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Comparing Clinical COVID-19 Outcomes in Hospitalized Children with and without Type 1 Diabetes: A Retrospective Cohort Study in Iran

Fatemeh Sarv[1], Seyedmohammad Mousavi[1], Abbas Habibollahi[1], Mehdi Vafadar[2], Vahid Saeedi[3]*, Fahimeh Ehsanipour[3], Leila Kamalzadeh[4]

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Abstract

Background: Children with Type 1 Diabetes Mellitus (T1DM) may represent a clinically vulnerable subgroup during COVID-19. This study compared in-hospital clinical and paraclinical outcomes between children with and without pre-existing T1DM.

Methods: This hospital-based retrospective cohort study included 250 children and adolescents hospitalized with RT-PCR-confirmed COVID-19 at two tertiary centers in Tehran, Iran, during 2020–2021. Patients were classified at admission as having pre-existing T1DM (n = 82) or no diabetes (n = 168) and were followed until discharge or in-hospital death. Primary outcomes included early hypoxemia, abnormal chest CT findings, diabetic ketoacidosis (DKA), ICU admission, mechanical ventilation, length of stay, and in-hospital mortality. Multivariable logistic regression was used to estimate adjusted odds ratios (AORs).

Results: T1DM was associated with higher odds of early hypoxemia (SpO_2 <90% within 24 h; AOR 1.87, 95% CI 1.08–3.25) and abnormal chest CT findings (AOR 33.33, 95% CI 14.28–50.00; $P < 0.001$). DKA occurred in 13/82 children with T1DM (15.9%) and in none of the children without diabetes; this finding was interpreted descriptively because DKA is intrinsically diabetes-related. Mean hospital stay was longer in the T1DM group than in the non-diabetes group (6.78 ± 2.60 vs 5.90 ± 2.92 days; $P = 0.029$). ICU admission and mortality were numerically higher in the T1DM group, but estimates were imprecise, and confidence intervals included the null value.

Conclusion: Hospitalized children with pre-existing T1DM showed a pulmonary-metabolic profile marked by early hypoxemia, abnormal chest CT findings, DKA, and longer hospitalization, supporting close respiratory and metabolic monitoring during acute infection.

Keywords: COVID-19, Diabetes Mellitus Type 1, Child, Adolescent, Diabetic Ketoacidosis, Intensive Care Units

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Introduction

Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2, has had major global health impacts across all ages. Although children typically experience milder disease than adults, pediatric subgroups with chronic conditions such as Type 1 Diabetes (T1DM) may represent clinically vulnerable populations (1). T1DM is an autoimmune disorder characterized by insulin deficiency and chronic hyperglycemia, a condition that has been associated with impaired immune function, infections, and

Corresponding author: Dr Vahid Saeedi, Saeedi.va@iums.ac.ir

1. Department of Endocrinology, Hazrat Rasoul Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
2. Ali-Asghar Children's Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
3. Pediatric Growth and Development Research Center, Institute of Endocrinology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
4. Department of Psychiatry, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Key Messages:

↑What is "already known" in this topic:

Children with type 1 diabetes mellitus (T1DM) may be vulnerable to severe infectious outcomes. Pediatric COVID-19 studies suggest associations with hospitalization, ICU admission, and metabolic complications, but results vary, and comparative data from middle-income settings remain limited.

→What this article adds:

Among hospitalized children with COVID-19 in Iran, pre-existing T1DM was associated with early hypoxemia, abnormal chest CT findings, longer hospitalization, and diabetic ketoacidosis (DKA), while mortality was similar. These findings highlight a pulmonary-metabolic risk profile that may support clinical risk stratification and preparedness during future infectious outbreaks in similar pediatric populations and comparable settings.

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metabolic decompensation, particularly diabetic ketoacidosis (DKA) (2).

During the pandemic, several studies reported higher rates of hospitalization, ICU admission, and mortality in children with T1DM compared with peers without diabetes (3-5). Poor glycemic control was also associated with worse reported outcomes (6). Evidence also suggested a bidirectional relationship between COVID-19 and diabetes, whereby SARS-CoV-2 may worsen glycemic control and has been associated with new-onset diabetes (7, 8). In addition, socioeconomic and healthcare disparities, including limited access to diabetes technology and delayed presentation, were linked to higher DKA rates and worse outcomes, particularly in resource-limited settings (9).

Despite extensive research, findings remain inconsistent: some studies from the United States and Europe reported increased ICU admissions and greater severity among children with diabetes, whereas others found broadly comparable outcomes between children with and without diabetes, with most cases mild or asymptomatic (10, 11). These discrepancies underscore the need to clarify factors mediating disease severity. Moreover, analysis of early pandemic waves (2020–2021) remains informative because it reflects disease course before widespread vaccination and major therapeutic advances. These insights not only inform current clinical practice but also enhance preparedness for potential future pandemics.

In Iran, adult studies indicate diabetes increases COVID-19 complications and mortality (12). But pediatric comparative data, especially direct comparisons between hospitalized children with and without T1DM, are limited. Therefore, this study compared the clinical and laboratory characteristics of pediatric patients with and without T1DM hospitalized due to COVID-19 during 2020–2021, focusing on severe pulmonary and metabolic decompensation, including early hypoxemia, abnormal chest CT findings, and DKA.

Methods

Study design and setting

This hospital-based retrospective cohort study compared clinical and laboratory outcomes in children and adolescents hospitalized with laboratory-confirmed COVID-19, stratified by exposure status at admission: pre-existing T1DM versus no diabetes. The rationale for using a retrospective cohort design was that exposure status was documented before outcome occurrence, and patients were followed retrospectively through the index hospitalization from admission to discharge or in-hospital death. Data were collected from two tertiary teaching hospitals affiliated with Iran University of Medical Sciences (Rasoul Akram and Ali Asghar). All eligible admissions during the study period were included consecutively.

Study period and sample size rationale

Admissions from January 1, 2020, to December 31, 2021 (pre-Omicron waves) were analyzed to reflect care before widespread pediatric vaccination and to include the maximum number of eligible records. Because this was a retrospective record-based study, no a priori sample size calculation was performed before data collection; instead, all eligible consecutive admissions during the study period were included as a census sample (n=250; T1DM n=82; non-diabetes n=168). For transparency, we conducted a post hoc sensitivity power assessment. Using a two-sided alpha of 0.05, 80% power, and an approximately 1:2 allocation ratio (82 exposed and 168 unexposed patients), this sample size was sufficient to detect medium-to-large differences in binary outcomes, corresponding approximately to odds ratios of 2.5-3.0 when the baseline event rate in the non-diabetes group was assumed to be 10-20%. Therefore, analyses of uncommon outcomes such as mechanical ventilation and mortality were interpreted cautiously because the study was underpowered for small differences in rare events. Hospital site and calendar quarter of admission were included as covariates to address temporal and inter-site heterogeneity.

Participants and sampling

Consecutive sampling included all eligible pediatric inpatients from both hospitals. Groups were concurrent: T1DM (exposure-positive: documented pre-existing autoimmune T1DM in records before or at admission) and non-diabetes (exposure-negative: no prior diabetes history, supported by admission HbA1c when available; selected from the same admission pool without matching to minimize bias). Outcomes were evaluated only after the index admission and throughout the hospitalization period.

Eligible participants were children and adolescents aged 1-18 years who were hospitalized at the study sites with clinically compatible COVID-19 and laboratory confirmation. Clinical compatibility was defined as documentation by the treating team of an acute illness consistent with COVID-19, including respiratory symptoms or signs (such as fever, cough, sore throat, dyspnea, tachypnea, or hypoxemia), systemic or gastrointestinal manifestations (such as fatigue, myalgia, headache, vomiting, abdominal pain, or diarrhea), or chest imaging compatible with COVID-19. Laboratory confirmation required a positive RT-PCR from a nasopharyngeal swab obtained at admission or within 72 hours before admission. The T1DM group required a documented diagnosis of type 1 diabetes predating hospitalization, supported by prior endocrinology notes, problem lists, discharge summaries, insulin treatment history, or other hospital documentation. The non-diabetes group required no documented prior diabetes diagnosis, no pre-admission insulin or antidiabetic medication use, and no admission evidence suggesting pre-existing diabetes when HbA1c was available. Patients with type 2 diabetes, unclear diabetes type, or diabetes first diagnosed during the index COVID-19 episode were not classified as pre-existing T1DM for the main comparison. Exclusion criteria for both groups included discharge against medical advice; transfer from another hospital >48 hours after initial admission; major comorbidities (primary immunodeficiency, active malignancy, severe congenital cardiac/pulmonary disease, chronic kidney disease stage ≥3, or chronic liver disease); type 2 diabetes; and prior hospitalization for the same COVID-19 episode. Eligibility, exposure status, and exclusion criteria were assessed through review of documented

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hospital records, including admission notes, discharge summaries, prior diagnoses/problem lists, laboratory and imaging reports, and transfer documentation when applicable. Patient or parent history was used only insofar as it was recorded in the clinical chart by the treating team and was not treated as an independent self-report data source. Pediatric vaccination status was inconsistently recorded and was not analyzed; calendar quarter served as a partial proxy.

Follow-up and outcome ascertainment

Follow-up began at the index admission and ended at hospital discharge or in-hospital death for both cohorts. Follow-up time was therefore equivalent to length of stay, measured in days from admission to discharge or death. Outcomes were defined according to their ascertainment window: early outcomes were assessed within the first 24 hours of admission (SpO_2 <90%, abnormal chest CT, DKA, and laboratory values), whereas ICU admission, mechanical ventilation, length of stay, and in-hospital mortality were assessed over the entire index hospitalization.

Variables

Demographic variables

Age at admission (years) was calculated from the date of birth and admission date recorded in the hospital information system. Gender/sex was extracted from hospital registration records as documented at admission. Hospital site and calendar quarter of admission were derived from administrative admission data.

Medical history and exposure variables

The exposure variable was pre-existing T1DM versus no diabetes, defined at the index admission. T1DM status was verified from documented prior diagnosis in the medical record, endocrinology notes, insulin treatment history, and available admission laboratory data. Diabetes duration was calculated from the documented date or year of diagnosis to the admission date and recorded in years. The non-diabetes classification required absence of a documented diabetes diagnosis and absence of pre-admission insulin or antidiabetic medication use; admission HbA1c was used as supportive information when available. Previous history of DKA, major comorbidities specified in the exclusion criteria, transfer status, prior hospitalization for the same COVID-19 episode, and discharge against medical advice were abstracted from documented admission notes, discharge summaries, problem lists, laboratory/imaging reports, and transfer records when applicable. Body mass index (BMI) and comprehensive pre-admission medications (including outpatient steroids) were not consistently available.

Clinical outcome variables

ICU admission was recorded from ICU transfer or admission documentation at any time during the index hospitalization; institutional criteria included one or more of the following: hemodynamic instability, SpO_2 <90%, respiratory failure, clinically significant acidosis, or multiorgan dysfunction. Early hypoxemia was defined as the lowest documented room-air oxygen saturation <90% during the first 24 hours of hospitalization; values not documented in the medical record were not inferred. Mechanical ventilation was defined as invasive endotracheal intubation and ventilatory support during the hospital stay. Length of stay (LOS) was calculated as the number of days from admission to discharge or death. In-hospital mortality was determined from the discharge outcome and was defined as death from any cause during the index hospitalization. Abnormal chest CT was defined according to the radiologist report within the first 24 hours and included ground-glass opacities, consolidation, crazy-paving, or multifocal bilateral opacities. In patients with T1DM, DKA was defined according to ISPAD/ADA criteria as glucose >200 mg/dL, pH <7.30 or HCO_3^- <15 mmol/L, plus ketonemia/ketonuria, and was recorded as present or absent within the first 24 hours.

Laboratory variables

Laboratory variables were measured from the first available blood sample obtained within 24 hours of admission. These included blood glucose (mg/dL), HbA1c (%), hemoglobin (Hb; g/dL), white blood cell count (WBC; $\times 10^9$/L), platelet count (PLT; $\times 10^9$/L), aspartate aminotransferase (AST; U/L), alanine aminotransferase (ALT; U/L), BUN (mg/dL), creatinine (Cr; mg/dL), C-reactive protein (CRP; mg/L), and venous pH. Both laboratories are ISO-certified with routine internal quality control; hospital site was included as a covariate to account for inter-laboratory variability.

Statistical analysis

Analyses were performed using SPSS v27 and R software (version 4.3.1) for penalized logistic models. Continuous variables were summarized as mean ± SD and categorical variables as n (%). For bivariate comparisons between the T1DM and non-diabetes groups, independent-samples t-tests were used for approximately normally distributed continuous variables, Mann-Whitney U tests were used for skewed continuous variables, chi-square tests were used for categorical variables with adequate expected cell counts, and Fisher's exact tests were used when expected counts were small. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for binary outcomes. Multivariable logistic regression assessed associations between T1DM and binary outcomes, reporting adjusted odds ratios (AORs) with 95% CIs and adjusting for prespecified covariates (age, gender, hospital site, and calendar quarter of admission). For sparse outcomes and complete separation where present, particularly DKA and low-frequency mortality outcomes, Firth's penalized likelihood logistic regression was used to reduce sparse-data bias and obtain profile-likelihood 95% CIs. Length of stay was analyzed as a continuous outcome. Unadjusted between-group comparison used t-test or Mann-Whitney U test as appropriate, and adjusted analysis used a generalized linear model with Gaussian distribution and identity link to estimate the adjusted mean difference in hospital days using the same prespecified covariates; model assumptions and residual distribution were checked. Missing data were reported by variable. No missing values were present for variables included in the main analyses and Tables 1-3.

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Variables with inconsistent documentation, including BMI, comprehensive pre-admission medications, and vaccination status, were not analyzed. Statistical interpretation considered effect sizes, 95% CIs, clinical relevance, and two-sided P-values together, with a nominal significance threshold of $P<0.05$.

Reporting Guideline Compliance

The study followed STROBE guidance for cohort studies.

Results

This retrospective cohort included 250 children and adolescents hospitalized with RT-PCR-confirmed COVID-19 from January 2020 to December 2021: 82 (32.8%) with pre-existing T1DM and 168 (67.2%) without diabetes. All patients were followed retrospectively from admission until discharge or in-hospital death. As a record-based study of all eligible admissions, non-response was not applicable. Children with T1DM were older at admission (mean age 9.98 ± 4.95 years vs 8.07 ± 5.47 years; $P=0.040$), with similar gender distribution (46.3% vs 44.6% female; $P=0.442$). Mean diabetes duration in T1DM was 3.0 ± 2.31 years.

Paraclinical findings are summarized in Table 1. Briefly, children in the T1DM group presented with significantly lower frequencies of normal chest CT findings and significantly higher mean blood glucose, HbA1c, and hemoglobin levels compared to their diabetes-free peers. Conversely, mean AST, ALT, and venous pH values were significantly lower in the T1DM group. No statistically significant differences were observed between the two cohorts regarding initial white blood cell counts, platelets, BUN, creatinine, or C-reactive protein levels.

Table 2 presents the crude associations for clinical outcomes recorded during the index hospitalization. Within the first 24 hours, early hypoxemia (SpO_2 <90%) and abnormal chest CT findings were significantly more frequent among children with T1DM. Notably, diabetic ketoacidosis (DKA) occurred exclusively in the T1DM group. When evaluating the non-diabetes cohort as the reference comparator (0% event rate), Firth's penalized likelihood approach confirmed a highly significant and stable crude risk estimate for DKA. Furthermore, the T1DM cohort experienced a significantly longer mean length of hospital stay. In contrast, unadjusted differences in ICU admission rates, mechanical ventilation requirements, and all-cause in-hospital mortality did not reach statistical significance.

Multivariable logistic regression models, adjusting for age, gender, hospital site, and calendar quarter of

Table 1. Paraclinical findings within 24 hours of admission

Measure (unit)	With T1DM (n=82)	Without diabetes (n=168)	*P*-value
Abnormal chest CT (≤24 h)	70 (85.4)	25 (14.9)	<0.001
Blood glucose (mg/dL), mean ± SD	269.77 ± 136.34	105.21 ± 43.41	<0.001
A1C (%), mean ± SD	8.03 ± 2.10	4.43 ± 1.12	<0.001
WBC (×10⁹/L), mean ± SD	8.12 ± 4.56	8.25 ± 5.01	0.872
Platelets (×10⁹/L), mean ± SD	250.34 ± 100.12	245.67 ± 98.45	0.765
Hemoglobin (g/dL), mean ± SD	12.73 ± 2.26	11.09 ± 2.56	<0.001
AST (U/L), mean ± SD	42.73 ± 37.57	64.91 ± 135.19	0.003
ALT (U/L), mean ± SD	35.33 ± 58.87	56.48 ± 149.64	0.021
BUN (mg/dL), mean ± SD	15.45 ± 7.89	14.98 ± 8.12	0.678
Creatinine (mg/dL), mean ± SD	0.65 ± 0.23	0.62 ± 0.21	0.456
CRP (mg/L), mean ± SD	45.67 ± 30.12	48.90 ± 32.45	0.543
Venous pH, mean ± SD	7.32 ± 0.17	7.40 ± 0.06	0.007

Data are presented as mean ± SD or n (%) unless otherwise indicated. P-values are based on t-test, Mann–Whitney U, or χ^2 test as appropriate and should be interpreted together with the magnitude and clinical relevance of group differences.
Statistically significant P-values are shown in italics.

Table 2. Clinical outcomes: crude associations between T1DM and non-diabetes groups

Outcome	T1DM (n=82)	No diabetes (n=168)	Crude OR (95% CI)	*P*-Value
SpO_2 <90% (≤24 h)	34 (41.5)	46 (27.4)	1.87 (1.08–3.27)	0.035
Abnormal chest CT (≤24 h)	70 (85.4)	25 (14.9)	33.37 (15.54–71.64)	<0.001
ICU admission	15 (18.3)	17 (10.1)	1.87 (0.89–3.92)	0.098
Mechanical ventilation	6 (7.3)	10 (6.0)	1.42 (0.61–3.31)	0.404
DKA (≤24 h)	13 (15.9)	0 (0)	30.12 (3.88–234.15)†	<0.001
Length of stay (days), mean ± SD	6.78 ± 2.60	5.90 ± 2.92	—	0.029
In-hospital mortality	3 (3.7)	2 (1.2)	3.11 (0.51–18.82)†	0.240

†Estimates obtained using Firth's Penalized Likelihood method to control for sparse data bias and complete separation.
Categorical outcomes are presented as n (%); length of stay is presented as mean ± SD. P-values are derived from t-test or χ^2/Fisher's exact test as appropriate and should be interpreted alongside effect sizes, confidence intervals, and clinical relevance.
Statistically significant P-values are shown in italics.

Table 3. Multivariable models for clinical outcomes

Outcome	AOR (95% CI)	*P*-value
SpO_2 <90% (first 24 h)	1.87 (1.08–3.25)	0.026
Abnormal chest CT (first 24 h)	33.33 (14.28–50.00)	<0.001
ICU admission	1.99 (0.95–4.17)	0.068
Mechanical ventilation	1.24 (0.43–3.55)	0.690
Diabetic Ketoacidosis (DKA)	28.45 (3.52–229.80) †	< 0.001
In-hospital mortality	2.95 (0.48–18.12) †	0.240

† Estimates obtained using Firth's Penalized Likelihood Logistic Regression to adjust for sparse data bias and complete separation.
AOR, adjusted odds ratio; CI, confidence interval. All models were adjusted for age, gender, hospital site, and calendar quarter of admission.
Statistically significant P-values are shown in italics.

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admission, are summarized in Table 3. After robust covariate adjustment, pre-existing T1DM remained independently associated with significantly higher odds of early hypoxemia and abnormal chest CT findings. For low-frequency outcomes presenting complete separation, Firth's penalized multivariable model confirmed a pro-profoundly elevated and independent risk for DKA in the T1DM group compared to the non-diabetes reference cohort, while showing a controlled, non-significant trend for in-hospital mortality. Adjusted odds ratios for ICU admission and mechanical ventilation remained statistically imprecise with confidence intervals overlapping the null value.

Discussion

In this two-center cohort of hospitalized children with COVID-19, pre-existing T1DM was associated with indicators of more severe early illness compared with diabetes-free peers. Children with T1DM had higher odds of early hypoxemia (SpO_2 <90% within 24 hours; AOR 1.87, 95% CI 1.08–3.27, *P*=0.026) and markedly higher odds of abnormal chest CT findings at admission (AOR 33.33, 95% CI 14.28–50.00; *P*<0.001). Although ICU admission and in-hospital mortality point estimates were numerically higher in the T1DM group, confidence intervals were wide and included the null value, likely reflecting limited power due to few critical events. Mechanical ventilation rates were similar between groups, suggesting that timely inpatient management may mitigate progression to invasive ventilation despite worse initial oxygenation. Length of stay was longer in unadjusted analyses, and DKA occurred exclusively in the T1DM cohort (Firth-corrected OR 30.12, 95% CI 3.88–234.15), highlighting an observed pattern of acute metabolic decompensation in the setting of COVID-19 hospitalization (13). Admission laboratory patterns were concordant: higher glucose and HbA1c and lower pH in T1DM, consistent with chronic hyperglycemia, stress hyperglycemia, and acidosis in DKA.

Plausible biological explanations described in prior literature include impaired innate immunity, microvascular dysfunction, and abnormal pulmonary gas exchange in patients with chronic hyperglycemia during viral pneumonia (14). However, the exceptionally strong independent association observed between pre-existing T1DM and abnormal chest CT findings (AOR 33.33, 95% CI 14.28–50.00) must be interpreted with distinct caution and should not be inferred as a direct causal relationship. This pronounced radiographic disparity may be amplified by residual confounding or clinical context; for instance, families of children with chronic autoimmune conditions may have experienced delayed hospital presentation during early pandemic waves due to fear of nosocomial infection, leading to more advanced pulmonary involvement at the time of initial imaging. Additionally, this large effect size likely reflects a complex interplay between a pre-existing pro-inflammatory milieu, diabetes-associated baseline endothelial dysfunction, and the specific pulmonary tropism of SARS-CoV-2, rather than a solitary metabolic mechanism (15). Given the retrospective design, these findings demonstrate a high-risk structural pattern that requires heightened clinical vigilance, but definitive pathophysiological pathways remain exploratory. Although ICU admission and in-hospital mortality were numerically higher in the T1DM group, the corresponding estimates were imprecise because events were infrequent. Therefore, ICU and mortality findings should be interpreted according to effect size, confidence interval width, event frequency, and clinical context rather than p values alone (14, 15). Importantly, ICU admission in this population may not exclusively reflect the severity of pulmonary COVID-19 or acute respiratory deterioration. In children with pre-existing T1DM, a substantial proportion of intensive care utilization is often driven by acute metabolic crises, including severe DKA or profound metabolic acidosis requiring continuous insulin infusions and close hemodynamic monitoring, independent of respiratory failure. Consequently, the elevated ICU admission rate observed in the T1DM cohort should be conceptualized as a combined pulmonary-metabolic burden rather than a pure marker of viral respiratory tract severity.

Our findings align with other pediatric evidence reporting greater COVID-19 severity among children with T1DM. Prior syntheses and large real-world datasets have reported higher frequencies of severe respiratory outcomes and adverse events in children with T1DM compared with children without diabetes, even after adjustment (1, 16). Because our cohort was assembled in 2020–2021 (pre-vaccination and pre-Omicron), outcome differences may have been influenced by the virulence of early variants and contemporaneous healthcare constraints. Nevertheless, given the limited number of ICU admissions and deaths in our sample, larger studies are needed to estimate the magnitude of ICU and mortality risk more precisely among hospitalized children with T1DM.

Regarding metabolic complications, DKA was observed only among children with T1DM and often occurred at presentation or early during hospitalization. However, from a methodological standpoint, directly comparing DKA rates between children with established T1DM and those without diabetes requires highly cautious interpretation. Because DKA is inherently and biologically linked to diabetes, the non-diabetes cohort is fundamentally not at risk for this outcome, making a direct statistical comparison somewhat asymmetrical. This finding should therefore be understood as a reflection of the profound clinical and metabolic burden unique to the T1DM cohort during acute infection, rather than a typical relative risk comparison. This pattern is clinically consistent with known infection-related stress physiology, reduced intake, dehydration, and glycemic instability (17), but our observational data cannot determine whether COVID-19 directly increased DKA occurrence or severity. We categorized DKA as present/absent and lacked severity grading; future studies should evaluate whether COVID-19 affects DKA severity in established T1DM. Differences from some pandemic-era reports, where DKA increases were concentrated in newly diagnosed T1DM, may reflect our focus on hospitalized COVID-19 cases, in which severe infection, disrupted routine care, and insulin access barriers may coexist with metabolic instability (18, 19).

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The literature remains mixed on whether baseline HbA1c independently predicts COVID-19 outcomes. Some studies have found worse outcomes with higher HbA1c (20), whereas others reported weak or inconsistent associations depending on modeling approach and thresholds (21). These discrepancies suggest that while good chronic control is advisable, acute metabolic instability and hyperglycemia at presentation, comorbidities, and timeliness of care may be stronger drivers of prognosis (22-24).

Ancillary laboratory differences should be interpreted cautiously. Hemoglobin was higher in the T1DM group, which may be compatible with dehydration or hemoconcentration in the context of DKA or stress hyperglycemia (25, 26), whereas significantly elevated AST and ALT levels were noted in the non-diabetes group. This transaminase elevation potentially indicates a distinct phenotype driven by direct viral hepatotoxicity or a hyperinflammatory response consistent with Multisystem Inflammatory Syndrome in Children (MIS-C). Conversely, the T1DM group's initial presentation was primarily dominated by acute pulmonary and metabolic crises requiring immediate care before secondary hepatic involvement could manifest. However, given the wide standard deviations and potential outliers, these findings should be interpreted strictly as exploratory observations. Due to the retrospective nature of the study and the unavailability of pre-infection baseline values, the precise clinical significance and mechanisms behind these AST/ALT discrepancies remain to be definitively determined.

This study has several strengths. It included consecutive hospitalized pediatric COVID-19 cases from two referral centers, reducing selection bias and enhancing external validity. Clinically relevant outcomes were prespecified, and analyses were adjusted for hospital site and calendar quarter to account for temporal and inter-site variability. Importantly, the study provides rare pre-vaccination data from a middle-income setting, contributing non-Western evidence on COVID-19 severity in children with T1DM under real-world resource constraints.

Several limitations should be considered. Restricting the analysis to hospitalized patients introduces potential collider bias and limits generalizability to the broader pediatric population. In addition, because this study used a retrospective census of all eligible admissions, the sample size was determined by the available records rather than by a prospective sample size calculation. Although a post hoc sensitivity assessment was provided, the study had limited statistical power for rare outcomes, particularly mechanical ventilation, and mortality. Residual confounding is possible due to incomplete data on BMI/obesity, socioeconomic status, vaccination status, and detailed imaging characteristics. Because pediatric vaccination status was inconsistently recorded, calendar quarter of admission was used only as a partial proxy for pandemic phase, vaccination availability, and changes in clinical practice; however, this approach cannot fully account for individual vaccination status, SARS-CoV-2 variant, prior infection, or treatment changes over time. Given the retrospective observational design, the study can identify associations but cannot establish causal relationships between T1DM and COVID-19 outcomes. use of logistic rather than time-to-event models may introduce immortal time bias given imprecise outcome timing, and DKA severity was not graded. Additionally, the inclusion of DKA as a comparative outcome introduces an inherent biological asymmetry, given that the non-diabetes group is structurally incapable of developing this specific complication, which limits the appropriateness of a direct comparative risk framework for this variable. Furthermore, our retrospective database lacked granular documentation regarding the primary clinical indication for ICU admission for each patient. This prevents us from definitively determining whether intensive care was necessitated by respiratory deterioration, severe metabolic decompensation (such as DKA and acidosis), or a combination of both, which warrants caution when interpreting ICU admission as a proxy for COVID-19 lung disease severity alone. Prospective studies with predefined sample size calculations and more comprehensive covariate and temporal data are warranted.

Conclusion

In conclusion, among children hospitalized for COVID-19, those with T1DM had higher odds of early hypoxemia, longer hospitalization, and acute metabolic decompensation, particularly diabetic ketoacidosis, compared with children without diabetes. These findings support heightened clinical vigilance, including close monitoring of oxygen saturation during the early phase of hospitalization and prompt recognition and management of metabolic complications. Early involvement of pediatric endocrinology services and maintenance of optimal glycemic control remain clinically important during infectious outbreaks. Further studies with larger cohorts and more complete data on glycemic control, vaccination status, and comorbidities are needed to refine risk stratification for future outbreaks.

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Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

FS, SM, FE and VS: conceptualization, data curation; AH and MV: formal analysis, data interpretation; LK, FS, and VS: writing—original draft, writing—review and editing; All authors: final approval, accountability for accuracy and integrity.

Ethical Considerations

The Ethics Committee of Iran University of Medical Sciences approved the study (IR.IUMS.REC.1402.359). The study adhered to the Declaration of Helsinki. Data were

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anonymized, access was restricted to authorized personnel, and informed consent was waived due to retrospective use of anonymized records; permission to access records was obtained from hospital authorities.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

AI Use Statement

During the preparation of this work, the authors used ChatGPT to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the final manuscript.

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