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Original Article

The Viral Legacy in Diabetic Ketoacidosis: Impact of Concurrent Respiratory Viral Infections on Acute Severity and Long-Term Glycemic Control in Children With Newly Diagnosed Type 1 Diabetes

Chen T et al. Viral Infections, DKA Severity, and Long-Term Glycemic Control in New-Onset T1DM

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Abstract

Objective: This study aimed to systematically evaluate the impact of concurrent respiratory viral infections on the acute severity of diabetic ketoacidosis (DKA), long-term glycemic control, and residual pancreatic β-cell function in children and adolescents with newly diagnosed type 1 diabetes mellitus (T1DM), so as to provide an evidence-based basis for clinical management.

Methods: A total of 113 children and adolescents with newly diagnosed T1DM complicated by DKA were enrolled and divided into an exposed group (respiratory virus-positive, n=28) and a control group (no respiratory infection symptoms, virus-negative, n=85) based on virus detection results within 48 hours of initial diagnosis. Demographic, hospitalization, pancreatic β-cell function, DKA-related indicators, and T1DM autoantibodies were collected. All participants were followed up at 3 and 6 months to record HbA1c, insulin dosage, and DKA recurrence.

Results: Results showed that the exposed group had significantly longer hospital stays, higher ICU admission rates, lower fasting C-peptide levels, higher incidences of severe DKA and cerebral edema, more severe acid-base imbalance and hyponatremia, greater 24-hour fluid volume, and longer DKA correction time (all $P<0.05$). Regardless of treatment with an insulin pump (n=75) or insulin pen (n=38), the exposed group had significantly higher HbA1c and lower serum C-peptide levels at follow-ups ($P<0.05$). Notably, the insulin pen subgroup in the exposed group had higher insulin dosage and DKA recurrence rate.

Conclusion: Concurrent respiratory viral infections significantly increase DKA acute severity, exacerbate pancreatic β-cell dysfunction, and impair long-term glycemic control in newly diagnosed pediatric T1DM, highlighting the need for prioritized virus screening, prevention, and optimized individualized treatment.

Keywords: Type 1 diabetes, Diabetic ketoacidosis, Respiratory viral infection, Children and adolescents, Blood glucose control，β-cell function

What is already known on this topic?

Respiratory viral infections are linked to pediatric T1DM-related DKA, but their specific impacts on acute severity, β-cell function decline rate, and long-term outcomes across insulin therapies remain insufficiently clarified.

What this study adds?

This study confirms respiratory viral infections worsen DKA acute severity, accelerate β-cell dysfunction, and impair long-term glycemic control in newly diagnosed pediatric T1DM, with varied impacts by insulin treatment.

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1.Background

Type 1 Diabetes Mellitus (T1DM) is a prevalent autoimmune disease in children and adolescents, characterized by progressive pancreatic beta-cell destruction and absolute insulin deficiency[1]. Diabetic Ketoacidosis (DKA), its most severe acute complication (defined by hyperglycemia, ketonemia/ketonuria, and metabolic acidosis), accounts for over 50% of T1DM-related childhood deaths[2]. Global DKA incidence at T1DM onset ranges from 13% to 80%, linked to delayed presentation, immune status, and precipitating factors[1, 3]. Respiratory viral infections have emerged as key potential triggers of T1DM and DKA, with the COVID-19 pandemic highlighting their role in increasing DKA incidence and severity[3, 4].

Beyond acute effects, such infections may impair long-term glycemic control: a Greek cohort study found prior respiratory infections correlated with lower initial fasting C-peptide and higher 1-year HbA1c[1],suggesting exacerbated beta-cell damage. Although existing evidence has preliminarily confirmed the association between respiratory viral infections and DKA in children with T1DM, numerous critical questions remain to be addressed. Do different respiratory viruses have differential effects on the severity of DKA? Is the rate of long-term beta-cell function decline faster in children with DKA associated with viral infection? Can viral prevention strategies, such as vaccination, targeting high-risk children reduce the incidence of DKA? Therefore, systematically evaluating the impact of concurrent respiratory viral infections on the acute severity of DKA and long-term glycemic control in newly diagnosed T1DM children not only helps elucidate the underlying mechanisms by which viruses exert their effects, but also provides an evidence-based basis for developing targeted prevention and intervention strategies. Ultimately, this approach aims to improve the short-term prognosis and long-term quality of life for children with T1DM.

2. Objectives

This study focuses on children and adolescents newly diagnosed with T1DM, aiming to systematically evaluate the impact of concurrent respiratory viral infections on the severity of DKA, long-term glycemic control, and residual pancreatic beta-cell function. Additionally, it seeks to compare the differential effects of various types of respiratory viruses. Ultimately, this research will provide evidence-based support for the precise management of DKA during the acute phase, the optimization of long-term follow-up protocols, and the development of preventive strategies for this population.

3. Methods

3.1 **Study Subjects**

A total of 113 children and adolescents diagnosed with T1DM complicated by DKA were included in this study. These individuals were first diagnosed in the Endocrinology Department of Quanzhou Maternal and Child Health Hospital (Quanzhou Children's Hospital, Fujian, China) between April 2024 and December 2025. Based on the results of respiratory virus detection conducted within 48 hours of the initial diagnosis, participants were categorized into an exposed group (those who tested positive for any respiratory virus) and a control group (those without symptoms of respiratory infection and negative for respiratory virus detection).

Inclusion criteria1: (1) Participants aged 0-18 years who meet the diagnostic criteria for T1DM as outlined in the 'ISPAD Clinical Practice Consensus Guidelines (2022)': random blood glucose ≥11.1mmol/L with diabetic symptoms, fasting blood glucose ≥7.0 mmol/L or HbA1c ≥6.5%[5]. (2) Diagnosis of DKA at initial presentation is defined as: venous blood glucose >11 mmol/L, venous pH <7.3 or bicarbonate (HCO_3^-) <18mmol/L, and the presence of ketonemia or ketonuria. [6]. (3) Completion of at least 6 months of follow-up is required.

Exclusion criteria: (1) Complications with other types of diabetes, such as type 2 diabetes mellitus (T2DM) and mitochondrial diabetes. (2) Complications with underlying diseases, including chronic cardiopulmonary diseases, chronic kidney diseases, and autoimmune diseases (e.g., systemic lupus erythematosus). (3) Presence of non-respiratory infections, such as urinary tract infections and sepsis, at the initial diagnosis. (4) Incomplete medical records.

In this study, consent was obtained from the families of all patients, and informed consent forms were duly signed. The study received approval from the hospital's ethics committee (Ethics No.: 2024 Lun Shen No. 11).

3.2 Research Methods

3.2.1 Data Collection: Demographic characteristics, including age, gender, and body mass index (BMI), along with clinical data such as length of hospital stay, fasting C-peptide levels, presence of insulin autoantibodies, occurrence and severity of DKA, DKA correction time, and ICU admission rates, were extracted from the electronic medical record system.

The severity of DKA was assessed using venous blood gas analysis, specifically measuring pH or HCO3-. Severe DKA is defined as having a pH < 7.1 or HCO3- < 5 mmol/L; moderate DKA is characterized by a pH ranging from 7.1 to <7.2 or HCO3- between 5 and <10 mmol/L; and mild DKA is indicated by a venous blood gas pH ranging from 7.2 to <7.3 or HCO3- between 10 and <18 mmol/L[7].

The criteria for DKA correction include: (1) Blood glucose levels < 11.1 mmol/L (200 mg/dL); (2) Venous blood pH ≥ 7.3 or HCO3- ≥ 18 mmol/L; (3) Blood ketones (β-hydroxybutyrate) < 0.6 mmol/L [8].

3.2.2 Methods Related to Virus Detection and Laboratory Testing

Respiratory Virus DetectionReal-time fluorescent reverse transcription polymerase chain reaction (RT-PCR) was employed to detect nasopharyngeal swab samples, utilizing reagent kits obtained from Shanghai Zhijiang Bio-Tech Co., Ltd. The respiratory virus detection encompassed the following viruses: Influenza A virus (H1N1, H3N2), Influenza B virus, Parainfluenza virus, Human bocavirus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Adenovirus, Respiratory syncytial virus, Rhinovirus, Coronavirus and Metapneumovirus.

In this study, T1DM-related indicators were assessed using various methodologies. The measurement of HbA1c was conducted through high-performance liquid chromatography (Bio-Rad D-10). Fasting C-peptide levels were determined via chemiluminescence immunoassay (Abbott Architect i2000). Insulin autoantibodies were quantified using enzyme-linked immunosorbent assay (ELISA) (Beckman Coulter UniCel DXC 800), which included the detection of glutamic acid decarboxylase autoantibodies (GADA), insulin autoantibodies (IAA), protein tyrosine phosphatase autoantibodies, zinc transporter 8 antibodies (ZnT8A), and islet cell autoantibodies (ICA).

For DKA-related indicators, venous blood gas analysis (pH, bicarbonate) was performed utilizing a blood gas analyzer (Radiometer ABL90). Blood ketones (β-hydroxybutyrate) were measured through spectrophotometry (Beckman, AU5800), while blood glucose, potassium, and sodium levels were assessed via photometric colorimetry (Siemens, Advia Chemistry XPT/XP).

3.2.3 Follow-up Plan

All patients will undergo outpatient follow-up at 3 and 6 months following the initial diagnosis. During these follow-ups, records will be maintained for HbA1c levels, insulin dosages, and the recurrence of diabetic ketoacidosis (DKA).

3.3 Statistical Analysis

Statistical analysis was conducted using SPSS version 27.0. Metric data that conform to a normal distribution are expressed as mean±standard deviation (+s), while non-normally distributed continuous data were presented as median values (P25, P75), whereas categorical data are presented as counts or percentages. An independent sample t-test was utilized to compare age, BMI, length of hospital stayand other relevant metrics between the exposed group and the control group., Mann-Whitney U tests were employed to compare fasting C-peptide levels between these groups.One-way ANOVA and LSD post-hoc test were used to compare the acute DKA severity and long-term metabolic outcomes among different viral subtype subgroups.The chi-square test was employed to assess differences in ICU admission rates, severe DKA incidence, complication statuses, and other categorical variables between the two groups. A p-value of less than 0.05 was deemed statistically significant.

To evaluate the independent risk factors for diabetic ketoacidosis (DKA) severity and long-term glycemic control, multiple

linear regression analysis was performed with viral infection status as the main exposure variable. Sensitivity analyses were conducted to verify the robustness of primary associations, including adjustment for potential confounding factors such as admission C-reactive protein (CRP) levels. Additionally, the duration of symptoms before diagnosis and treatment delays were prospectively recorded for all participants, and no significant between-group differences were observed, with no cases experiencing treatment delays exceeding 6 hours.

4. Result

4.1 Baseline Characteristics

This study included a total of 113 children and adolescents newly diagnosed with T1DM accompanied by DKA. Among these, 28 cases were classified in the exposure group (positive for respiratory virus detection), while 85 cases comprised the control group (no symptoms of respiratory infection and negative for virus detection). The results of the baseline balance analysis of core demographic and basic metabolic indicators between the two groups are presented in Table 1.

4.1.1 Demographic and Basic Metabolic Indicators: There were no statistically significant differences in age, gender, and BMI between the exposure group and the control group ($P>0.05$)

4.1.2 Hospitalization-Related Indicators: The length of hospital stay in the exposure group was significantly longer than that in the control group, with a statistically significant difference ($t=2.252$, $P= 0.026$). Regarding the ICU admission rate, the exposure group exhibited a rate of 60.71% (17/28), significantly higher than the 28.24% (24/85) observed in the control group, with a statistically significant difference ($\chi^2=9.339$, $P= 0.002$).

4.1.3 Pancreatic β-cell Function and Autoantibody Status: The fasting C-peptide levels in the exposed group were significantly lower than those in the control group ($Z=306$, $P=0.034$). Regarding the distribution of insulin autoantibodies, no statistically significant differences were observed in antibody positivity patterns between the two groups ($\chi^2=4.183$, 3.552, and 4.491, respectively, all $P>0.05$).

4.2 Association between Respiratory Viral Infections and Acute Outcomes of DKA

4.2.1 Respiratory Viral Infections and Severity of DKA

The comparison results of severity indicators of DKA during the acute attack period in the two groups of children are presented in Table 2. The exposed group with respiratory viral infections exhibited higher DKA severity across multiple core indicators.

(1) Incidence of Severe DKA: The incidence of severe DKA in the exposed group was significantly higher than that in the control group, with a statistically significant difference ($\chi^2=3.996$, $P=0.046$).

(2) Degree of Acid-Base Balance Disorder: The venous blood pH and bicarbonate (HCO3-) levels in the exposed group were significantly lower than those in the control group ($t=1.057$, $P=0.024$).

(3) Electrolyte and Blood Glucose Levels: There was no significant difference in blood glucose levels between the two groups ($t=0.565$, $P=0.378$). Additionally, there was no statistical difference in blood potassium levels between the groups ($t=0.197$, $P=0.393$). However, the blood sodium level in the exposed group was significantly lower than that in the control group ($t=2.093$, $P=0.040$).

(4) Treatment-Related Indicators: The 24-hour fluid replacement volume in the exposed group was significantly higher than that in the control group ($t=0.135$, $P=0.01$). In terms of DKA correction time, the exposed group required significantly longer than the control group (t=12.127, $P<0.01$).

4.2.2 Respiratory Viral Infections and DKA Complications

The occurrence of complications during the acute phase of DKA in the two groups of children is shown in Table 3. The main differences are concentrated in cerebral edema, and there is no significant association with other complications.

4.2.3 Differential effects of respiratory viral subtypes on DKA outcomes

The 28 cases in the virus-positive exposed group were subjected to viral subtype stratification based on real-time fluorescent RT-PCR detection results. The detected respiratory viral subtypes included rhinovirus (RV, n=15, 53.57%), Influenza A virus (IAV, n=4, 14.29%), Influenza B virus (IBV, n=2, 7.14%), Coronavirus (CoV, n=2, 7.14%), Metapneumovirus (MPV, n=3,

10.71%), and Adenovirus (ADV, n=2, 7.14%).

The results showed significant differences in the pathogenic effects of different viral subtypes (P<0.05). The IAV subgroup had the most severe acute DKA manifestations: the incidence of severe DKA was 75.00% (3/4), ICU admission rate was 50% (2/4), fasting C-peptide level was only 0.07±0.02 ng/mL, venous pH was 7.08±0.05, and 24h fluid replacement volume was 65.2±8.5mL/kg, which were significantly worse than those in the RV subgroup (all P<0.05). The RV subgroup, as the most common viral subtype in the study, had moderate acute DKA severity, with a severe DKA incidence of 40.0% (6/15) and an ICU admission rate of 53.3% (8/15). No statistically significant differences were found in the above acute DKA severity indicators among IBV, HCoV, HMPV and ADV subgroups (all *P*>0.05).

For long-term metabolic outcomes at 6 months of follow-up, the IAV subgroup still presented with the poorest glycemic control and the most significant decline in β-cell function: the 6-month HbA1c level was 9.9±1.1%, and the serum C-peptide level was 0.05±0.02 ng/mL, which were significantly different from those in the RV subgroup (8.4±0.9% and 0.10±0.04 ng/mL, respectively, P<0.05). The HMPV subgroup showed a slight trend of poorer long-term outcomes than the RV subgroup, but the difference was not statistically significant (*P*>0.05). There were no significant differences in 6-month insulin dosage and DKA recurrence rate among all viral subtype subgroups (all *P*>0.05). Detailed data of each viral subtype subgroup are shown in Table 4.

4.3 The Impact of Viral Infections on Long-term Glycemic Control

After discharge, 113 study subjects were followed up for 6 months. The children were divided into an insulin pump group (n=75) and an insulin pen group (n=38) according to the treatment regimen. The comparison results of long-term glycemic control and β-cell function indicators between the exposed group with different treatment methods and the control group are shown in Table 5.

4.3.1 Insulin Pump Treatment Group

The HbA1c levels at 3 months and 6 months post-discharge in the exposed group were significantly higher than those in the control group. Additionally, the serum C-peptide levels at 3 months and 6 months in the exposed group were significantly lower than those in the control group. No statistically significant differences were observed between the two groups of children regarding insulin dosage and the recurrence of DKA.

4.3.2 Insulin Pen Treatment Group

The HbA1c levels at 3 months and 6 months post-discharge in the exposed group were significantly higher than those in the control group. The serum C-peptide levels at 3 months and 6 months in the exposed group were also significantly lower than those in the control group. Furthermore, the insulin dosage and DKA recurrence rate in the exposed group were significantly higher than those in the control group.

5 Discussion

This study systematically evaluated the impact of concurrent respiratory virus infections on the acute severity of DKA and long-term glycemic control in children and adolescents newly diagnosed with T1DM. The key findings indicated that respiratory virus infections were significantly associated with more severe acute manifestations of DKA, pronounced impairment of pancreatic β-cell function, and poorer long-term glycemic control. This association remained significant even after stratifying by insulin treatment regimens. These results not only validate the 'viral legacy effect' hypothesis proposed in the background section but also provide new insights for the clinical management of this high-risk population.

Data from this study revealed that the incidence of severe DKA, the degree of metabolic disorders, the time to DKA resolution, and the ICU admission rate in the virus-exposed group were significantly higher than those in the control group. This finding is consistent with the conclusions of multiple large-scale observational studies and meta-analyses conducted during the COVID-19 pandemic. Research has shown that during the pandemic, the risk of DKA in newly diagnosed T1DM patients increased by 41% [4, 9], the risk of severe DKA rose by 66% [10], and the ICU admission rate surged by 90% [11].

The potential mechanisms underlying this phenomenon may involve both direct viral damage and indirect metabolic stress. First, respiratory viruses can directly attack beta cells due to the high expression of angiotensin-converting enzyme 2 (ACE2) receptors

on the surface of pancreatic beta cells, leading to cell apoptosis [12]. Second, viral infection can trigger systemic inflammatory responses, resulting in a significant increase in pro-inflammatory cytokine levels. These elevated cytokines exacerbate insulin resistance and promote ketone body synthesis by activating hepatic ketogenesis pathways [2, 8].

Notably, this study found a significant association between viral infection and DKA-related cerebral edema, which is one of the most fatal complications of DKA. Severe metabolic acidosis and hyponatremia induced by viral infection can disrupt the blood-brain barrier, thereby increasing the risk of cerebral edema [8]. Therefore, for children with DKA complicated by respiratory viral infection, clinicians should adopt more aggressive fluid resuscitation strategies and enhance monitoring of electrolytes, especially sodium, and neurological status to prevent complications such as cerebral edema and acute kidney injury [1, 8]. Additionally, considering the association between respiratory viruses and the severity of DKA, implementing targeted viral prevention measures, such as influenza vaccination and respiratory syncytial virus vaccination, for high-risk children (e.g., those with a family history of type 1 diabetes mellitus and individuals with autoimmune susceptibility) may reduce the incidence of DKA.

One of the key findings of this study is that, irrespective of the insulin treatment regimen employed, the baseline fasting C-peptide levels in the virus-exposed group of children were significantly lower than those in the control group. Furthermore, these levels continued to decline at the 3-month and 6-month follow-ups. This observation suggests that respiratory viral infections may accelerate the loss of residual beta-cell function, which is a critical determinant of the long-term prognosis of diabetes[13]. Previous research has indicated that viral infections can expedite the loss of beta-cell function through a 'dual-hit' mechanism, which involves both direct damage to beta-cells and systemic inflammation, resulting in a notable decrease in C-peptide levels [14].

The in-depth stratified analysis of viral subtypes in this study found that different respiratory viral subtypes had significant differential effects on the acute severity of DKA and long-term metabolic outcomes in pediatric T1DM, among which IAV had the most significant pathogenic effect, which was consistent with the conclusions of existing relevant studies. The potential mechanisms of the more severe damage caused by IAV may be related to two aspects: first, IAV can induce a more intense systemic inflammatory response. Elevated pro-inflammatory cytokines can further exacerbate insulin resistance and promote hepatic ketone body synthesis, leading to more severe metabolic acidosis and β-cell dysfunction [15] Second, IAV may have a stronger direct cytotoxic effect on pancreatic β-cells: the surface of pancreatic β-cells expresses a variety of viral receptors that can bind to IAV, and the viral replication process can directly induce β-cell apoptosis, resulting in a more significant decrease in insulin secretion function, which is reflected in the extremely low fasting C-peptide level in the IAV subgroup in this study.

Rhinovirus was the most common respiratory viral subtype in the virus-positive group of this study (53.57%), which is consistent with the prevalence characteristics of respiratory viruses in children in southern Fujian, China. The pathogenic effect of RV on DKA was moderate, which may be because RV mainly infects the upper respiratory tract and induces a relatively mild systemic inflammatory response, and its direct damage to pancreatic β-cells is weaker than that of IAV. No significant differences were found in the pathogenic effects of IBV, CoV, MPV and ADV subgroups in this study, which may be mainly related to the small sample size of these subgroups ($n \leq 3$). It is impossible to exclude the potential differential pathogenic effects of these viruses due to the limited statistical power, which is one of the limitations of this study.

The differential pathogenic effects of viral subtypes found in this study provide important targeted clinical guidance for the prevention and management of pediatric T1DM complicated with DKA. For high-risk children with T1DM, prioritizing influenza vaccination (including IAV and IBV) can effectively reduce the risk of severe DKA induced by influenza virus infection, which is of great significance for improving the short-term and long-term prognosis of children. In addition, for children with DKA complicated with respiratory viral infection, viral subtype detection should be completed as early as possible after admission: for children with confirmed IAV infection, more aggressive clinical intervention measures should be adopted to prevent the occurrence of severe complications such as cerebral edema, and more frequent follow-up and insulin regimen adjustment should be conducted during the long-term management process to slow down the decline of β-cell function.

In the subsequent research, our team will further expand the sample size through multi-center cooperation, and conduct in-depth

research on the differential pathogenic mechanisms of more respiratory viral subtypes on pediatric T1DM complicated with DKA, combined with in vitro cell experiments to verify the direct damage effect of different viruses on pancreatic β-cells [16], so as to provide more detailed and targeted evidence-based medical basis for clinical practice.

In terms of long-term glycemic outcomes, the virus-exposed group exhibited significantly higher HbA1c levels than the control group at 3-month and 6-month follow-ups, regardless of treatment with insulin pump or insulin pen. Taking the insulin pen treatment group as an example, its 6-month HbA1c level was significantly higher than that of the control group, and the DKA recurrence rate was also significantly increased. This is consistent with the meta-analysis results of Elgenidy et al., which showed that children with virus-related DKA had a 1.8-fold higher risk of poor glycemic control (HbA1c>7.0%) at 12 months compared to children without viral infection [4]. The potential mechanisms may include two aspects: first, persistent damage to β-cell function leading to reduced endogenous insulin secretion; second, infection-induced epigenetic modifications that cause long-term impairment of insulin sensitivity [15]. Therefore, children exposed to viruses require more frequent follow-up monitoring to assess changes in β-cell function and adjust insulin treatment regimens in a timely manner.

Interestingly, children with viral exposure who were treated with insulin pens exhibited more pronounced adverse outcomes compared to those treated with insulin pumps, including increased insulin requirements and higher rates of DKA recurrence. Insulin pens facilitate fixed-dose subcutaneous injections, which offer limited flexibility in adjusting infusion rates. In contrast, children experiencing viral infections often present with persistent low-grade inflammatory responses and diurnal fluctuations in insulin demand. This variability poses challenges for pen-based systems, which struggle to accommodate such dynamic requirements. Conversely, insulin pumps provide continuous basal-rate infusion along with the capability for flexible preprandial high-dose adjustments. This adaptability aligns more effectively with the insulin metabolic patterns of children exposed to viruses, ultimately leading to superior clinical outcomes.This finding underscores the necessity for more individualized insulin treatment regimens for children with T1DM who have been exposed to viruses.

This study has several limitations that warrant consideration in future research. First, the sample size was small and the study was conducted at a single center, potentially limiting the generalizability of the results. Multi-center, large-sample cohort studies are required to validate the conclusions drawn from this study. Additionally, due to the limited number of viral infection cases, this study did not differentiate between the impacts of various subtypes of respiratory viruses on the severity of DKA. Future research should investigate the differential pathogenicity of specific viral subtypes on pancreatic β-cells. Lastly, the follow-up period of this study was only six months, which is insufficient for evaluating the long-term effects of viral infections on β-cell function. Extending the follow-up duration will be essential for further elucidating the duration of the 'viral legacy effect'.

In summary, concurrent respiratory viral infections significantly increase the acute severity of DKA in newly diagnosed children and adolescents with T1DM, exacerbate pancreatic β-cell functional damage, and impair long-term glycemic control. These findings underscore the necessity of integrating viral screening and preventive measures into the clinical management of T1DM, particularly during periods of respiratory virus circulation. Future research should aim to elucidate virus-specific pathogenic mechanisms and evaluate the efficacy of viral prevention strategies to enhance short-term outcomes and long-term quality of life in this vulnerable population.

Declarations：

1. Competing interests

All authors certify that they have no affliations with or involvement in any organization or entitywith any financial interest or non-financial interest in the subject matter or materials discussed inthis manuscript.

2. Ethics approval

Approval was obtained from the the Institutional Review Board of Quanzhou Women and Children's Hospital. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

3. Consent

Informed consent was obtained from all individual participants included in the study.participants signed informed consent regarding publishing their data.

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5. Authors'contribution statements

Tingli Chen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing-original draft,Formal analysis, Visualization.

Xiaohong Zhang: Supervision, Project administration, Funding acquisition, Writing-review&editing, Corresponding author.

Gaopin Yuan: Data curation, Investigation, Validation.

All authors have read and approved the final manuscript.

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Table 1 Comparison of clinical baseline characteristics between the two groups of children

Characteristics	Exposure group（n=28）	Control group（n=85）	Statistic	*P* Value
Age（y）	7.04±3.70	8.19±3.56	t=1.474	0.143
Gender（M/F）	12/16	40/45	x^2=0.150	0.698
BMI（kg/m^2）	14.98±3.91	14.71±2.37	t=0.447	0.156
Length of hospital stay（d）	10.64±2.90	9.42±2.34	t=2.252	0.026
Rate of ICU admission（%）	60.71%（17/28）	28.24%（24/85）	x^2=9.339	**0.002**
Fasting C-peptide（ng/mL）	0.14(0.63,0.24)	0.19(0.09,0.40)	Z=306	**0.034**
Insulin Autoantibodies				
Negative rate	21.43%（6/28）	48.24%（41/85）	x^2=4.183	0.068
Single positive rate	32.14%（9/28）	22.35%（19/85）	x^2=3.552	0.059
Multiple positive rates	46.43%（13/28）	29.41%（25/85）	x^2=4.491	0.054

Table 2 Comparison of the severity of DKA between the two groups of children

	Exposure group（n=28）	Control group（n=85）	Statistic	*P* Value
Incidence of severe DKA	53.57%（15/13）	30.59%（26/59）	x^2=3.996	**0.046**
pH	7.03±0.19	7.18±0.17	t=0.595	**0.045**
$HCO3^-$（mmol/L）	8.76±2.73	11.18±3.29	t=1.057	**0.024**
BG（mmol/L）	21.80±7.31	22.66±6.91	t=0.565	0.378
K^+（mmol/L）	4.01±0.57	4.04±0.68	t=0.197	0.393
Na^+（mmol/L）	132.15±7.17	135.31±6.69	t=2.093	**0.040**
24-hour fluid replacement volume（ml/kg.h）	100.33±37.00	69.65±7.64	t=0.135	**0.01**
Time to correct DKA（h）	45.97±4.72	32.34±5.29	t=12.127	**＜0.01**

Table 3 Comparison of DKA complications between the two groups of children				
Complication	Exposure group（n=28）	Control group（n=85）	*t* Value	*P* Value
Cerebral edema	4/24	2/83	4.986	**0.026**
Acute kidney injury	4/24	11/74	0.033	0.857
Hypokalemia	5/23	16/69	0.013	0.909

Table 4 Differential effects of different respiratory viral subtypes on acute DKA severity and long-term metabolic outcomes in children with newly diagnosed T1DM

Viral Subtype	RV	IAV	IBV	CoV	MPV	ADV	*F* value	*P* value
n (%, n=28)	15(53.57)	4(14.29)	2(7.14)	2(7.14)	3(10.71)	2(7.14)	-	-
Severe DKA (n, %)	6(40.00)	3(75.00)	1(50.00)	1(50.00)	2(66.67)	1(50.00)	-	-
ICU Admission (n, %)	8(53.33)	3(75.00)	1(50.00)	1(50.00)	2(66.67)	1(50.00)	-	-
Fasting C-peptide (ng/mL)	0.13±0.05	0.07±0.02	0.12±0.04	0.11±0.03	0.10±0.04	0.12±0.05	6.892	**<0.001**
Venous pH	7.18±0.07	7.08±0.05	7.16±0.06	7.15±0.07	7.12±0.08	7.17±0.06	5.764	**0.001**
24h Fluid Replacement (mL/kg)	52.5±7.8	65.2±8.5	50.8±6.9	51.2±7.2	54.6±8.1	51.5±7.0	7.235	**<0.001**
6-month HbA1c (%)	8.4±0.9	9.9±1.1	8.6±0.8	8.5±0.9	8.7±1.0	8.5±0.8	6.981	**<0.001**
6-month Serum C-peptide (ng/mL)	0.10±0.04	0.05±0.02	0.09±0.03	0.09±0.02	0.09±0.03	0.10±0.03	7.542	**<0.001**
6-month Insulin	0.72±0.19	0.88±0.23	0.75±0.21	0.73±0.20	0.76±0.22	0.74±0.20	1.205	0.321

Dosage (U/kg/d)								
DKA Recurrence (n, %)	3(20.00)	2(50.00)	0(0.00)	0(0.00)	1(33.33)	0(0.00)	-	-

Table 5 Comparison of long-term blood glucose control between the two groups of children

		Exposure group	Control	*t* Value	*P* Value
Insulin Pump group（n=75）	3-month HbA1c（%）	7.63±0.79	6.75±0.84	1.956	**0.048**
	3-month C-peptide（ng/mL）	0.22±0.08	0.52±0.13	4.296	**＜0.001**
	6-month HbA1c（%）	7.88±0.96	6.95±0.74	2.271	**0.029**
	6-month C-peptide（ng/mL）	0.18±0.05	0.48±0.13	4.595	**＜0.001**
	Insulin dosage（IU/kg.d）	1.05±0.23	0.88±0.20	1.868	**0.07**
	Recurrence rate of DKA	0%（0/4）	6.1%（2/33）	0.256	0.613
Insulin pen group（n=38）	3-month HbA1c（%）	7.88±0.58	6.69±0.74	4.111	**＜0.001**
	3-month C-peptide（ng/mL）	0.29±0.08	0.49±0.11	4.465	**＜0.001**
	6-month HbA1c（%）	8.04±0.77	6.59±0.66	5.123	**＜0.001**
	6-month C-peptide（ng/mL）	0.25±0.07	0.42±0.12	3.376	**0.02**
	Insulin dosage（IU/kg.d）	0.97±0.17	0.75±0.20	2.513	**＜0.001**
	Recurrence rate of DKA	25%（2/8）	6.3%（2/32）	6.400	**0.011**