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Research article

Increased risk of diabetic ketoacidosis in an Urban, United States, safety-net emergency department in the COVID-19 era

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Abstract: Aims: The incidence of diabetic ketoacidosis (DKA) increased during the COVID-19 pandemic but estimates from low-resource settings are limited. We examined the odds of DKA among emergency department (ED) visits in the Los Angeles County Department of Health Services (DHS) (1) during the COVID-19 pandemic compared to the pre-COVID era, (2) without active COVID infections, and (3) stratified by effect modifiers to identify impacted sub-groups. **Methods:** We estimated the odds of DKA from 400,187 ED visits pre-COVID era (March 2019–Feb 2020) and 320,920 ED visits during the COVID era (March 2020–Feb 2021). Our base model estimated the odds of DKA based on the COVID era. Additional specifications stratified by effect modifiers, controlled for confounders, and limited to visits without confirmed COVID-19 disease. **Results:** After adjusting for triage acuity and interaction terms for upper respiratory infections and payor, the odds of DKA during the COVID era were 27% higher compared to the pre-COVID era (95%CI 14–41%, p < 0.001). In stratified analyses, visits with private payors had a 112% increased odds and visits with Medicaid had a 20% increased odds of DKA during the COVID era (95%CI 7–36%, p = 0.003). **Conclusions:** We identified increased odds of DKA during the COVID pandemic, robust to a variety of specifications. We found differential effects by the payor; with increased odds during COVID for privately-insured patients.

1. Introduction

Diabetic ketoacidosis (DKA) is an endocrine emergency, commonly triggered by infection, cardiovascular events, catecholamine surges such as with extreme stress, or discontinuation of insulin administration. During the COVID-19 pandemic, the incidence of DKA has increased [1–3]. This increase is postulated to be due to several reasons: increased rates of new diagnosis of type I diabetes after acute COVID-19 infection, inflammatory responses to COVID in patients with existing diabetes, and with secondary factors related to the pandemic such as inadequate access to care or acute stress [4–6]. However, our understanding of the relationship of these factors is limited in low-resource and adult populations, which might be more susceptible to ambulatory care-sensitive conditions, such as DKA and hyperglycemia. Understanding their relative importance will allow for better planning for future pandemics as well as preparing for the transition of this pandemic to the endemic phase.

To better understand the causes of the increased incidence of DKA in an urban safety-net population living in the US, we examined trends in DKA at a large public health system in the context of the COVID-19 pandemic. We first examined if the odds of a diagnosis of DKA increased among adult emergency department (ED) patient visits in the COVID era compared to the pre-COVID era, after adjusting for relevant confounders. We then examined if these increased odds of DKA were sensitive to the removal of visits from patients with active COVID infections. Lastly, we evaluated the odds of DKA stratified by significant effect modifiers to identify sub-groups most impacted by the phenomena.

2. Methods

2.1. Study design and setting

This is a retrospective analysis of all ED encounters in the Los Angeles County Department of Health Services (DHS) for the one-year period preceding the arrival of the community spread of COVID-19 in Los Angeles County (March 2019 to February 2020) and the first one-year period of the COVID-19 pandemic and associated social distancing measures in Los Angeles County (March 2020 to February 2021). COVID vaccinations were not widely available until after the study period ended. Adult patients 18 years or older at the time of the ED visit were included. Outcomes and patient visit characteristics were collected from the electronic health records (EHR) of patients during these visits. The Los Angeles County DHS system contains 3 EDs located in separate medical centers.

2.2. Measures

The primary outcome of this study was the categorization of an ED visit as having been caused by DKA as identified by an ED ICD-10 diagnosis in the EHR. We categorized an ED encounter as a DKA case if the first five listed diagnoses included Diabetic Ketoacidosis (ICD10 codes E10.10, E11.10, E11.11, E13.10, or E13.11). The primary independent variable of interest was the time period

of exposure. The "pre-COVID" period was defined as March 2019 to February 2020, while the "COVID"-era period was defined as March 2020 to February 2021.

As described in prior work with this dataset [7], patient reported demographic characteristics were collected from patients during ED registration, including patient age; gender; race or ethnicity, primary language and Emergency Severity Index (ESI) triage category. The presence of a respiratory illness was defined by ICD-10 diagnosis, and our methodology for this categorization has been described previously [7]. These patient and encounter-level characteristics are presented as the count or proportion of all weekly ED visits accounted for by these categories. We defined a COVID infection as a positive PCR or antigen test from medical center laboratory records. All patients with DKA were tested for COVID infection prior to admission. Patients were not retested while hospitalized per hospital policy.

2.3. Statistical analysis

Patient and visit characteristics were described in tables and graphically displayed using histograms. All administrative variables had less than 2% missingness and were included with a plan for listwise deletion for multivariate models. ESI/triage acuity scale was categorized as 1–2 (indicating high acuity), 3 and 4–5 (indicating lower acuity) given the low numbers in triage category 1 and 5. The primary language was categorized as English, Spanish and "Other" give the low numbers of individual languages other than English or Spanish. Insurance was categorized as Medicaid, Medicare, Private, None and Other Government according to algorithms used in our previous work [7].

We examined the patient and patient visit characteristics across and between the study period with descriptive analysis (Table 1). We then used logistic regression models to estimate the odds of DKA from the pre-COVID period (March 2019–Feb 2020) vs the COVID-era period (March 2020–Feb 2021). We started with a base model of the probability of a patient visit being diagnosed as DKA modeled on time period alone (Figure 1, Bar 1). We then checked for potential confounding by modifying the base model with each individual potential confounder. Terms that changed the regression coefficient for time period by a substantial amount (greater than 15%) from the base model were retained in the final model. We examined insurance payor, patient age, ESI triage acuity, gender, presence of respiratory infection, patient reported race and ethnicity and patient primary language as potential confounders. We also examined these candidate variables as potential effect modifiers with interaction terms, retaining them if the Wald test for the interaction term regression coefficient was statistically significant. We calculated odds ratios stratified by subgroups for significant effect modifiers. Lastly, we conducted a sub-analysis to examine the indirect effects of the COVID pandemic on the odds of DKA—such as reduced access to ambulatory care—by removing patients who had a confirmed diagnosis of COVID19. We used a p-value of <0.05 to indicate statistical significance. For multiple comparisons in the subgroup analysis of significant effect modifiers, we used the Bonferroni correction.

2.4. Ethics approval of research

This work was approved by the University of Southern California Institutional Review Board, approval UP-20-00344-AM002.

3. Results

Among 720,477 Adult ED visits identified in the EHR in the study period, there were 1,395 cases of DKA (Table 1), with a similar number of cases of recurrent DKA. The pre-COVID era population was of similar age to the COVID era population and was slightly more likely to be male. The COVID era population had the same rate of Medicaid insurance, higher rates of Medicare and private insurance and lower rates of no insurance and other government program insurance than the pre-COVID population. The COVID era population had higher proportions of triage acuity (ESI) scores in the ranges of 1–2 indicating higher acuity, and a higher proportion of visits attributable to upper respiratory infections (Table 1). The odds of a patient visit having a diagnosis of DKA were 40% higher in the COVID era than in the pre-COVID era (95% CI 1.26–1.55, $p < 0.001$; Figure 1, Bar 1).

Table 1. Visit and study population characteristics.

Visit characteristics	Pre-COVID-era Mar 2019–Feb 2020	COVID-era Mar 2020–Feb 2021	Combined eras
Total number of Visits	400,187	320,290	720,477
Visits with DKA diagnosis	658	737	1,395
Unique patients with DKA	368	367	689***
Visits for recurrent DKA	452	447	899
Visits with COVID diagnosis	0	10,624	10,624
Age (mean, sd)	46.94 (16.46)	46.60 (16.36)	46.78 (16.42)
Female Gender, % (n)	46.4% (185,547)	44.1% (141,076)	45.3% (326,623)
Race and Ethnicity, % (n)			
Hispanic/Latino	66.3% (265,176)	66.2% (212,058)	66.2% (477,234)
Black	12.6% (50,447)	12.8% (41,135)	12.7% (91,582)
Other and multi racial	11.4% (45,602)	11.5% (36,971)	11.5% (82,573)
Asian/Pacific Islander	4.9% (19,514)	4.4% (13,953)	4.6% (33,467)
Non-Hispanic White	4.9% (19,448)	5.1% (16,173)	4.9% (35,621)
Language, % (n)			
English	52.4% (209,645)	53.1% (169,920)	52.7% (379,565)
Spanish	43.5% (174,009)	42.9% (137,432)	43.2% (311,441)
Other	2.7% (10,857)	2.6% (8,426)	2.7% (19,283)
Missing	1.4% (5,676)	1.4% (4,512)	1.4% (10,188)
Insurance, % (n)			
Medicaid	67.3% (269,238)	67.3% (215,541)	67.3% (478,241)
Medicare	9.0% (36,034)	10.0% (32,085)	9.5% (67,161)
Private	5.6% (22,575)	6.4% (20,619)	6.0% (34,480)
Other	10.9% (43,737)	9.3% (29,753)	10.2% (72,651)
None	6.4% (25,461)	5.9% (18,847)	6.2% (31,248)
Missing	0.8% (3,142)	1.1% (3,445)	0.9% (6,587)

Visit characteristics	Pre-COVID-era Mar 2019–Feb 2020	COVID-era Mar 2020–Feb 2021	Combined eras
Triage Acuity Score, % (n)			
1–2	19.0% (76,182)	23.2% (74,421)	20.9% (150,603)
3	57.1% (228,620)	56.0% (179,243)	56.6% (407,863)
4–5	22.2% (88,872)	19.1% (61,142)	20.8% (150,014)
Missing	1.6% (6,513)	1.7% (5,484)	1.7% (11,997)
Presence of Upper Respiratory Infection, % (n)	6.7% (26,761)	9.8% (31,268)	8.1% (58,029)

***As 46 patients were diagnosed with DKA in both the pre-COVID and COVID eras, combined total is less than the sum of the two columns.

In our multivariate analysis, 17,704 visits (2.5% of visits) were excluded for missing one or more data points. We found the triage acuity score and the presence of respiratory infection diagnosis to substantially confound the association between the study period and DKA diagnosis, decreasing the regression coefficient by 29% and 42% respectively. Additionally, we found medical insurance type and the presence of respiratory infection diagnosis to be significant effect modifiers of the relationship between the study period and DKA diagnosis. Our final model included terms for triage acuity score and presence of respiratory infection as confounders and interaction terms for insurance type and presence of respiratory infection diagnosis as effect modifiers. After adjusting for triage acuity score and interaction terms for the presence of upper respiratory infections and type of insurance, the adjusted odds of DKA in the COVID period were attenuated to a 27% increased odds of DKA compared to the pre-COVID era (95%CI 14–41%, $p < 0.001$; Figure 1, bar 2).

In stratified analysis by insurance type, (Figure 1, bars 4–8) we found that visits with private insurance had a 112% increased odds of DKA in the COVID-era compared to the pre-COVID era (95%CI 40–220% increased odds, $p < 0.001$, $p_{Bonferroni} \leq 0.001$). Visits with Medicaid insurance had a 20% increased odds of DKA in the COVID era (95%CI 7–36%, $p = 0.003$, $p_{Bonferroni} = 0.015$). Visits with other insurance had a 60% increased odds of DKA in the COVID era, however, this was not significant after adjusting for multiple comparisons (95%CI 6–142%, $p = 0.027$, $p_{Bonferroni} = 0.054$). There were no significant changes in the odds of DKA between the study periods for visits with Medicare or no insurance.

We examined the role of respiratory infection on odds of DKA by stratified analysis by respiratory infection followed by a sensitivity analysis excluding COVID cases. In stratified analysis by the presence of respiratory infection (Figure 1, bars 8&9), visits with respiratory infection had a 92% (95%CI 33–177%) increased odds of DKA in the COVID era, while visits without respiratory infection had a 21% (10–36%) increased odds of DKA in the COVID period. In our sensitivity analysis removing the 10,499 visits with COVID diagnosis from the COVID period, using the final multivariate regression model, we found a persistent 13% increased odds of DKA in the COVID period (95%CI 0.2–30%, $p = 0.045$; Figure 1, bar 3).
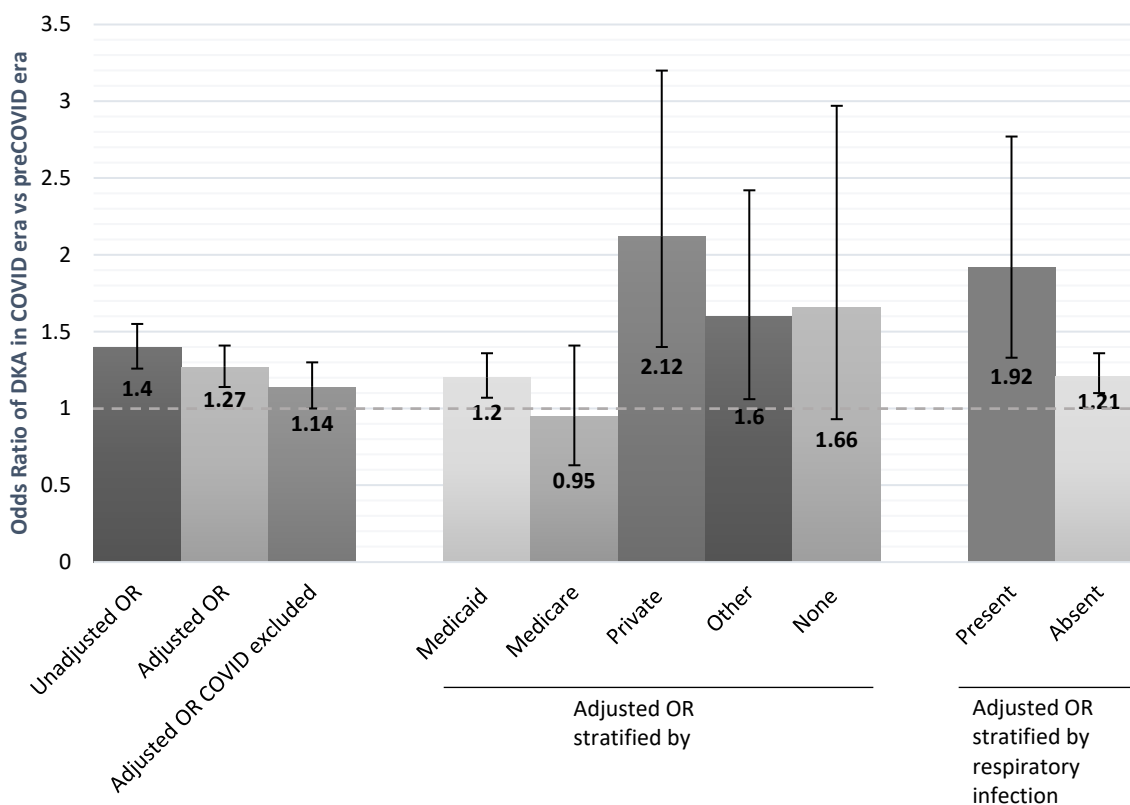
Figure 1. Unadjusted, Adjusted and Stratified Odds Ratios of DKA in COVID era vs Pre-COVID Era.

4.   Discussion and conclusions

In this novel analysis conducted in a low-resource population, we found increased odds of DKA in the COVID era compared to the pre-COVID era, robust to controlling for confounders and subgroup analysis removing visits with COVID infection. Additionally, we found different odds ratios for different medical insurance types; increased odds of DKA in the COVID era were significantly higher for private medical insurance.

The observed increased odds of DKA were robust to controlling for relevant confounders, and also to a sensitivity analysis removing COVID-era patient visits with a diagnosis of COVID. These findings suggest that it is not the pro-inflammatory response to COVID infection alone that caused increased DKA, but also non-physiologic factors such as reduced access to care, or patients delaying care due to fear of obtaining a COVID infection in a healthcare setting, factors seen in varying degrees in other populations [8–11]. The increased odds of DKA were most pronounced among patients with private insurance, suggesting that differential access to care associated with clinic closures and patients delaying care was greatest for those with private insurance, leading to increased DKA rates, while those with less access to care prior to the pandemic had less change with clinic closures.

While access to care may have a role in the increase in DKA found in our population, direct infection by COVID likely played a role as well. Effect modification by the presence of a respiratory infection (including COVID infection) does indicate there is a large role of the pathologic inflammation seen in patients with active COVID infections, as has been seen in other

populations [2,8,12,13]. Additionally, there is published data to support likely a role of new onset diabetes associated with direct beta cell destruction as well as an autoimmune response to COVID infection [12,14–18].

While presenting important findings on access to care in an underrepresented population, there are several limitations to our study, primarily related to observational nature of the study and the EHR/administrative dataset. The data source of ED-based EHR records results in underreporting of chronic conditions, and we do not know if patient visits for DKA represent a new diagnosis of diabetes or exacerbations of existing diagnoses. Additionally, chronic conditions and comorbidities that might predispose to DKA were not systematically captured in the EHR. This missing information includes prior insulin use and type of diabetes, limiting our ability to examine the phenomena of DKA in people with previously non-insulin dependent diabetes. Prospective studies in this population would improve this understanding, especially of the time-lag between COVID infection and development of DKA. This dataset was limited to the year immediately preceding the first COVID year, and we could not assess for previous trends in DKA. Lastly, our findings cannot be interpreted as causal relationships, but should inspire future work to better understand the rising rates of DKA in the COVID era.

Our findings on the role of access to care in the increased rates of DKA are important for health system leaders as the United States heads towards and endemic phase of COVID. The US has greatly increased telehealth capacity, especially for chronic diseases, and these changes must be sustained. However, increased rates of DKA directly related to COVID infection must also be considered, given the high level of nursing care required by DKA patients, particularly with current staffing shortages and prolonged boarding in the ED by ICU patients. Additional nursing resources and training are potentially necessary maybe necessary to plan for potential COVID surges in the coming year as we move to an endemic pattern of COVID-19 infection.

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Conflict of interest

The authors confirm that there are no conflicts of interest in this article's content.

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