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ORIGINAL ARTICLE

Comorbidities increase COVID-19 hospitalization in young people with type 1 diabetes

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Abstract

Objectives: We evaluated COVID-19 outcomes in children and young adults with type 1 diabetes (T1D) to determine if those with comorbidities are more likely to experience severe COVID-19 compared to those without.

Research Design and Methods: This cross-sectional study included questionnaire data on patients <25 years of age with established T1D and laboratory-confirmed COVID-19 from 52 sites across the US between April 2020 and October 2021. We examined patient factors and COVID-19 outcomes between those with and without comorbidities. Multivariate logistic regression analysis examined the odds of hospitalization among groups, adjusting for age, HbA1c, race and ethnicity, insurance type and duration of diabetes.

Results: Six hundred fifty-one individuals with T1D and COVID-19 were analyzed with mean age 15.8 (SD 4.1) years. At least one comorbidity was present in 31%, and more than one in 10%. Obesity and asthma were the most frequently reported comorbidities, present in 19% and 17%, respectively. Hospitalization occurred in 17% of patients and 52% of hospitalized patients required ICU level care. Patients with at least one comorbidity were almost twice as likely to be hospitalized with COVID-19 than patients with no comorbidities (Odds ratio 2.0, 95% CI: 1.3–3.1). This relationship persisted after adjusting for age, HbA1c, race and ethnicity (minority vs nonminority), insurance type (public vs. private), and duration of diabetes.

Conclusions: Our findings show that comorbidities increase the risk for hospitalization with COVID-19 in children and young adults highlighting the need for tailored COVID-19 prevention and treatment strategies in T1D.

KEYWORDS
comorbidities, COVID-19, type 1 diabetes

Abbreviations: AYA, adolescents and young adults; COVID-19, Coronavirus disease 2019 associated with SARS-CoV2; T1D, type 1 diabetes.

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1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) primarily causes lower respiratory tract infections, and clinical manifestations are diverse, ranging from no symptoms to fever, cough, and dyspnea or gastrointestinal symptoms to severe respiratory compromise. Severe COVID-19 has been defined as infection requiring inpatient care for treatment and respiratory support.[1] The few reports on outcomes for children or adults with type 1 diabetes (T1D) are mixed in terms of severity of disease and mortality compared to people without diabetes.[2–6] For adults with type 1 diabetes (T1D), having a co-existing medical diagnosis such as cardiovascular disease, hypertension, or renal disease increases the risk of suffering from severe COVID-19 and adverse outcomes.[4,5,7–11] However, few published studies examine the relationship between comorbidities and severity of COVID-19 infection in children with T1D.

While most children with COVID-19 either experience mild or no symptoms, severe complications including acute respiratory distress syndrome (ARDS), multisystem inflammatory syndrome (MIS-C) and death can occur.[12–16] A meta-analysis found that children with underlying chronic conditions were at increased risk of severe COVID-19 and mortality.[17] Obesity was the most prevalent diagnosis in this cohort and was independently associated with an increased risk of severe COVID-19. Children with asthma are also suggested to have an increased risk of severe COVID-19.[18] As obesity and asthma have been proposed risk factors for severe COVID-19 in children, it is possible these comorbidities increase the risk of hospitalization for children with T1D who develop COVID-19. We evaluated characteristics and outcomes of COVID-19 in children, adolescents, and young adults (AYA) with T1D to determine if children and AYA with established T1D and comorbidities are more likely to experience severe COVID-19 compared to those without comorbidities.

2 | METHODS

The T1D Exchange QI Collaborative,[19] a population health research network, sponsored a cross-sectional study of 52 adult and pediatric endocrinology clinics across the United States. A central review board, the Western IRB, deemed the study as exempt. Participating sites also obtained local institutional review board approvals as appropriate.

A designated representative from each participating site submitted data using the online survey software via Qualtrics, version XM (www.qualtrics.com). One questionnaire was completed for every patient known to the local clinical team with a previously established diagnosis of T1D and a laboratory confirmed case of COVID-19 between April 2020 and October 2021. During this timeframe, the Centers for Disease Control recommended clinicians work with local and state health departments to coordinate COVID-19 testing through public health laboratories for individuals with signs and symptoms compatible with COVID-19.[20] The questionnaires collected deidentified data using 33 pre-coded and free text questions, and the complete questionnaire is available in Appendix 1. The coordinating center reviewed questionnaires for possible errors in data entry or incomplete information and performed random data validation for quality assurance. Details of the questionnaire and data from the T1D COVID-19 registry have been previously reported.[12,21–26]

2.1 | Inclusion criteria

All patients submitted by participating centers with COVID-19 and T1D ages 0–24 years at time of reporting were included in this study. Emerging adults ages 19–24 years were included in this analysis because many pediatric endocrinology clinics follow patients through this age, and explore how this population is affected by COVID-19. An individual was entered into the registry as COVID-19 positive if they tested positive by molecular testing (reverse transcription-polymerase chain reaction) from nasopharyngeal swabs, throat swabs, sputum, or other bodily fluid testing. We excluded from this analysis any patients that were newly diagnosed with T1D during their COVID-19 illness, and these cases are described separately.[23]

2.2 | Comorbidities

Participating centers entered comorbidity data for each patient by selecting one or more diagnoses from a pre-populated list. The list included obesity, asthma, cardiovascular disease, other chronic lung disease, hypertension, and celiac disease, among others. There was also an opportunity to add free text or to select none.

2.3 | Primary outcome

The primary outcome was hospitalization during COVID-19 illness in individuals with known T1D as a marker of severe COVID-19.[1] As a binary outcome, hospitalization was defined as admission to general inpatient care or an intensive care unit as the highest level of care received during COVID-19 illness. Non-hospitalization was defined as receiving care in a clinic, urgent care, or emergency department setting or receiving care at home.

2.4 | Additional covariates

Patient-specific information was collected on additional variables of interest that included sociodemographic information (age, sex,

and health insurance type), and diabetes characteristics (most recent HbA1c, duration of T1D, use of continuous glucose monitoring [CGM] or insulin pump). Race and ethnicity were also collected as a social construct rather than genetic or biological categories. Adverse outcomes collected included diabetic ketoacidosis (DKA), severe hypoglycemia, death, and an option to write in others.

2.5 | Statistical analyses

Descriptive statistics were used to describe the study population and summarize study data. Patient outcomes, comorbidities, and demographics were analyzed as categorical variables when appropriate. Race and ethnicity information were collected in the questionnaire as a categorical variable with potential responses including: Non-Hispanic White, Non-Hispanic Black, Asian, Hispanic, more than one race, other, or unknown per US Census criteria.[27] The race and ethnicity variable for this analysis was constructed with 4 groups: Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Hispanic, and other. Health insurance type was classified as either public, private, or unknown. Duration of diabetes was collected as a categorical variable with potential responses including: less than 1 year, 1–5 years, or greater than 5 years. Use of an insulin pump and use of CGM were also analyzed as binary (yes/no) variables. The use of both an insulin pump and CGM in the same patient was analyzed separately. Patient age and last reported HbA1c value were collected and analyzed as continuous variables. Continuous variables were analyzed using mean (SD) or median (IQR) as appropriate based on data distribution. Categorical variables were shown as the percentage of patients. *p*-values were calculated using the Fisher exact or chi-square tests to examine the association between the categorical variables.

Logistic regression was used to evaluate the association between hospitalization and the presence of comorbidities. Patients were excluded from this analysis if hospitalization status was unknown. Comorbidities were analyzed individually and collectively, each as a binary (yes/no) variable. Models were adjusted for age, HbA1c, race and ethnicity, insurance type, and duration of diabetes. The socially constructed variables of race and ethnicity were chosen for model adjustment because of the differential burden of COVID-19 disease in minoritized populations.

TABLE 1 Patient characteristics values reported as % unless otherwise indicated

	Total ($n = 651$)	Any comorbidity ($n = 199$)	No comorbidities ($n = 452$)	*p*-value of comorbidity vs no comorbidity
Median age, years (Q1-Q3)	16.0 (13.0–19.0)	17.0 (14.0–20.0)	16.0 (13.0–19.0)	<0.001
Female sex	52.1	56.3	50.2	0.2
Race/ethnicity				0.005
NHW	61.0	51.3	65.3	<0.001
NHB	12.6	15.1	11.5	0.3
Hispanic	20.6	27.6	17.5	0.004
Other	5.8	6.0	5.8	0.9
Health insurance type				0.2
Public	40.1	44.7	38.1	0.1
Private	56.7	52.8	58.4	0.2
Unknown	3.2	2.5	3.5	0.9
HbA1c Median (Q1–Q3)	8.4 (7.3–10.2)	8.6 (7.5–10.1)	8.4 (7.3–10.2)	0.2
Duration of T1D, years				<0.001
<1	7.7	4.5	9.1	0.06
1–5	41.3	31.7	45.6	0.001
> 5	51.0	63.8	45.4	<0.001
CGM use	67.0	60.3	70.0	0.02
Insulin pump use	49.0	47.2	49.8	0.6
Highest level of care				0.01
Hospitalized	16.7	23.1	13.9	0.01
Inpatient	8.9	12.6	7.3	0.1
ICU	7.8	10.6	6.6	0.04
Non-Hospitalized	83.3	76.9	86.1	0.005
DKA at COVID-19 diagnosis	12.3	15.1	11.1	0.4

TABLE 2 Comorbidities by Race and Ethnicity (% of patients in race/ethnic group)

	Total ($n = 651$)	NHW ($n = 397$)	NHB ($n = 82$)	Hispanic ($n = 134$)	Other ($n = 38$)	p-value comparing race/ethnic groups
Number of patients with any comorbidity (n)	199	102	30	55	12	0.005
Number of comorbidities						
1	68.3	71.6	60.0	69.1	58.3	0.5
2–4	28.6	27.5	33.3	27.3	33.3	0.9
5+	3.0	1.0	6.7	3.6	8.3	0.1
Type of comorbidity						
Obesity	18.6	16.7	20.0	21.8	8.3	0.7
Asthma	16.6	11.8	36.7	14.5	16.7	0.02
Celiac disease	10.1	12.7	6.7	1.8	33.3	0.005
Thyroid disease	14.1	18.6	0.0	12.7	16.7	0.03
Hospitalization (yes)	23.1	15.7	50.0	23.6	16.7	0.002

TABLE 3 Comorbidities by insurance Type (% of patients in insurance type group)

	Total ($n = 651$)	Public insurance ($n = 261$)	Private insurance ($n = 369$)	p-value
Number of patients with any comorbidity (n)	199	89	105	0.3
Number of comorbidities				
1	68.3	69.7	66.7	0.8
2–4	28.6	25.8	31.4	0.6
5+	3.0	3.4	1.9	0.1
Type of comorbidity				
Obesity	18.6	25.8	13.3	0.05
Asthma	16.6	24.7	9.5	0.01
Celiac disease	10.1	4.5	13.3	0.01
Thyroid disease	14.1	11.2	15.2	0.1
Hospitalization (Yes)	13.1	34.8	13.3	0.001

3 | RESULTS

A total of 651 individuals ages 0–24 years with established T1D and confirmed COVID-19 were included in this analysis. Mean age was 15.8 years (4.1 SD), 52% female sex, and 40% had public health insurance. Median (Q1–Q3) HbA1c was 8.4% (7.3, 10.2) and 67% were using CGM. At least one comorbidity was present in 31%, and 10% had more than one comorbidity. Demographics, diabetes characteristics, comorbidities and outcomes are summarized in Table 1.

The most frequently reported comorbidities were obesity and asthma, present in 19% and 17% of those with comorbidities, respectively (Table 2). Compared to patients without comorbidities, those with comorbidities were older (mean age 16.7 ± 4.0 vs. 15.4 ± 4.3 years) and less likely to use CGM (60% vs. 70%, $p = 0.02$). Frequency of comorbidities also varied by race and ethnicity: 26% in NHW, 37% in NHB, and 41% in Hispanic patients. Of those with comorbidities, asthma prevalence varied by race and ethnicity affecting 37% of NHB, 12% of NHW and 15% of Hispanic patients ($p = 0.02$). Obesity prevalence did not vary significantly by race and ethnicity. There was no difference in comorbidities in patients with public versus private insurance (34% vs. 29%, p = 0.3) (Table 3).

Hospitalization occurred in 17% of patients with COVID-19 and T1D, and 52% of hospitalized patients required ICU level care. DKA occurred in 12% of all patients, and there were no deaths, as previously described.[8] Patients with at least one comorbidity had higher rates of hospitalization and ICU level care (23% vs. 14%, $p = 0.01$ and 11% vs. 7%, $p = 0.04$, respectively) (Table 1). Rates of hospitalization among patients with comorbidities varied by race and ethnicity, occurring in 50% of NHB patients compared to 24% of Hispanic patients and only 16% of NHW patients ($p = 0.002$) (Table 2). Among patients with comorbidities, hospitalization occurred in 35% of those with public insurance, compared to only 13% of those with private insurance ($p = 0.001$) (Table 3).

Logistic regression analyses examining the association between the presence of any comorbidity and hospitalization among patients with confirmed COVID-19 and T1D are presented in Table 4. Patients with at least one comorbidity had almost twice the odds of being hospitalized with COVID-19 than did patients with no comorbidities

TABLE 4 Logistic regression for hospitalization among patients with confirmed COVID-19 and type 1 diabetes

	Model A	Model B	Model C	Model D
Any comorbidity	2.00 (1.29, 3.08)	2.12 (1.28,3.54)	2.02 (1.20, 3.37)	1.98 (1.18, 3.34)
	0.001	0.003	0.007	0.009
Number of comorbidities (continuous)	1.33 (1.08, 1.63)	1.47 (1.15, 1.86)	1.41 (1.10, 1.79)	1.37 (1.07, 1.74)
	0.005	0.001	0.004	0.01
Obesity	1.45 (0.60, 3.14)	0.90 (0.33, 2.22)	0.83 (0.30, 2.07)	7.26 (0.25 1.85)
	0.3	0.8	0.7	0.5
Asthma	2.90 (1.31, 6.12)	2.68 (1.07, 6.41)	2.33 (0.91, 5.61)	2.14 (0.82, 5.28)
	0.006	0.03	0.06	0.1
Celiac disease	0.29 (0.01, 1.46)	0.24 (0.01, 1.42)	0.27 (0.01, 1.62)	2.20 (0.01, 1.41)
	0.3	0.2	0.2	0.2

Note: $N = 628$ Values presented as odds ratio with 95% CI. Model A: Unadjusted. Model B: Adjusted for age and a1c. Model C: Adjusted for age, a1c, race and ethnicity, insurance. Model D: Adjusted for age, a1c, race and ethnicity, insurance, duration of diabetes.

(odds ratio [OR] 2.0, 95% CI: 1.3–3.1). This relationship persisted after adjusting for age, HbA1c, race and ethnicity (minoritized populations vs. NHW), insurance type (public vs private), and duration of diabetes. Those with asthma had nearly three times the odds of hospitalization (OR 2.9, 95% CI: 1.3–6.1). This significantly increased odds persisted with adjustment for age and HbA1c (adjusted OR 2.7, 95% CI 1.1–6.4), but was no longer significant when adjusted for race and ethnicity (minoritized populations vs. NHW), insurance type (public vs private), and duration of diabetes. Obesity was not associated with odds of hospitalization. The number of comorbidities present in an individual patient (continuous variable) was also associated with hospitalization (adjusted odd ratio 1.4, 95% CI 1.1–1.7).

4 | DISCUSSION

This study examines a large, diverse cohort of children, adolescents and young adults with T1D and COVID-19 from across the US, and therefore offers novel insight into COVID-19 in this population. These findings demonstrate that children, adolescents and young adults with T1D and a coexisting medical condition have an additional risk for severe COVID-19 compared to those with T1D and no other chronic conditions. This finding is consistent with other studies in children without diabetes and in adults with diabetes in whom chronic medical conditions confer increased risk of severe COVID-19.[4,5,7,8,17,18,28]

Similar to many diseases, COVID-19 has disproportionately impacted children from racial and ethnic minority groups due to complex factors including systemic and structural racism.[29,30] Although COVID-19 affects children to a lesser extent than adults, NHB and Hispanic children have been hospitalized at higher rates with COVID-19 than have NHW children.[13,31] For people with T1D, racial and ethnic disparity also exists in adverse outcomes and severity of illness with COVID-19. Previously published data from this registry shows higher rates of DKA in NHB pediatric and adult patients with COVID-19.[24] Also from this registry, patients under 19 years of age were hospitalized at higher rates with COVID-19 if from a minoritized racial or ethnic group.[22] Understanding what drives disparity in outcomes and COVID-19 illness is critical to help identify at-risk populations, target vaccination strategies, and support equitable resource utilization. Nearly 1 in 3 youth with T1D in this cohort had at least one comorbidity, and comorbidities disproportionately affected those from racial and ethnic minority groups. This disparity has been suggested previously in an early cohort of 576 children without diabetes hospitalized with COVID-19 with higher rates of underlying conditions in Hispanic and NHB children (45.7% and 29.8%, respectively) compared to NHW children (14.9%).[13] Demonstrating racial and ethnic disparities in rates of comorbidities and a relationship between comorbidities and hospitalization may provide more understanding about the complex interplay of risk factors in the COVID-19 pandemic.

Asthma affects 7% of children in the US and disproportionately affects racial and ethnic minority groups and those living in poverty.[32,33] Asthma-related morbidity and mortality also disproportionately impact NHB Americans.[34] Asthma was the second most prevalent comorbidity in this population of children, adolescents, and young adults with T1D, and it was the only independent comorbidity found to be a risk factor for hospitalization. Asthma was disproportionately present in NHB patients and those with public health insurance. When adjusted for race, ethnicity and insurance type, asthma did not maintain its significance as a risk factor for hospitalization. As this relationship between asthma and severity of COVID-19 seems to be modified by other factors, more work is needed to understand the factors underlying these social constructs influence this association.

Like studies of children hospitalized with COVID-19 who do not have diabetes, this study found obesity as the most prevalent underlying medical condition in this cohort with T1D.[13,35,36] Childhood obesity is becoming increasingly prevalent in the US, now estimated to affect nearly one in every five children and is disproportionately affecting NHB and Hispanic children.[37] In youth with T1D, most recent estimates from the T1D Exchange[38] show obesity and overweight affecting more than one in three adolescents with T1D (13.1% and 22.9%, respectively).[39] Obesity is well recognized as a risk factor for severe COVID-19 in adults, and given the rising prevalence in children, understanding how obesity

impacts severity of COVID-19 illness in children is imperative.[7] Obesity was not an independent risk factor for severe COVID-19 in this study, and further case-control studies would help elucidate the effect of obesity on COVID-19 disease course in youth with T1D.

Celiac disease is more common individuals with type 1 diabetes compared those without, and has been associated with an increased susceptibility to bacterial and viral infections, and some reports have identified worse outcomes for these infections.[40–42] Similar to a large population-based study from Sweden,[43] this analysis found no association between Celiac disease and COVID-19 severity in this population.

Limitations of this study include its cross-sectional nature. While we cannot identify any causation between comorbidities and severity of COVID-19 disease in young people with T1D, the demonstrated relationships do allow identification of high-risk groups. Comorbidity data were entered into the study questionnaires based on electronic health record data, so some comorbidities may have been missed as diagnoses may not have been in the system at the time of data entry. To ensure collection of complete comorbidity data, there was no mechanism to grade severity of individual comorbidities. Therefore, the complex pathophysiology and etiology of asthma results in heterogenous disease and, as such, future work should evaluate the relationship and severity modifiers for comorbidities as they relate to COVID-19 infection. Some of the comorbidities included can be associated with other complications that may be associated with COVID-19 outcomes. For example, non-alcoholic liver disease associated with obesity has been associated with severity of COVID-infection in adults.[44] COVID-19 illness severity was based on highest level of care received at the time of data entry so patients who required escalating care after entry may have been missed. Finally, this study period encompassed a few waves of different COVID-19 variants, and as the nature of COVID-19 variants continues to change and COVID-19 vaccination is more available than during this study, it is uncertain how accurately these data extrapolate to future variants.

Finally, while investigators actively sought out COVID-19 cases in local populations, it is likely not all local cases were included given limitations of testing and reporting. Specifically, those not requiring hospitalization, and those with asymptomatic infection,[45] may have been missed. Therefore, this report likely overestimates hospitalization rate for children and AYA with T1D.

5 | CONCLUSION

This is the first multi-institutional surveillance study of children, adolescents, and young adults with T1D evaluating the impact of comorbidities on COVID-19 severity. Our findings show that comorbidities increase the risk for hospitalization with COVID-19, and racial, ethnic, and socioeconomic disparity may modify this risk. Our findings highlight the importance of tailoring COVID-19 prevention and treatment strategies in type 1 diabetes.

AUTHOR CONTRIBUTORS

Osagie Ebekozien conceptualized and designed the study, reviewed and revised the manuscript. Elizabeth A. Mann drafted the initial manuscript, reviewed and revised the manuscript. Osagie Ebekozien, Mary Pat Gallagher and Guy Todd Alonso are co-principal investigators for the surveillance study. They designed the data collection instruments, coordinated, and supervised data collection, and reviewed and revised the manuscript. Saketh Rompicherla performed the data analyses and reviewed and revised the manuscript. Mary Pat Gallagher, Guy Todd Alonso, Naomi R. Fogel, Simmons, Jamie R. Wood, Jenise C. Wong, Nudrat Noor, Patricia Gomez and Mark Daniels critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

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.

ETHICS STATEMENT

A central review board, the Western IRB, deemed the study as exempt. Participating sites also obtained local institutional review board approvals as appropriate.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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