failure	480 (3.5)	157 (12.3)	323 (2.6)	<0
Liver failure	109 (0.8)	51 (4.0)	58 (0.5)	<0
Neurological failure	687 (5.0)	153 (12.0)	534 (4.3)	<0
Hematological failure	302 (2.2)	110 (8.6)	192 (1.5)	<0
In-hospital mortality	132 (1.0)	55 (4.3)	77 (0.6)	<0
Resource utilization	Resource utilization			
Length of hospital stay (days)	2.6±3.3	5.2±6.3	2.3±2.7	<0
Hospitalization cost ($)	18089.6±29478.8	42696.7±68065.2	15579.8±20430.0	<0

Continuous variables are reported as mean ± standard deviation; categorical variables are reports as counts (percentages)

Table 2 Factors associated with acute kidney injury in salicylate intoxication patients

Variables	Univariable analysis	Univariable analysis	Multivariable analysis
	Crude odds ratio (95%CI)	P-value	Adjusted odds ratio (95%CI)
Age (years)			
<20	1 (reference)		1 (reference)
20-29	2.45 (1.91-3.15)	<0.001	1.90 (1.47-2.45)
30-39	4.08 (3.17-5.26)	<0.001	2.93 (2.25-3.80)
40	8.30 (6.68-10.30)	<0.001	4.54 (3.59-5.74)
Male	2.63 (2.34-2.96)	<0.001	2.59 (2.28-2.95)
Race			
Caucasian	1 (reference)		1 (reference)
African American	1.10 (0.92-1.32)	0.29	1.19 (0.97-1.46)
Hispanic	0.46 (0.35-0.59)	<0.001	0.70 (0.53-0.93)
Asian or Pacific Islander	0.97 (0.61-1.55)	0.91	1.35 (0.82-2.23)
Other	0.72 (0.62-0.84)	<0.001	1.16 (0.98-1.37)
Year of data collection			
2003-2006	1 (reference)		1 (reference)
2007-2010	2.60 (2.20-3.08)	<0.001	2.23 (1.86-2.67)
2011-2014	3.86 (3.28-4.54)	<0.001	3.19 (2.68-3.80)
Alcohol drinking	1.08 (0.93-1.26)	0.32	
Obesity	1.34 (1.02-1.76)	0.04	
Anemia	3.52 (2.98-4.16)	<0.001	2.31 (1.90-2.80)
Diabetes Mellitus	2.56 (2.13-3.09)	<0.001	
Hypertension	3.12 (2.74-3.54)	<0.001	1.19 (1.02-1.39)
Dyslipidemia	2.73 (2.26-3.29)	<0.001	
Coronary artery disease	3.54 (2.87-4.36)	<0.001	
Congestive heart failure	4.55 (3.42-6.04)	<0.001	1.67 (1.20-2.32)
Atrial flutter/fibrillation	3.76 (2.66-5.30)	<0.001	
Chronic kidney disease	18.78 (13.99-25.20)	<0.001	7.00 (5.03-9.73)
Liver cirrhosis	2.86 (1.84-4.45)	<0.001	
Volume depletion	4.16 (3.49-4.95)	<0.001	3.48 (2.87-4.23)
Sepsis	9.28 (6.51-13.23)	<0.001	5.61 (3.79-8.29)
Seizure	1.34 (1.03-1.74)	0.03	
Gastrointestinal bleeding	1.79 (1.33-2.39)	<0.001	
Ventricular arrhythmia/cardiac arrest	3.80 (2.41-5.99)	<0.001	1.72 (1.01-2.91)
Gastric lavage	0.76 (0.51-1.15)	0.20	

Table 3 The association of acute kidney injury with in-hospital treatment, complications, outcomes, and resource utilization in salicylate intoxication patients

Variables	Univariable analysis	Univariable analysis	Multivariable analysis	Mul
	Crude odds ratio (95%CI)	P-value	Adjusted odds ratio* (95%CI)	P-va
Treatments				
Non-invasive ventilation	7.27 (4.41-11.98)	<0.001	3.06 (1.72-5.45)	<0.0
Invasive mechanical ventilation	5.85 (4.97-6.89)	<0.001	3.99 (3.28-4.86)	<0.0
Blood component transfusion	5.14 (4.09-6.47)	<0.001	2.70 (2.03-3.59)	<0.0
Renal replacement therapy	9.94 (8.51-11.61)	<0.001	7.25 (6.07-8.67)	<0.0
Complications and outcomes				
Respiratory failure	5.95 (5.12-6.92)	<0.001	4.08 (3.41-4.89)	<0.0
Circulatory failure	5.28 (4.32-6.45)	<0.001	2.76 (2.18-3.50)	<0.0
Liver failure	8.92 (6.09-13.05)	<0.001	6.30 (4.05-9.81)	<0.0

Variables	Univariable analysis	Univariable analysis	Multivariable analysis	Mul
Neurological failure	3.05 (2.52-3.68)	<0.001	2.05 (1.65-2.55)	<0.0
Hematological failure	6.04 (4.74-7.69)	<0.001	3.48 (2.63-4.61)	<0.0
In-hospital mortality	7.24 (5.10-10.28)	<0.001	4.93 (3.15-7.71)	<0.0
Resource utilization	Coefficient (95% CI)	P-value	Adjusted co efficient* (95% CI)	P-va
Length of hospital stay (days)	2.9 (2.7-3.0)	<0.001	1.7 (1.6-1.9)	<0.0
Hospitalization cost ($)	27117 (25469-28765)	<0.001	17013 (15386-18640)	<0.0

*adjusted for age, sex, race, year of hospitalization, alcohol drinking, obesity, anemia, diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, congestive heart failure, atrial fibrillation, chronic kidney disease, liver cirrhosis, volume depletion, sepsis, seizure, gastrointestinal bleeding, ventricular arrhythmia/cardiac arrest and gastric lavage