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Clinical Research Article

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Cardiovascular Events in Patients with Thyroid Storm

Zainulabedin Waqar,[1] Sindhu Avula,[2] Jay Shah,[1,2] and Syed Sohail Ali[2]

[1]Department of Internal Medicine, Mercy St. Vincent Medical Center, Toledo, OH 43608, USA; and [2]Department of Cardiology, Mercy St Vincent Medical Center, Toledo, OH 43608, USA

ORCiD number: 0000-0001-8101-9691 (Z. Waqar).

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Abstract

Context: Thyroid storm can present as a multitude of symptoms, the most significant being cardiovascular (CV). It is associated with various manifestations such as cardiac arrhythmia, heart failure, and ischemia. However, the frequencies of events and characteristics associated with patients that experience these events are not known.
Methods: Study cohort was derived from the National Inpatient Sample database from January 2012 to September 2015. Total hospitalizations of thyroid storm were identified using appropriate ICD-9 diagnostic codes. The analysis was performed using SAS.
Objective: To better understand the frequency and characteristics CV occurrences associated with thyroid storm, through a retrospective analysis of thyroid storm hospital admissions.
Design: The study cohort was derived from the National Inpatient Sample database from January 2012 to September 2015.
Setting: Total hospitalizations of thyroid storm were identified using International Classification of Diseases (ICD)-9 diagnostic codes. The analysis was performed using Statistical Analysis System (SAS).
Results: A total of 6380 adult hospitalizations were included in the final analysis, which includes 3895 hospitalizations with CV events (CEs). Most frequently associated CEs were arrhythmia (N = 3770) followed by acute heart failure (N = 555) and ischemic events (N = 150). Inpatient mortality was significantly higher in patients with CEs compared with those without CEs (3.5% vs 0.2%, $P < 0.005$). The median length of stay was also higher in patients with CEs compared with those without CEs (4 days vs 3 days, $P < 0.0005$). Atrial fibrillation was the most common arrhythmia type, followed by nonspecified tachycardia.
Conclusions: In patients who were hospitalized due to thyroid storm and associated CEs significantly increased in-hospital mortality, length of stay, and cost. Patients with obesity, alcohol abuse, chronic liver disease, and COPD were more likely to have CEs. Patients with CV complications were at higher risk for mortality. In-hospital mortality

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increased with ischemic events and acute heart failure. Further evaluation is needed to further classify the type of arrhythmias and associated mortality.

Key Words: thyroid storm, arrhythmia, cardiovascular disease

Thyroid storm represents an uncommon endocrine emergency [1]. Causes can vary but are generally initiated by Graves' disease, amiodarone toxicity, toxic multinodular goiter, or autoimmune thyroiditis [1]. Patient presentations for thyroid storm vary and affect multiple organ systems [1, 2]. Patients can present with agitation, altered mental status, lethargy, coma, or dyspnea on exertion; they may also be seen with flushing, vitiligo, or hyperpigmentation [1, 2]. Sinus tachycardia, atrial fibrillation, or a heart blockage can also be observed on telemetry [2]. Gastrointestinal symptoms can vary but commonly noted are nausea, vomiting, diarrhea, and generalized abdominal pain [2]. The diagnosis of thyroid storm is made by clinical judgment but can be quantified using Burch and Wartofsky's diagnostic parameters [1, 3, 4]. These parameters illustrate a culmination of multiple symptoms, which help a clinician assess when a patient may be in thyroid storm [2, 3]. Burch and Wartofsky parameters have adjusted values for atrial fibrillation, heart failure, and tachycardia, which influence the parameters of thyroid storm but do not quantify the occurrence of such issues [1, 4].

One of the most disruptive clinical effects of thyroid dysfunction is its impact on the cardiovascular (CV) system and the heart, specifically [5]. Excess thyroid hormone increases the number of Beta adrenergic receptors in the myocardium and makes it more susceptible to vagal and sympathetic stimulation [5, 6]. Activation of triiodothyronine (T3) binds to thyroid hormone nuclear receptors, activating sodium and calcium channels (in both cell membranes, as well as the sarcoplasmic reticulum), resulting in increased contractility [7]. Free T3 also stimulates the renin angiotensin-aldosterone axis, triggering systemic vascular resistance, higher diastolic blood pressure, cardiac chronotropy, and ionotropy, ultimately causing an increase in cardiac output [3, 7, 8].

Thyroid storm may often cause arrhythmia in patients; however, it may also cause severe dilated cardiomyopathy, one of the leading causes of death in patients [1, 3].

In this study, we sought to define characteristics of patients admitted with thyroid storm and assess the impact of associated CV events (CEs) with their outcomes.

Methods

The study cohort was derived from the National Inpatient Sample (NIS) database collected from January 2012 to September 2015, which is derived from the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality. Thyroid storm as primary diagnosis was identified using International Classification of Diseases, Clinical Modification (ICD-9-CM) codes (242.91, 242.01, 242.11, 242.21, 242.31, 242.41, 242.81). A total of 6830 adult hospitalizations with thyroid storm as the primary diagnosis were included in the final analysis, as depicted in Fig. 1. A total of 3895 cases were found to have thyroid storm hospitalizations that included CEs (defined as ischemia, acute heart failure, and/or arrhythmia) and were compared with the remaining 2935 thyroid storm hospitalizations that did not have any documented CEs. Of the 3895 hospitalizations, 150 were found to be hospitalizations with ischemic events, 555 hospitalizations were associated with acute heart failure documented, and 3770 hospitalizations were documented with arrhythmia.

SAS software was used to convert the NIS database data to generate patient data by the HCUP recommendations and was performed using multivariate analysis.

The extracted thyroid storm hospitalizations were additionally classified by gender, race, comorbidities, household income, admission type, and hospital demographics. Patients were also categorized by their insurance status and type to identify Medicare and Medicaid recipients. The admitting hospitals were classified as rural, urban, teaching, and nonteaching hospitals based on the number of beds. Hospitals were organized by geographical locations as follows: the northeast, northwest, southern, and western regions. Admissions were also classified as either elective or emergent and/or urgent, where emergent and urgent were combined in our analysis. In-hospital mortality was determined based on patient expiring prior to discharge.

Results

Cardiovascular events after hospitalization with thyroid storm were significantly associated with increased age, as seen in Table 1 (44.2 years vs 38.6 years in those without CEs). Though there was not an apparent difference in gender, more females were diagnosed with thyroid storm than males in those with and without CEs. There were more white patients diagnosed with CEs than without (41.1% vs 37.5%), while the inverse was true for black

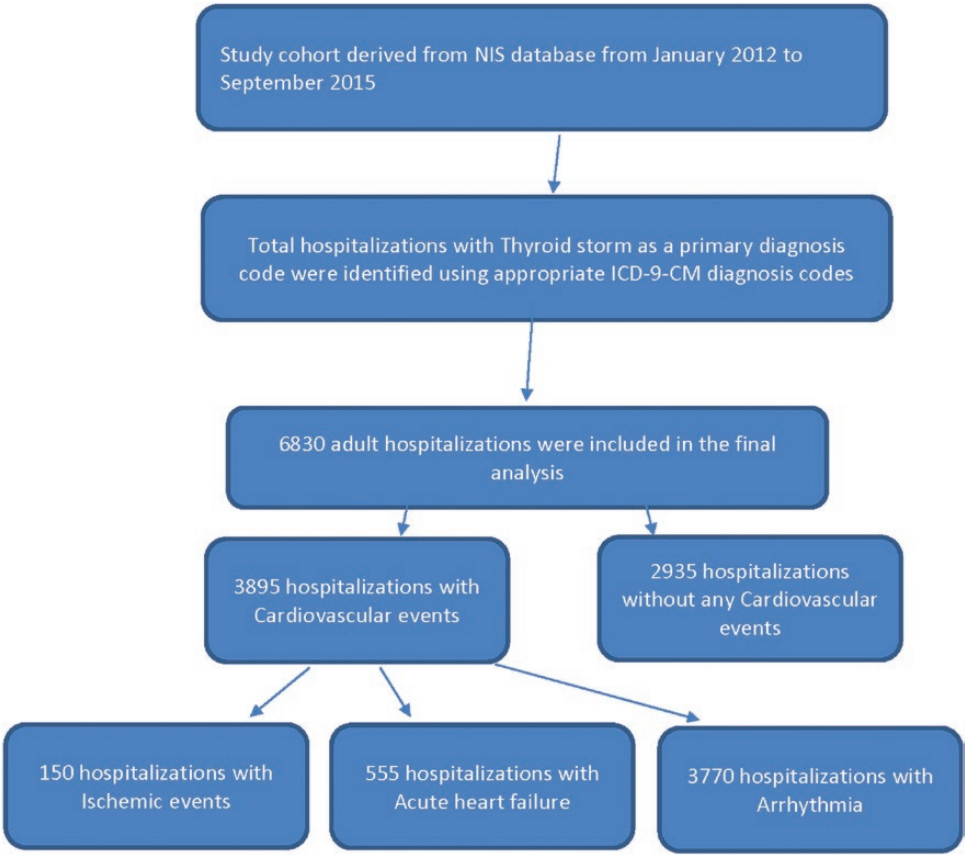

Figure 1. Selection criteria from using the NIS database. Also describing the subclassification of patients with cardiovascular events and thyroid storm and the division in acute ischemic events, acute heart failure, and arrhythmias.

patients (32.1% with CE vs 34.8% without) and other races (26.8% with CE vs 27.8% without), to a significant degree (P = 0.008).

When further subclassifying cardiac events divided in Table 2, patients noted with arrhythmia were noted to be younger than those with ischemic events or acute heart failure (44.1 years, 51.4 years, and 50.7 years, respectively).

Patients with obesity and chronic obstructive pulmonary disease (COPD) were more likely to experience CEs (obesity 6.9% vs 5.3%, P = 0.005; COPD, 16.3% vs 13.5%, P = 0.0014). When further analyzed, obesity was noted to be associated with a higher percentage of patients with ischemic events (13.3%). Chronic liver disease was also noted as being present in a greater proportion of patients with CEs (2.6% vs 1.7%, P = 0.02) and in a higher proportion of patients with acute heart failure (5.4%). Smokers were also more likely to have CEs (35.2% vs 32.2%, P = 0.01) and had about the same percentage of patients with ischemic events, acute heart failure, and arrhythmia (33.3%, 36%, and 35.3%, respectively).

No significant difference was noted for patients with hypertension, diabetes, and chronic renal disease when comparing patients with CV disease wth those without CV disease. However, hypertension and diabetes were noted to be more common in patients with ischemic events (63.3% and 26.7%, respectively) compared with acute heart failure or arrhythmias (38.7% and 39%; 6.3% and 11.4%, respectively). There was no difference in patients hospitalized with thyroid storm experiencing CEs in patients with a median income or on the location of hospital, but it was noted to have a higher percentages of patients in the lowest income quartile; also noted to have the higher percentage of patients treated in the southern region (45.3% of total patients with no CEs and 45.7% of total patients with CEs).

Interestingly, alcohol abuse was noted in patients without CV disease but not in those with CV disease (4.6% vs 3.3%, P = 0.008). When subclassified in CEs, a larger portion were noted to have ischemic events.

Outcomes for patients with CEs and those without CEs, patients were noted to have higher mortality, length of stay, and hospitalizations costs as seen in Table 3. A larger portion of ischemic events had a higher mortality rate (16.7%), a significantly longer median length of stay (8.5 days), as well as the highest hospitalization costs.

Table 1. Subclassification of patients diagnosed with thyroid storm and comparing those with and without cardiovascular events

Variable	No CV Event (N = 2935)	CV Events Present (N = 3895)	*P*-value
Age (years), mean, SD	38.6 ± 15.1	44.2 ± 15.6	<0.0001
Gender			0.98
Males	730 (24.9)	970 (24.9)	
Females	2205 (75.1)	2925 (75.1)	
Race			0.008
White	1100 (37.5)	1600 (41.1)	
Black	1020 (34.8)	1250 (32.1)	
Others	815 (27.8)	1045 (26.8)	
Comorbidities			
Hypertension	1095 (37.3)	1535 (39.4)	0.08
Diabetes mellitus	335 (11.4)	440 (11.3)	0.9
Obesity	155 (5.3)	270 (6.9)	0.005
COPD	395 (13.5)	635 (16.3)	0.001
Chronic renal disease	75 (2.6)	115 (3)	0.32
Chronic liver disease	49 (1.7)	100 (2.6)	0.02
Alcohol abuse	135 (4.6)	130 (3.3)	0.008
Smoker	945 (32.2)	1370 (35.2)	0.01
Primary payer			0.72
Medicare/Medicaid	1290 (44)	1750 (44.9)	
Private insurance	800 (27.3)	1145 (26.8)	
Other	845 (28.8)	1100 (28.2)	
Median household income (in percentile)			0.1
0–25th	1165 (40.4)	1570 (41.2)	
26–50th	730 (25.3)	890 (23.4)	
51–75th	585 (20.3)	750 (19.7)	
76–100th	405 (14)	600 (15.8)	
Admission type			0.08
Elective	180 (6.1)	200 (5.2)	
Emergent/urgent	2750 (93.9)	3685 (94.9)	
Hospital region			0.43
Northeast	490 (16.7)	645 (16.6)	
Midwest	510 (17.4)	720 (18.5)	
South	1330 (45.3)	1780 (45.7)	
West	605 (20.6)	750 (19.3)	
Hospital teaching status			<0.0001
Rural	165 (5.6)	350 (9)	
Urban, nonteaching	820 (27.9)	1110 (28.5)	
Urban, teaching	190 (66.4)	2435 (62.5)	
Hospital bed size			0.15
Small	310 (10.6)	470 (12.1)	
Medium	835 (28.5)	1090 (28)	
Large	1790 (61)	2335 (60)	

Numbers in parenthesis designate percentages.
Abbreviations: COPD, chronic obstructive pulmonary disease; CV, cardiovascular; SD, standard deviation.

Arrhythmia types are subclassified in Table 4, with the largest number of patients with atrial fibrillation (1790) followed by tachycardia (890) and atrial flutter (260).

Discussion

Hyperthyroidism is due to excessive endogenous thyroid hormone production and thyrotoxicosis as a result of excess thyroid hormone, which can be secondary to either endogenous thyroid hormone production (hyperthyroidism) or due to exogenous thyroid hormone replacement [5].

Thyroid crisis or thyroid storm, on the other hand, is an extreme manifestation of thyrotoxicosis, which is characterized by amplified manifestations. It is most commonly caused by Grave's disease or toxic multinodular goiter, but in rare occasions can be from subacute thyroiditis or due to intentional thyroid hormone overdose [9].

Table 2. Classification of patient's who have been diagnosed with cardiovascular events and further identified as ischemic events, acute heart failure, and arrhythmia

Variable	Ischemic Event	Acute Heart Failure	Arrhythmia
	(N = 150)	(N = 555)	(N = 3770)
Age (years)	51.4 ± 12.7	50.7 ± 14.4	44.1 ± 15.6
Gender			
Males	55 (36.7)	160 (28.8)	950 (25.2)
Females	95 (63.3)	395 (71.2)	2820 (74.8)
Race			
White	65 (43.3)	240 (43.2)	1550 (41.1)
Black	55 (36.7)	210 (37.8)	1190 (31.6)
Others	30 (20)	105 (18.9)	1030 (27.3)
Comorbidities			
Hypertension	95 (63.3)	215 (38.7)	1470 (39)
Diabetes mellitus	40 (26.7)	35 (6.3)	430 (11.4)
Obesity	20 (13.3)	70 (5.6)	245 (6.5)
COPD	20 (13.3)	100 (18)	630 (16.7)
Chronic renal disease	15 (10)	45 (8.1)	110 (2.9)
Chronic liver disease	5 (3.3)	30 (5.4)	90 (2.4)
Alcohol abuse	20 (13.3)	20 (3.6)	130 (3.5)
Smoker	50 (33.3)	200 (36)	1330 (35.3)
Primary payer			
Medicare/Medicaid	70 (46.7)	285 (51.4)	1695 (45)
Private insurance	35 (23.3)	130 (23.4)	1015 (26.9)
Other	45 (30)	140 (25.2)	1060 (28.1)
Median household income (in percentile)			
0–25th	45 (30)	40 (44.9)	1505 (40.8)
26–50th	30 (20)	80 (15)	870 (23.6)
51–75th	35 (23.3)	135 (25.2)	725 (19.7)
76–100th	40 (26.7)	80 (15)	858 (15.9)
Admission type			
Elective	15 (10)	10 (1.8)	195 (5.2)
Emergent/urgent	135 (90)	545 (98.2)	3565 (94.8)
Hospital region			
Northeast	25 (16.7)	55 (9.9)	625 (16.6)
Midwest	35 (23.3)	120 (21.6)	700 (18.6)
South	80 (53.3)	295 (53.2)	1700 (45.1)
West	10 (6.7)	85 (15.3)	745 (19.8)
Hospital teaching status			
Rural	15 (10)	65 (11.7)	340 (9)
Urban, nonteaching	45 (30)	140 (25.2)	1065 (28.3)
Urban, teaching	90 (60)	350 (63.1)	2365 (62.7)
Hospital bed size			
Small	30 (20)	50 (9)	465 (12.3)
Medium	45 (30)	145 (26.1)	1055 (29)
Large	75 (50)	360 (64.9)	2250 (59.7)

Numbers in parenthesis designate percentages.
Abbreviation: COPD, chronic obstructive pulmonary disease.

Thyroid storm can occur with solitary toxic adenoma or toxic multinodular goiter and less commonly with thyroid-secreting pituitary adenomas, hypersecretory thyroid carcinomas, teratomas, and with hydatiform moles. It can also be associated with thyrotoxicosis induced by interleukin-2 or α-interferon [10]. Several other conditions such as diabetic ketoacidosis, myocardial infarction, congestive heart failure, trauma, surgery, infection, and intense emotional stress can serve as triggers for thyroid storm in patients with thyrotoxicosis [11].

Thyroid storm is a clinical emergency, with a mortality rate of 20% to 30% [12]. Its incidence rate was

Table 3. Patient outcomes of those diagnosed with and without cardiovascular events

Outcome	CV Events Present (N = 3895)	No CV Event (N = 2935)	*P*-value
In-hospital mortality	135 (3.5%)	5 (0.2)	<0.001
Adjusted mortality	19 (7.7–46.6)		<0.001
Length of stay in days (median)	4 (2–7)	3 (2–5)	<0.001
Cost in $$ (median)	7744 (4581–14674)	5380 (3435–8641)	<0.001
	Ischemic Event (N = 150)	**No CV Event (N = 2935)**	
In-hospital mortality	25 (16.7%)	5 (0.2)	<0.001
Adjusted mortality	23.9 (13.2–43.2)		<0.001
Length of stay (median)	8.5 (5–25)	3 (2–5)	<0.001
Cost (median)	25622 (15542–64894)	5380 (3435–8641)	<0.001
	Acute Heart Failure (N = 555)	**No CV Event (N = 2935)**	
In-hospital mortality	20 (3.6%)	5 (0.2)	<0.001
Adjusted mortality	1.3 (0.8–2.1)		0.37
Length of stay (median)	7 (4–11)	3 (2–5)	<0.001
Cost (median)	13511 (8645–28155)	5380 (3435–8641)	<0.001
	Arrhythmia (N = 3770)	**No CV Event (N = 2935)**	
In-hospital mortality	120 (3.2%)	5 (0.2)	<0.001
Adjusted mortality	4.5 (2.8–7.4)		<0.001
Length of stay (median)	4 (2–7)	3 (2–5)	<0.001
Cost (median)	7646 (4539–15606)	5380 (3435–8641)	<0.001

Table 4. Subclassification of arrhythmia types in patients with cardiovascular events

Arrhythmia Types	Number of Diagnosis
Atrial fibrillation	1790
Atrial flutter	260
Supraventricular tachycardia	55
Ventricular tachycardia	185
Ventricular fibrillation	20
Cardiac arrest	150
Paroxysmal atrial/ventricular tachycardias	245
Premature beats	50
Tachycardia (nonspecific)	890
Palpitations	195

0.57 to 0.76 per 100 000 persons and 4.8 to 5.6 per 100 000 hospitalized patients per year, as found in a US-based survey [13]. It constituted 16% of patients hospitalized with thyrotoxicosis and has 12 times the mortality compared with thyrotoxicosis without storm [13]. The study showed that although its incidence rate did not change significantly spanning the years 2003 to 2014, the hospitalization costs had increased. Our analysis, which included the interval years 2012 to 2015, showed that among hospitalized patients with thyroid storm, any CE was associated with higher mortality, length of stay (LOS), and hospitalization costs. The longer LOS and hospitalization costs remained significant even upon conducting a subgroup analysis among various subtypes of CEs, such as ischemic events, heart failure, or arrhythmias. There were significantly more patients with obesity, liver disease, and smoking in the group that had CV events, which is not unexpected, as these are the traditional CV risk factors.

Thyroid disorders, both thyroid hormone excess or deficiency, are well known to have myriad effects on the CV system. These include heart failure, atrial and ventricular arrhythmias, and atherosclerosis [14]. There is growing evidence that suggests that even subclinical thyrotoxicosis or hypothyroidism could be associated with CV risk and arrhythmias [14, 15]. Cardiovascular manifestations are the most severe demonstration of thyrotoxicosis [16]. There is a hyperdynamic state that consists of an increased resting heart rate, increased blood volume, and enhanced left ventricular contractility, but reduced systemic vascular resistance [17, 18]. Reduced exercise tolerance is the most common manifestation, though in rare cases patients can have severe symptomatic congestive heart failure [19, 20]. Previous studies have shown that about 6% of patients with thyrotoxicosis develop heart failure and that reduced ejection fraction occurs in about 1% of patients. In our study, about 8% of thyroid storm patients had acute heart failure. However, the type of heart failure, whether with or without reduced ejection fraction, could not be deciphered. Isolated right heart failure can also occur with thyrotoxicosis, which is usually a result of pulmonary hypertension [18]. However, both right and left heart failure can be reversed with the rapid treatment of thyrotoxicosis [21, 22]. A small rise in troponin in thyroid storm may be due to tachycardia [23], coronary artery spasm [24], or Takotsubo cardiomyopathy [25, 26] and not necessarily due to atherosclerotic coronary artery disease.

Sinus tachycardia is the most common abnormal rhythm, which is found in a majority of patients with hyperthyroidism [27, 28]. Atrial fibrillation is the most commonly identified arrhythmia in patients with thyrotoxicosis, with a prevalence rate of 13.8% compared with 2.3% in euthyroid patients [29, 30]. From the Danish registry data, it was found that male gender, congestive heart failure, ischemic and valvular heart disease were at highest risk for atrial fibrillation. However, in unselected patients with atrial fibrillation, the prevalence of overt hyperthyroidism was <1% [5, 31]. In our study, atrial fibrillation was the commonly associated arrhythmia followed by nonspecific tachycardia. As sinus tachycardia is a rather benign finding, there is a good chance that several cases of sinus tachycardia might not have been coded into a patient's diagnoses list. Atrial flutter was the next most commonly found arrhythmia, followed by ectopy, including parosyxmal atria complexes (PACs) or parosyxmal ventricular arrhythmias (PVCs).

Thyrotoxicosis has traditionally been known to cause supraventricular arrhythmias, whereas hypothyroidism has been indicted in ventricular arrhythmias, albeit with lesser evidence to its support [30]. Ventricular arrhythmias tend to occur in patients with intrinsic cardiac disease and are rarely associated with isolated thyrotoxicosis [12]. There are a few isolated case reports where thyrotoxicosis was associated with ventricular fibrillation [32–34]. Of these, 2 case reports had negative cardiac work-up that ruled out any intrinsic cardiac disease [33, 34]. In our study, ventricular tachycardia was the 5th most common arrhythmia after PACs/PVCs.

About 150 cardiac arrests were registered, but only 20 observations were ventricular fibrillation, which was also the least common arrhythmia seen in the database.

Limitations to the data include not having data to subclassify heart failure with or without preserved ejection fraction, and subclassification of arrhythmias was based on documented ICD-9 codes and could not be further stratified. ICD-9 codes were available but not ICD-10 codes. Due to the nature of the data used, it was not possible to decipher if the same patient had multiple hospitalizations, which could potentially skew the data. Exact levels of thyroid stimulating hormone (TSH), free T3, and free thyroxine T4 were not readily available, nor was any analysis of the Burch-Wartofsky scale in any patients analyzed in this data.

Additional Information

Correspondence: Zainulabedin Waqar, Department of Internal Medicine, Mercy Saint Vincent Medical Center, 2213 Cherry Street, Internal Medicine, Toledo, OH 43608, USA. E-mail: zawaqar@mercy.com.

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Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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