ORIGINAL ARTICLE

Retrospective Study

COVID-19 infection and inactivated vaccination: Impacts on clinical and immunological profiles in Chinese children with type 1 diabetes

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Abstract

BACKGROUND
The coronavirus disease 2019 (COVID-19) pandemic has been linked to an increased incidence of diabetes and diabetic ketoacidosis (DKA). However, the relationship between COVID-19 infection and progression to type 1 diabetes (T1D) in children has not been well defined.

AIM
To evaluate the influence of COVID-19 infection and inactivated vaccine administration on the progression of T1D among Chinese children.

METHODS
A total of 197 newly diagnosed patients with T1D were retrospectively enrolled from Children's Hospital of Fudan University between September 2020 and December 2023. The patients were divided into three groups based on their history of COVID-19 infection and vaccination: the infection group, the vaccination-only group, and the non-infection/non-vaccination group. Comprehensive clinical assessments and detailed immunological evaluations were performed to delineate the characteristics and immune responses of these groups.

RESULTS
The incidence of DKA was significantly higher in the COVID-19 infection group (70.2%) compared to the non-infection/non-vaccination group (62.5%) and vaccination-only group (45.6%; $P = 0.015$). Prior COVID-19 infection was correlated with increased DKA risk (OR: 1.981, 95%CI: 1.026-3.825, $P = 0.042$), while vaccination was associated with a reduced risk (OR: 0.558, 95%CI: 0.312-0.998, $P = 0.049$). COVID-19 infection mildly altered immune profiles, with modest dif-

ferences in autoantibody positivity, lymphocyte distribution, and immunoglobulin levels. Notably, *HLA-DR3* positive children with a history of COVID-19 infection had an earlier T1D onset and lower fasting C-peptide levels than the *HLA-DR3* negative children with a history of infection (both *P* < 0.05).

CONCLUSION
COVID-19 infection predisposes children to severe T1D, characterized by enhanced DKA risk. Inactivated vaccination significantly lowers DKA incidence at T1D onset. These findings are valuable for guiding future vaccination and T1D risk surveillance strategies in epidemic scenarios in the general pediatric population.

Key Words: COVID-19 infection; Diabetic ketoacidosis; Type 1 diabetes; Vaccination; Immune profiles

Core Tip: Much remains unknown regarding the association between the infection and vaccination of coronavirus disease 2019 (COVID-19) and the progression of type 1 diabetes (T1D). In this study, we analyzed the features of newly diagnosed T1D children after COVID-19 infection and inactivated vaccination in China. A history of COVID-19 infection was associated with a greater risk of DKA at the onset of T1D, whereas inactivated vaccination significantly lowered DKA incidence. Furthermore, HLA-DR3 positive children with COVID-19 infection had earlier T1D onset and lower fasting C-peptide levels, suggesting that COVID-19 infection predisposes HLA-DR3 positive children to severe T1D.

INTRODUCTION

Type 1 diabetes (T1D) is caused by chronic cell-mediated autoimmune destruction of the pancreatic β-cells, resulting in partial or absolute insulin deficiency[1,2]. The etiology of T1D is multifactorial, involving genetic risk, environmental triggers, and the immune system[2]. Epidemiological, clinical, and pathological research has implicated viral infections as pivotal etiological factors in T1D development[3]. Notably, the TEDDY study revealed that viral triggers can precipitate islet autoimmunity, potentially accelerating the transition to clinical T1D[4]. Furthermore, another study found that respiratory infections were associated with initiating of T1D autoimmunity[5].

The emergence of coronavirus disease 2019 (COVID-19), attributable to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), marked a global pandemic with profound health implications. The association between viral infections and the onset of T1D has been the subject of considerable research. The mechanisms by which viral infection causes pancreatic β-cells destruction include direct infection of islets by viruses, indirect damage of the islet through microvascular inflammation, a hypercoagulable state, thrombosis of pancreatic blood vessels, and development of autoimmunity due to molecular mimicry, loss of immunologic self-tolerance, bystander activation, epitope spreading and persistent infections[6,7]. Enterovirus infection, particularly coxsackieviruses B infections is strong associated with T1D[8], and a phase 2 randomized trial revealed that antiviral treatment may preserve the β-cell function in new-onset T1D children[9]. Given its recent emergence, there is significant research interest in exploring any potential links between SARS-CoV-2 and the development of T1D. Epidemiological evidence had indicated a rise in diabetes incidence during the pandemic, surpassing the pre-existing rates[10-14]. *Ex vivo* research has implicated SARS-CoV-2 in the direct infection of pancreatic β-cells, potentially precipitating insulin secretion decline, β-cell apoptosis, and trans-differentiation[13,15-17]. Furthermore, a meta-analysis of 124597 children with diabetes found that the incidental risk of diabetic ketoacidosis (DKA) significantly increased during the COVID-19 pandemic in newly diagnosed T1D patients[18] , and a study on Korean children also found the same results[19].

Current investigations into the link between COVID-19 infection and DKA incidence in pediatric and adolescent populations have focused predominantly on the European and the United States regions[13,16,17,20,21], with a dearth of data from Asian cohorts[19,22]. Our study addressed the critical gap in the knowledge concerning not only the correlation between COVID-19 infection and the risk of DKA in new-onset Chinese pediatric T1D patients but also the clinical and immunological characteristics of post-COVID-19-onset T1D children. Furthermore, apprehensions regarding the possible relationship between COVID-19 vaccination and the onset of hyperglycemia and DKA have emerged[23,24]. In light of these considerations, this study aimed to elucidate the differential impacts of inactivated COVID-19 vaccine administration and natural infection on T1D, providing early intervention clues for potential adverse reactions that might arise from vaccination campaigns during similar future epidemics.

MATERIALS AND METHODS

Study population

This study retrospectively collected data on children with diabetes who were admitted to the Children's Hospital of Fudan University between September 2020 and December 2023. The research covered important time points before and after mass infection in the population and the wide acceptance of COVID-19 vaccination for children to better understand the impact of COVID-19 infection and vaccination on pediatric T1D. A total of 277 patients under the age of 18 with newly diagnosed diabetes were included in the study. The diagnosis of T1D was based on the criteria of the International Society for Pediatric and Adolescent Diabetes[2]. Patients were excluded from the study if they were less than one year old, had a disease course longer than one month, tested negative for diabetes-related autoantibodies, were diagnosed with other types of diabetes, or lacked important data including COVID-19 infection or vaccination history (Supplementary Figure 1).

This study was approved by the Ethics Commission of Children's Hospital of Fudan University (No. 2022-183). All participants and their guardians, who were included in this study, signed a consent form upon admission, confirming that their clinical data during hospitalization could be utilized for research purposes.

Data collection and measurements

The hospital information system obtained the clinical characteristics of patients with T1D. These characteristics included sex, age, time of visit, fasting blood glucose, glycated hemoglobin (HbA1c), fasting serum C-peptide, human leukocyte antigen (HLA) genotype, and history of COVID-19 infection and vaccination. A history of COVID-19 infection was defined as the presence of symptoms and positive self-tested antigen or nucleic acid tests. Autoantibodies, including glutamic acid decarboxylase antibody (GADA), autoantibodies against insulin (IAA), protein tyrosine phosphatase antibody (IA-2A), islet cell antibodies (ICA), and zinc transporter 8 autoantibodies (ZnT8A), were tested. GADA was detected *via* the chemiluminescence method, IA-2A was detected using radioimmunoassay, ICA and ZnT8A were detected by immunoblotting, and IAA was detected *via* the radioligand assay.

HLA genotyping

HLA-DR/DQ genotypes were analyzed upon admission. The *HLA* genes were sequenced *via* polymerase chain reaction sequence-based typing and analyzed according to the IMGT/HLA database[25]. A total of 23 *HLA-DRB1* alleles, 13 *HLA-DQA1* alleles, and 14 *HLA-DQB1* alleles were detected.

Statistical analysis

The patients were classified into three groups based on their COVID-19 infection and vaccination history: The infection group (those with a history of COVID-19 infection), the vaccination-only group (those without a history of COVID-19 infection but with a history of COVID-19 vaccination), and the non-infected/non-vaccination group (those with neither a history of COVID-19 infection nor a history of COVID-19 vaccination). Statistical analysis was conducted using SPSS (v26). Categorical variables were compared *via* χ^2 tests. Differences between two groups for normally distributed continuous variables were compared using Student's *t*-test and one-way ANOVA, while the Mann-Whitney *U* test and the Kruskal-Wallis *H* test were used for variables that were not normally distributed. To assess the impact of COVID-19 infection and vaccination on the incidence rate of DKA individually, univariate binary logistic regression models were constructed. A multivariate binary logistic regression model was subsequently developed to evaluate the combined effect of a history of COVID-19 infection and vaccination on the DKA incidence rate, adjusting for potential confounders such as age and sex. *P* < 0.05 was considered significant.

RESULTS

Basic characteristics

Over the study period, our center admitted 277 patients with diabetes for their initial visit. Among these, 197 patients were included in the analysis, comprising 94 girls (47.7%) and 103 boys (52.3%). The average age of onset was 8.10 ± 3.47 years (ranging from 1.3 to 16.6 years). DKA was the initial presentation in 116 patients, presenting 58.9% of the study population. The mean HbA1c level was 11.92% ± 1.83%, and the mean fasting C-peptide level was 0.24 ± 0.22 ng/mL.

The association between COVID-19 infection/vaccination and the onset of T1D

Among the 197 children in our study, 57 (28.9%) had a documented COVID-19 infection preceding the diagnosis of T1D, and 110 (55.8%) had received COVID-19 vaccination. The mean age at T1D onset was significantly lower in the non-infection/non-vaccination group (6.53 ± 3.41 years) than in the COVID-19 infected (8.75 ± 3.65 years) and vaccination-only groups (9.21 ± 2.75 years; *P* < 0.001). However, baseline HbA1c levels (11.83% ± 1.71% in the infected group, 12.02% ± 1.85% in the vaccinated group, and 11.90% ± 1.92% in the non-infection/non-vaccination group; *P* = 0.838) and fasting C-peptide levels (0.26 ± 0.25 ng/mL in the infected group, 0.26 ± 0.18 ng/mL in the vaccinated group, and 0.22 ± 0.21 ng/mL in the non-infection/non-vaccination group; *P* = 0.365) showed no significant intergroup differences (Table 1).

Notably, the prevalence of DKA peaked in the COVID-19 infected group at 70.2% (40/57), surpassing the non-infection/non-vaccination (62.5%, 45/72) and vaccination-only groups (45.6%, 31/68; *P* = 0.015). The subgroup analysis of the COVID-19 infected group revealed that children with a vaccination history had a lower prevalence of DKA than those

Table 1 Clinical characteristics of newly-onset type 1 diabetes children with and without coronavirus disease 2019 infection history

Variables	Total (*n* = 197)	Infection group[1] (*n* = 57)	Vaccination only group[2] (*n* = 68)	Non-infection/non-vaccination group[3] (*n* = 72)	*P* value
Female, *n* (%)	94 (47.7)	29 (50.9)	30 (44.1)	35 (48.6)	0.739
Age (year)	8.10 ± 3.47	8.75 ± 3.65	9.21 ± 2.75	6.53 ± 3.41	< 0.001
HbA1c (%)	11.92 ± 1.83	11.83 ± 1.71	12.02 ± 1.85	11.90 ± 1.92	0.838
Fasting C-peptide (ng/mL)	0.24 ± 0.22	0.26 ± 0.25	0.26 ± 0.18	0.22 ± 0.21	0.365
DKA, *n* (%)	116 (58.9)	40 (70.2)	31 (45.6)	45 (62.5)	0.015
Autoantibodies, *n* (%)					
GADA	142 (72.1)	32 (56.1)	52 (76.5)	58 (80.6)	0.005
IAA	50 (25.4)	14 (24.6)	15 (22.1)	21 (29.2)	0.618
IA-2A	140 (71.1)	44 (77.2)	48 (70.6)	48 (66.7)	0.422
ICA	13 (6.6)	5 (8.8)	5 (7.4)	3 (4.2)	0.551
ZnT8A	8 (4.1)	2 (3.6)	1 (1.5)	5 (6.9)	0.256

[1]Infection group: Children with coronavirus disease 2019 (COVID-19) infection history.

[2]Vaccination only group: Children with COVID-19 vaccination history but without COVID-19 infection history.

[3]Non-infection/non-vaccination group: Children had neither COVID-19 vaccination history nor COVID-19 infection history.

Values are expressed as mean ± SD or frequencies (%). DKA: Diabetic ketoacidosis; GADA: Glutamic acid decarboxylase antibody; IAA: Autoantibodies against insulin; IA-2A: Protein tyrosine phosphatase antibody; ICA: Islet cell antibodies; ZnT8A: Zinc transporter 8 autoantibodies.

without a vaccination history [64.3% (27/42) *vs* 86.7% (15/17)]. However, the difference was not statistically significant (*P* = 0.104). Regardless of vaccination status, univariate binary logistic regression analysis revealed that the risk of DKA among children with prior COVID-19 infection was significantly elevated, 1.981-fold higher compared to children without a history of COVID-19 infection (95%CI: 1.026-3.825, *P* = 0.042). Conversely, vaccination was associated with a reduced risk of DKA (OR: 0.558, 95%CI: 0.312-0.998; *P* = 0.049). After adjusting for age and sex, these associations persisted when the history of infection and the history vaccination were included in the same model (Supplementary Table 1).

COVID-19 infection correlated with variations in the seropositivity of autoantibodies related to T1D. Specifically, the rate of GADA seropositivity was significantly lower in the COVID-19 infected group (56.1%) compared to the non-infection/non-vaccination (76.5%) and the vaccinated-only groups (80.6%, *P* = 0.005; Table 1). Additionally, GADA titers peaked in the non-infection/non-vaccination group and decreased sequentially throughout the vaccinated and infected groups (*P* = 0.002) (Figure 1). While the seropositivity rates of IAA and IA-2A did not differ significantly across the groups, the titers of IAA were notably higher in the non-infection/non-vaccination group (*P* < 0.001), and IA-2A titers were elevated in the infected group (*P* = 0.021).

COVID-19 infection promotes the onset of T1D among HLA-DR3 positive children

Given the established link between the *HLA* genotype and immune function, and its implications in infectious and autoimmune diseases, we further analyzed the effect of COVID-19 infection on T1D development across various *HLA* genotypes. Among the 197 enrolled patients, *HLA* class II alleles, specifically *HLA-DRB1*, *HLA-DQB1*, and *HLA-DQA1*, were genotyped in 147 cases. Our analysis did not reveal a correlation between specific *HLA* types and T1D onset following COVID-19 infection or vaccination. Nonetheless, within the COVID-19 infected subgroup, individuals positive for *HLA-DR3* exhibited an earlier age of T1D diagnosis (mean age 7.67 years ± 3.80 *vs* 9.88 years ± 3.10, *P* = 0.030) and lower fasting C-peptide levels (mean 0.16 ± 0.13 ng/mL *vs* 0.35 ± 0.31 ng/mL, *P* = 0.007) compared to the non-*HLA-DR3* individuals (Figure 2). However, among children without a history of COVID-19 infection, there were no significant differences in the age of onset or fasting C-peptide level between patients who were *HLA-DR3* positive and those who were negative. These findings suggest a potentially accelerated T1D pathogenesis in HLA-DR3 positive individuals post-COVID-19 infection.

The impact of COVID-19 infection and vaccination on the immune spectrum

Our analysis revealed that COVID-19 infection and vaccination moderately influence on lymphocyte subpopulations and immunoglobulin profiles. Children with a documented COVID-19 infection exhibited reduced CD16+/CD56+ T cell counts compared to their non-infected counterparts (Figure 3A and Supplementary Table 2). The CD4+ to CD8+ T cell ratio was the lowest in the vaccinated cohort, followed by the infected and non-infection/non-vaccination groups following in succession. Additionally, both COVID-19 infected and vaccinated children presented elevated IgG and IgA levels (Figure 3B and C and Supplementary Table 2)
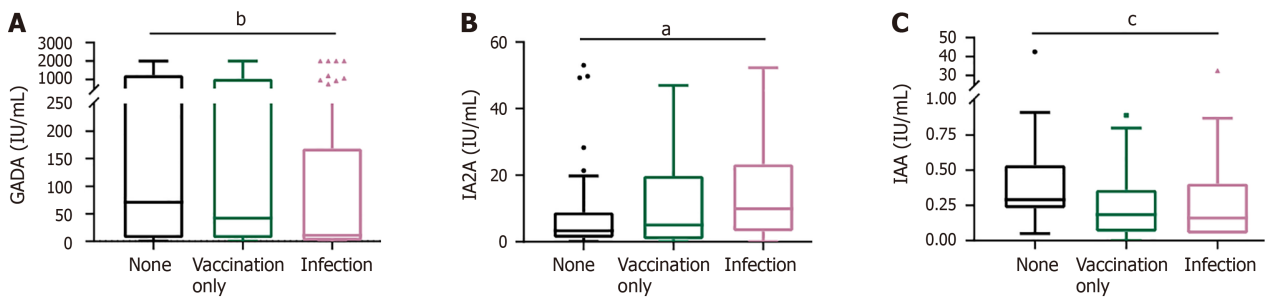
Figure 1 Titers of diabetes related antibodies among type 1 diabetes patients with and without coronavirus disease 2019 infection/vaccination history. A: Difference in glutamic acid decarboxylase antibody titers; B: Difference in tyrosine phosphatase antibody titers; C: Difference in autoantibodies against insulin titers. $^aP < 0.05$, $^bP < 0.01$, $^cP < 0.001$. GADA: Glutamic acid decarboxylase antibody; IA2A: Tyrosine phosphatase antibody; IAA: Autoantibodies against insulin. None: The non-infection/non-vaccination group [those with neither a history of coronavirus disease 2019 (COVID-19) infection nor a history of COVID-19 vaccination]; Vaccination only: The vaccination-only group (those without a history of COVID-19 infection but with a history of COVID-19 vaccination); Infection: The infection group (those with a history of COVID-19 infection).
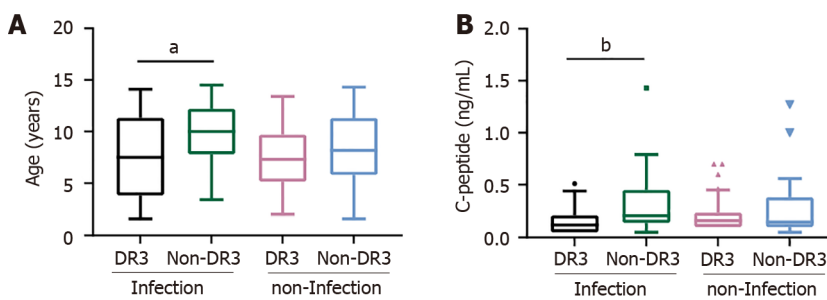

Figure 2 Clinical profiles of DR3-positive and DR3-negative patients with and without the coronavirus disease 2019 infection history. A: The difference of onset age between DR3 positive and DR3 negative patients with and without the coronavirus disease 2019 (COVID-19) infection history; B: The difference of onset age and fasting C-peptide level between DR3 positive and DR3 negative patients with and without the COVID-19 infection history. $^aP < 0.05$, $^bP < 0.01$.
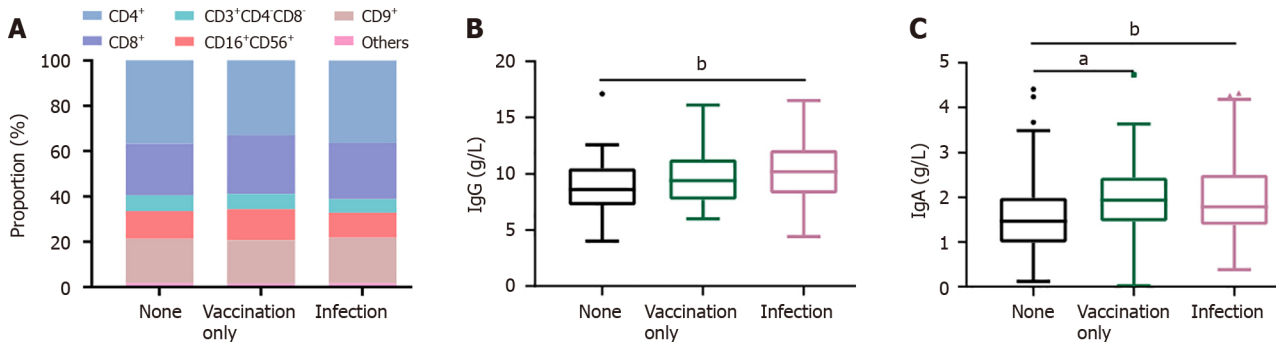

Figure 3 Immune spectrum of type 1 diabetes patients with and without a history of coronavirus disease 2019 infection/vaccination. A: Proportion of different lymphocyte types; B: Differences in IgG; C: Differences in IgA. None: The non-infection/non-vaccination group [those with neither a history of coronavirus disease 2019 (COVID-19) infection nor a history of COVID-19 vaccination]; Vaccination only: The vaccination-only group (those without a history of COVID-19 infection but with a history of COVID-19 vaccination); Infection: The infection group (those with a history of COVID-19 infection). $^aP < 0.05$, $^bP < 0.01$.

DISCUSSION

Our study offered novel insights into the clinical and immunological profiles at the onset of T1D in Chinese pediatric patients during the COVID-19 pandemic. We further explored the correlation between these clinical manifestations and a history of COVID-19 infection or receipt of inactivated vaccines. Notably, our findings indicated that COVID-19 infection was associated with a more aggressive T1D phenotype, characterized by an increased risk of DKA, earlier age of disease onset, and reduced fasting C-peptide levels in *HLA-DR3*-positive individuals. Conversely, we reported for the first time that inactivated COVID-19 vaccination is linked to a diminished risk of DKA at T1D presentation.

Our study indicated that children with a preceding COVID-19 infection were at a significantly greater risk of DKA at T1D onset, with an observed incidence 3.203 times greater than in non-infected peers. This observation was corroborated

by studies from Italy, Canada, and Iran, which reported a marked increase in DKA incidence among children with new-onset diabetes during the COVID-19 pandemic[10,26,27]. While the precise mechanisms remain elusive, potential contributors include pandemic-driven lifestyle alterations and healthcare system disruptions that might delay diagnosis. However, the viral infection itself is implicated in β-cell destruction and the modulation of the autoimmune response. Notably, COVID-19 infection is associated with an exaggerated pro-inflammatory cytokine response, particularly IL-6, which may precipitate DKA[28,29]. Furthermore, evidence suggests that SARS-CoV-2 can directly impact pancreatic β-cells, as indicated by the detection of viral antigens in autopsy samples and the observed cellular trans-differentiation and reduced insulin expression mediated by the eIF2 pathway[30]. *In vitro* studies have also demonstrated β-cell death and impaired insulin secretion following SARS-CoV-2 infection[31]. We propose that SARS-CoV-2-induced pancreatic β-cell apoptosis could contribute to the elevated incidence of DKA observed in individuals with new-onset T1D following COVID-19 infection. The link between COVID-19 and DKA is supported primarily by anecdotal clinical case reports, lacking definitive evidence of causality. Future research should delve into the underlying mechanisms, and comparative analyses of DKA incidence after infection by other pathogens could provide valuable insights into the distinct association between COVID-19 and DKA precipitation.

Genetic and immunological heterogeneity likely influences the risk and severity of T1D following COVID-19 infection. Prior research has indicated that specific *HLA* genotypes, such as low heterozygosity for *HLA* class I loci, might be linked to increased COVID-19 severity[32], and specific high-risk *HLA* genotypes are correlated with a propensity for DKA at T1D onset[33]. These findings suggest that distinct populations could be predisposed to DKA or more severe T1D following COVID-19 infection. While our study did not identify HLA genotypes predictive of DKA risk, we observed that children with *HLA-DR3* exhibited earlier T1D onset and reduced fasting C-peptide levels post-infection, potentially related to the antigen presentation processes. Further research is warranted to delineate the attributes of populations particularly vulnerable to T1D and DKA following COVID-19.

Concurrently, the impact of COVID-19 vaccination on T1D and DKA incidence is under scrutiny. Isolated reports described vaccine-induced hyperglycemia and DKA, with cases of type 2 diabetes and hyperosmolar hyperglycemic syndrome emerging shortly after mRNA COVID-19 vaccination[34,35]. Additionally, instances of hyperglycemic hyperosmolar syndrome (HHS) and DKA have been documented in three UK patients within 20-36 days post-vaccination with an adenoviral COVID-19 vaccine, including two with a prediabetes history[23]. Interestingly, in contrast to existing case reports, our study revealed a reduced risk of DKA at the onset of diabetes among children vaccinated against COVID-19. This observation suggested that distinct vaccine formulations might influence the risk of DKA during initial diabetes presentation. Given that our cohort exclusively received inactivated COVID-19 vaccines, the only type authorized for children aged 3-17 years in China in 2021, our findings contrast with data on other vaccine platforms. mRNA vaccines, known to elicit robust neutralizing antibody and T-cell responses, may confer quicker immune protection but have been associated with a shorter interval to HHS and/or DKA onset based on case reports. Conversely, inactivated vaccines, which typically induce a less vigorous immune reaction, were associated with a lower DKA risk in our patient population. The milder immune response potentially afforded by inactivated vaccines could underlie the observed reduction in DKA risk post-vaccination.

Our study revealed subtle yet noteworthy alterations in the immunological profiles of children with T1D who had a prior COVID-19 infection and/or vaccination, characterized by elevated IgA and IgG levels and diminished CD16+CD56+ natural killer (NK) cell counts. Both the absolute numbers and function of NK cells were reported to be compromised by COVID-19 infection[36]. Consistent with these observations, an immunocytochemistry assessment conducted in Kuwait in 2022 revealed a marked reduction in CD56+ NK cells among COVID-19 patients compared to healthy controls and vaccinated individuals[37]. Persistent NK cell reduction is a characteristic of severe COVID-19 infection, and the more severe the infection is, the longer it takes for the NK cell function to return to normal[38,39]. A notable reduction in the presence of NK cells was observed in newly-onset patients with T1D, and this diminution persisted throughout the phases of partial remission and disease progression. The observed decrease in peripheral NK cells could be attributed to their active translocation toward the pancreas and draining nodes, potentially playing a pivotal role in the immunopathogenesis of T1D[40,41]. The reduction of peripheral blood NK cells in T1D patients with a history of COVID-19 infection might be associated with the migration of a greater number of functional NK cells to the peri-pancreatic region. This may explain why these patients might exhibit a more severe pancreatic inflammatory response, potentially leading to the onset of a more severe form of the disease, such as presenting with DKA. Future mechanistic research would further validate this hypothesis. Additionally, more refined subtyping of immune cells in the future could provide a better understanding of how COVID-19 infection participates in the pathogenesis of T1D by affecting the immune system. Additionally, the observed elevation in IgA and IgG merits consideration, especially given evidence that T1D patients exhibit heightened serum IgA levels, which might be implicated in β-cell autoimmunity through the modulation of mucosal immunity[42,43]. Infection and vaccination may affect the structure of the gut microbiota and IgA mucosal immunity. Future studies are needed to further analyze the mechanism behind these phenomena.

Our study had several limitations. Firstly, this was a single-center retrospective study, and the study population might not be representative enough due to the geographical location and selection bias. However, as one of the largest tertiary centers in China, our results may represent the condition in eastern China to some extent. Future population-based cohort studies or multicenter prospective studies will provide more persuasive evidence. Secondly, as the history of COVID-19 infection was obtained from the hospital information system with symptoms reported by parents and positive self-tested antigen or nucleic acid tests, there was possibility of missing COVID-19 infection history due to asymptomatic infection or underreporting. However, we believe that the impact of underreporting on the overall results was minimal due to the low population COVID-19 infection rate and strict monitoring measures in Shanghai during most of the study period. Thirdly, as a retrospective study, the clinical data for analysis were obtained through the hospital information system, and the exact duration of COVID-19 infection could not be obtained. However, our study is one of the few studies in

children to show that the incidence of DKA was significantly higher in patients with new-onset T1D after COVID-19 infection, while history of inactivated COVID-19 vaccination did not affect the risk of DKA.

CONCLUSION

Our findings, which revealed modest changes in the immune profiles of children with a history of COVID-19 infection, suggested that the virus could modulate immune responses, potentially leading to a more severe onset of T1D, especially in *HLA-DR3* positive children. Moreover, our study found that inactivated COVID-19 vaccination was associated with a significantly reduced incidence of DKA at T1D onset. Our results advocate for the inclusion of T1D risk assessment in the post-COVID-19 public health surveillance, especially among *HLA DR3* positive individuals with a history of COVID-19. They also provide valuable insights that could guide future research to explore the long-term effects of COVID-19 and the impact of different vaccination strategies on immune function, T1D incidence and severe T1D presentations, in order to inform the development of targeted public health policies and optimize vaccination strategies during epidemic scenarios.

FOOTNOTES

Author contributions: Luo FH and Zhang MY contribute equally to this study as co-corresponding authors. Zhang MY, Xu ZR and Luo FH designed the study, analyzed and interpreted data, wrote and revised the manuscript; Xi L contributed to patient management and data collection; Wu J and Ni JW contributed to acquisition of data and drafting the article; all authors contributed to final approval of the version to be published.

Institutional review board statement: This study was approved by the Ethics Commission of Children's Hospital of Fudan University (No. 2022-183).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data retrospectively. All included patients signed informed consent forms during hospitalization and agreed to use their clinical data for future research.

Conflict-of-interest statement: No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Data sharing statement: Data of the current study are available from the corresponding author on reasonable request.

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