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RESEARCH ARTICLE

The Effect of Atrial Fibrillation on Mortality Outcomes in Patients Admitted With Diabetic Ketoacidosis

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Abstract

This study aims to identify the effect of atrial fibrillation on mortality in patients admitted with DKA. We used the National Inpatient Sample Database for the year 2018 and 2019 to identify patients hospitalized with DKA. Association of atrial fibrillation was confirmed using the International Classification of Disease, Tenth Edition (ICD 10 CM). We performed a retrospective analysis on this database using STATA (Stata Corp, College Station, TX). The primary outcome was mortality in DKA. Length of stay (LOS) and total hospitalization charge were the secondary outcomes.

There was a total of 447,570 DKA patients out of which 12,770 had associated atrial fibrillation in the year 2018−2019. The mean age of patients with DKA and AFIB was 62 years. Approximately 46% of patients were female in DKA with AFIB group. The multivariate logistic analysis showed increased mortality in patients with DKA and AFIB (OR = 1.4, $p = 0.048$). Predictors of increased mortality were older age and teaching status of hospitals in metropolitan areas (OR = 1.0, $p < 0.001$ and OR = 1.4, $p = 0.031$ respectively). LOS was lower in patients with DKA and AFIB compared to DKA alone (3.1 day and 5.2 days respectively, OR = 0.82, $p < 0.001$). Total hospitalization charge was higher for patient in DKA with AFIB (USD 53,576 and USD 32,533 respectively, coefficient = 10,513, $p < 0.001$).

Patients hospitalized with DKA and AFIB had higher mortality compared to patients without AFIB, while they showed lower LOS but increased hospitalization cost. Further research in this direction would be helpful to better understand this association.

Keywords: National In patient Sample, Atrial fibrillation, Diabetic ketoacidosis, Outcome

1. Introduction

Diabetes ketoacidosis (DKA) is characterized by triad of uncontrolled hyperglycaemia, metabolic acidosis, and increased total body ketone concentration. The overall mortality of DKA in adults is <1% however elderly populations and those with concomitant life-threatening illnesses are known to have higher mortality (>5%).[1] Atrial fibrillation is defined as a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction.[2] The overall prevalence of atrial fibrillation has tripled in the last 50 years and contributes towards increased mortality in DKA patients.[3] Notwithstanding the rising prevalence of diabetes and atrial fibrillation there is a dearth of studies specifically assessing the effect of atrial fibrillation on mortality outcomes of hospitalized patients with DKA.

2. Methods

National Inpatient Sample (NIS) is the largest publicly available all-payer inpatient healthcare database available in the United States of America (USA) and is maintained by the Agency for Healthcare Research and Quality. The 2019 NIS includes discharge data from hospitals in 47 states and the District of Columbia in the USA. These diagnoses are documented as International Classification of Diseases Tenth Edition Clinical Modification (ICD-10-CM) and clinically meaningful

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clusters of ICD-10 CM codes. NIS data is publicly available, and as per the recommendations of this database, institutional review board certification was not required for research use.[4]

We used the NIS Database for years 2018 and 2019 to identify our patient population hospitalized with DKA. Association of atrial fibrillation was confirmed using the International Classification of Disease, Tenth Edition (ICD 10 CM). Patients with the principal diagnosis of DKA were identified by ICD-10 code E11.1. For the diagnosis of atrial fibrillation, we used various different ICD-10 codes, in order to identify and capture patients with various types of atrial fibrillation (Table 1). Patient and hospital characteristics of patients with Atrial Fibrillation with DKA are detailed in Table 2. As the NIS is an administrative database, and we use loop command to obtain atrial fibrillation as secondary diagnosis, it was not possible to further classify if patients presented with new onset versus known atrial fibrillation. We obtained patient socio-economic demographics such as gender, race/ethnicity, age, median annual income, and insurance type. In terms of hospital characteristics, we reviewed hospital region, hospital location, hospital size based on number of beds, and teaching hospital status. We included the Charlson Comorbidity Index Score (CCS) to assist with presenting risk of mortality. Severity of comorbidity was categorized into 3 grades. CCS score of 1–2 was considered mild, 3–4 was considered moderate, and a score is more than 5 was considered severe. The outcome variables studied were (1) in-hospital mortality, (2) duration of stay; and (3) total expenditure (Table 3). We performed a retrospective analysis of this database using STATA version 15 (Stata Corp, College Station, TX). A p-value of 0.05 was considered statistically significant. The primary outcome was mortality in DKA. Length of stay (LOS) and total hospitalization charge were the secondary outcomes.

3. Results

There was a total of 447,570 patients who were admitted with DKA from 2018 to 2019. Out of which (2.8%) 12,770 had an associated diagnosis of atrial fibrillation. The mean age of patients with DKA was 39 years, while the mean age of patients with DKA and AFIB was significantly higher, 62 years. Approximately 46% of patients were female in DKA with AFIB group. Most of the patients were Caucasians in both the groups (56% in DKA and 70% in DKA with AFIB). In-hospital mortality was noted in 1.4% of patients with DKA and AFIB as compared to 0.3% in patients with DKA alone. The multivariate logistic analysis showed increased mortality in patients with DKA and AFIB (OR = 1.4, p = 0.048) (Table 3). Predictors of increased mortality were older age and teaching status of hospitals in metropolitan areas (OR = 1.0, p = 0.000 and OR = 1.4, p = 0.031 respectively). Other variables such as race, median annual income, Charlson Comorbidity Index, education or teaching status of the hospitals, or medical insurance did not have any association with mortality.

Table 1. Types of atrial fibrillation and ICD Codes.

ICD-10 code	Type of Atrial Fibrillation
I48.0	Paroxysmal atrial fibrillation
I48.11	Longstanding persistent atrial fibrillation
I48.19	Other persistent atrial fibrillation
I48.21	Permanent atrial fibrillation
I48.9	Unspecified atrial fibrillation and atrial flutter
I48.91	Unspecified atrial fibrillation

Table 2. Patient and hospital characteristics of patients with Atrial Fibrillation with DKA.

Patient characteristics	
No. (%) of patients	12,770
Gender	
Female, no. (%)	5890 (46.1)
Race/ethnicity, no. (%)	
White	8913 (69.8)
Black	2439 (19.1)
Hispanic	919 (7.2)
Asian or Pacific Islander	166 (1.3)
Native American	89 (0.7)
Other	243 (1.9)
Mean age, year, (95% CI)	62.5 (61.9–63.1)
Median annual income in patient's zip code, US$, no (%)	
1-47,999	4201 (32.9)
48,000–60,999	3525 (27.6)
61,000–81,999	2899 (22.7)
≥82,000+	2145 (16.8)
Insurance type, no. (%)	
Medicare	7662 (60)
Medicaid	2171 (17)
Private	2324 (18.2)
Self	613 (4.8)
Hospital characteristics	
Hospital region, no. (%)	
Northeast	2260 (17.7)
Midwest	3001 (23.5)
South	5172 (40.5)
West	2337 (18.3)
Hospital bed size, no. (%)	
Small	2963 (23.2)
Medium	4048 (31.7)
Large	5759 (45.1)
Hospital location	
Rural	1264 (9.9)
Urban	11,506 (90.1)
Teaching status	
Non-teaching hospital	3882 (30.4)
Teaching hospital	8888 (69.6)

Abbreviations: CI- Confidence Interval, DKA-Diabetic Keto Acidosis.

Table 3. Factors associated with mortality.

Factors associated with Mortality	Odds Ratio	S. E	P value	[95% CI]	
Atrial fibrillation	1.429	0.258	0.048	1.003	2.035
AGE	1.049	0.004	0.001	1.041	1.057
FEMALE	0.913	0.099	0.402	0.738	1.130
Race (Reference- White)					
Black	1.039	0.139	0.772	0.800	1.351
Hispanic	1.022	0.200	0.912	0.696	1.501
Asian or Pacific Islander	1.837	0.612	0.068	0.955	3.531
Native American	0.839	0.611	0.810	0.201	3.501
Other	1.320	0.461	0.428	0.665	2.619
Median annual income US$ (Reference-1 - 47,999)					
48,000–60,999	1.118	0.155	0.420	0.852	1.467
61,000–81,999	1.016	0.157	0.920	0.750	1.375
82,000+	0.841	0.163	0.373	0.575	1.231
Charlson comorbidity Index					
1	0.177	0.185	0.096	0.023	1.363
2	0.221	0.230	0.147	0.029	1.699
≥3	0.372	0.385	0.339	0.049	2.824
Urban hospitals (Reference-rural)					
	0.861	0.200	0.519	0.546	1.357
Hospital region (Reference- Northeast)					
Midwest	1.018	0.196	0.924	0.699	1.484
South	1.100	0.188	0.575	0.788	1.538
West	1.079	0.203	0.687	0.746	1.558
Hospital bed-size (Reference small)					
Medium	1.202	0.181	0.223	0.894	1.615
Large	1.152	0.164	0.319	0.872	1.522
HOSP_TEACH (Reference non-teaching					
Teaching	1.373	0.202	0.031	1.029	1.832
Insurance (Reference Medicare)					
Medicaid	0.922	0.162	0.643	0.653	1.301
Private	0.893	0.155	0.514	0.634	1.256
Self-pay	1.107	0.256	0.660	0.703	1.743

Abbreviations: CI: Confidence Interval, SE: Standardized Error.

Length of stay (LOS) was lower in patients with DKA and AFIB compared to DKA alone (3.1 day and 5.2 days respectively, OR = 0.82, p = 0.001). Predictors of increased LOS were older age and female gender. Median annual income, insurance status of the patient, and Charlson Comorbidity Index did not have any association with increased length of stay (Table 4). However, the difference in the length of stay was significant across different races, hospital regions, bed size and teaching status of the hospital.

Total hospitalization charge was higher for patient in DKA with AFIB (USD 53,576 and USD 32,533 respectively, coefficient = 10,513, p = 0.000) (Table 5). There was no significant association in total charges and factors like median annual income, Charlson Comorbidity Index, teaching status of the hospital, hospital bed size, and hospital region.

Table 4. Length of stay analysis.

Factors associated with length of stay	Coef.	S.E.	P	[95% C.I.]	
Atrial fibrillation	0.821	0.098	0.000	0.629	1.014
AGE	0.029	0.001	0.000	0.027	0.031
FEMALE	0.157	0.025	0.000	0.108	0.206
Race (Reference- White)					
Black	0.209	0.032	0.000	0.146	0.273
Hispanic	0.159	0.037	0.001	0.087	0.231
Asian or Pacific Islander	0.284	0.122	0.020	0.045	0.524
Native American	0.140	0.110	0.205	0.076	0.356
Other	0.234	0.067	0.001	0.102	0.366
Median annual income US$ (Reference-1 - 47,999)					
48,000–60,999	0.016	0.033	0.623	0.080	0.048
61,000–81,999	0.043	0.035	0.218	0.112	0.026
82,000+	0.079	0.040	0.049	0.157	0.000

(*continued on next page*)

Table 4. (continued)

Factors associated with length of stay	Coef.	S.E.	P	[95% C.I.]	
Insurance (Reference-Medicare)					
Medicaid	0.098	0.051	0.055	0.002	0.199
Private	0.157	0.047	0.001	0.250	0.065
Self-pay	1.107	0.256	0.660	0.703	1.743
Charlson comorbidity Index					
1	0.359	0.422	0.395	1.186	0.468
2	0.106	0.423	0.801	0.722	0.935
≥3	0.970	0.424	0.022	0.139	1.800
Urban hospitals (Reference-rural) Urban	0.340	0.039	0.000	0.263	0.417
Hospital region (Reference- Northeast)					
Midwest	0.404	0.052	0.000	0.506	0.303
South	0.188	0.050	0.000	0.286	0.089
West	0.460	0.055	0.000	0.568	0.352
Hospital bed-size (Reference-small)					
Medium	0.164	0.032	0.000	0.102	0.227
Large	0.494	0.032	0.000	0.431	0.557
Hospital teaching status (Reference-non-teaching)	0.292	0.031	0.000	0.230	0.353

Abbreviations: Coef.: Coefficient, CI: Confidence Interval, SE: Standardized Error.

Table 5. Total charges analysis.

Factors associated with total charges	Coefficient	Linearized Standard Error	P	[95% C.I.]	
Atrial fibrillation	10512.69	1236.29	0.000	8089.26	12936.12
AGE	235.72	12.99	0.000	210.26	261.19
FEMALE	1693.62	302.74	0.000	1100.17	2287.07
Race (reference = White)					
Black	1734.18	485.07	0.000	783.32	2685.04
Hispanic	6223.27	573.73	0.000	5098.62	7347.92
Asian or Pacific Islander	6564.41	2749.912	0.017	1173.9	11954.91
Native American	3510.89	1181.09	0.003	5826.12	1195.66
Other	6857.93	1085.6	0.000	4729.89	8985.97
Insurance provider (reference = Medicare)					
Medicaid	1190.5	592.69	0.045	28.68	2352.31
Private	748.05	577.35	0.195	383.7	1879.81
Self-pay	618.27	579.7	0.286	518.08	1754.61
Median annual income in patient's zip code, US$ (reference 1–47,999)					
48,000–60,999	549.89	452.65	0.224	1437.18	337.41
61,000–81,999	237.72	555.82	0.669	1327.26	851.81
82,000+	1305.99	689.29	0.058	45.19	2657.16
Charlson comorbidity score					
1	379.68	3073.62	0.902	5645.35	6404.71
2	4699.39	3086.52	0.128	1350.94	10749.72
≥3	14577.41	3091.7	0.000	8516.93	20637.89
Urban hospitals (reference-rural)	10996.78	639.52	0.000	9743.16	12250.4
Hospital region (reference Northeast)					
Midwest	8631.17	1083	0.000	10754.12	6508.23
South	4189.47	1079.9	0.000	6306.34	2072.6
West	7361.49	1230.58	0.000	4949.25	9773.73
Hospital bed-size (reference small)					
Medium	2944.69	625.65	0.000	1718.25	4171.12
Large	4671.01	625.97	0.000	3443.96	5898.07
Hospital teaching status (reference non-teaching)					
Teaching	1179.39	634.77	0.063	64.92	2423.69

4. Discussion

This population based, epidemiological study evaluated the effect of atrial fibrillation on mortality in patients admitted for diabetic ketoacidosis (DKA) using the NIS database from 2018 to 2019. DKA is a potentially fatal complication of uncontrolled diabetes.[5] The global prevalence of atrial fibrillation has tripled in the last 50 years with an increasing

prevalence of diabetes as one of the attributable risk factors.[3,6] The age-adjusted hospitalization rate for DKA in adults above the age of 18 years old has doubled in the USA for 20 years between 2000 and 2019 as shown by CDC's United States Diabetes Surveillance System. A study using the NIS database showed advances in early diagnosis and better inpatient care have reduced the mortality and length of stay from DKA. However, the costs of hospitalizations have increased significantly between 2003 and 2014.[7]

The Framingham Heart Study showed diabetes mellitus is associated with an increased risk of developing atrial fibrillation with OR of 1.4 for men and 1.6 for women.[8] The incidence of AF among diabetics can be as high as 14.9%.[9] An estimated 15% of patients with diabetes have atrial fibrillation, whereas 30% of patients with atrial fibrillation have diabetes.[10] A dose–response effect has been shown between greater exposure to hyperglycemia causing increased risk of atrial fibrillation which argues for causality.[11] The excess risk of atrial fibrillation in individuals with type 2 diabetes increases with worsening glycemic control and renal complications.[12] In diabetic rat models, structural remodelling of the atrium by diffuse interstitial fibrosis is a substrate for atrial fibrillation.[13] The acidosis and electrolyte imbalances in DKA can be arrhythmogenic. On the other hand, atrial fibrillation causes the release of stress hormones which can cause a relative deficiency of insulin, potentially tilting the balance towards DKA.[14] Interestingly, diabetes has also been shown to cause the expansion of epicardial fat adjoining the left atrium, also leading to atrial fibrillation.[15]

The prevalence of AFIB among the hospitalized DKA patients in our study was 2.85%. This showed an increasing prevalence of AFIB among hospitalized DKA patients in comparison with two previous studies.[16,17] The mean age of patients with DKA was 39 years, while the mean age of patients with DKA and AFIB was significantly higher, 62 years. The incidence of DKA is higher in Type 1 diabetes than in Type 2 diabetes, hence this difference explains the younger mean age of DKA patients. The mean age group of patients with DKA in our group correlates well with a previous study that showed that the age group below 45 years old had the highest rate of increase in hospitalization from 2009 to 2014.[18] The finding of our study also correlates with the general prevalence of AFIB, which tends to increase with age in diabetics more than those without diabetes.[19] Inpatient mortality rates for DKA are generally low, <1%.[1] However, our study showed increased mortality in DKA patients with AFIB than those without AFIB (OR = 1.4, p = 0.048). Generally, the combination of diabetes and AFIB increases the mortality rate two-fold compared to the general population, and over fivefold at ages below 65.[20] Not surprisingly, this pattern is again noted in our study. In patients with DKA and AFIB, older age is another predictor that increases mortality in our study. Age is shown as an independent predictor of mortality in hyperglycemic emergencies as well.[21]

Multiple mechanisms have been postulated regarding the increase of mortality in patients with AFIB in DKA:

1. A prior study by Yang et al.[17] had shown that patients with AFIB had higher risk of septic shock, worsening lung function, increased neurological, hepatic, cardiac deterioration, and requirement of mechanical ventilation. They postulated that these complications contributed to higher overall mortality.[17]
2. Acute AFIB could increase release of stress hormones, which can cause relative deficiency of insulin and further worsening of severity of DKA. Similarly, new onset AFIB might be a marker of severe DKA.[1,17]
3. Patients with DKA and AFIB have been known to have a higher prevalence of hypertension, obesity, CKD, CHF, and prior MI, which could independently increase complications in patients with AFIB. The higher number of comorbidities in the elderly could predisposes them to higher risks of complications and hence higher mortality rate from DKA as well.

Our study showed that the teaching status of hospitals in metropolitan areas is a predictor of higher mortality rates among patients admitted for DKA. Two previous NIS database studies in 2017 and 2018 respectively showed contradicting findings in this regard, however, the findings were not statistically significant.[22,23] One of the factors could be the generally sicker population of DKA patients in a teaching hospital compared to a non-teaching hospital. Certainly, more studies are needed to clarify this important finding. In terms of length of stay, unlike the two previous NIS-based studies, our study showed that the length of stay was shorter in patients with DKA and AFIB compared to DKA alone. A prior study by Yang et al. in similar subset of patients had shown longer length of stay in the patients with DKA and AFIB (5.5 days) as compared to DKA alone (3.3 days). The unexpected finding of shorter length of stay in DKA patients with AFIB in our study and whether this is related to potential treatment for AF such as electrical or

pharmacological cardioversion is yet to be studied. While it is possible that patient with DKA and AFIB have received additional procedures including continuous telemonitoring, transthoracic echocardiogram, transoesophageal echocardiogram and cardioversion, thus increasing the cost of stay. Whether this intervention would implicate faster recovery and reduction of duration of stay is uncertain. In addition, relationship between length of stay and hospitalization charges are non-linear and generally depend on various factors.[24] Hence, more study is certainly needed to clarify the effect of treatment of AF on length of stay in patients with both AF and DKA.[27]

Our study had multiple limitations. First, it did not distinguish between newly diagnosed AFIB and pre-existing AFIB. Second, the NIS database is a billing-based database and hence can have erroneous coding. This database also lacks details on laboratory results which makes it difficult to stratify the severity of the DKA and ascertain the confounding effects of the severity of DKA on the mortality of patients with DKA and AFIB. However, despite these limitations, this study reiterates the increased prevalence of AFIB in patients admitted with DKA and demonstrated that patients hospitalized with DKA and a history of AFIB have a higher mortality compared to patients without AFIB, and this combination is also associated with increased hospitalization cost. We are unable to ascertain if additional investigational and therapeutics procedures would implicate faster recovery and reduction of stay. Further research should focus on confirming the above associations, and better defining the prognostic implications of various subtypes of DKA and their outcomes in patients with AFIB. Similarly, studies should focus on outcome of these subset of patients with the different management strategies.[25,26] Further research in this direction would be helpful to better understand this association.

Informed consent

NA.

Authors contributions

AM, AJ formulated the study. AM, AJ obtained the data, AM, UT, AJ completed the manuscript. AG, DL supervised the study and guided the study and revised the manuscript.

Ethics approval

NA.

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Conflicts of interests

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