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Short communication

Epidemiology of acute coronary syndrome co-existent with allergic/hypersensitivity/anaphylactic reactions (Kounis syndrome) in the United States: A nationwide inpatient analysis☆

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ABSTRACT

Background: The nationwide epidemiological data on Kounis Syndrome (KS), still remains indistinct in the United States (US) after it was first reported in 1991.
Methods: We assessed the prevalence of KS among patients primarily hospitalized for allergic/hypersensitivity/anaphylactic reactions. We then compared baseline demographics, comorbidities, and outcomes of KS with patients with only allergic/hypersensitivity/anaphylactic reactions using the National Inpatient Sample, 2007–2014.
Results: The cohort comprised of 235,420 patients primarily hospitalized with allergy/hypersensitivity/anaphylactic reactions. Of these, 2616 [1.1%; 0.2% unstable angina, 0.2% ST-elevation myocardial infarction & 0.7% non-ST-elevation myocardial infarction] patients experienced ACS and were identified as having KS. Patients with KS were older (mean 65.9 ± 14.1 vs. 57.2 ± 17.8 yrs), more often White (71.1% vs. 58.6%), male (46.4% vs. 39.9%) and Medicare enrollees (58.9% vs. 41.5%) admitted non-electively (96.8% vs. 95.3%) as compared to non-KS group ($p < 0.001$). The hospitalizations with KS demonstrated higher all-cause in-hospital mortality (7.0% vs. 0.4%, $p < 0.001$), prolonged hospitalization stay (mean 5.8 ± 6.0 vs. 3.0 ± 3.9 days, $p < 0.001$), higher hospitalization charges ($52,656 vs. $20,487, $p < 0.001$) and more frequent transfers to other facilities. The rates of stroke (1.0% vs. 0.2%), arrhythmias (30.4% vs. 12.4%), venous thromboembolism (1.6% vs. 1.0%), and diagnostic and therapeutic coronary interventions were also found to be significantly higher in patients with KS ($p < 0.05$). Patients with KS had increased odds of in-hospital mortality [unadjusted OR: 18.52; 95% CI: 15.74–21.80, $p < 0.001$ & adjusted OR: 9.74, 95% CI: 8.08–11.76, $p < 0.001$] compared to non-KS group.
Conclusions: Overall US prevalence of KS among patients hospitalized for allergic/hypersensitivity/anaphylactic reactions is 1.1% with a subsequent all-cause inpatient mortality rate of 7.0%.

1. Introduction

Kounis syndrome (KS) is defined as the concurrence of acute coronary syndromes (ACS) with conditions associated with allergic reactions or hypersensitivity induced by exposure to drugs, food, coronary stents, and other environmental triggers [1]. The condition was first described as "allergic angina" by Dr. Nicholas Kounis in 1991 [2]. The pathophysiology of KS involves transient/persistent coronary artery spasms (type 1), atheromatous plaque rupture (type 2), or stent-related allergic coronary events (type 3) [1,3]. KS typically results from allergic reactions causing mast cell degranulation with subsequent release of inflammatory mediators such as histamine, platelet activating factor, cytokines, chemokines, and other protease substances [4]. It is

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imperative to understand that KS is a rare condition and usually underdiagnosed, or difficult to diagnose in emergency departments [5]. Furthermore, the syndrome has been mostly encountered in Southern Europe, mainly in Greece, Turkey, Italy, and Spain where physicians are aware of its existence [1]. The incidence rate of KS has been estimated to be 0.002%–3.4% [6,7]. However, these results were based on a small geographic region and specific population groups. No studies have investigated the prevalence of fatal KS in a larger population. There is a need for accurate epidemiological and outcomes data on KS to establish a preventive strategy against allergic reactions leading to development of ACS. The aim of this study was to investigate the prevalence and in-hospital outcomes of KS among patients primarily hospitalized with allergic/hypersensitivity/anaphylactic reactions using a national cohort in the United States (US).

2. Methods

2.1. Data source

We acquired the publicly accessible National Inpatient Sample (NIS) databases (2007–2014), which are funded by the Agency for Healthcare Research and Quality (AHRQ) as a part of Healthcare Cost and Utilization Project (HCUP) [8]. The NIS represents a nationally stratified 20% sample of discharges from over 1000 US community hospitals of 44 states, representing 95% of the US population. Discharge weight included in this dataset was used to produce national estimates of hospital inpatient stays. The study was exempted from IRB review due to deidentified nature of data.

2.2. Study design

We assessed primarily adult hospitalizations for allergy/hypersensitivity/anaphylaxis caused by any agent using the International Classification of Diseases-9th revision, Clinical Modification (ICD-9 CM) codes 4771 5186 5583 6910 6918 6920 6921 6922 6923 6924 6925 6926 69270 69271 69272 69273 69274 69279 69281 69282 69283 69284 69289 6929 6930 6931 6938 6939 708.x 9950 9951 9953 9956x 9957 9994 V071 V727. In-hospital ACS, inclusive of ST elevation myocardial infarction (STEMI), NSTEMI and unstable angina (UA), were identified using ICD-9 CM codes 410.x and 411.x. Co-existing comorbidities, outcomes, and coronary interventions were identified using the ICD-9 codes as detailed in prior studies [9,10].

2.3. Study outcomes

The primary outcome was the prevalence of KS (ACS among all patients primarily hospitalized for allergic, hypersensitivity or anaphylactic reactions), demographic attributes of the affected population, and consequent rate and odds of all-cause in-hospital mortality. Co-primary outcomes were rates of arrhythmia, stroke, venous thromboembolic events (VTE), and interventions including diagnostic coronary angiography, percutaneous coronary interventions, and coronary artery bypass grafting. Secondary outcomes were the mean length of stay (LOS, days), total hospital charges and discharge disposition.

2.4. Statistical analysis

Weighted discharges were utilized to analyze national estimates. Cases with missing values were excluded from the final analysis. Student's *t*-test and Pearson's chi-square test were used to compare continuous and categorical variables, respectively. Continuous and categorical variables were expressed as mean ± standard deviation and percentages, respectively. A two-tailed *p*-value≤0.05 was considered statistically significant. SPSS v22 (IBM Corp, Armonk, NY, USA) was used for all analyses.

3. Results

3.1. Baseline demographics and hospital characteristics

The study cohort comprised of 235,420 patients primarily hospitalized with allergy/hypersensitivity/anaphylactic reactions. Of these, 2616 [1.1%; 0.2% UA, 0.2% STEMI & 0.7% NSTEMI] patients experienced in-hospital ACS and were identified as having KS. KS patients were older (mean age years 65.9 ± 14.1 vs. 57.2 ± 17.8), more often White (71.1% vs. 58.6%), males (46.4% vs. 39.9%) and Medicare enrollees (58.9% vs. 41.5%) admitted non-electively (96.8% vs. 95.3%) as compared to non-KS ($p < 0.001$). Further, over half of the hospitalizations with KS were of elderly patients ≥65 years (55.5% vs. 44.5%, $p < 0.001$) compared to non-KS. Midwest region hospitals (21.2% vs. 17.7%, $p < 0.001$) and rural hospitals (11.2% vs. 9.7%, $p < 0.001$) showed more frequent KS hospitalizations (Table 1).

3.2. Primary outcomes

Overall prevalence of KS among patients primarily admitted for allergic reactions was 1.1% [0.2% UA, 0.2% STEMI & 0.7% NSTEMI] with a subsequent all-cause inpatient mortality of 7.0%. The hospitalizations with KS demonstrated higher all-cause in-hospital mortality (7.0% vs. 0.4%, $p < 0.001$) as compared to those with non-KS. Patients with KS had increased odds of in-hospital mortality (unadjusted OR: 18.52; 95% CI: 15.74–21.80, $p < 0.001$). After adjusting for demographics, comorbidities and hospital-level characteristics, odds of in-hospital mortality in hospitalized KS patients were higher (OR 9.74, 95% CI 8.08–11.76, $p < 0.001$) as compared to non-KS. Other co-primary outcomes such as rates of stroke (1.0% vs.0.2%, $p < 0.001$), arrhythmias (30.4% vs.12.4%, $p < 0.001$) and VTE (1.6% vs. 1.0%, $p = 0.003$), and coronary interventions including diagnostic coronary angiography (24.8% vs. 0.4%, $p < 0.001$), PCI (6.1% vs. 0.03%, $p < 0.001$) and CABG (1.3% vs. <11, $p < 0.001$) were found to be significantly higher in patients with KS compared to patients with allergic reactions without co-existent ACS (Table 2).

3.3. Secondary outcomes

Patients with KS had a prolonged LOS (mean 5.8 ± 6.0 vs. 3.0 ± 3.9 days), higher hospitalization charges ($52,656 vs. $20,487) and more frequent transfers to short term hospitals (3.9% vs. 0.9%), other transfers (SNF, ICF, other facility) (13.2% vs. 6.9%) or home health care (10.3% vs. 7.0%) as compared to non-KS ($p < 0.001$).

4. Discussion

To our knowledge, this is the first nationwide study of the KS and related in-hospital outcomes in the US. The major findings of this cross-sectional analysis are as follows. 1) majority of patients with KS were white older males, more frequently admitted to rural large bed-size hospitals, with a higher admission rate in the Midwest region 2) Patients with KS had a higher rate of hypertension, diabetes, peripheral vascular disorders, cardiopulmonary comorbidities, and a previous history of MI/PCI/CABG 3) Prevalence of KS was 1.1% with subsequent inpatient all-cause mortality rate of 7.0% 4) Patients with KS have significantly higher rates of all-cause in-hospital mortality, arrhythmia, and stroke, VTE, and coronary interventions including diagnostic coronary angiography, PCI, and CABG.

Epidemiologic studies indicate a lifetime prevalence of anaphylaxis around 1.6% and food allergy around 10.8% with >50% of them having severe food allergy reaction [11,12]. Another retrospective study using electronic medical records reported a higher incidence rate of penicillin allergy and other drug-induced anaphylaxis cases with cardiorespiratory failure occurring in 23% of hospitalized cases [13,14]. It is not surprising that the risk of drug-induced anaphylaxis increases with age, and most likely related to multiple drug use [15]. It could explain the higher rate of KS in the older age group as noted in our study. More recent updates on KS suggest that the syndrome has been observed in every race, age group and geographic location [1]. However, there was no detailed information available on the prevalence of KS within age and race subgroups. With a larger population, we have found that KS is more common in whites and older males.

Since the majority of the population with KS had higher comorbid conditions, it is plausible that they could have a higher stress level due to the bidirectional relationship between chronic conditions and stress [16]. Stress could also precipitate allergy by releasing inflammatory mediators, which could trigger coronary mast cells leading to cardiac events [17]. Furthermore, studies have shown that the attack of "angina" occurs during the episodes of anaphylaxis frequently in patients

Table 1
Baseline characteristics of hospitalizations for allergic, hypersensitivity or anaphylactic reactions without vs. with in-hospital acute coronary syndrome (KS).

Variables	(Allergy/hypersensitivity/anaphylaxis $N = 235,420$)				p
	No ACS ($N = 232,804$)		Yes ACS (KS) ($N = 2616$)		
Age (yrs) at hospitalization					<0.001
Mean ± SD	57.2 ± 17.8		65.9 ± 14.1		
18–44	55,890	(24.0%)	241	(9.2%)	
45–64	92,572	(39.8%)	922	(35.3%)	
≥65	84,342	(36.2%)	1453	(55.5%)	
Sex					<0.001
Male	92,871	(39.9%)	1214	(46.4%)	
Female	139,933	(60.1%)	1402	(53.6%)	
Race					<0.001
White	136,391	(58.6%)	1861	(71.1%)	
Black	63,458	(27.3%)	442	(16.9%)	
Hispanic	20,380	(8.8%)	190	(7.3%)	
Asian or Pacific Islander	4745	(2.0%)	51	(2.0%)	
Native American	1165	(0.5%)	14	(0.5%)	
Others	6665	(2.9%)	58	(2.2%)	
Type of admission					<0.001
Non-elective	221,762	(95.3%)	2532	(96.8%)	
Elective	11,042	(4.7%)	84	(3.2%)	
Admission day					0.024
Weekday	169,586	(72.8%)	1958	(74.8%)	
Weekend	63,218	(27.2%)	659	(25.2%)	
Median household income national quartile for patient's ZIP Code					0.022
0–25th	75,324	(32.4%)	784	(30.0%)	
26–50th	55,547	(23.9%)	659	(25.2%)	
51–75th	52,422	(22.5%)	577	(22.0%)	
76–100th	49,511	(21.3%)	597	(22.8%)	
Primary expected payer					<0.001
Medicare	96,502	(41.5%)	1541	(58.9%)	
Medicaid	29,839	(12.8%)	181	(6.9%)	
Private including HMO	78,406	(33.7%)	681	(26.0%)	
Self-pay	17,768	(7.6%)	130	(5.0%)	
No charges	2013	(0.9%)	15	(0.6%)	
Others	8275	(3.6%)	69	(2.7%)	
Bed size of hospital					0.005
Small	30,711	(13.2%)	295	(11.3%)	
Medium	62,143	(26.7%)	679	(26.0%)	
Large	139,951	(60.1%)	1642	(62.7%)	
Location/teaching status of hospital					0.010
Rural	22,507	(9.7%)	294	(11.2%)	
Urban nonteaching	91,575	(39.3%)	977	(37.4%)	
Urban teaching	118,721	(51.0%)	1345	(51.4%)	
Region of hospital					<0.001
Northeast	61,894	(26.6%)	694	(26.5%)	
Midwest	41,263	(17.7%)	554	(21.2%)	
South	93,635	(40.2%)	951	(36.4%)	
West	36,012	(15.5%)	417	(15.9%)	
Baseline comorbidities					
Alcohol abuse	9523	(4.1%)	114	(4.4%)	0.493
Deficiency anemias	29,132	(12.5%)	473	(18.1%)	<0.001
Rheumatoid arthritis/collagen vascular diseases	8242	(3.5%)	99	(3.8%)	0.502
Chronic blood loss anemia	650	(0.3%)	46	(1.8%)	<0.001
Congestive heart failure	17,767	(7.6%)	646	(24.7%)	<0.001
Chronic pulmonary disease	52,787	(22.7%)	634	(24.2%)	0.058
Coagulopathy	7302	(3.1%)	178	(6.8%)	<0.001
Diabetes, uncomplicated	54,434	(23.4%)	798	(30.5%)	<0.001
Diabetes with chronic complications	7703	(3.3%)	161	(6.1%)	<0.001
Drug abuse	7469	(3.2%)	69	(2.6%)	0.099
Hypertension	142,312	(61.1%)	1987	(76.0%)	<0.001
Hypothyroidism	25,159	(10.8%)	391	(14.9%)	<0.001
Liver disease	4813	(2.1%)	51	(1.9%)	0.671
Fluid and electrolyte disorders	47,834	(20.5%)	934	(35.7%)	<0.001
Obesity	30,004	(12.9%)	425	(16.3%)	<0.001
Peripheral vascular disorders	7734	(3.3%)	276	(10.5%)	<0.001
Pulmonary circulation disorders	3704	(1.6%)	80	(3.0%)	<0.001
Renal failure	23,475	(10.1%)	487	(18.6%)	<0.001
Valvular heart disease	7053	(3.0%)	251	(9.6%)	<0.001
Dyslipidemia	63,587	(27.3%)	1175	(44.9%)	<0.001
Previous MI PCI CABG	18,550	(8.0%)	825	(31.5%)	<0.001
Smoking	56,679	(24.3%)	752	(28.7%)	<0.001

$p < 0.05$ indicates statistical significance.
KS = Kounis syndrome, ACS = acute coronary syndrome, HMO = health maintenance organization, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting.

Table 2
Outcomes of Kounis syndrome-related hospitalizations.

Outcomes	No ACS (n = 232,804)		Yes ACS (n = 2616)		p
All-cause in-hospital mortality	949	(0.4%)	184	(7.0%)	<0.001
Arrhythmia	28,895	(12.4%)	797	(30.4%)	<0.001
Stroke	466	(0.2%)	25	(1.0%)	<0.001
Venous thromboembolism	2284	(1.0%)	41	(1.6%)	0.003
Diagnostic coronary angiography	982	(0.4%)	650	(24.8%)	<0.001
Percutaneous coronary intervention	76	(0.03%)	160	(6.1%)	<0.001
Coronary artery bypass grafting	<11[a]		35	(1.3%)	<0.001
Length of stay (days) Mean ± SD	3.0 ± 3.9		5.8 ± 6.0		<0.001
Total hospital charges (Mean)	$ 20,487		$ 52,656		<0.001
Disposition					<0.001
Routine	194,282	(83.5%)	1698	(64.9%)	
Transfer to short-term hospital	1979	(0.9%)	103	(3.9%)	
Other transfers (SNF, ICF, other facility)	16,055	(6.9%)	345	(13.2%)	
Home Health Care	16,240	(7.0%)	270	(10.3%)	

$p < 0.05$ indicates statistical significance, ACS = Acute Coronary Syndrome, SNF = Skilled Nursing Facility, ICF = Intermediate Care Facility.

[a] Cell counts <11 are not reported as per the privacy guidelines by HCUP.

with prior coronary diseases [18]. Our study showed a significantly higher rate of all-cause mortality, arrhythmia, stroke, VTE, and coronary interventions in patients hospitalized with KS. Interestingly, there are no studies in literature with an incidence rate of any of the mentioned outcomes. However, it is established that cardiac arrhythmia, pulmonary edema, and cardiac failure can increase the odds of death following KS [19].

The implications of our findings are important for cardiologists to realize the presence of KS even though it's rare. There are no guidelines or recommended treatments established for KS which makes it complicated to prioritize treatment based on the severity of either by anaphylaxis or acute coronary syndrome [20]. It is also important to find the triggering allergen in case of KS, to avoid such future events.

The findings of this study should be inferred considering its limitations. The precise cause-to-effect relationship cannot be established considering retrospective nature of the NIS data. There is a possibility of administrative coding errors. Since we have selected patients primarily admitted for allergy/hypersensitivity/anaphylaxis, it is unlikely that in-hospital ACS incidence was due to some other reasons without any role of allergic reactions. However, it is certainly possible that other factors might have also contributed to ACS in addition to allergic reactions in some cases. In addition, 3 subtypes of KS cannot be differentiated using this data source. Nonetheless, this large study presents the first ever data on the nationwide prevalence of KS and in-hospital outcomes in the US.

Declaration of Competing Interest

None.

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