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Diabetic Ketoacidosis Was Associated with High Morbidity and Mortality in Hospitalized Patients with COVID-19 in the NYC Public Health System

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Abstract: Background: COVID-19 has been associated with a higher risk of death in patients with diabetes mellitus (DM). However, there is a dearth of data regarding the effects of diabetic ketoacidosis (DKA) in these patients. We explored the in-hospital outcomes of patients who presented with COVID-19 and DKA. Methods: A propensity score-matched observational retrospective cohort study was conducted in hospitalized patients with COVID-19 in the public healthcare system of New York City from 1 March 2020 to 31 October 2020. Patients were matched, and a subgroup analysis of patients with DKA and COVID-19 and patients without COVID-19 was conducted. Results: 13,333 (16.0%) patients with COVID-19 and 70,005 (84.0%) without COVID-19 were included in the analysis. The in-hospital mortality rate was seven-fold in patients with DKA and COVID-19 compared to patients with COVID-19 and without DKA (80 (36.5%) vs. 11 (5.4%), $p < 0.001$). Patients with COVID-19 and DKA had a two-fold higher likelihood for in-hospital death (OR: 1.95; 95% CI: 1.41–2.70; $p < 0.001$) after adjusting for multiple variables. Conclusions: DKA was associated with significantly higher in-hospital mortality in hospitalized patients with COVID-19.

Keywords: coronavirus disease 2019; COVID-19; severe acute respiratory syndrome coronavirus 2; SARS-CoV-2; diabetes; diabetic ketoacidosis; DKA; hyperglycemia; mortality; innate immunity; cytokine storm; angiotensin-converting enzyme 2; pancreatic β-cell damage

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1. Introduction

New-onset diabetes and severe metabolic complications such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) have been observed in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) [1], the virus that causes Coronavirus disease 2019 (COVID-19). Initially, DKA was more commonly associated with patients with type 1 diabetes mellitus (T1DM) as compared to type 2 diabetes mellitus (T2DM). However, some studies have shown that patients with T2DM can present with DKA, but they are usually older, require more insulin, and tend to have a longer course of stay [2,3]. Interestingly, patients with COVID-19 have presented with DKA without a previously known diagnosis of DM [4,5]. Since the beginning of the pandemic, there have been reports of worse outcomes and increased mortality in patients with DKA and COVID-19 [6,7]. It has been proposed that the higher mortality in these patients can be attributed to advanced age, the higher severity of COVID-19, and the use

of steroids [8,9]. COVID infection resulted in an increased incidence of DKA in patients with T2DM. These patients required a longer ICU stay and were found to have worse mortality [10]. We previously reported significantly higher mortality in patients with COVID-19 that presented with DKA compared to the previously known mortality rate of DKA [11]. In this study, we compared the in-hospital outcomes of patients with DKA prior to the start of the COVID-19 pandemic in our hospital system to the mortality of patients that presented with DKA in the setting of COVID-19 during the first phase of the pandemic in 2020.

2. Materials and Methods

2.1. Study Design and Patient Population

This was a propensity score-matched observational cohort study performed at the eleven acute care hospitals of the New York City Health + Hospitals (NYC H + H) system. The study group included patients ≥18 years of age who presented to the emergency room and were admitted to any inpatient service, including intensive care units (ICU), with laboratory-confirmed COVID-19 from 1 March 2020 to 31 October 2020. The control group included patients that were admitted from 1 July 2019 to 31 December 2019, before the pandemic was declared and prior to the first diagnosed case of COVID-19 in the USA. These populations were matched, and a subgroup analysis of patients with COVID-19 and DKA and patients with DKA but without COVID-19 was performed. DKA was defined as blood glucose > 250 mg/dL, pH < 7.3, a bicarbonate level of <18 mEq/L, an elevated anion gap, and positive ketones in blood or urine [12]. Laboratory-confirmed COVID-19 was defined as a SARS-CoV-2 positive result in the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of nasopharyngeal or nasal swab samples (Bio Reference Laboratories, Elmwood Park, NJ, USA). We excluded patients that had the following criteria: patients that were discharged from the emergency department, patients without laboratory-confirmed COVID-19, and patients who were still hospitalized at the time of data collection. The study was approved by the Biomedical Research Alliance of New York Institutional Review Board with a waiver of informed consent (IRB #20-12-318-373). The data were fully de-identified and anonymized before they were accessed, and IRB waived the requirement for informed consent.

2.2. Data Sources

The study data were obtained from electronic health records via appropriate diagnostic codes (Epic systems, Verona, WI, USA). The dataset was reviewed by two independent investigators for missing data and completeness. The extracted data included baseline demographic variables (age, sex, race), clinical characteristics (body mass index (BMI), history of tobacco use, hypertension, hyperlipidemia, asthma, coronary artery disease (CAD), heart failure, stroke/transient ischemic attack (TIA), chronic kidney disease (CKD), end-stage renal disease (ESRD)), medication list (including insulin, biguanides, dipeptidyl peptidase- 4 (DPP-4) inhibitors, glucagon like peptide-1 (GLP-1) agonists, sulfonylureas, insulin, angiotensin-converting enzyme (ACE) inhibitors, and statins), laboratory data (hemoglobin A1C,C-reactive protein (CRP), lactate dehydrogenase (LDH), Ferritin, D-Dimer, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT)), and outcomes including invasive mechanical ventilation, admission to the intensive care unit (ICU), the need for renal replacement therapy (RRT), and death from all causes. The data were processed and analyzed without any personal identifiers to maintain patient confidentiality, as per the Health Insurance Portability and Accountability Act (HIPAA).

2.3. Exposure of Interest and Outcomes

The primary outcome was the in-hospital mortality in patients with COVID-19 and DKA. The secondary outcomes were length of stay (LOS), invasive mechanical ventilation, admission to the ICU, and need for RRT.

2.4. Statistical Analysis

Propensity score matching was conducted to create comparable groups controlling for imbalances of covariates [13] [Supplemental Material Figures S1 and S2]. The propensity score was estimated using a logistic regression model and is the subject-specific probability of being infected with COVID-19, in which the following covariates were used: age, sex, BMI, race, DKA, comorbidities (history of diabetes mellitus, hypertension, hyperlipidemia, Chronic obstructive pulmonary disease (COPD), asthma, CAD, heart failure, stroke TIA, ESRD, CKD), and medications (biguanides, DPP4 inhibitors, SGLT2 inhibitors, GLP-1 agonists, insulin, ACE inhibitors, sulfonylureas, and statins). A nearest-neighbor matching without replacement was performed using a caliper of 0.2, which has been found to be optimal [14,15].

A stepwise logistic regression model identified the baseline variables associated with in-hospital mortality, invasive mechanical ventilation/intubation [Tables S1–S3] admission to ICU [Tables S4–S6], and the need for RRT [Tables S7–S9] in three different data panels: (a) matched groups (COVID-19 and control), (b) COVID-19 group, and (c) DKA group. Univariate analysis was performed, and four multivariate models with different definitions of our variable of interest are presented for robustness: model 1: age, sex, and BMI; model 2: age, sex, BMI, and all comorbidities; model 3: age, sex, BMI, all comorbidities, and diabetes medications; model 4: age, sex, BMI, all comorbidities, diabetes medications, and all medications used during inpatient status. Additional variables are included in the multivariable models 1–4 for every different panel, specifically: for panel (a), models 1–4 also include positive COVID-19 status and the presence of DKA; for panel (b), models 1–4 also include the presence of DKA; and for panel (c), models 1–4 also include positive COVID-19 status.

T-tests compared continuous variables, while Chi-Square tests compared discrete variables. Continuous data are presented as median values with the interquartile range (IQR) specified, and categorical data are presented as absolute and relative frequencies. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Descriptive Analyses

3.1.1. Baseline Characteristics

A flowchart of the analysis is presented in Figure 1. In total, 83,338 patients were included in our analysis. A total of 13,333 (16.0%) were patients with COVID-19, and 70,005 (84.0%) were patients without COVID-19. The propensity score matching between the COVID-19 and control groups yielded a cohort of 22,694 patients (COVID-19 group: 11,347 and control group: 11,347). In the COVID-19 group, 58.8% were men, the median age was 62 (IQR 49–74) years, and the median BMI was 28.1 (24.4–32.8) kg/m^2. From the non-COVID-19 group, 57.8% were men, the median age was 62 (IQR 48–75) years, and the median BMI was 27.9 (23.8–33.3) kg/m^2. The matching in DKA patients yielded a cohort of 422 patients (DKA/COVID-19 group: 219 and control group: 203). In the DKA/COVID-19 group, 63.5% were men, the median age was 56 (69–41) years, and the median BMI was 25.7 (22.6–30.2) kg/m^2. In the DKA/non-COVID-19 group, 67.0% were men, the median age was 50 (38–63) years, and the median BMI was 26.1 (22.4–30.8) kg/m^2. Detailed baseline characteristics are included in Table 1.

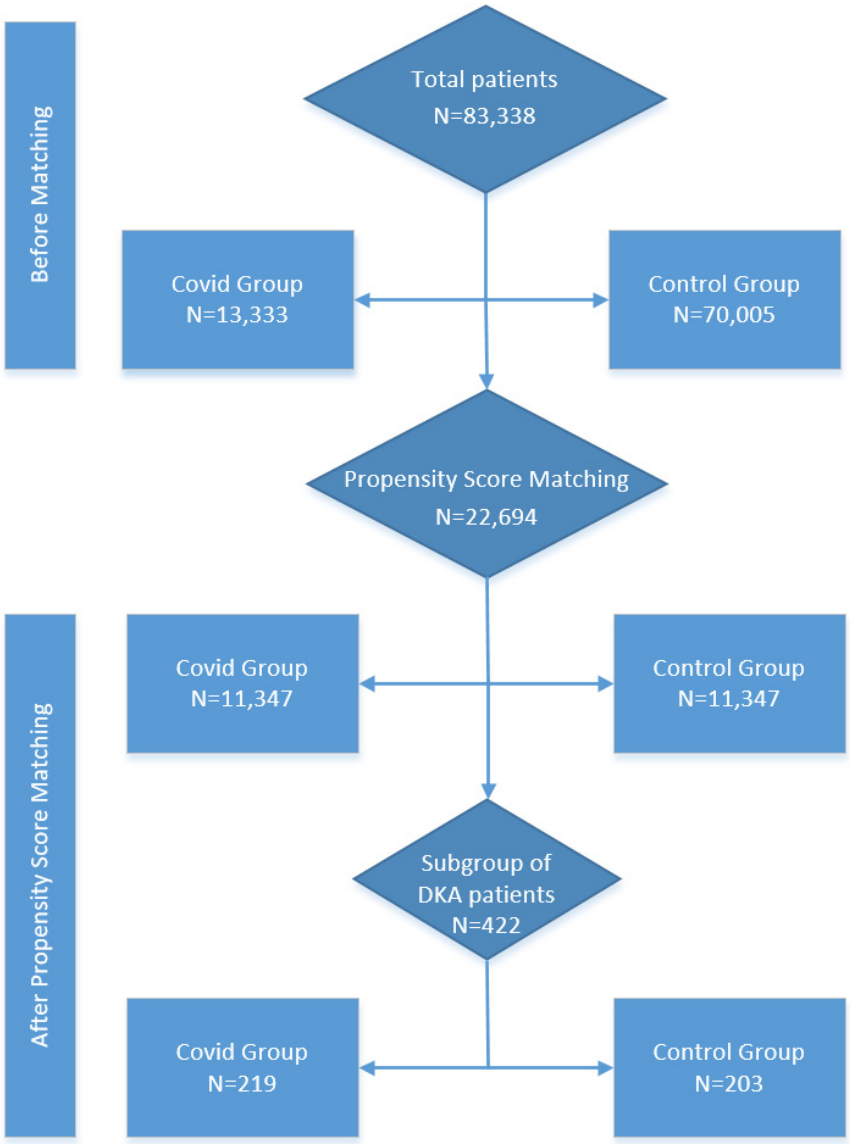

Figure 1. Flowchart of the analysis.

Table 1. Baseline characteristics.

	COVID-19 and Control Group				DKA/COVID-19 vs. DKA/Non-COVID-19			
	Total (N = 22,694)	**COVID-19 Group (N = 11,347)**	**Control Group (N = 11,347)**	***p*-Value**	**Total (N = 422)**	**COVID-19 Group (N = 219)**	**Control Group (N = 203)**	***p*-Value**
Male sex—no. (%)	13,224 (52.2)	6672 (58.8)	6552 (57.7)	0.106	275 (65.1)	139 (63.4)	136 (67.0)	0.448
Age—years—Median (IQR)	62 (48–74)	62 (49–74)	62 (48–75)	0.233	53 (40–66)	56 (41–69)	50 (38–63)	0.004
BMI—kg/m^2—Median (IQR)	27.9 (24.1–33.1)	28.1 (24.4–32.8)	27.9 (23.8–33.3)	0.063	25.8 (22.5–30.4)	25.7 (22.6–30.2)	26.1 (22.4–30.8)	0.429
Race/Ethnicity—no. (%)								
Asian	1395 (6.21)	643 (5.7)	752 (6.7)	<0.001	16 (3.8)	9 (4.1)	7 (3.5)	0.255
Black	7264 (32.3)	3577 (31.8)	3687 (32.8)		153 (36.7)	74 (34.1)	79 (45.2)	
White	3003 (13.3)	1174 (10.4)	1829 (16.3)		40 (9.6)	17 (7.8)	23 (11.5)	
Other/Latino	10,791 (48.0)	5846 (52.0)	4945 (44.1)		207 (49.7)	117 (53.9)	90 (45.2)	
Coexisting disorder—no. (%)								
Diabetic Ketoacidosis	422 (1.8)	219 (1.9)	203 (1.7)	0.432	422 (100)	219 (100)	203 (100)	-
History of DM	9951 (43.8)	4938 (43.5)	5013 (44.1)	0.316	422 (100)	219 (100)	203 (100)	-

Table 1. *Cont.*

	COVID-19 and Control Group				DKA/COVID-19 vs. DKA/Non-COVID-19			
	Total (N = 22,694)	**COVID-19 Group (N = 11,347)**	**Control Group (N = 11,347)**	***p*-Value**	**Total (N = 422)**	**COVID-19 Group (N = 219)**	**Control Group (N = 203)**	***p*-Value**
Type 1 Diabetes	139 (0.6)	61 (0.5)	78 (0.6)	0.148	93 (22.0)	44 (20.0)	49 (24.1)	0.316
HTN	5127 (22.5)	2532 (22.3)	2595 (22.8)	0.317	99 (23.4)	46 (21.0)	53 (26.1)	0.216
HLD	2114 (9.3)	1042 (9.1)	1072 (9.4)	0.493	45 (10.6)	24 (10.9)	21 (10.3)	0.838
Pulmonary HTN	108 (0.4)	45 (0.4)	63 (0.5)	0.083	1 (0.2)	1 (0.4)	0 (0.0)	0.335
COPD	474 (2.0)	218 (1.9)	256 (2.2)	0.078	1 (0.2)	0 (0.0)	1 (0.4)	0.298
Asthma	976 (4.3)	474 (4.1)	502 (4.4)	0.360	13 (3.0)	4 (1.8)	9 (4.4)	0.121
CAD	707 (3.1)	347 (3.0)	360 (3.1)	0.619	5 (1.1)	4 (1.8)	1 (0.4)	0.206
Heart Failure	1225 (5.4)	592 (5.2)	633 (5.5)	0.228	16 (3.7)	8 (3.6)	8 (3.9)	0.877
Stroke/TIA	304 (1.3)	163 (1.4)	141 (1.2)	0.204	3 (0.7)	2 (0.9)	1 (0.4)	0.607
ESRD	1032 (4.5)	513 (4.5)	519 (4.5)	0.848	18 (4.2)	9 (4.1)	9 (4.4)	0.869
Chronic Kidney Disease	1339 (5.9)	660 (5.8)	679 (5.9)	0.592	29 (6.8)	12 (5.4)	17 (8.3)	0.241

Notes: BMI in kg/m^2. *p*-values refer to t-test or Chi-Square test between COVID-19 and control groups. Significance at *p*-value < 0.05. Abbreviations and symbols: BMI = body mass index; kg = kilograms; m = meter; N = no = number; IQR = interquartile range; DKA = Diabetic Ketoacidosis; DM = Diabetes Mellitus; HTN = hypertension; HLD = hyperlipidemia; COPD = Chronic Obstructive Pulmonary Disease; CAD = coronary artery disease; TIA = Transient Ischemic Attack; ESRD = End-Stage Renal Disease.

3.1.2. Inflammatory Markers

The baseline concentrations of the available inflammatory markers are presented in Table 2. The median values of LDH, D-dimer, ferritin, and CRP were higher in patients with COVID-19 compared to patients without COVID-19 ($p < 0.001$). Significant and consistent differences in the baseline concentrations of inflammatory markers among patients with DKA/COVID-19 compared to patients with DKA but not COVID-19 were not noted.

Table 2. Laboratory values.

	COVID-19 vs. Non COVID-19				DKA with COVID-19 vs. DKA without COVID-19			
Inflammatory Markers	**Total (N = 22,694)**	**COVID-19 Group (N = 11,347)**	**Control Group (N = 11,347)**	***p*-Value**	**Total (N = 422)**	**COVID-19 Group (N = 219)**	**Control Group (N = 203)**	***p*-Value**
CRP (mg/L)—Median (IQR)	18.1 (5.7–602)	18.7 (6–60.1)	11.5 (2.98–61)	0.035	13.1 (4.4–52.3)	12.7 (4.4–52.3)	14.1 (6.3–20.7)	0.247
LDH (U/L)—Median (IQR)	388 (279–568)	399 (290–577)	271 (197–402)	<0.001	424 (301–619)	427 (309–631.5)	268 (169–584)	0.141
Ferritin (ng/mL)—Median (IQR)	631 (263–1310)	731 (344–1418)	212 (72–593)	<0.001	820 (454–1501)	914 (490.6–1606)	410 (158–655)	0.026
D-Dimer (ng/mL)—Median (IQR)	721 (333–2272.5)	736 (351–2314)	471 (236–1331.5)	0.008	1143 (471–2698)	1093 (481.5–2774.5)	1686.8 (294.5–2284)	0.491
Creatinine (mg/dL)—Median (IQR)	0.9 (0.7–1.3)	0.9 (0.7–1.6)	0.9 (0.7–1.2)	<0.001	0.9 (0.6–1.5)	1 (0.6–2.2)	0.8 (0.6–1.12)	<0.001
AST (U/L)—Median (IQR)	30 (20–52)	38 (25–65)	24 (17–36)	<0.001	28 (18–50)	35 (21–66)	22 (15–37)	0.017
ALT (U/L)—Median (IQR)	25 (15–47)	33 (19–60)	19 (13–32)	<0.001	22 (15–43)	24 (16–48)	20 (14–34)	0.041
HbA1c (%)—Median (IQR)	6.4 (5.7–8.2)	6.6 (5.8–8.6)	6.3 (5.6–7.9)	<0.001	12.8 (10.8–14.8)	13.1 (10.7–15.2)	12.4 (10.8–14.6)	0.371
Vitamin D (ng/mL)/Admission—Median (IQR)	21.3 (14–29.8)	20.8 (13–29.8)	22 (14.7–29.8)	0.768	14.3 (9.4–29.5)	13.6 (9.7–29)	17.8 (9–30)	0.892
Vitamin D (ng/mL)/Pre COVID-19—Median (IQR)	24.9 (16.5–33.5)	24.9 (16.5–33.5)			23.7 (15–32.3)	23.7 (15–32.3)		

Note: *p*-values refer to T-test between COVID-19 and control groups. Significance at *p*-value < 0.05. Abbreviations and symbols: N = number; IQR = interquartile range; U/L = unit/liter; mg = milligram; ng = nanogram; ml = milliliter; dL = deciliter; DKA = Diabetic Ketoacidosis; CRP = C-Reactive Protein; LDH = Lactate Dehydrogenase; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; HbA1c = Hemoglobin A1c.

3.1.3. Outcomes

The median LOS in patients with COVID-19 was 6 days vs. 4 days in the control group ($p < 0.001$). In total, 9.1% of patients with COVID-19 required intubation compared to 3.3% in the non-COVID-19 control group ($p < 0.001$). ICU admission happened for 23.4% of patients in the COVID-19 group vs. 14.7% of patients in the non-COVID-19 group ($p < 0.001$). A total of 8.5% of patients with COVID-19 required RRT compared to 4.2% in the control group ($p < 0.001$). In-hospital death occurred in 26.0% of patients with COVID-19 compared to 9.3% in the control group ($p < 0.001$). Outcomes are presented in Table 3 and Figure 2.

Table 3. Outcomes in COVID-19 patients vs. control group.

Outcomes	COVID-19 vs. Non COVID-19			
	Total (N = 22,694)	**COVID-19 Group (N = 11,347)**	**Control Group (N = 11,347)**	***p*-Value**
Length of Stay—Median (IQR)	5 (2–10)	6 (3–13)	4 (2–8)	<0.001
Death—no. (%)	4007 (17.6)	2949 (25.9)	1058 (9.3)	<0.001
Intubation—no. (%)	1413 (6.2)	1034 (9.1)	379 (3.3)	<0.001
ICU Admission—no. (%)	4324 (19.0)	2658 (23.4)	1666 (14.6)	<0.001
Renal Replacement Therapy—no. (%)	1445 (6.3)	967 (8.5)	478 (4.2)	<0.001

Notes: *p*-values refer to T-test or Chi-Square test between COVID-19 and control groups. Significance at *p*-value < 0.05. Abbreviations and symbols: N = no = number; IQR = interquartile range; ICU = Intensive Care Unit.

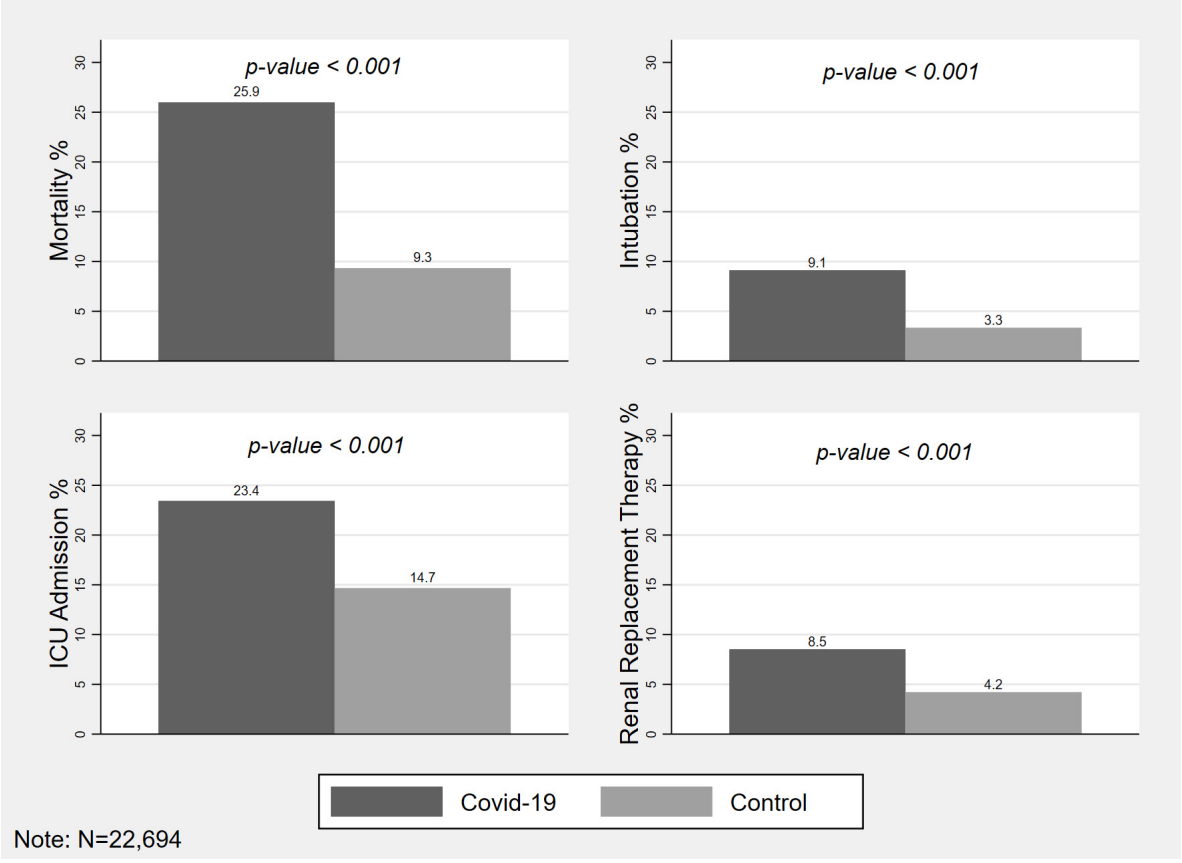

Figure 2. Outcomes in COVID-19 vs. control groups after propensity score matching.

3.2. Subgroup Analysis for Patients with DKA

In patients with DKA and COVID-19, the LOS was 7 days compared to 4 days in patients with DKA and without COVID-19. Intubation happened for 14.6% of patients with DKA and COVID-19 vs. 5.9% of patients with DKA and without COVID-19 ($p = 0.003$). The mortality rates were 36.5% for patients with DKA and COVID-19 compared to 5.4% for patients with DKA and without COVID-19 ($p < 0.001$). The rate of requiring RRT was significantly higher in the DKA/COVID 19 group compared to the DKA/non-COVID-19 group ($p = 0.005$). There was no statistical significance of ICU admission between the two groups ($p = 0.207$). The outcomes of the subgroup analysis are presented in Table 4 and Figure 3.

Table 4. Outcomes in DKA patients with COVID-19 vs. without COVID-19.

Outcomes	DKA with COVID-19 vs. DKA without COVID-19			
	Total (N = 422)	**COVID-19 Group (N = 219)**	**Control Group (N = 203)**	***p*-Value**
Length of Stay—Median (IQR)	5 (3–10)	7 (4–13)	4 (2–7)	0.003
Death—no. (%)	91 (21.5)	80 (36.5)	11 (5.4)	<0.001
Intubation—no. (%)	44 (10.4)	32 (14.6)	12 (5.9)	0.003
ICU Admission—no. (%)	242 (57.3)	132 (60.2)	110 (54.1)	0.207
Renal Replacement Therapy—no. (%)	38 (9.0)	28 (12.7)	10 (4.9)	0.005

Notes: *p*-values refer to T-test or Chi-Square test between COVID-19 and control groups. Significance at *p*-value < 0.05. Abbreviations and symbols: N = no = number; IQR = interquartile range; ICU = Intensive Care Unit; DKA = Diabetic Ketoacidosis.

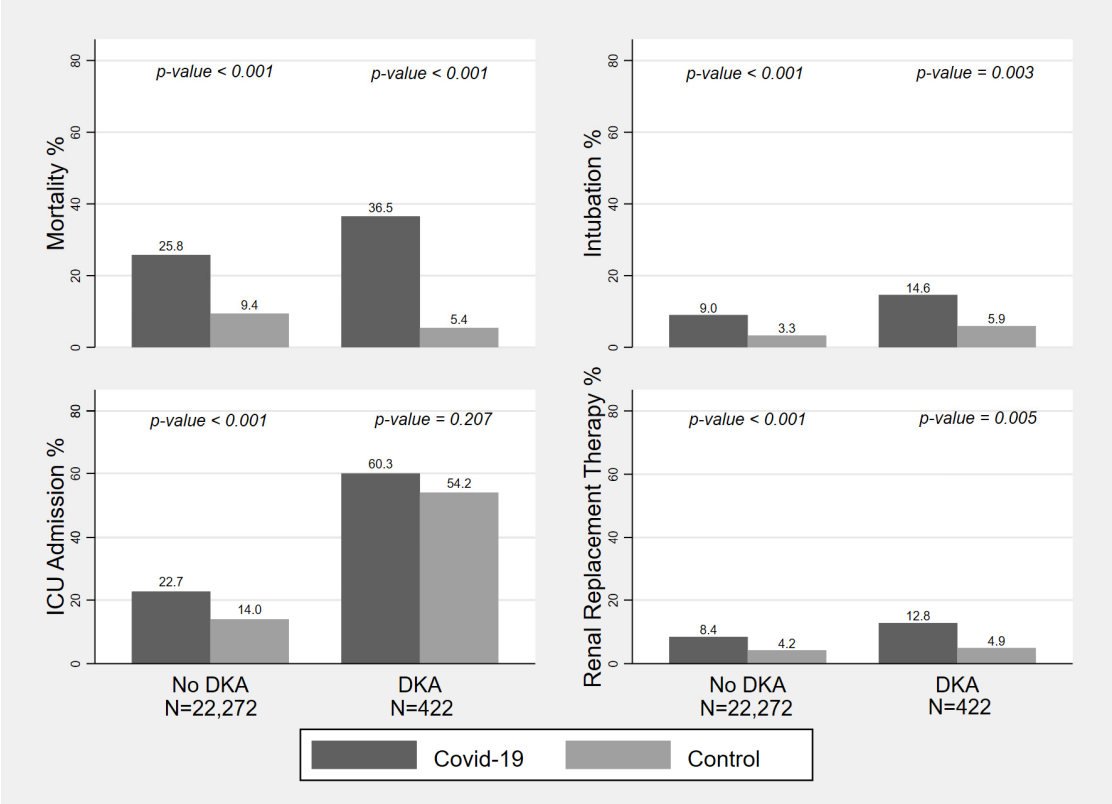

Figure 3. Outcomes in DKA vs. no DKA and COVID-19 vs. control groups after propensity score matching.

3.3. Logistic Regression Analysis

3.3.1. Matched Cohort (COVID-19 and Non-COVID-19)

Univariate associations with in-hospital mortality were examined for the available baseline demographic and clinical characteristics and are presented in Table 5. Older age, male sex, higher BMI, ESRD, COVID-19, diabetes mellitus, and DKA were all associated with a higher likelihood for in-hospital mortality in all models. Hypertension, CAD, asthma, and a history of stroke were shown to have an inverse association with in-hospital death. The use of biguanides, DPP4-inhibitors, ACE inhibitors, sulfonylureas, and statins were also shown to have an inverse association with in-hospital death.

Table 5. Baseline patient characteristics: univariate and multivariate logistic regression analysis for the outcome of mortality.

	Univariate Analysis	**Multivariate Analysis**	**Multivariate Analysis**	**Multivariate Analysis**	**Multivariate Analysis**
		Model 1	**Model 2**	**Model 3**	**Model 4**
		***n* = 22,694**	***n* = 22,694**	***n* = 22,694**	***n* = 22,694**
Variables	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**
Age per 10 years	1.49 ** (1.46–1.52) $p < 0.001$	1.64 ** (1.60–1.67) $p < 0.001$	1.63 ** (1.59–1.68) $p < 0.001$	1.66 ** (1.61–1.70) $p < 0.001$	1.66 ** (1.62–1.71) $p < 0.001$
Male sex	1.18 ** (1.10–1.26) $p < 0.001$	1.42 ** (1.31–1.53) $p < 0.001$	1.40 ** (1.29–1.51) $p < 0.001$	1.42 ** (1.31–1.53) $p < 0.001$	1.33 ** (1.23–1.45) $p < 0.001$
BMI	1.00 (0.99–1.00) $p = 0.693$	1.03 ** (1.02–1.03) $p < 0.001$	1.03 ** (1.02–1.03) $p < 0.001$	1.03 ** (1.02–1.03) $p < 0.001$	1.03 ** (1.02–1.03) $p < 0.001$
COVID-19	3.41 ** (3.17–3.68) $p < 0.001$	3.95 ** (3.64–4.28) $p < 0.001$	4.11 ** (3.78–4.46) $p < 0.001$	4.10 ** (3.78–4.45) $p < 0.001$	3.62 ** (3.30–3.98) $p < 0.001$
Diabetic Ketoacidosis	1.29 * (1.02–1.63) $p = 0.034$	1.89 ** (1.47–2.43) $p < 0.001$	1.50 ** (1.14–1.96) $p = 0.003$	1.51 ** (1.15–1.99) $p = 0.003$	1.46 ** (1.10–1.94) $p = 0.009$
History of DM	2.02 ** (1.88–2.16) $p < 0.001$		1.88 ** (1.74–2.04) $p < 0.001$	2.17 ** (1.97–2.38) $p < 0.001$	1.68 ** (1.52–1.85) $p < 0.001$
Type 1 Diabetes	0.40 ** (0.22–0.74) $p = 0.004$		0.52 (0.26–1.03) $p = 0.061$	0.50 (0.25–1.00) $p = 0.051$	0.56 (0.28–1.14) $p = 0.112$
Hypertension	0.93 (0.85–1.01) $p = 0.079$		0.64 ** (0.58–0.71) $p < 0.001$	0.69 ** (0.62–0.77) $p < 0.001$	0.70 ** (0.63–0.78) $p < 0.001$
Hyperlipidemia	0.88 * (0.78–0.99) $p = 0.035$		0.77 ** (0.67–0.89) $p < 0.001$	0.87 (0.75–1.01) $p = 0.064$	0.95 (0.82–1.11) $p = 0.544$
Pulmonary Hypertension	1.56 * (1.01–2.41) $p = 0.047$		1.61 (0.95–2.73) $p = 0.079$	1.56 (0.91–2.67) $p = 0.109$	1.55 (0.87–2.77) $p = 0.138$
COPD	1.19 (0.95–1.49) $p = 0.135$		1.15 (0.89–1.49) $p = 0.275$	1.19 (0.92–1.54) $p = 0.176$	0.96 (0.73–1.26) $p = 0.781$
Asthma	0.51 ** (0.41–0.63) $p < 0.001$		0.60 ** (0.48–0.75) $p < 0.001$	0.61 ** (0.48–0.76) $p < 0.001$	0.51 ** (0.40–0.64) $p < 0.001$
CAD	1.03 (0.85–1.25) $p = 0.751$		0.74 ** (0.59–0.93) $p = 0.009$	0.78 * (0.62–0.99) $p = 0.038$	0.81 (0.63–1.03) $p = 0.085$
Heart Failure	1.31 ** (1.14–1.50) $p < 0.001$		1.00 (0.84–1.19) $p = 0.973$	1.08 (0.90–1.29) $p = 0.398$	1.21 * (1.00–1.46) $p = 0.045$
Stroke/TIA	0.87 (0.64–1.19) $p = 0.390$		0.62 ** (0.44–0.87) $p = 0.006$	0.66 * (0.46–0.93) $p = 0.019$	0.73 (0.50–1.05) $p = 0.093$
ESRD	1.84 ** (1.60–2.12) $p < 0.001$		2.11 ** (1.76–2.53) $p < 0.001$	2.03 ** (1.69–2.44) $p < 0.001$	1.76 ** (1.45–2.15) $p < 0.001$
Chronic Kidney Disease	1.47 ** (1.29–1.68) $p < 0.001$		1.06 (0.90–1.25) $p = 0.460$	1.06 (0.89–1.25) $p = 0.510$	1.12 (0.94–1.34) $p = 0.215$
Biguanides	0.65 ** (0.57–0.74) $p < 0.001$			0.63 ** (0.54–0.73) $p < 0.001$	0.72 ** (0.62–0.85) $p < 0.001$

Table 5. *Cont.*

	Univariate Analysis	Multivariate Analysis	Multivariate Analysis	Multivariate Analysis	Multivariate Analysis
		Model 1	Model 2	Model 3	Model 4
		n = 22,694	*n* = 22,694	*n* = 22,694	*n* = 22,694
Variables	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**
DPP4 inhibitors	0.86 * (0.76–0.99) $p = 0.031$			0.75 ** (0.64–0.87) $p < 0.001$	0.77 ** (0.65–0.91) $p = 0.002$
SGLT-2 inhibitors	0.60 (0.24–1.52) $p = 0.278$			0.93 (0.35–2.48) $p = 0.881$	0.83 (0.24–2.82) $p = 0.764$
GLP-1 agonists	0.80 (0.52–1.22) $p = 0.297$			0.92 (0.56–1.51) $p = 0.742$	0.95 (0.57–1.57) $p = 0.842$
Insulin	1.48 ** (1.38–1.59) $p < 0.001$			1.08 (0.99–1.19) $p = 0.100$	1.09 (0.99–1.20) $p = 0.092$
ACE inhibitors	0.86 ** (0.79–0.94) $p = 0.001$			0.71 ** (0.64–0.78) $p < 0.001$	0.75 ** (0.67–0.83) $p < 0.001$
Sulfonylureas	0.75 * (0.57–0.99) $p = 0.046$			0.72 * (0.53–0.97) $p = 0.033$	0.78 (0.56–1.08) $p = 0.129$
Statins	1.34 ** (1.25–1.43) $p < 0.001$			0.83 ** (0.76–0.90) $p < 0.001$	0.79 ** (0.72–0.86) $p < 0.001$
Heparin	2.14 ** (2.00–2.30) $p < 0.001$				1.51 ** (1.38–1.65) $p < 0.001$
Enoxaparin	1.37 ** (1.28–1.47) $p < 0.001$				0.92 (0.84–1.01) $p = 0.096$
Apixaban	1.27 ** (1.15–1.41) $p < 0.001$				0.61 ** (0.54–0.69) $p < 0.001$
Steroids	3.84 ** (3.57–4.13) $p < 0.001$				2.71 ** (2.48–2.97) $p < 0.001$
Tocilizumab	3.44 ** (2.92–4.06) $p < 0.001$				1.49 ** (1.22–1.82) $p < 0.001$
Remdesivir	1.61 ** (1.29–2.02) $p < 0.001$				0.54 ** (0.42–0.71) $p < 0.001$
Convalescent Plasma	3.97 ** (3.34–4.72) $p < 0.001$				1.10 (0.88–1.39) $p = 0.406$
Cefepime	5.63 ** (5.15–6.17) $p < 0.001$				3.06 ** (2.74–3.41) $p < 0.001$

Notes: Table 5 shows univariate analysis and four multivariate models with different definitions of our variable of interest. Model 1 includes the variables: age, sex, BMI, diabetic ketoacidosis, and COVID-19. Model 2 includes the variables: age, sex, BMI, diabetic ketoacidosis, COVID-19, and comorbidities including a history of diabetes, hypertension, hyperlipidemia, pulmonary hypertension, chronic obstructive pulmonary diseases, asthma, coronary artery disease, heart failure, stroke/TIA, end-stage renal disease, and chronic kidney disease. Model 3 includes the variables: age, aex, BMI, diabetic ketoacidosis, COVID-19, comorbidities including a history of diabetes, hypertension, hyperlipidemia, pulmonary hypertension, chronic obstructive pulmonary diseases, asthma, coronary artery disease, heart failure, stroke/TIA, end-stage renal disease, and chronic kidney disease, and antidiabetic medication classes including biguanides, DPP4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, insulin, ACE inhibitors, sulfonylureas, and statins. Model 4 includes the variables: age, sex, BMI, diabetic ketoacidosis, COVID-19, comorbidities including a history of diabetes, hypertension, hyperlipidemia, pulmonary hypertension, chronic obstructive pulmonary diseases, asthma, coronary artery disease, heart failure, stroke/TIA, end-stage renal disease, and chronic kidney disease, antidiabetic medication classes including biguanides, DPP4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, insulin, ACE inhibitors, sulfonylureas, and statins, and all the medications used during inpatient status: heparin, enoxaparin, apixaban, steroids, tocilizumab, remdesivir, convalescent plasma, and cefepime. ** $p < 0.01$, * $p < 0.05$.

Abbreviations and symbols: n = number; BMI in kg/m^2; DM = Diabetes Mellitus; DKA = Diabetic Ketoacidosis; COPD = Chronic Obstructive Pulmonary Disease; CAD = coronary artery disease; TIA = Transient Ischemic Attack; ESRD = End-Stage Renal Disease; DPP 4 = Dipeptidyl Peptidase 4; GLP 1 = Glucagon-like peptide 1; SGLT 2 = Sodium Glucose Transporter 2; ACE = Angiotensin-Converting Enzyme

3.3.2. COVID-19 Cohort

Univariate associations with in-hospital mortality for the COVID-19 cohort were examined for the available baseline demographics and clinical characteristics and are presented in Table 6. Older age, male sex, higher BMI, diabetes mellitus, and DKA were associated with a higher likelihood for in-hospital death in all models. A history of type 1 diabetes, hypertension, asthma, heart failure, and stroke/TIA were shown to have an inverse association with in-hospital mortality. The use of biguanides, DPP4-inhibitors, and ACE inhibitors was also inversely associated with in-hospital mortality.

Table 6. COVID-19 Cohort: univariate and multivariate logistic regression analysis for the outcome of mortality.

	Univariate Analysis	**Multivariate Analysis**	**Multivariate Analysis**	**Multivariate Analysis**	**Multivariate Analysis**
		Model 1	**Model 2**	**Model 3**	**Model 4**
		***n* = 11,371**	***n* = 11,371**	***n* = 11,371**	***n* = 11,371**
Variables	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**
Age per 10 years	1.61 ** (1.57–1.65) $p < 0.001$	1.67 ** (1.62–1.72) $p < 0.001$	1.69 ** (1.63–1.74) $p < 0.001$	1.71 ** (1.65–1.77) $p < 0.001$	1.76 ** (1.70–1.83) $p < 0.001$
Male sex	1.18 ** (1.10–1.28) $p < 0.001$	1.47 ** (1.34–1.61) $p < 0.001$	1.46 ** (1.32–1.61) $p < 0.001$	1.47 ** (1.33–1.62) $p < 0.001$	1.34 ** (1.20–1.48) $p < 0.001$
BMI	1.00 (1.00–1.01) $p = 0.154$	1.04 ** (1.03–1.04) $p < 0.001$	1.03 ** (1.03–1.04) $p < 0.001$	1.04 ** (1.03–1.04) $p < 0.001$	1.03 ** (1.03–1.04) $p < 0.001$
Diabetic Ketoacidosis	1.94 ** (1.51–2.49) $p < 0.001$	2.57 ** (1.92–3.43) $p < 0.001$	1.95 ** (1.42–2.68) $p < 0.001$	1.95 ** (1.41–2.70) $p < 0.001$	1.95 ** (1.37–2.76) $p < 0.001$
History of DM	2.09 ** (1.93–2.26) $p < 0.001$		2.09 ** (1.90–2.30) $p < 0.001$	2.54 ** (2.28–2.85) $p < 0.001$	1.85 ** (1.64–2.09) $p < 0.001$
Type 1 Diabetes	0.65 (0.36–1.19) $p = 0.166$		0.36 * (0.16–0.81) $p = 0.014$	0.35 * (0.15–0.82) $p = 0.016$	0.37 * (0.16–0.88) $p = 0.024$
Hypertension	0.73 ** (0.66–0.80) $p < 0.001$		0.53 ** (0.46–0.60) $p < 0.001$	0.59 ** (0.51–0.68) $p < 0.001$	0.56 ** (0.48–0.65) $p < 0.001$
Hyperlipidemia	0.80 ** (0.69–0.92) $p = 0.001$		0.85 (0.71–1.01) $p = 0.064$	0.96 (0.80–1.16) $p = 0.658$	1.09 (0.90–1.33) $p = 0.376$
Pulmonary Hypertension	0.95 (0.49–1.83) $p = 0.871$		1.06 (0.47–2.35) $p = 0.895$	0.99 (0.43–2.26) $p = 0.982$	1.02 (0.37–2.83) $p = 0.962$
COPD	1.02 (0.77–1.35) $p = 0.904$		1.19 (0.86–1.65) $p = 0.288$	1.25 (0.90–1.75) $p = 0.190$	1.06 (0.73–1.53) $p = 0.773$
Asthma	0.49 ** (0.38–0.62) $p < 0.001$		0.64 ** (0.49–0.84) $p = 0.001$	0.66 ** (0.50–0.87) $p = 0.003$	0.56 ** (0.42–0.75) $p < 0.001$
CAD	0.97 (0.77–1.21) $p = 0.773$		0.85 (0.64–1.12) $p = 0.249$	0.93 (0.69–1.24) $p = 0.615$	0.98 (0.72–1.34) $p = 0.919$
Heart Failure	0.78 ** (0.65–0.94) $p = 0.010$		0.62 ** (0.49–0.79) $p < 0.001$	0.68 ** (0.54–0.87) $p = 0.002$	0.83 (0.64–1.07) $p = 0.144$
Stroke/TIA	0.66 * (0.46–0.97) $p = 0.032$		0.48 ** (0.31–0.75) $p = 0.001$	0.51 ** (0.33–0.81) $p = 0.004$	0.56 * (0.35–0.91) $p = 0.018$
ESRD	1.33 ** (1.11–1.59) $p = 0.002$		1.63 ** (1.29–2.07) $p < 0.001$	1.58 ** (1.24–2.02) $p < 0.001$	1.15 (0.89–1.49) $p = 0.295$
Chronic Kidney Disease	1.24 * (1.05–1.46) $p = 0.010$		1.05 (0.85–1.29) $p = 0.677$	1.02 (0.82–1.27) $p = 0.864$	1.08 (0.86–1.37) $p = 0.497$

Table 6. *Cont.*

	Univariate Analysis	Multivariate Analysis	Multivariate Analysis	Multivariate Analysis	Multivariate Analysis
		Model 1	Model 2	Model 3	Model 4
		n = 11,371	*n* = 11,371	*n* = 11,371	*n* = 11,371
Variables	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**
Biguanides	0.55 ** (0.47–0.65) $p < 0.001$			0.57 ** (0.47–0.69) $p < 0.001$	0.70 ** (0.57–0.87) $p = 0.001$
DPP4 inhibitors	0.75 ** (0.64–0.88) $p < 0.001$			0.78 * (0.64–0.95) $p = 0.014$	0.84 (0.68–1.03) $p = 0.100$
SGLT-2 inhibitors	0.77 (0.28–2.07) $p = 0.601$			1.13 (0.33–3.89) $p = 0.847$	0.86 (0.16–4.60) $p = 0.858$
GLP-1 agonists	1.03 (0.65–1.64) $p = 0.896$			1.22 (0.66–2.24) $p = 0.523$	1.35 (0.71–2.57) $p = 0.364$
Insulin	1.34 ** (1.24–1.45) $p < 0.001$			0.94 (0.84–1.06) $p = 0.343$	0.95 (0.84–1.08) $p = 0.434$
ACE inhibitors	0.69 ** (0.62–0.76) $p < 0.001$			0.58 ** (0.51–0.65) $p < 0.001$	0.61 ** (0.53–0.70) $p < 0.001$
Sulfonylureas	0.77 (0.58–1.04) $p = 0.088$			0.83 (0.57–1.21) $p = 0.334$	0.86 (0.57–1.29) $p = 0.460$
Statins	1.28 ** (1.19–1.39) $p < 0.001$			0.92 (0.82–1.02) $p = 0.109$	0.85 ** (0.76–0.95) $p = 0.004$
Heparin	2.69 ** (2.48–2.91) $p < 0.001$				2.02 ** (1.81–2.26) $p < 0.001$
Enoxaparin	0.92 * (0.85–0.99) $p = 0.036$				0.98 (0.87–1.11) $p = 0.760$
Apixaban	0.97 (0.86–1.09) $p = 0.588$				0.52 ** (0.44–0.61) $p < 0.001$
Steroids	3.51 ** (3.23–3.81) $p < 0.001$				3.01 ** (2.69–3.38) $p < 0.001$
Tocilizumab	2.07 ** (1.76–2.42) $p < 0.001$				1.37 ** (1.11–1.69) $p = 0.003$
Remdesivir	0.93 (0.74–1.17) $p = 0.557$				0.54 ** (0.41–0.71) $p < 0.001$
Convalescent Plasma	2.38 ** (2.00–2.83) $p < 0.001$				1.05 (0.82–1.34) $p = 0.708$
Cefepime	4.52 ** (4.08–5.02) $p < 0.001$				3.13 ** (2.74–3.58) $p < 0.001$

Notes: Table 6 shows univariate analysis and four multivariate models with different definitions of our variable of interest. Model 1 includes the variables: age, sex, BMI, and diabetic ketoacidosis. Model 2 includes the variables: age, sex, BMI, diabetic ketoacidosis, and comorbidities including a history of diabetes, hypertension, hyperlipidemia, pulmonary hypertension, chronic obstructive pulmonary diseases, asthma, coronary artery disease, heart failure, stroke/TIA, end-stage renal disease, and chronic kidney disease. Model 3 includes the variables: age, sex, BMI, diabetic ketoacidosis, comorbidities including a history of diabetes, hypertension, hyperlipidemia, pulmonary hypertension, chronic obstructive pulmonary diseases, asthma, coronary artery disease, heart failure, stroke/TIA, end-stage renal disease, and chronic kidney disease, and antidiabetic medication classes including biguanides, DPP4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, insulin, ACE inhibitors, sulfonylureas, and statins. Model 4 includes the variables: age, sex, BMI, diabetic ketoacidosis, comorbidities including a history of diabetes, hypertension, hyperlipidemia, pulmonary hypertension, chronic obstructive pulmonary diseases, asthma, coronary artery disease, heart failure, stroke/TIA, end-stage renal disease, and chronic kidney disease, antidiabetic medication classes including biguanides, DPP4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, insulin, ACE inhibitors, sulfonylureas, and statins, and all the medications used during inpatient status: heparin, enoxaparin, apixaban, steroids, tocilizumab, remdesivir, convalescent plasma, and cefepime. ** $p < 0.01$, * $p < 0.05$.

Abbreviations and symbols: n = number; BMI in kg/m^2; DM = Diabetes Mellitus; DKA = Diabetic Ketoacidosis; COPD = Chronic Obstructive Pulmonary Disease; CAD = coronary artery disease; TIA = Transient Ischemic Attack; ESRD = End-Stage Renal Disease; DPP 4 = Dipeptidyl Peptidase 4; GLP 1 = Glucagon-like peptide 1; SGLT 2 = Sodium Glucose Transporter 2; ACE = Angiotensin-Converting Enzyme

3.3.3. DKA Cohort

Univariate associations with in-hospital mortality for the DKA cohort were examined for the available baseline demographics and clinical characteristics and are presented in Table 7. Older age, higher BMI, and hyperlipidemia were associated with a higher likelihood for in-hospital mortality in all models. COVID-19, in this cohort, was associated with an almost ten-fold likelihood for in-hospital mortality in all cohorts. In this cohort, no association between other comorbidities or the use of medications and in-hospital death was noted.

Table 7. DKA Cohort: univariate and multivariate logistic regression analysis for the outcome of mortality.

	Univariate Analysis	**Multivariate Analysis**	**Multivariate Analysis**	**Multivariate Analysis**	**Multivariate Analysis**
		Model 1	**Model 2**	**Model 3**	**Model 4**
		***n* = 422**	***n* = 422**	***n* = 422**	***n* = 422**
Variables	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**
Age per 10	1.61 ** (1.38–1.88) $p < 0.001$	1.64 ** (1.38–1.94) $p < 0.001$	1.67 ** (1.37–2.05) $p < 0.001$	1.72 ** (1.40–2.12) $p < 0.001$	1.81 ** (1.44–2.27) $p < 0.001$
Male	0.87 (0.54–1.41) $p = 0.568$	1.35 (0.73–2.49) $p = 0.333$	1.47 (0.75–2.85) $p = 0.261$	1.70 (0.86–3.39) $p = 0.130$	2.08 (0.92–4.70) $p = 0.079$
BMI	1.02 (1.00–1.05) $p = 0.100$	1.05 ** (1.02–1.08) $p = 0.003$	1.05 ** (1.02–1.09) $p = 0.002$	1.05 ** (1.02–1.09) $p = 0.003$	1.04 (1.00–1.09) $p = 0.074$
COVID-19	10.05 ** (5.15–19.59) $p < 0.001$	10.08 ** (4.91–20.70) $p < 0.001$	10.31 ** (5.12–20.76) $p < 0.001$	10.26 ** (4.91–21.40) $p < 0.001$	8.56 ** (3.23–22.74) $p < 0.001$
Type 1 Diabetes	0.32 ** (0.16–0.67) $p = 0.002$		0.67 (0.28–1.62) $p = 0.379$	0.63 (0.25–1.56) $p = 0.317$	0.66 (0.23–1.90) $p = 0.440$
Hypertension	0.83 (0.47–1.46) $p = 0.513$		0.50 (0.24–1.05) $p = 0.066$	0.62 (0.29–1.32) $p = 0.216$	0.57 (0.24–1.32) $p = 0.188$
Hyperlipidemia	2.22 * (1.15–4.30) $p = 0.018$		3.13 * (1.13–8.66) $p = 0.028$	3.84 ** (1.44–10.28) $p = 0.007$	6.91 ** (2.49–19.22) $p < 0.001$
Asthma	0.65 (0.14–3.01) $p = 0.585$		1.06 (0.35–3.25) $p = 0.914$	1.04 (0.29–3.73) $p = 0.955$	0.43 (0.11–1.76) $p = 0.241$
CAD	0.91 (0.10–8.25) $p = 0.932$		0.25 (0.01–7.41) $p = 0.422$	0.18 (0.01–6.28) $p = 0.343$	0.17 (0.01–3.43) $p = 0.246$
Heart Failure	0.51 (0.11–2.28) $p = 0.378$		0.20 (0.01–2.91) $p = 0.241$	0.18 (0.01–3.64) $p = 0.261$	0.58 (0.05–6.33) $p = 0.655$
ESRD	1.04 (0.33–3.25) $p = 0.945$		2.54 (0.22–29.04) $p = 0.455$	2.98 (0.19–46.75) $p = 0.437$	5.62 (0.76–41.46) $p = 0.090$
CKD	0.74 (0.28–2.01) $p = 0.559$		0.58 (0.12–2.92) $p = 0.513$	0.60 (0.10–3.84) $p = 0.594$	0.46 (0.04–4.67) $p = 0.509$
Biguanides	0.87 (0.42–1.82) $p = 0.718$			1.00 (0.42–2.41) $p = 0.999$	1.35 (0.53–3.43) $p = 0.532$

Table 7. *Cont.*

	Univariate Analysis	Multivariate Analysis	Multivariate Analysis	Multivariate Analysis	Multivariate Analysis
		Model 1	Model 2	Model 3	Model 4
		n = 422	*n* = 422	*n* = 422	*n* = 422
Variables	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**	**OR (95% CI), *p*-Value**
DPP4 inhibitors	0.78 (0.43–1.42) $p = 0.421$			0.50 (0.22–1.12) $p = 0.094$	0.52 (0.21–1.27) $p = 0.153$
GLP-1 agonists	1.83 (0.16–20.44) $p = 0.624$			1.54 (0.26–9.04) $p = 0.634$	0.78 (0.13–4.53) $p = 0.780$
Insulin	0.67 (0.41–1.09) $p = 0.109$			0.89 (0.48–1.67) $p = 0.721$	1.05 (0.52–2.12) $p = 0.893$
ACE inhibitors	0.52 * (0.29–0.91) $p = 0.022$			0.51 (0.23–1.10) $p = 0.085$	0.46 (0.19–1.14) $p = 0.093$
Sulfonylureas	1.47 (0.28–7.69) $p = 0.652$			2.01 (0.42–9.66) $p = 0.384$	3.38 (0.46–24.84) $p = 0.232$
Statins	1.10 (0.69–1.75) $p = 0.699$			0.89 (0.48–1.63) $p = 0.706$	0.91 (0.44–1.89) $p = 0.808$
Heparin	1.78 * (1.08–2.94) $p = 0.024$				1.66 (0.79–3.46) $p = 0.178$
Enoxaparin	1.51 (0.93–2.44) $p = 0.094$				0.96 (0.40–2.32) $p = 0.929$
Apixaban	1.84 (0.86–3.94) $p = 0.116$				0.35 (0.11–1.16) $p = 0.086$
Steroids	10.44 ** (6.12–17.82) $p < 0.001$				9.15 ** (4.25–19.73) $p < 0.001$
Tocilizumab	7.16 ** (2.33–21.96) $p = 0.001$				2.39 (0.36–15.97) $p = 0.370$
Remdesivir	3.70 (0.51–26.67) $p = 0.195$				1.54 (0.13–18.66) $p = 0.735$
Convalescent Plasma	4.51 ** (1.48–13.80) $p = 0.008$				0.16 * (0.03–0.89) $p = 0.037$
Cefepime	5.87 ** (3.29–10.48) $p < 0.001$				2.85 ** (1.40–5.79) $p = 0.004$

Notes: Table 7 shows univariate analysis and four multivariate models with different definitions of our variable of interest. Model 1 includes the variables: age, sex, BMI, and COVID-19. Model 2 includes the variables: age, sex, BMI, COVID-19, and comorbidities including a history of diabetes, hypertension, hyperlipidemia, pulmonary hypertension, chronic obstructive pulmonary diseases, asthma, coronary artery disease, heart failure, stroke/TIA, end-stage renal disease, and chronic kidney disease. Model 3 includes the variables: age, sex, BMI, COVID-19 comorbidities including a history of diabetes, hypertension, hyperlipidemia, pulmonary hypertension, chronic obstructive pulmonary diseases, asthma, coronary artery disease, heart failure, stroke/TIA, end-stage renal disease, and chronic kidney disease, and antidiabetic medication classes including biguanides, DPP4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, insulin, ACE inhibitors, sulfonylureas, and statins. Model 4 includes the variables: age, sex, BMI, COVID-19, comorbidities including a history of diabetes, hypertension, hyperlipidemia, pulmonary hypertension, chronic obstructive pulmonary diseases, asthma, coronary artery disease, heart failure, stroke/TIA, end-stage renal disease, and chronic kidney disease, antidiabetic medication classes including biguanides, DPP4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, insulin, ACE inhibitors, sulfonylureas, and statins, and all the medications used during inpatient status: heparin, enoxaparin, apixaban, steroids, tocilizumab, remdesivir, convalescent plasma, and cefepime. ** $p < 0.01$, * $p < 0.05$.

Abbreviations and symbols: n = number; BMI in kg/m^2; DM = Diabetes Mellitus; DKA = Diabetic Ketoacidosis; COPD = Chronic Obstructive Pulmonary Disease; CAD = coronary artery disease; TIA = Transient Ischemic Attack; ESRD = End-Stage Renal Disease; DPP 4 = Dipeptidyl Peptidase 4; GLP 1 = Glucagon-like peptide 1; SGLT 2 = Sodium Glucose Transporter 2; ACE = Angiotensin-Converting Enzyme

4. Discussion

Diabetic ketoacidosis is a severe metabolic complication attributable to severe insulin deficiency. From previous studies, it is well established that COVID-19 is associated with ketosis, ketoacidosis, and diabetic ketoacidosis [16]. Our study investigated the association of DKA with in-hospital outcomes among patients admitted with COVID-19 in the largest public health care system of the United States. The key findings of our descriptive analysis showed that the mortality rate was seven times higher in patients with DKA and COVID-19 compared to the DKA control group, i.e., patients without COVID-19. The likelihood of death in patients with DKA and COVID-19 was found to be significantly higher compared to patients with DKA and without COVID-19.

Khan et al. reported a cohort of 14,900 patients across the eleven hospitals of New York City Health + Hospitals, which showed that the mortality rate in DKA/COVID-19 patients was almost 50% [17]. To further elucidate these findings, we adjusted for common conditions and treatments that could influence mortality. Our analysis found that diabetes was associated with a two-times-higher likelihood of death among patients with COVID-19 after adjustment for variables such as common co-morbidities, DKA, and anti-hyperglycemic medications. This is similar to the meta-analysis by Kumar et al. (33 studies, 16,003 patients) which demonstrated that diabetes in patients with COVID-19 was associated with a two-fold increase in mortality as compared to patients without diabetes [18]. This is in line with our previous meta-analysis of 18,506 patients that also showed a higher mortality in patients with diabetes and COVID-19 as compared to those without diabetes [19]. In our analysis, COVID-19 was associated with a four-times-higher likelihood for death in the matched cohort (COVID-19/control), which became ten-fold in the DKA group. Hyperosmolar hyperglycemic syndrome (HHS) and DKA can be precipitated in patients with new onset DM or with previously adequate glycemic control [20]. Some case reports described that patients with both HHS and DKA who required mechanical ventilation had a poor prognosis with 100% mortality [21]. However, the effects of long-COVID on the rates of mortality in DKA are unknown. Several plausible mechanisms have been suggested in the development of SARS-CoV-2-mediated acute diabetes and diabetic ketoacidosis. This includes damage to the pancreatic β-cell, which could either be direct, by the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) receptors on the pancreatic islets, immune-mediated from alterations in the self-antigens, or by β-cell death resulting from the release of inflammatory markers such as tumor-necrosis factor-α (TNFα) and interferon-γ by a SARS-CoV/SARS-CoV-2-infected exocrine pancreas [22–24]. Damage to the pancreatic β-cell in the setting of relative (Type 2 DM) or absolute (Type 1 DM) insulin deficiency can lead to an imbalance in the insulin:glucagon ratio. This imbalance causes an increase in glucose synthesis, reduced glucose utilization, and excessive lipolysis, leading to hyperglycemic ketoacidosis [25,26]. The production of interferon (IFN) gamma can lead to resistance to insulin on muscles, leading to hyperinsulinemia in order to maintain a euglycemic state. However, patients with a reduced production of insulin or an increased resistance to insulin might fail this compensatory mechanism if they are affected by COVID-19 [27].

Diabetes in COVID-19 can lead to severe disease and increase the overall mortality. Some of the possible explanations for this include: (a) compromised innate immunity, which is the first line of defense against COVID-19. Uncontrolled diabetes leads to reduced innate immunity, which gives rise to the unhindered proliferation of the virus [28,29]. (b) Exaggerated cytokine storm response: even in the absence of immune stimulation, diabetes is associated with a pro-inflammatory state characterized by increased levels of

interleukin (IL)-1, IL-6, tumor-necrosis factor (TNF)-α, and ferritin. This cytokine response is exaggerated when there is an appropriate stimulus such as COVID-19 viral infection leading to acute respiratory distress syndrome (ARDS) and rapid deterioration [30–32]. (c) Increased oxidative stress: ACE2 is a membrane glycoprotein expressed in the lungs, kidneys, intestine, and blood vessels. It is known to break down angiotensin II and angiotensin I to smaller peptides such as angiotensin (Ang) (1–7) and angiotensin (1–9), respectively. ACE2/Ang (1–7) plays a crucial role as anti-inflammatory mechanism and antioxidant protecting lungs against ARDS. ACE2 is under-expressed in diabetes patients, possibly due to glycosylation, which explains the increased susceptibility to severe lung injury and ARDS in COVID-19 patients [33,34]. However, even the over-expression of ACE2 would be detrimental, as SARS-CoV-2 utilizes ACE2 as a receptor for entry into the host pneumocytes [35]. It is also interesting to note that there have been a few cases of patients presenting with DKA after being vaccinated against COVID-19 [36,37]. These authors have attributed DKA after vaccination to poor oral intake or the inability to titrate insulin requirements, especially in patients with T1DM combined with the vaccine-induced enhancement of a robust systemic immune-inflammatory response [36,38].

To our knowledge, this study is the largest to date assessing the impact of DKA on the in-hospital outcomes of patients with COVID-19 of different sexes, age groups, and racial/ethnic backgrounds. We should acknowledge that our study has several limitations. First, this was a retrospective cohort involving electronic medical records; hence, there are risks related to observational bias and unmeasured confounding. Second, our cohort is unique in that it is enriched with immigrant populations, Medicaid-Medicare recipients, and the uninsured, which may have unique unidentified confounding factors; therefore, our findings cannot be easily generalized to patient populations with other characteristics.

5. Conclusions

In summary, our study of a large cohort of hospitalized patients with COVID-19 in a public healthcare system showed that DKA and diabetes were associated with increased in-hospital death after adjusting for DKA/diabetes-related potentially confounding factors. This demonstrates that the presence of DKA is associated with worse outcomes of coronavirus infection. We propose that the enhanced prevention of COVID-19 infection in persons with diabetes by known preventive measures such as masks, social distancing, and vaccination—and, more importantly, the enhanced monitoring of COVID-19 patients with DKA/diabetes during their hospitalization—may help reduce mortality.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diabetology3030036/s1, Graphs concerning the quality of the matching technique used: Figure S1. Extent of covariate imbalance in terms of standardized percentage differences before and after matching. Figure S2. Propensity scores, subject-specific probability of mortality (A) before matching and (B) after matching. Statistics: Table S1. Correlation matrix of disorders. Table S2. Correlation matrix of disorders in the DKA cohort. Regression analysis for the outcome of intubation: Table S3. Baseline patient characteristics: univariate and multivariate logistic regression analysis for the outcome of intubation. Table S4. COVID-19 cohort: univariate and multivariate logistic regression analysis for the outcome of intubation. Table S5. DKA cohort: univariate and multivariate logistic regression analysis for the outcome of intubation. Regression analysis for the outcome of ICU admission: Table S6. Baseline patient characteristics: univariate and multivariate logistic regression analysis for the outcome of ICU admission. Table S7. COVID-19 cohort: univariate and multivariate logistic regression analysis for the outcome of ICU admission. Table S8. DKA cohort: univariate and multivariate logistic regression analysis for the outcome of ICU admission. Regression analysis for the outcome of Renal Replacement Therapy: Table S9. Baseline patient characteristics: univariate and multivariate logistic regression analysis for the outcome of Renal Replacement Therapy. Table S10. COVID-19 cohort: univariate and multivariate logistic regression analysis for the outcome of Renal Replacement Therapy. Table S11. DKA cohort: univariate and multivariate logistic regression analysis for the outcome of Renal Replacement Therapy.

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