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Diabetic Ketoacidosis Prevalence and Clinical Presentation in Diabetic-Covid Comorbidity in Nangarhar Afghanistan

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ABSTRACT

Background: Diabetic ketoacidosis (DKA) as an acute complication of diabetes mellitus is a life threatening medical emergency causing mortality and morbidity in patients. The aim of the study was to find out DKA prevalence and existing clinical presentation in diabetic-covid comorbidity.

Materials and Methods: The retrospective cross sectional study included 791 both male and female diabetic patients with a confirmed diagnosis of covid 19 based on purposive sampling for a period of one year from Aug 2021 to Aug 2022 from two centers (Corona Center and Nangarhar Regional Hospital) in Nangarhar, Afghanistan.

Findings: The study included 300 (37.9%) male and 491 (62.1%) female patients, 45 (5.7%) Type 1, 746 (94.3%) Type 2 diabetic patients, 511 (64.6%) old diabetes, and 280 (35.4%) new onset diabetes patients. Mean age at the study was 58.7±13, BMI was31.2±4, Systolic BP128.3±24.4, oxygen was 79.1±15.4, glycaemia was 297.5±8, and mean hospital stay was 8.8±8.1 days. In fact, 149 out of 791 patients (19%) had diabetic ketoacidosis (DKA) of which 140 patients out of 149 (93.96%) were hyperglycemic and 9 out of 149 patients (6%) were euglycemic DKA. Furthermore, DKA was more prevalent in males 58.4% vs 41.6% in females, young age (20-39 years) 31.2%, Type 1 diabetes 33.3% vs 21.9% type 2 diabetes, and old diabetes 19.5% vs 17.6% new onset diabetes. Moreover, clinical presentation included dyspnea 143 (96%), abdominal pain 124 (83.2%), nausea/vomiting 121 (81.2%), tachycardia 105 (70.5%), polydipsia of diabetic classic symptoms 70 (47%), and crepitation in chest auscultation though not significant 77 (51.7%). Pneumonia 92 (61.7%), and ARDS 54 (36.2%) were respectively the most prevalent clinical and X-ray findings in DKA patients. In addition, hospitalization duration was comparatively higher for females (10 vs 9), T2DM (10 vs 6), and new onset DM (14 vs 7) and it increased with advancing age (most for patients of ≥ 80 years) in DKA. Death and referral measures were significantly different across DKA positive and DKA negative patients i.e. 37.6% vs 14.8% and 16.1% vs 8.1% respectively. While, discharge status with home rest was more prevalent in DKA negative patients i.e. 46.3% vs 77.1%.

Conclusion: We concluded that DKA prevalence has increased almost two fold in diabetic patients suffering from corona virus affecting in-hospital mortality, hospital stay, morbidity and the preexisting clinical picture. In fact, obesity, hypertension, young age and male gender were significant factors contributing to the prevalence. In addition, mortality and referral rates to specialty specific centers were significantly higher in DKA positive patients with the aforementioned factors being the leading contributors.

Keywords: Diabetes, Diabetic Ketoacidosis, DKA, Covid 19, Afghanistan

INTRODUCTION

The novel corona virus infected pneumonia (NCIP) first appeared in Wuhan, China, with the number of cases increasing over periods of time causing lockdowns in the city then in the whole country leaving great impact on social life (Wang et al., 2020). In Afghanistan, approximately ten million people (31.5% of the whole country) were reported to suffer from either a pre-existing or a new Covid disease up to July 2020 (Saeedzai et al., 2022). In fact, 7321 deaths were reported on 10th Dec 2021 in association with Covid (Shah et al., 2022) which may be an underestimated figure representing the whole country since there were numerous rumors about the virus and it is still an under-looked topic. Shutdown of healthcare centers due to lack of financial aid and lack of in-hospital beds, oxygen supply, ventilators and professional staff were the leading contributors to the increased number of mortality in a small population residing country (Shah et al., 2022).

Diabetes Mellitus is an independent risk factor for in-hospital complications in Covid patients, which include hyperglycemic medical emergencies as diabetic ketoacidosis (DKA) and others as well as increased hospitalization and hospital stays in comparison with controls (Erratum, 2022). Increased ACE2 (Angiotensin converting enzyme 2) expression and later downregulation specifically after the virus entry (Roca et al., 2017), increased Furin expression (Fernandez et al., 2018), impaired T cell function (Kulcsar et al., 2019) and increased interleukin 6 appearance (Maddaloni et al., 2020) in diabetic patients are the known pathophysiologic mechanisms predisposing to Covid 19 and the subsequent lung injury and ARDS.On the other hand, binding of SARS Corona virus to the receptors (ACE2 and Furin), causes pancreatic damage which in turn results in acute diabetes calling it a bidirectional relationship (Yang et al., 2010).

Despite the recent explosion of articles on the topic, Covid, still little is known about Covid-DM comorbidity and its sequences and local data on the prevalence of diabetic ketoacidosis and its associated characteristics during the comorbidity lacks, so we aimed to conduct the study to find out the prevalence of diabetic ketoacidosis in Covid further elaborating its associated factors, clinical trends, types of diabetes, hospital stay and mortality.

MATERIALS AND METHODS

It is a retrospective cross-sectional multicenter (Nangarhar Regional Hospital, Nangarhar Corona Center) study, which is based on purposive sampling including 791 patients for a period of one year from Aug 2021 to Aug 2022. Patients of either gender with either type of diabetes regardless of age but with a positive Covid test (real time PCR on a nasopharyngeal swab) were included in the study and patients with diagnosis other than Covid and other known KDA predisposing factors such as insulin withdrawal, infection/stress, infarction and etc were excluded from the study. Patients' identity was secured for ethical purpose and the study was registered at the ethical committee as IRB-3121. In fact, Diabetes mellitus was diagnosed under the criteria, two positive tests or a single positive tests plus classic clinic. And DKA was defined according to the American Diabetic Association as PH <7.35, bicarbonate <18 mEq/L, positive serum or urine ketones and serum glucose >250 mg/dl (Dhatariya, 2007). Patients' demographics, baseline characteristics and other variables of interest achieved via thorough approach including history, physical exam and labs were analyzed using both qualitative and quantitative measures after verifying the data normality via Kolmogorov test by SPSS version 26. Mean ± standard deviation was used for continuous variables while frequencies percentages for categorical variables.

RESULTS

The study included 791 both female and male (300 males & 491 females) patients with known Diabetes Mellitus and Covid 19 with most cases coming from Nangarhar province where Corona health centers are located. 407 (51.45%) of the cases were obese, 253 (31.98%) were overweight and 131 (16.56%) were of normal weight. Further demographic characteristics of the study participants are described in Table 1.

Table 1. Demographics

Parameter		**Frequency (%)**
Gender	Male	300 (37.9%)
	Female	491 (62.1%)
Age	20-39	48 (6.1%)
	40-59	304 (38.4%)
	60-79	376(47.5%)
	>=80	63(8%)
Marital Status	Single	6(0.8%)
	Married	785(99.2%)
BMI	Normal weight	131(16.7%)
	Overweight	253(32%)
	Obese	407(51%)
Economic Status	Poor	369(46.6%)
	Fair	234(29.6%)
	Good	188(23.8%)
DM Type	Type1	45(5.7%)
	Type2	746(94.3%)
Residence	Nangarhar	659(83.3%)
	Laghman	59(7.5%)
	Kunar	26(3.3%)
	Other Provinces	47(5.9%)
Diabetes Onset	Old onset Diabetes	511(64.6%)
	New onset Diabetes	280(35.4%)

Mean age of the cases during study was 58.7±13 years, mean glycaemia 297.48±8 mg/dl and mean hospital stay was 8.8±8.1 days. Table 2 describes the baseline characteristics of the study participants (patient values at the time of admission under diabetic ketoacidosis like age, blood pressure, BMI and etc).

Table 2. Baseline Characteristics

Parameter	**Mean**	**Minimum**	**Maximum**
Age	58.7±13	20	100
BMI	31.2±4	24.7	48.5
Heart Rate	111.8±26	65	180
Respiratory Rate	25.1±4	16	36
Temperature	37.7±0.6	35.6	40
Systolic BP	128.3±24.4	70.0	190
Oxygen saturation	79.1±15.4	30	96
Glycaemia	297.5±8	69	610
ALT	79.4±6	6	328
AST	51±34	10	230
Hemoglobin	12 ±1.3	7	16
Total Leukocytes	13298±5660	3500	42300
Creatinine	1.63±1	0.1	5.50
Potassium	3.8±0.4	2.2	5.80

pH	7.3±0.4	6.7	7.90
Hospital stay duration	8.8±8.1	0	75

BMI= Body mass index, BP= Blood pressure, ALT= Alanine transaminase, AST=Aspartate transaminase, pH= Power of hydrogen

In fact, 149 cases (19%) out of 791 diabetic-covid 19 patients were complicated to diabetic ketoacidosis as shown in Figure 1.

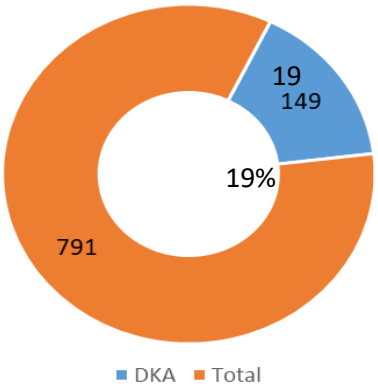

Figure 1. Ketoacidosis Prevalence

DKA was significantly more prevalent in males i.e. 87 out of 300 (29%) compared to females, 62 out of 491 (12.6%). In addition, 33.3% of Type 1 DM and 21.9% of Type 2 DM were complicated to DKA during the comorbidity. However, DKA prevalence was not significantly different across different age groups as shown in Table 2. In fact, 67.1% cases of DKA were diagnosed as having old DM while the rest 32.9% had new onset DM. 58.3% of the DKA positive patients were males and the rest 41.7% were females despite knowing that majority of the cases included in the study were females. 140 patients out of 149 (93.96%) were diagnosed with hyperglycemic DKA while 9 out of 149 patients (6%) were diagnosed with euglycemic DKA.

Table 3. DKA Prevalence across gender, age groups, and diabetes types

Parameters		**Total Count**	**DKA Positive**
Gender	Male	300	87 (29%)
	Female	491	62 (12.6%)
Age Groups	20-39	48	15 (31.2%)
	40-59	304	62 (20.4%)
	60-79	376	63 (16.7%)
	>=80	63	9 (14.3%)
Diabetes Mellitus	Type 1	45	15 (33.3%)
	Type 2	612	134 (21.9%)
Old/New Diabetes	Old	511	100 (19.6%)
	New	280	49 (17.5%)
Glycemic status	Hyperglycemic DKA	444	140 (24%)
	Euglycemic DKA	198	9 (4.34%)

Moreover, DKA was analyzed over glycemic status as whether DKA was euglycemic or hyperglycemic; euglycemic DKA was defined as having blood glycemic level less than 250 mg/dl at the time of diagnosis. Nine out of 149 (6.04%) cases were euglycemic while 140 out of 149 (93.96%) were hyperglycemic were diagnosed with hyperglycemic DKA. Surprisingly, we did not have any euglycemic DKA event in males and Type 1 DM while we had 9 (6.04%) euglycemic DKA events in females and Type 2 DM. However, 4 out of 9 euglycemic DKA events were foundin patients with old DM and the rest in new onset DM.

Dyspnea and tachypnea were respectively the most frequent clinical findings followed by abdominal pain and up to some range, the classic clinic of diabetes mellitus such as polydipsia, polyuria and weight loss as describedin Table 4. Almost half of the patients revealed crepitation during their chest auscultation followed by rhonchi.

Table 4. Frequency of signs and symptoms across DKA positive Covid patients

Parameter		**Frequency**
Tachycardia		105 (70.5%)
Tachypnea		133 (89.3%)
Dyspnea		143 (96%)
Kussmaul Breathing		102 (68.5%)
Abdominal pain		124 (83.2%)
Nausea/Vomiting		121 (81.2%)
Dehydration		97 (65.1%)
	No Symptoms	27 (18.1%)
	Polydipsia	70(47%)
DM Classic symptoms	Polyuria	25(16.8%)
	Weight loss	3(2%)
	Multiple Symptoms	24(16.1%)
	NAF	10(6.7%)
	Crepitation	77(51.7%)
Chest Auscultation	Rhonchi	16(10.7%)
	Wheezing	15(10.1%)
	Combined	31(20.8%)

Mean serum potassium level, pH, Creatinine, Total Leukocytes, ALT, AST, Glycaemia, systolic BP,and Oxygen saturation on a pulse oximeter were all comparatively high in DKA positive Covid 19 patients (3.6507±0.43, 7.2914±0.3, 1.9643±1.13, 26300±13457, 110±83, 73.14±47.7, 384±82, 130±30, 72%±20 respectively).

Pneumonia (Table 5) was the most prevalent x ray finding in both DKA negative and DKA positive patients as seen in 500 patients (63.2.8%) vs 92 (11.6%) followed by the findings of ARDS 120 (15.2%) vs 54 (6.8%), pleural effusion 6 (0.8%) vs 3 (0.4%) , fibrosis 7 (0.9%) vs 0 (0.0%) and hyperinflation 6 (0.8%) vs 0 (0.0%).

Table 5. Chest X-ray (PA) changes across DKA

X ray findings	**DKA negative**	**DKA positive**
Normal	3 (0.5%)	0 (0%)
Pneumonia	500 (77.9%)	92 (61.7%)
ARDS	120 (18.7%)	54 (36.2%)
Hyperinflation	6 (0.9%)	0 (0%)
Fibrosis	7 (1.1%)	0 (0%)
Pleural Effusion	6 (0.9%)	3 (2%)
Total	642 (100%)	149 (100%)

The following medicines were used in patients: Tocilizumab 24 (3%), Remdesivir 230(29.1%), steroid 105 (13.3%) and anticoagulant 212 (26.8%). Mortality is calculated out of 100% for each medicine group across DKA positive and DKA negative patients; being the least in both DKA positive and negative patients who received tocilizumab as shown in Table 6.

Table. 6. Mortality across different drugs

Medicine		Mortality	
		DKA negative	DKA positive
Tocilizumab	No	92 (96.8%)	47 (83.9%)
	Yes	3 (3.2%)	9 (16.1%)
Remdesivir	No	77 (81.1%)	40 (71.4%)
	Yes	18 (18.9%)	16 (28.6%)
Steroid	No	77 (81.1%)	47 (83.9%)
	Yes	18 (18.9%)	9 (16.1%)
Anticoagulant	No	62 (65.3%)	44 (78.6%)
	Yes	33 (34.7%)	12 (21.4%)

DKA= Diabetic Ketoacidosis

Ventilator was used in 35% of DKA positive patients in comparison to 15% of DKA negative patients.

Mean hospital stay in days was comparatively high though not significant in DKA positive Covid patients (10 vs 9). Hospitalization duration in Covid-DKA patients across gender, age groups and diabetes type is shown in Figure2.

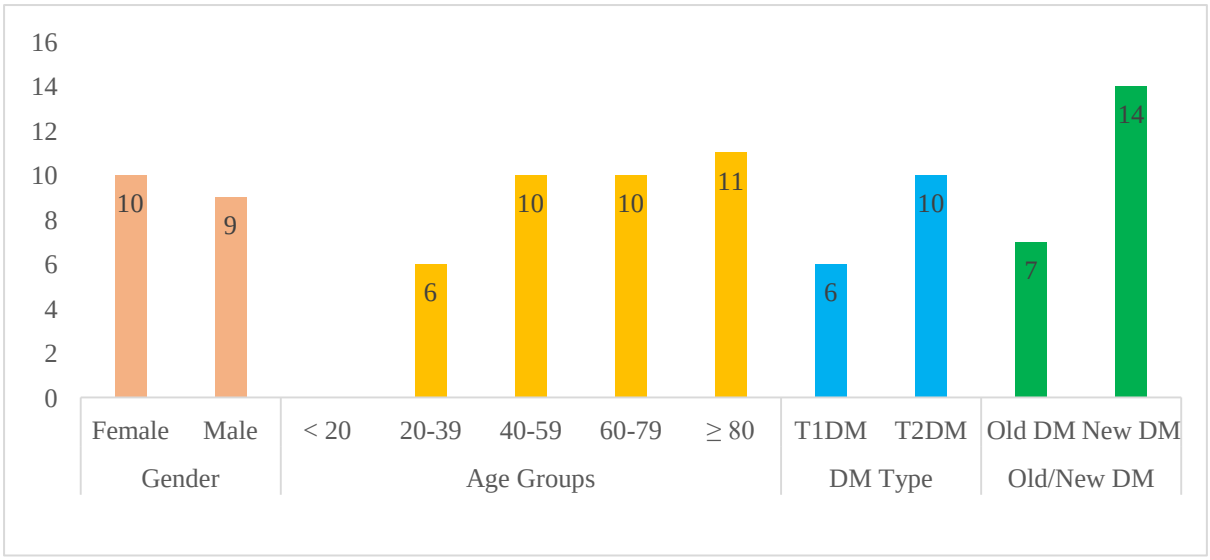

Figure 2. Mean Hospital Stay (Days) in DKA Positive Patients

Figure 2 shows that hospitalization duration was comparatively high for females (10 vs 9), T2DM (10 vs 6), and new onset DM (14 vs 7) and it increased with advancing age (most for patients of ≥ 80 years).

76 patients out of 791 (9.6%) died regardless of diabetic ketoacidosis in which mortality almost doubled. Dischargestatus across diabetic ketoacidosis patients is shown in Figure 3.

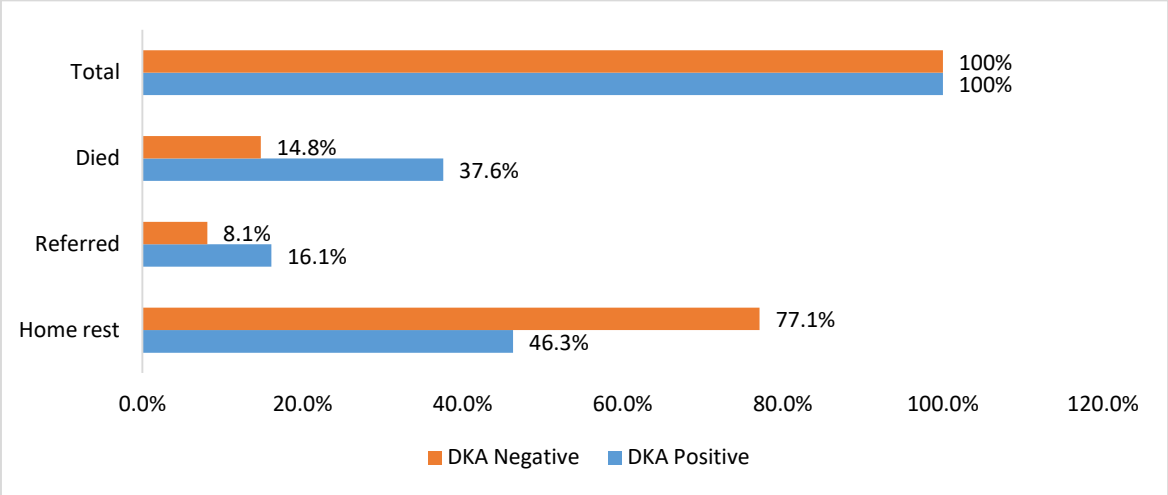

Figure 3. Discharge Status in Covid-DKA Patients

Death and referral measures were significantly different across DKA positive and DKA negativepatients i.e. 37.6% vs 14.8% and 16.1% vs 8.1% respectively. While discharge status with home rest was moreprevalent in DKA negative patients i.e. 46.3% vs 77.1%. In fact, referral was made to tertiary care or specialty specific care centers for kidney disease, heart diseases such as infarction and heart failure, cerebrovasculardiseases such as stroke, etc. Mortality rate was higher in obese diabetic ketoacidosis patients suffering from Corona viral disease i.e. mortality rate almost doubled in obese DKA patients compared with non DKA patients 29 (35.8%) vs 49 (14.4%) as in Table 7. However, mortality was not significantly different across overweight and normal weight patients despite being higher in the respective groups across DKA.

Table. 7. DKA mortality across BMI groups

Discharge Status	**DKA negative**			**DKA positive**		
	Normal Weight	Overweight	Obese	Normal Weight	Overweight	Obese
Home rest	94 (83.9%)	148 (74.4%)	240 (73.6%)	7 (36.8%)	22 (44.9%)	40 (49.3%)
Referred	11 (9.8%)	34 (17.1%)	39 (12%)	3 (15.8%)	9 (18.1%)	12 (14.8%)
Died	7 (6.3%)	17 (8.5%)	47 (14.4%)	9 (47.4%)	18 (36.7%)	29 (35.8%)
Total	112 (100%)	199 (100%)	326 (100%)	19 (100%)	49(100%)	81 (100%)

DISCUSSION

The major findings of the study include diabetic ketoacidosis prevalence in diabetic patients suffering from recent covid, old vs new onset diabetes mellitus, euglycemic vs hyperglycemic diabetic ketoacidosis, and clinical presentation in the comorbidity complicating to diabetic ketoacidosis.

New onset diabetes prevalence was higher in hypertensive, young age, and male patients as comparable with a study by Heaney A. et al in the United States of America (Heaney et al., 2020).

DKA was more prevalent in diabetic patients suffering from Covid; this is consistent with the findings of a study by Faraz khan et al. in USA revealing that DKA prevalence doubled during the pandemic (Khan et al., 2022).

DKA was significantly more prevalent in males despite the large number of the female patients in the study, hypertensive, obese and young age and it is comparable with the studies by Rimesh Pal et al. in India (Pal et al., 2020) and Heaney A. et al in USA (Heaney et al., 2020).

Most of the DKA positive covid patients were diagnosed as having preexisting diabetes while a minority of patients had new onset DM which is compatible with the findings of a study by Rimesh Pal et al. (Pal et al., 2020) stating that 77% of DKA positive covid patients had preexisting diabetes.

A minority of the cases in our study had euglycemic DKA; in fact, euglycemic DKA in a study by Rebecca et al. in Massachusetts was shown to be due to sodium glucose cotransporter 2 inhibitors and they prosed the medicine to be counselled for discontinuation during Covid infection (Vitale et al., 2021).

Mortality was significantly higher in DKA positive arm compared with DKA negative arm such that it doubled in diabetic covid patients complicated to DKA which is comparable with numerous studies in United Kingdom, India, and America (Dhatariya et al., 2007, Pal et al., 2020, Chamorro et al., 2020). Furthermore, DKA mortality was higher in elderly males and obese patients i.e. almost half of the obese DKA patients died which is consistent with a study by Francisco et al. in 17 different states of America (Pasquel et al., 2021). Lack of hospital beds, Corona specific hospitals, political instability, and lack of ventilators and experienced technicians were the leading factors contributing to the high number of mortality in the eastern Afghanistan due to corona-diabetes comorbidity complicated to DKA. However, mortality has recently decreased. In addition, referral rate was also double in the DKA patients who were referred to tertiary care or specialty specific care centers due to kidney disease, heart diseases such as infarction and heart failure, cerebrovascular disease such as stroke,etc.

Remdesivir, Tocilizumab and steroid were used for severe cases in the study and mortality was significantly lower in patients receiving Tocilizumab and Remdesivir. Tocilizumab, an IL 6 antagonist, expressed in a study by Zhang et al. in China, (Zhang et al., 2020) and steroids are effective in proinflammatory status (cytokine storm) which is a known key element in the pathogenesis of Covid 19 in a study by Maddaloni et al. in Italy (Maddaloni et al., 2020). The combination of Tocilizumab with steroid showed efficacy in decreasing mortality compared with Tocilizumab alone and the control group in a study by Mahmood Mousazadeh et al. in France (Mossazadeh et al., 2022). On the other hand, Remdesivir in a study by Tchesnokov et al. in Canada is known to inhibit viral replication of SARS COV2 (Tchesnokov et al., 2020).

There were a few limitations in the study despite the interesting results and the realistic topic but the contributors in the study have made their outmost efforts to collect clean data and to reduce bias. First, confounders in the retrospective descriptive study may have affected the results; for example, stress, hypertension, ischemic heart disease and etc. all alleviate glycemic level and may predispose diabetic patients to diabetic ketoacidosis, on the other hand we know that all the aforementioned factors could be due to either diabetes or covid, so we were hesitant to exclude them from the study. Second, Absence of database resulted in loss of a few variables of interest we planned to include in the study such as HBA1C levels, Ketones quantitative measures and etc.; and loss of follow up being the last one which may have increased the prevalence of diabetic ketoacidosis in diabetes-covid comorbidity in the future.

We recommend that clinicians should screen diabetic or diabetic ketoacidosis patients for covid 19, isolate them in case being positive to avoid transmission to other patients or healthy individuals, properly educate their patients, and provide them with prompt and proper management to avoid or decrease morbidity and mortality. In addition, policy makers and program managers to provide free insulin, ventilators, and the medicines shown in

literature to decrease mortality in such patients. They should also design and run awareness programs on social media, hire new staff, design special capacity building programs for them, and provide grants for large analytical studies on the topic on the country level.

CONCLUSION

We concluded that DKA prevalence has increased almost two fold in diabetic patients suffering from Corona virus affecting in-hospital mortality, hospital stay, morbidity and the preexisting clinical picture. In fact, obesity, hypertension, young age and male gender were significant factors contributing to the prevalence. In addition, mortality and referral rates to specialty specific centers were significantly higher in DKA positive patients with the aforementioned factors being the leading contributors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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