Eman Monir Sherif, Yasmine Ibrahim Elhenawy*, Randa Mahmoud Matter, Hanan Hassan Aly, Rasha Adel Thabet and Yasmeen Abdelaziz Fereig

Clinical characteristics and outcome of hospitalized children and adolescent patients with type 1 diabetes during the COVID-19 pandemic: data from a single center surveillance study in Egypt

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Abstract

Objectives: COVID-19 pandemic significantly impacted the diagnosis of type 1 diabetes and its acute complications. Thus, the study aimed to evaluate the characteristics of pediatric patients with type 1 diabetes hospitalized during the first wave of the pandemic and the prevalence of new onset diabetes among patients with evidence of COVID-19 infection.

Methods: A single-center surveillance study included all patients with diabetes admitted to Children's Hospital, Ain Shams University, in Egypt between May to August 2020. Data were collected to evaluate patients' clinical and laboratory characteristics as well as their outcomes.

Results: Thirty-six patients were admitted during the study period. The mean age was 8.4 ± 3.8 years. Patients presented late to the emergency department with a mean delay of 3.05 ± 1.19 days from onset of symptoms. 34/36 patients presented in diabetic ketoacidosis (DKA), 50% presenting in severe DKA. Almost 81% of the patients were newly diagnosed. During the study period, SARS-CoV-2 PCR was found positive in four patients, COVID Ig M antibodies were positive in another two patients; all were symptomatic requiring ICU admission. Four patients showed a picture suggestive of the multi-inflammatory syndrome (MIS-C); cardiac affection was a constant feature.

Conclusions: The pandemic affected both the prevalence and severity of DKA among pediatric patients. The increased prevalence of severe DKA could be partly related to delayed hospital admission or the effect of COVID-19 in triggering DKA. Efforts should be done to continuously raise awareness about diabetes in children as well as the importance of seeking timely medical guidance.

Keywords: COVID-19; diabetic ketoacidosis; multi-inflammatory syndrome; type 1 diabetes.

***Corresponding author: Yasmine Ibrahim Elhenawy**, Division of Pediatric and Adolescent Diabetes Unit (PADU), Department of Pediatrics, Faculty of Medicine, Ain Shams University, 26 Hassan Ibrahim Hassan Street, Nasr City, Cairo, Egypt, Phone: +20 1006714334, E-mail: dr_yasmi@yahoo.com

Eman Monir Sherif, Randa Mahmoud Matter, Hanan Hassan Aly, Rasha Adel Thabet and Yasmeen Abdelaziz Fereig, Division of Pediatric and Adolescent Diabetes Unit (PADU), Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Introduction

Since being declared as a pandemic by the World Health Organization on 11 March 2020, coronavirus disease 2019 (COVID-19) became a global catastrophe [1].

Poor glycemic control among patients with diabetes, especially those hospitalized with infectious disease, is significantly associated with higher long-term mortality risk [2]. Epidemiological and surveillance studies, defining comorbidity associated with COVID-19, have frequently highlighted diabetes as major comorbidity in adult patients [3, 4].

The association between the onset of type 1 diabetes and viral infection preceding the development of overt diabetes have been well recognized, viruses could cause type 1 diabetes either by infecting beta-cell and/or altering the immune system [5, 6].

Although data in the pediatric age group is scarce, children with well-controlled diabetes do not appear to have an increased risk of infection with SARS-CoV-2 or progress to severe disease [7].

The extent to which clinical and laboratory features of patients modifies both the outcome and severity of the

disease seems entirely unclear and few studies in the pediatric age group aimed to map the characteristics and presentations of patients with type 1 diabetes during the pandemic [8–10].

To the best of our knowledge, this is the first study evaluating the impact of the first wave of the pandemic on an Egyptian cohort of pediatric and adolescent patients with type 1 diabetes. The primary objective of the current study is to map the clinical and laboratory characteristics of pediatric patients with type 1 diabetes hospitalized during the COVID-19 pandemic. The study aimed to explore the relationship between diabetes and the severity of COVID-19 infection as well as the impact of COVID-19 on the clinical presentation and outcome in patients with type 1 diabetes. The study as well maps the prevalence of new-onset diabetes among pediatric patients with evidence of COVID-19 infection.

Methods

The current surveillance study is a single-center retrospective observational study approved by the local ethical committee of Ain Shams University and registered in the Clinical Trials Government (NCT 01763658). Participants included all patients with type 1 diabetes admitted to Children's Hospital, Ain Shams University in the period between the first of May till the end of August 2020.

The following case definitions were used in the current study:

- Newly diagnosed diabetes was defined as two or more blood glucose levels ≥200 mg/dL with glycated hemoglobin (HbA_{1c}) ≥6.5% [11]. Diabetic ketoacidosis (DKA) was defined as the presence of acidosis (pH < 7.3, HCO3 < 15 mmol/L), high blood or urine ketones, and blood glucose level ≥ 200 mg/dL. Severe DKA was defined as pH < 7.1 [12].
- Confirmed COVID-19 cases were diagnosed biologically by a positive PCR in suspected cases.
- Clinical severity of COVID-19 infection was classified as defined by Qiu et al. [13]:

The mild disease was defined if the patients are either asymptomatic or show a short duration of upper respiratory symptoms with a positive RT-PCR test for SARS-CoV-2. Patients with the moderate disease show mild pneumonia with no complications or manifestations related to severe conditions. The presence of any manifestations suggesting disease progression defines severe disease. Manifestations of disease progression include any of the following: rapid breath, hypoxia, lack of consciousness, depression, coma, convulsions, dehydration, gastrointestinal dysfunction, myocardial injury, elevated liver enzymes, coagulation dysfunction, and any other manifestations suggesting injuries to vital organs. Patients with the critical illness include patients with rapid disease progression, associated with either any manifestation of respiratory failure, septic shock, or organ failure that needs monitoring in the ICU.

- Multisystem inflammatory syndrome in children (MIS-C) was defined if the patient meets the following criteria [14],
  - "Fever >38.0 °C for ≥24 h, or report of subjective fever lasting ≥24 h, and
  - Laboratory evidence of inflammation (including, but not limited to, one or more of the following: neutrophilia; lymphopenia; hypoalbuminemia; and elevated levels of C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], fibrinogen, D-dimer, ferritin, lactic acid dehydrogenase [LDH], or interleukin 6 [IL-6]), and
  - Evidence of clinically severe hospitalized illness among children aged <21 years with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological), and
  - One of the following:
    (1) SARS-CoV-2 positive RT-PCR test
    (2) SARS-CoV-2 positive antibody test
    (3) SARS-CoV-2 negative RT-PCR and antibody tests but with identified COVID exposure within the four weeks prior to the onset of symptoms.

Data of the studied cohort were extracted from inpatient files and reports. The data were revised and completed by attending physicians in the Pediatric and Adolescent Diabetes Unit, Children's Hospital, Ain Shams University.

The clinical characteristics variables evaluated in the studied cohort included time between symptoms' onset and hospital admission, history of contact with confirmed cases of COVID-19, presence of fever, and respiratory symptoms. For patients presenting in DKA, the following variables were considered initial pH and HCO3 level, total duration on an insulin drip, the time to closure of anion gap, and the presence of persistent metabolic acidosis. Manifestations of multisystem affection were evaluated thoroughly with a special emphasis on cardiovascular involvement, renal, central nervous system, thromboembolic, and mucocutaneous manifestations. The following was used to define cardiovascular involvement and included the need for vasopressor support, the presence of any evidence of pulmonary edema or manifestations of cardiac arrhythmia. Echocardiographic changes and elevated cardiac troponins as well were included. Echocardiographic changes included ejection fraction of less than 55%, maximum z score of right coronary artery of at least 2.5, pericarditis or pericardial effusion, or evidence of valve affection [14, 15]. Acute kidney injury (AKI) was defined if creatinine level was elevated above the following values: infants: 0.6 mg/dL, 1–10 years: 1.05 mg/dL and in children ≥11 years: >1.5 mg/dL [14, 15].

The laboratory data were extracted from medical files and admission laboratory records. The evaluated variables included random blood sugar on admission, HbA1c, kidney function test, and electrolytes including serum creatinine, BUN, potassium, sodium, and phosphorus, liver function tests including ALT, AST, and serum albumin, acute phase reactant including CRP, LDH, ferritin, and D-dimer. Laboratory records of blood pictures were reviewed with special emphasis on lymphocyte count and neutrophil count as well. Cardiac troponin was done for patients with a/the manifestation of cardiovascular affection and IL-6 was done for selected patients. Chest X-ray and CT chest were done for suspected cases and confirmed positive case. For all suspected cases, the SARS-CoV-2 PCR test was done to confirm positive cases. COVID-19 antibody testing (IgG and IgM) was done if patients showed a highly suspected picture in spite of a negative PCR testing. Antibodies were done as well when MIS-C was suspected.

The following outcome measures were evaluated and included data about the total duration of hospital stay, the need for ICU admission and subsequent management, total stay at ICU, total daily dose of insulin during the hospital stay, on discharge, and outcome of patients.

Statistical analysis

Analysis of data was done using Statistical Program for Social Science version 23 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean, SD, median and inter-quartile range (IQR), and qualitative variables were described as number and percent. Comparison of nonparametric variables was carried out using Mann–Whitney tests. Categorical variables were compared using the Chi-square (X^2) test. The one-way analysis of variance was used to determine whether there are any statistically significant differences between the means of three or more independent groups. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, a Spearman correlation test was performed. Logistic regression analysis was performed by estimating the Odds ratio (OR) and 95% confidence interval (CI) to define independent variables for ICU admission. A *p*-value <0.05 was considered significant in all analyses.

Results

Thirty-six patients with type 1 diabetes were admitted during the study period. The clinical and demographic data of the studied cohort is highlighted in Table 1. The age of the patients ranged from 2–15 years with a mean age of 8.4 ± 3.8 years, with male predominance (52.8%). Thirty-four patients (94.4%) presented in DKA, 50% presented in severe DKA with pH < 7.1. The median duration of hospital admission was 3 days (IQR 2–10).

All patients presented late to the emergency department with a mean delay of 3.05 ± 1.19 days from the onset of symptoms. The delay to hospital admission was found to be negatively correlated with patients' pH at presentation (r=−0.54, p=0.001) (Figure 1).

Twenty-nine patients (80.6%) were newly diagnosed. All presented in DKA except one female patient that presented in hyperglycemia with mild to moderate ketonuria. The mean HbA_{1c} was 11.7 ± 2.4%, the mean time to hospital admission from the onset of symptoms was 3.21 ± 1.2 days. In patients with DKA, the median time needed for resolution of DKA with the closure of anion gap was 24 h (IQR 12–48). Almost 55% of newly diagnosed patients were admitted to ICU and 13 patients (44.8%) required circulatory support. AKI and echocardiographic changes were reported in seven (24.1%) and eight patients (27.6%) respectively. Seven patients (24.1%) had persistent metabolic acidosis with AKI and cardiac involvement with impaired contractility requiring circulatory support (Table 1).

Seven patients (19.4%) were known cases of type 1 diabetes. The mean age was 9.29 ± 3.25 years with female predominance (57.1%). The mean disease duration was 2.29 ± 1.38 years, all patients were poorly controlled with an average HbA_{1c} of 11.1 ± 1.1% and none of the patients had neither associated comorbidities nor any diabetes-related complications. Like newly diagnosed patients, patients presented late to the hospital with a mean delay to hospital admission from the onset of symptoms of 2.43 ± 0.98 days. Six patients presented in DKA and these patients spent a median of 12 h (IQR 12–24 h) on an insulin drip. Three known patients required ICU admission with respiratory and circulatory support (Table 1).

Nineteen patients (52.8%) required ICU admission, clinical and laboratory characteristics of the patients admitted to ICU were mapped and compared with patients not requiring ICU admission and is highlighted in Table 2. Almost 42% of patients admitted to ICU required respiratory support either due to respiratory distress or due to persistent metabolic acidosis with impaired cardiac contractility.

Regression analysis to identify determinants of ICU admission showed that the presence of respiratory symptoms and the need for supplemental oxygen therapy were significantly associated with ICU admission. Furthermore, the following laboratory characteristic (pH at presentation ≤ 7.1, HCO3 ≤ 8.3 mmol/L, serum albumin < 3 g/dL, CRP > 15 mg/L, lactate dehydrogenase (LDH) > 181 IU/L, and D-dimer > 0.3 μg/mL) were significantly associated with ICU admission as well. The time needed for resolution of DKA and closure of anion gap significantly attributed to the need for ICU admission (Table 3). All patients with AKI were admitted to ICU, all showed significantly lower pH at presentation, HCO3 level, and serum albumin level (p<0.05) (Figure 2).

Subset analysis of patients with positive PCR is highlighted in Table 4. All four cases were symptomatic presenting with persistent fever and either respiratory symptoms (three cases) or gastrointestinal symptoms (one case). Two of the newly diagnosed cases, with positive SARS-CoV-2 PCR, had a history of contact with confirmed cases. Three of the four cases were newly diagnosed patients presenting in DKA, the fourth patient is a known case that presented with hyperglycemia and mild to moderated ketonuria. Baseline laboratory characteristics of patients with positive PCR showed significantly lower lymphocyte counts and higher ferritin levels compared to patients with negative PCR (p<0.05). All required ICU admission with a median of 4 days (IQR 1–14), the median duration on insulin drip was 48 h (24–72). Two patients had elevated D-dimer

Table 1: Clinical and laboratory characteristics of the studied cohort.

	All studied patients No. = 36	Known cases with 1 diabetes No. = 7	Newly diagnosed cases No. = 29	p-Value[d]
Gender Female	17 (47.2%)	3 (42.9%)	14 (48.3%)	0.797
Male	19 (52.8%)	4 (57.1%)	15 (51.7%)	
Age (mean ± SD)	8.4 ± 3.8	9.29 ± 3.25	8.14 ± 3.99	0.486
Duration of diabetes (mean ± SD)		2.29 ± 1.38		
DKA on first presentation n, %	34 (94.4%)	6 (85.7%)	28 (96.6%)	0.261
Severe DKA n, %	18 (50%)	2 (28.6%)	16 (55.2%)	0.206
Associated comorbidities n, %	1 (2.8%)	0 (0.0%)	1 (3.4%)	0.618
Time to hospital admission/days[a] (mean ± SD)	3.05 ± 1.19	2.43 ± 0.98	3.21 ± 1.21	0.123
Contact with confirmed cases n, %	4 (11%)	1 (14.3%)	3 (10.3%)	0.766
Fever n, %	13 (36.1%)	2 (28.6%)	11 (37.9%)	0.643
Disturbed conscious n, %	18 (50%)	3 (42.9%)	15 (51.7%)	0.673
Nausea/vomiting n, %	14 (38.9%)	4 (57.1%)	10 (34.5%)	0.269
Abdominal pain n, %	10 (27.8%)	2 (28.6%)	8 (27.6%)	0.958
Hepatitis n, %	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
CNS affection n, %	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Skin rashes n, %	1 (2.8%)	1 (14.3%)	0 (0.0%)	0.039
Musculoskeletal affection n, %	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Respiratory symptoms n, %	8 (22.2%)	3 (42.9%)	5 (17.2%)	0.143
Supplemental O2 n, %	19 (52.8%)	3 (42.9%)	16 (55.2%)	0.558
Respiratory support n, %	8 (22.2%)	1 (14.3%)	7 (24.1%)	0.574
Cardiac affection n, %	10 (27.8%)	2 (28.6%)	8 (27.6%)	0.958
Need for inotropes n, %	16 (44.4%)	3 (42.9%)	13 (44.8%)	0.925
Arrhythmia n, %	1 (2.8%)	0 (0.0%)	1 (3.4%)	0.618
Acute kidney injury n, %	9 (25%)	2 (28.6%)	7 (24.1%)	0.808
HbA_{1C}, % (IFCC) (mean ± SD)	11.6 ± 2.2 (103 ± 1)	11.1 ± 1.1 (98)	11.7 ± 2.4 (104 ± 3)	0.534
PH at presentation (mean ± SD)	7.09 ± 0.12	7.12 ± 0.11	7.08 ± 0.11	0.39
PCO2, mmHg (mean ± SD)	22 ± 4.94	22.63 ± 4.88	21.54 ± 4.87	0.619
HCO3, mmol/L (mean ± SD)	8.96 ± 3.73	8.90 ± 3.41	8.53 ± 3.02	0.789
Creatinine, mg/dL (median [IQR])	0.7 (0.6–1)	0.7 (0.6–1.6)	0.7 (0.6–1)	0.488
BUN, mg/dL (median [IQR])	14 (11–24)	13 (12–17)	15 (11–23)	0.703
Sodium, mmol/L (mean ± SD)	134.44 ± 5.33	134.86 ± 5.96	134.34 ± 5.27	0.823
Potassium, mmol/L (mean ± SD)	3.71 ± 0.8	4.26 ± 1.13	3.57 ± 0.64	0.038
Phosphorus, mg dL (mean ± SD)	2.52 ± 1.02	3.03 ± 1.23	2.40 ± 0.95	0.144
Magnesium, mg/dL (mean ± SD)	1.91 ± 0.31	2.07 ± 0.18	1.87 ± 0.32	0.123

Table 1: (continued)

	All studied patients No. = 36	Known cases with 1 diabetes No. = 7	Newly diagnosed cases No. = 29	p-Value[d]
ALT, IU/L (median [IQR])	15 (14–24)	16 (11–21)	20 (14–31)	0.118
AST, IU/L (median [IQR])	35 (23–45)	29 (16–36)	39 (29–45)	0.144
S. Albumin, g/dL (mean ± SD)	3.5 ± 0.63	3.47 ± 0.74	3.52 ± 0.64	0.869
C-reactive protein, mg/L (median [IQR])	12 (4–39)	20 (5–40)	11 (4–28)	0.254
LDH, IU/L (median [IQR])	185 (167–544)	300 (170–544)	181 (161–305)	0.379
Ferritin, ng/mL (median [IQR])	99 (46–256)	78 (45–213)	110 (56–256)	0.412
D-dimer, ug/mL (median [IQR])	0.25 (0.023–0.5)	0.27 (0.23–0.56)	0.2 (0.02–0.41)	0.496
WBC (median [IQR])	10.2 (6.6–14.8)	11 (9.9–15.1)	10 (6.1–13.7)	0.298
Lymphocyte count. (median [IQR])	2.2 (2–3.9)	3.3 (1.9–8.1)	2.1 (2.04–3.3)	0.470
ANC (median [IQR])	6.85 (3.9–13)	7.9 (4.2–13.8)	6.6 (3.9–8.7)	0.617
HB, g/dL (mean ± SD)	11.93 ± 1.35	11.41 ± 1.32	12.05 ± 1.36	0.270
PLT (mean ± SD)	307.97 ± 132.52	363.43 ± 168.22	294.59 ± 122.20	0.222
Troponin-I, ng/mL (median [IQR])	0.02 (0.001–0.035)	0.028 (0.001–0.459)	0.015 (0.001–0.04)	0.747
SARS-CoV-2 PCR n, %	4 (11%)	1 (14.3%)	3 (10.3%)	0.766
SARS-CoV-2 antibody (Ig G) n, %	4 (11%)	0 (0.0%)	4 (13.8%)	0.973
SARS-CoV-2 antibody (Ig M) n, %	2 (5.6%)	0 (0.0%)	2 (6.9%)	0.475
Chest imaging[b] n, %	7 (19.4%)	2 (28.6%)	5 (17.2%)	0.497
Need for anti-coagulation n, %	6 (17%)	1 (14.3%)	5 (17.2%)	0.851
Need for supplemental treatment[c]	5 (13.9%)	2 (28.6%)	3(10.3%)	0.143
ICU admission n, %	19 (52.8%)	3 (42.9%)	16 (55.2)%	0.558
Total duration on insulin drip (HRS) (median [IQR])	24 (12–48)	12 (12–24)	24 (12–48)	0.460
Duration at ICU, days (median [IQR])	3 (1–7)	4 (1–4)	2.5 (1–7)	0.953
Total duration at hospital, days (median [IQR])	3 (2–10)	2 (1–7)	3 (2–8)	0.322
Total daily dose of insulin at ICU, unit/kg/day Mean ± SD	1.67 ± 0.26	1.27 ± 0.38	1.4 ± 0.61	0.577
Total daily dose of insulin at discharge, unit/kg/day Mean ± SD	1.1 ± 0.21	0.97 ± 0.23	1.1 ± 0.46	0.349

BUN, blood urea nitrogen; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, lactate dehydrogenase; WBC, White blood cell; ANC, Absolute neutrophil count; HB, Hemoglobin concentration; PLT, platelet; CT, computed tomography. [a]Symptoms included either fever, vomiting and/or respiratory complains. [b]Chest findings: Ground-glass opacity on either chest X-ray (radiograph) or lung CT imaging. CO-RADS score 4 or 5. [c]Supplemental treatment included: methylprednisolone, intravenous immunoglobulin. [d]p-value = difference between patients with known cases with type 1 diabetes and newly diagnosed patients.

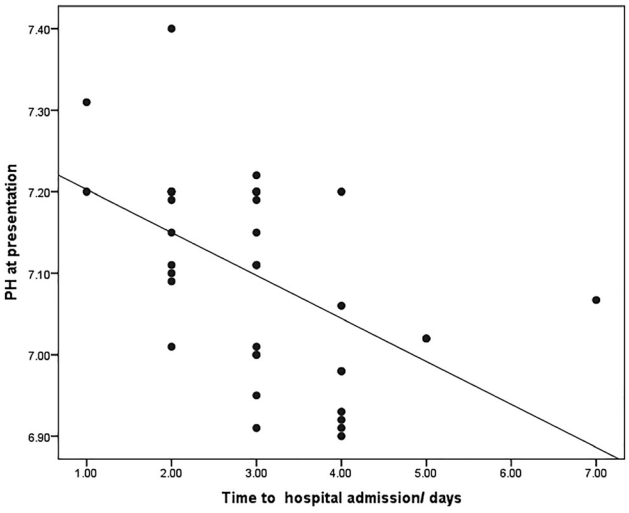

Figure 1: Correlation between time to hospital admission and patients' pH at initial presentation. A significant negative correlation was noticed between patients' pH at presentation and time delayed to hospital admission from onset of symptoms (r=−0.54, p=0.001).

that required anticoagulation and all patients required circulatory and ventilatory support as well. All patients presenting with respiratory complaints, showed significant radiological findings consistent with pulmonary COVID affection.

Two patients had positive COVID Ig M antibodies, antibody testing was done in these patients because, in spite of a negative PCR, patients were highly suspected with a history of contact with a confirmed case and both cases were newly diagnosed presenting in DKA. Both presented critically shocked with severe metabolic acidosis and respiratory distress requiring ICU admission and circulatory support. One of the two cases showed CT chest findings consistent with COVID pulmonary affection (Table 4).

COVID Ig G antibodies were positive in four cases and all were newly diagnosed, three of the four cases were presented with an MSI-C-like picture with a negative PCR, so antibody testing was done to complete the criteria for diagnosis. The fourth case with positive antibody testing gave a history of hospital admission for appendectomy 15 days before the onset of DKA.

Four of the studied cohort (11%) showed a picture suggestive of MIS-C. All had a persistent fever lasting ≥24 h associated with laboratory evidence of inflammation (elevated CRP), D-dimer, ferritin, LDH. All were critically ill requiring ICU admission with multisystem involvement with evidence of SARS-CoV-2 infection either a positive PCR or positive antibody testing. The clinical and laboratory characteristics of patients with MIS-C are illustrated in Supplementary Table 1.

Three out of four patients with MSI-C were newly diagnosed, all presenting in DKA. All the patients required ventilatory and circulatory support as well as anticoagulation. The four patients had cardiovascular involvement either in the form of valve affection, pericardial effusion, or impaired systolic function, besides the previous changes, one patient had bright coronaries with dilated left main coronary artery. Cardiac troponin was elevated in all patients. Renal affection reported in the patients was in the form of elevated serum creatinine. Besides elevating serum creatinine levels, one patient showed persistent metabolic acidosis requiring maintenance bicarbonate associated with low-grade proteinuria. One of the patients, a known case of type 1 diabetes, had cutaneous affection in the form of skin rash involving both hands and feet. All patients required adjuvant treatment with intravenous methylprednisolone and intravenous immunoglobulin was given to two patients (Supplementary Table 1).

Discussion

Although reports showed that children with well-controlled diabetes do not appear to have an increased risk of infection with SARS-CoV-2 [7], however, data are scarce regarding the extent to which patients' clinical phenotype could modify the severity and the outcome of the disease.

The current surveillance study highlighted the apparent cluster of newly diagnosed cases with diabetes that presented late in severe DKA. Four patients were positive for SARS-CoV-2 PCR, SARS-CoV-2 Ig M was positive in another two patients. All patients were symptomatic requiring ICU admission. This data is consistent with previous findings highlighting the impact of the pandemic on both diagnosis of type 1 diabetes and its acute complications with increased frequency of patients presenting in severe DKA [8–10, 16].

Efforts done to fight the overwhelming pandemic have significantly burdened health services systems with services focusing on COVID-19. Besides the huge burden, patients are afraid of contracting the infection from hospital settings. Similar to an anecdotal report from different countries, it was noticeable that patients in the current study were arriving late to the emergency department with a spectrum of severe and challenging clinical presentations of DKA [9, 16, 17].

Similar to data from the current surveillance study, reports from two multicenter studies showed high rates of DKA at presentation among newly diagnosed patients. Beliard et al. reported that the high incidence of DKA was independent of the viral infection and they postulated that

Table 2: Phenotypic features and laboratory parameters of patients requiring ICU admission and patients not requiring ICU admission.

		No ICU admission No. = 17	ICU admission No. = 19	p-Value
Age	Mean ± SD	9.12 ± 3.24	7.68 ± 4.28	0.270
Gender	Female	9 (52.9%)	8 (42.1%)	0.516
	Male	8 (47.1%)	11 (57.9%)	
Known patients with type 1 diabetes n, %		4 (57.1%)	3 (42.9%)	0.558
Newly diagnosed n, %		13 (76.5%)	16 (84.2%)	0.558
DKA on first presentation n, %		16 (94.1%)	18 (94.7%)	0.935
Time to hospital admission/days (mean ± SD)		2.71 ± 1.36	3.37 ± 0.96	0.097
Respiratory symptoms n, %		1 (5.9%)	17 (89.5%)	0.000
Supplemental O2 n, %		1 (5.9%)	18 (94.7%)	0.000
Respiratory support n, %		0 (0.0%)	8 (42.1%)	0.002
Cardiac affection n, %		0 (0.0%)	10 (52.6%)	0.000
Need for inotropes n, %		0 (0.0%)	16 (84.2%)	0.000
Arrhythmia n, %		0 (0.0%)	1 (5.3%)	0.337
Acute kidney injury n, %		0 (0.0%)	9 (47.4%)	0.001
HbA_{1C}, % (IFCC) (mean ± SD)		12.0 ± 1.2 (108)	11.2 ± 2.8 (99 ± 7)	0.248
PH at presentation (mean ± SD)		7.17 ± 0.07	7.01 ± 0.09	0.000
HCO3, mmol/L (mean ± SD)		10.40 ± 3.02	6.88 ± 1.88	0.000
Creatinine, mg/dL (mean ± SD)		0.68 ± 0.142	1.17 ± 0.899	0.034
BUN, mg/dL (median [IQR])		13 (11–16)	19 (12–26)	0.075
Sodium, mmol/L (mean ± SD)		133.65 ± 4.94	135.16 ± 5.69	0.403
Potassium, mmol/L (mean ± SD)		3.75 ± 0.62	3.66 ± 0.93	0.739
Phosphorus, mg/dL (mean ± SD)		2.84 ± 0.76	2.24 ± 1.16	0.079
Magnesium, mg/dL (mean ± SD)		1.99 ± 0.31	1.84 ± 0.30	0.146
ALT, IU/L (median [IQR])		16 (14–21)	21 (13–32)	0.221
AST, IU/L (median [IQR])		32 (29–39)	42 (18–55)	0.303
S. Albumin, g/dL (mean ± SD)		3.92 ± 0.26	3.14 ± 0.67	0.000
C-reactive protein, mg/L (median [IQR])		6 (4–12)	22 (6–42)	0.017
LDH, IU/L (median [IQR])		167 (159–178)	300 (198–678)	0.000
Ferritin, ng/mL (median [IQR])		57 (46–78)	213 (108–321)	0.001
D-dimer, ug/mL (median [IQR])		0.12 (0.01–0.27)	0.37 (0.1–1.5)	0.002
WBC (median [IQR])		9.2 (6.6–13)	10.3 (7.1–15.1)	0.234
Lymphocyte count. (Median [IQR])		2.4 (2.1–3.3)	2.1 (1.6–3.9)	0.259
ANC (median [IQR])		5 (3.4–8.2)	7.2 (5.9–14.5)	0.076
HB, g/dL (mean ± SD)		12.23 ± 1.23	11.66 ± 1.44	0.211
PLT (mean ± SD)		285.12 ± 90.60	328.42 ± 160.98	0.335
Troponin-I, ng/mL (median [IQR])		0.0105 (0.001–0.02)	0.02 (0.001–0.3)	0.446
SARS-CoV-2 PCR n, %		0 (0%)	4 (21.1%)	0.045
SARS-CoV-2 antibody (Ig G) n, %		0 (0%)	4 (21.1%)	0.045
SARS-CoV-2 antibody (Ig M) n, %		0 (0%)	2 (10.5%)	0.169
Chest imaging[a] n, %		0 (0%)	7 (36.8%)	0.005
Need for anticoagulation n, %		0 (0.0%)	6 (31.6%)	0.011
Need for supplemental treatment[b] n, %		0 (0.0%)	5 (26.3%)	0.022
Total duration on insulin drip, hours Median (IQR)		12 (12–24)	48 (24–48)	0.000
Duration at ICU, days (median [IQR])		–	3 (1–7)	–
Total duration at hospital (median [IQR])		2 (2–3)	7 (3–11)	0.001
MIS-C n, %		0 (0.0%)	4 (21.1%)	0.045

BUN, blood urea nitrogen; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, lactate dehydrogenase; WBC, White blood cell; ANC, Absolute neutrophil count; HB, Hemoglobin concentration; PLT, platelet; MIS-C, multi-inflammatory syndrome in children; CT, computed tomography. [a]Chest findings: Ground-glass opacity on either chest X-ray (radiograph) or lung CT imaging. CO-RADS score 4 or 5. [b]Supplemental treatment included: methylprednisolone, intravenous immunoglobulin.

Table 3: Logistic regression analysis for factors associated with ICU admission.

	B	S.E.	Wald	p-Value	Odds ratio (OR)	95% C.I. for OR	
						Lower	Upper
Respiratory symptoms	4.913	1.273	14.885	**0.000**	136.000	11.212	1,649.620
Supplemental O2	5.663	1.455	15.141	**0.000**	288.000	16.619	4,991.053
Severe DKA	3.961	1.178	11.302	**0.001**	52.500	5.215	528.474
pH at presentation ≤7.1							
HCO3 ≤8.3	2.788	0.853	10.694	**0.001**	16.250	3.056	86.414
S.Albumin <3	3.802	1.155	10.838	**0.001**	44.800	4.658	430.904
C-reactive protein >15	2.079	0.794	6.853	**0.009**	8.000	1.686	37.951
LDH >181	3.689	0.981	14.138	**0.000**	40.000	5.848	273.621
D-dimer >0.3	2.554	0.890	8.226	**0.004**	12.857	2.245	73.634
Total duration on insulin drip, hours >12	3.091	0.950	10.576	**0.001**	22.000	3.415	141.733

LDH, Lactate dehydrogenase; DKA, Diabetic ketoacidosis. Bold values indicate the significant values.

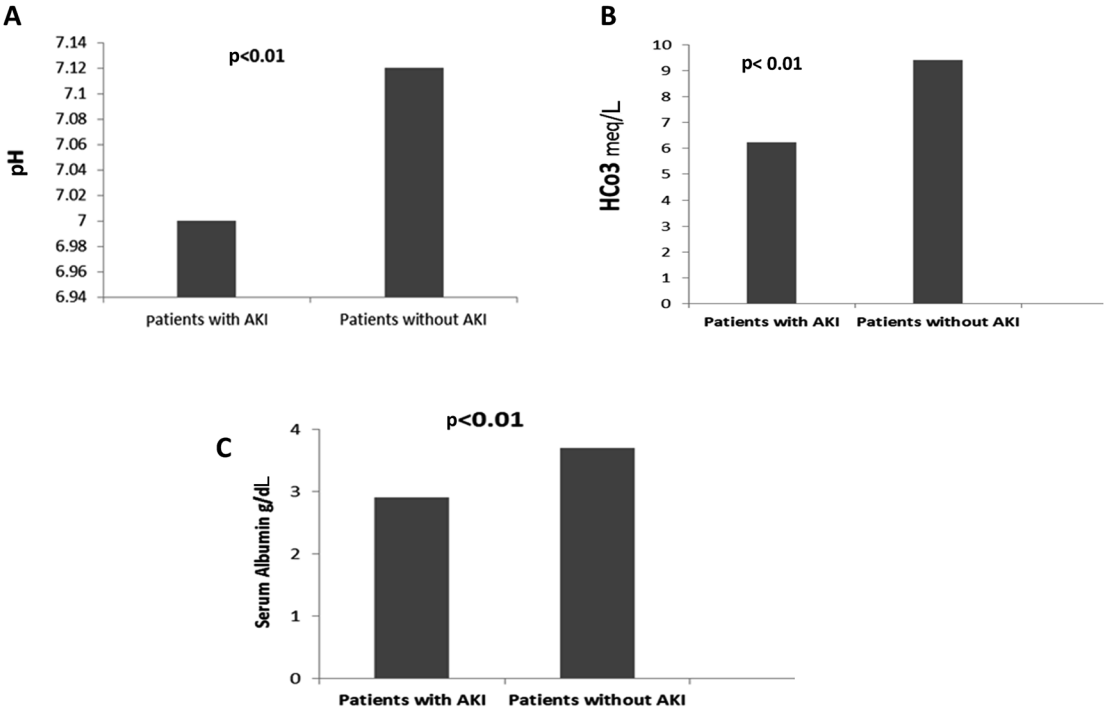

Figure 2: PH level, bicarbonate and serum albumin levels among both patients presenting with AKI and those not presenting with AKI. All patients with AKI were admitted to ICU, all showed significantly lower pH at presentation, HCO3 level, and serum albumin level (p<0.05).

patients' late presentation with DKA was mainly contributed to the reduction of hospital and health care visits [18]. However, Unsworth and his colleagues didn't notice a delay in patients' presentation and attributed that severe presentation of type 1 diabetes could be due to prior SARS-CoV-2 exposure [10].

The link between COVID-19 and diabetes remains controversial and whether diabetes itself indeed increases the susceptibility of infection or COVID-19 infection alters the subsequent risk of new-onset diabetes remains the main question [19].

The interplay between SARS-CoV-2 and the endocrine pancreas needs more detailed studies to delineate the possible risk of development of new-onset diabetes. The effect of SARS-CoV-2 on the pancreatic angiotensin system and islet-cells could provide a novel insight into the pathophysiology of diabetes. Besides being highly expressed in the lungs, angiotensin-converting enzyme 2 (ACE2) is

Table 4: Clinical and laboratory characteristics of patients with diabetes with/without evidence of COVID-19 infection.

		Evidence of COVID-19 Infection[c] No. = 10	No evidence of COVID-19 Infection No. = 26	p-Value
Age (mean ± SD)		9.18 ± 3.97	8.00 ± 3.81	0.403
Gender	Female	6 (60.0%)	12 (46.2%)	0.556
	Male	4 (40.0%)	14 (53.8%)	
Known patients with type 1 diabetes **n, %**		1 (10.0%)	6 (23.0%)	0.899
Newly diagnosed **n, %**		9 (90.0%)	20 (77.0%)	0.539
Time to hospital admission/days[a] (Mean ± SD)		3.27 ± 0.90	2.96 ± 1.31	0.477
Contact with confirmed cases **n, %**		4 (40.0%)	0 (0%)	0.001
Fever **n, %**		10 (100%)	3 (11.5%)	<0.001
Disturbed conscious **n, %**		9 (90.0%)	9 (34.6%)	0.002
Nausea/vomiting **n, % 14**		4 (40.0%)	10 (38.5%)	0.933
Pancreatitis/Hepatitis **n, %**		0 (0.0%)	0 (0.0%)	NA
CNS affection **n, %**		0 (0.0%)	0 (0.0%)	NA
Skin rashes **n, %**		1 (10.0%)	0 (0.0%)	0.101
Musculoskeletal affection **n, %**		0 (0.0%)	0 (0.0%)	NA
Respiratory symptoms **n, %**		8 (80.0%)	0 (0.0%)	<0.001
Supplemental O2 **n, %**		10 (100%)	9 (34.6%)	0.001
Respiratory support **n, %**		8 (80.0%)	0 (0.0%)	<0.001
Cardiac affection **n, %**		9 (90.0%)	1 (3.8%)	<0.001
Need for inotropes **n, %**		12 (37.5%)	4 (100%)	<0.001
Arrhythmia **n, %**		1 (10.0%)	0 (0.0%)	0.101
Acute kidney injury **n, %**		6 (60.0%)	3 (11.5%)	0.002
HbA_{1C} % (IFCC) (mean ± SD)		10.96 ± 3.65	11.87 ± 1.02	0.253
PH at presentation (mean ± SD)		7.02 ± 0.09	7.11 ± 0.11	0.027
HCO3, mmol/L (mean ± SD)		7.28 ± 1.86	9.12 ± 3.28	0.107
Creatinine, mg/dL (median [IQR])		0.7 (0.6–1.8)	0.7 (0.6–0.8)	0.293
Sodium, mmol/L (mean ± SD)		135.64 ± 5.48	133.92 ± 5.28	0.381
Potassium, mmol/L (mean ± SD)		3.78 ± 1.17	3.67 ± 0.58	0.707
Phosphorus, mg/dL (mean ± SD)		2.60 ± 1.19	2.48 ± 0.96	0.759
Magnesium, mg/dL (mean ± SD)		1.90 ± 0.37	1.91 ± 0.29	0.917
ALT, IU/L (median [IQR])		23 (15–34)	16 (13–22)	0.091
AST, IU/L (median [IQR])		41 (29–78)	35 (21–44)	0.130
S. Albumin, g/dL (mean ± SD)		3.01 ± 0.79	3.72 ± 0.46	0.002
C-reactive protein, mg/L (median [IQR])		78 (16–112)	11 (4–20)	0.016
LDH, IU/L (median [IQR])		570 (295–757)	178 (161–198)	0.001
Ferritin, ng/mL (median [IQR])		273 (121–468)	60 (45–110)	<0.001
D-dimer, ug/mL (median [IQR])		0.41 (0.31–3.9)	0.12 (0.02–0.27)	0.001
WBC (median [IQR])		10 (6.1–11)	10.3 (7.4–14.8)	0.429
Lymphocyte count (Median [IQR])		1.1 (0.89–2.3)	2.8 (2.1–3.8)	0.030
ANC (median [IQR])		6.9 (5.07–13)	6.8 (3.9–8.9)	0.744
HB, g/dL (mean ± SD)		11.37 ± 1.68	12.17 ± 1.14	0.104
PLT (mean ± SD)		309.91 ± 189.41	307.12 ± 103.24	0.955
Troponin-I, ng/mL (median [IQR])		0.04 (0.01–0.459)	0.0035 (0.001–0.02)	0.049
Total duration on insulin drip, hours (median [IQR])		48 (24–72)	12 (12–24)	0.006
Chest imaging n, %		7 (70%)	0 (0.0%)	<0.001
Need for anticoagulation n, %		6 (60.0%)	0 (0.0%)	<0.001

Table 4: (continued)

	Evidence of COVID-19 Infection[c] No. = 10	No evidence of COVID-19 Infection No. = 26	p-Value
Need for supplemental treatment[b] n, %	6 (60%)	0 (0.0%)	<0.001
ICU admission n, %	10 (100%)	9 (34.6%)	<0.001
Total duration at hospital, days (Median [IQR])	7 (3–21)	3 (2–4)	0.013

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, lactate dehydrogenase; WBC, White blood cell; ANC, Absolute neutrophil count; HB, Hemoglobin concentration; PLT, platelet; CT, computed tomography. [a]Chest findings: Ground-glass opacity on either chest X-ray (radiograph) or lung CT imaging. CO-RADS score 4 or 5. [b]Supplemental treatment included: methylprednisolone, intravenous immunoglobulin. [c]Evidence of COVID-19 infection either by a positive SARS-CoV-2 PCR or antibody testing.

expressed as well in the pancreas and could serve as an entry point for SARS-CoV-2 that could potentiate beta-cell injury [20].

Elevated levels of angiotensin II in COVID-19 patients could decrease blood flow to beta-cells delaying insulin secretion and may induce a local inflammatory reaction decreasing beta-cell proliferation and causing apoptosis [21]. Furthermore, cytokine release and T cell activation induced by viral infection could trigger the development of type 1 diabetes in genetically predisposed individuals [22].

Although well-controlled patients with type 1 diabetes don't show an increased risk of infection, however, special consideration should be directed to patients with poor glycemic control who are at increased risk of infection in general because of the defective immune systems [7, 19]. Studies showed that poor glycemic control or hyperglycemia are associated with increased risk of COVID-19 complications in patients with diabetes [23].

The pandemic significantly impacted the spectrum of clinical presentations of DKA among the studied cohort. Nineteen patients (58.6%) showed a spectrum of challenging presentation with persistent metabolic acidosis, AKI, and/or cardiac involvement which required ICU admission.

A strong association between the severity of acidosis and the risk for severe AKI in DKA was defined. A serum bicarbonate level below 10 mEq/L on presentation was found to be associated with a five-fold increased risk for the development of AKI and this could be due to renal vasoconstriction induced by the severe acidosis [24].

AKI has been reported in up to 25% of critically-ill patients with SARS-CoV-2 infection, especially those with associated comorbidities. Besides several nonspecific mechanisms of AKI in critically – ill patients, the pathophysiology of COVID-19 associated kidney injury could include a direct viral injury, an imbalanced renin-angiotensin-aldosterone system with the accumulation of angiotensin II, or elevated levels of pro-inflammatory cytokines and procoagulants [25].

Few reports have addressed the incidence of myocardial dysfunction in DKA, especially among children. The exact mechanism remains unclearly understood, however multiple theories have been postulated [26].

Acidosis and electrolyte abnormalities could contribute to cardiac contractile dysfunction [27, 28]. Another theory postulated that severe DKA could initiate the synthesis of autoantibodies to cardiac antigens, which can lead to the development of cardiomyopathy [29].

The possibility of infectious myocarditis couldn't be ruled out. In the era of COVID-19, the possible effect and association of SARS-CoV-2 should be always questioned. Studies highlighted that SARS-CoV-2 induced cardiac damage could be due to direct myocardial cells injury, myocardial oxygen supply/demand mismatch or it could a part of a systemic inflammatory response of severe COVID-19 disease [30, 31].

On May 14, an online Health Advisory was released by the Centers for Disease Control and Prevention (CDC) addressing the hyper-inflammatory syndrome associated with COVID-19 infection and they outlined a case definition of MIS-C [15].

There are few reports of COVID-19 post-inflammatory response in children with type 1 diabetes [32, 33]. Interestingly in the current study, four patients presented with a picture consistent with MIS-C.

Naguib et al. reported a child presenting with both MIS-C and new-onset diabetes mellitus. Another case was reported in a Saudi child, a known case of type 1 diabetes, presenting with MIS-C and evidence of COVID-19 infection [32, 33].

Patients with MIS-C in the current study had at least two organs affection. Cardiac affection was a constant feature in the four cases, and this is in accordance with data from previous studies showing that cardiac involvement is a primary determinant of MIS-C involving 80–85% of cases [14, 34, 35]. Similar to previous reports, the spectrum of cardiac findings included impaired contractility, valvular affection, pericardial effusion, coronary affection, and elevated cardiac troponins [14, 35, 36].

Early identification of patients at risk of complications would be an important step for better management during the clinical course of DKA and hence reducing the morbidity. Early screening of cardiac function and AKI in cases of severe DKA may be warranted.

The main limitation of the current study is the small sample size and the retrospective nature of the study. Another important limitation of the current study is the absence of comparative data regarding patients' presentation at the same time in previous years. More detailed multicenter studies are required to better map the clinical and laboratory characteristics of COVID-19 in Egyptian pediatric patients with type 1 diabetes. Furthermore, studies on larger scales are required to better understand the possible link between COVID-19 and the endocrine pancreas.

Conclusion

The clinical and laboratory characteristics of patients with type 1 diabetes at the onset of presentation significantly impact the patients' outcomes and strongly influence their management. The increased prevalence of severe DKA nowadays, whether partly related to delayed hospital admission or related to the effect of COVID-19 in exacerbating and/or triggering DKA, possess a real challenge in managing patients; a challenge that requires special considerations when evaluating the differential diagnoses and management protocols of patients. Efforts should be done to continuously raise awareness about diabetes in children as well as the importance of seeking timely medical guidance.

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