Title

Congenital anomalies and predisposition to severe COVID-19 among pediatric patients in the United States.

Journal

Pediatric Research, 96(3)

Authors

Goodman, Laura
Yu, Peter
Guner, Yigit
et al.

Publication Date

2024-08-01

DOI

10.1038/s41390-024-03076-9

Peer reviewed

APS European Society for Paediatric Research SPR Society for Pediatric Research

POPULATION STUDY ARTICLE OPEN

Check for updates

Congenital anomalies and predisposition to severe COVID-19 among pediatric patients in the United States

Laura F. Goodman[1,2]✉, Peter T. Yu[1,2], Yigit Guner[1,2], Saeed Awan[1,2], Akhil Mohan[3], Kevin Ge[4], Mathew Chandy[5], Mario Sánchez[4] and Louis Ehwerhemuepha[1,6]

BACKGROUND AND OBJECTIVE: Congenital heart defects are known to be associated with increased odds of severe COVID-19. Congenital anomalies affecting other body systems may also be associated with poor outcomes. This study is an exhaustive assessment of congenital anomalies and odds of severe COVID-19 in pediatric patients.

METHODS: Data were retrieved from the COVID-19 dataset of Cerner® Real-World Data for encounters from March 2020 to February 2022. Prior to matching, the data consisted of 664,523 patients less than 18 years old and 927,805 corresponding encounters with COVID-19 from 117 health systems across the United States. One-to-one propensity score matching was performed, and a cumulative link mixed-effects model with random intercepts for health system and patients was built to assess corresponding associations.

RESULTS: All congenital anomalies were associated with worse COVID-19 outcomes, with the strongest association observed for cardiovascular anomalies (odds ratio [OR], 3.84; 95% CI, 3.63–4.06) and the weakest association observed for anomalies affecting the eye/ear/face/neck (OR, 1.16; 95% CI, 1.03–1.31).

CONCLUSIONS AND RELEVANCE: Congenital anomalies are associated with greater odds of experiencing severe symptoms of COVID-19. In addition to congenital heart defects, all other birth defects may increase the odds for more severe COVID-19.

Pediatric Research (2024) 96:792–798; https://doi.org/10.1038/s41390-024-03076-9

IMPACT:

- All congenital anomalies are associated with increased odds of severe COVID-19.
- This study is the largest and among the first to investigate birth defects across all body systems.
- The multicenter large data and analysis demonstrate the increased odds of severe COVID19 in pediatric patients with congenital anomalies affecting any body system. These data demonstrate that all children with birth defects are at increased odds of more severe COVID-19, not only those with heart defects. This should be taken into consideration when optimizing prevention and intervention resources within a hospital.

INTRODUCTION

Congenital anomalies are structural or functional anomalies present at birth[1,2] that can affect any body system including the respiratory, cardiovascular, gastrointestinal, and neurologic systems. The World Health Organization estimates that 6% of children worldwide have a congenital anomaly,[2] while the Centers for Disease Control and Prevention (CDC) estimate the rate to be 3% among US newborns.[3] In the US, 20% of children affected by congenital anomalies die in infancy, and such anomalies are the most common cause of mortality in the first year of life.[4,5] In some cases, these congenital anomalies, such as those affecting the cardiovascular system, Trisomy 21, and gastroschisis,[6] are increasing in incidence annually.[7]

The SARS-CoV-2 virus or Coronavirus 2019 (COVID-19) pandemic has exacerbated the health burden of children with certain preexisting conditions.[8–12] Previous work by our group showed a strong association between congenital heart disease (CHD) and COVID-19 severity in children,[8] but there is a dearth of large multicenter studies on congenital anomalies affecting other body systems. Therefore, there is a need to investigate the influence of congenital anomalies on the clinical course of SARS-CoV-2 infection in order to optimize prevention efforts and allocate hospital resources to those at increased risk for severe COVID-19.[8]

In this study, we exhaustively assessed the association between congenital anomalies and severity of COVID-19 among pediatric patients. We hypothesized that, in addition to those affecting the cardiovascular system[8], other congenital anomalies may be associated with worse outcomes, and that there would be significant differences in the magnitude of association according to the physiologic system affected.

[1]Children's Hospital of Orange County, Orange, CA, USA. [2]University of California-Irvine Department of Surgery, Orange, CA, USA. [3]University of Arizona, Tucson, AZ, USA. [4]Emory University, 201 Dowman Dr, Atlanta, GA, USA. [5]University of Connecticut, Storrs, CT, USA. [6]Chapman University, School of Computational and Data Sciences, Orange, CA, USA. ✉email: lgoodman@choc.org

Received: 19 July 2023 Revised: 6 December 2023 Accepted: 7 January 2024
Published online: 16 February 2024

METHODS

This retrospective cohort study was approved by the Children's Hospital of Orange County Institutional Review Board (IRB #2008107).

Data sources

Cerner® Real-World Data (CRWD)—a large multicenter electronic health records (EHR) database—was used for this study. As of March 2022, the CRWD system houses data from 120 health systems and over 1.4 billion encounters from all care settings in the United States. It is a clinical data warehouse powered by Cerner's EHR-neutral and insights platform (HealtheIntent).[13,14] HealtheIntent retrieves data from the EHR of individual health systems. This data is combined across health systems, de-identified, encrypted, and secured in compliance with the Health Insurance Portability and Accountability Act of 1996 privacy regulation.[13,14]

Patients and variables

In this study, we used the COVID-19 dataset from CRWD and retrieved records for COVID-19 encounters that occurred between March 1, 2020 and February 28, 2022 for patients less than 18 years of age. Congenital anomalies were obtained by searching all relevant diagnosis codes in the database. International Statistical Classification of Disease, Version 10, Codes (ICD-10-CM) were used to identify congenital anomalies affecting organs or body systems such as the nervous system (Q00-Q07), eye, ear, face and neck (Q10-Q18), circulatory system (Q20-Q28), respiratory system (Q30-Q34), cleft lip and cleft palate (Q35-Q37), other digestive system organs (Q38-Q45), genital organs (Q50-Q56), urinary system (Q60-Q64), musculoskeletal system (Q65-Q79), other congenital malformations such as congenital ichthyosis, epidermolysis bullosa, phakomatoses, congenital malformation of the spleen, etc.[15] (Q80-Q89), and chromosomal abnormalities (Q90-Q99). These large groups of congenital anomalies, based on the organ/body systems affected, were selected, a priori, to make the study feasible and as a guide for investigation of more specific conditions encompassed within them. All body systems for which a patient may have a congenital malformation were accounted for. Data on patient diagnoses were provided in the database from the year 2015. If the diagnosis was reported and resolved prior to 2015, the patient may not have been designated as having a congenital anomaly.

Complex chronic conditions in pediatric patients have been previously classified using both diagnosis and procedure codes into broad classes of chronic conditions.[16] We adopted the definitions published by Feudtner et al. (2014) for pediatric chronic conditions encompassing neurologic/neuromuscular, cardiovascular, respiratory, renal/urologic, gastrointestinal, hematologic/immunologic, metabolic, prematurity/neonatal, and devices and transplants.[16]

We retrieved important demographic and related variables to be controlled for in a multivariable model including sex, race, age at encounter, and health insurance payor. This model also controlled for number of non-congenital chronic conditions affecting the neurologic/neuromuscular, cardiovascular, respiratory, renal/urologic, gastrointestinal, hematologic/immunologic, and metabolic body systems, as well as malignancy, prematurity/neonatal chronic conditions,[16] and obesity status (determined using the 95th percentile body mass index (BMI) threshold, respective to age). If BMI was not reported, the presence of a diagnosis code was used to determine obesity status.[8]

COVID-19 severity was defined as an ordinal variable by the level of respiratory support administered to the patient during the hospital encounter.[8,17,18] Patients who required invasive oxygen therapy (such as mechanical ventilation and extracorporeal membrane oxygenation) or died were defined as having had severe COVID-19. Patients discharged alive who received noninvasive oxygen therapy (such as bilevel positive airway pressure, continuous positive airway pressure, nasal cannula, or high-flow nasal cannula) were defined as having had moderate COVID-19. All other patients, those who were discharged alive and did not receive oxygen therapy, were defined as having had asymptomatic or mild COVID-19. The use of oxygen supplementation as an indicator of COVID-19 severity was selected based on existing literature.[8,17,18]

Statistical analysis

Matching between patients with congenital anomalies and their peers with no congenital anomalies was carried out to reduce both measured and unmeasured bias. This was achieved using one-to-one propensity score matching on age at encounter and number of other classes of chronic conditions with exact matching on race, sex, month of encounter, and health system. Consequently, matching was performed at the encounter level such that encounters occurring during the same month (or period) of the pandemic were matched to reduce unmeasured bias that may be associated with differences in variants of SARS-CoV-2, availability of vaccines and vaccination status, changes in treatment, and changes in public health policies. Furthermore, matching on health system was performed to reduce unmeasured bias associated with differences in local treatment patterns, local surges, and community response to the virus. Caliper width on the logit of the propensity scores was set to 0.2 standard deviations of the logit—a value based on extensive series of Monte Carlo simulations.[19] The goal of matching was to reduce baseline differences between children with congenital anomalies and their peers with no anomalies.

A cumulative link mixed-effects model (based on the proportion odds assumption) was used for modeling because COVID-19 severity was defined as an ordinal variable, patients were clustered within their respective health systems, and some patients had more than one encounter (reinfection) during the study period. Random intercepts for health systems and patients were introduced to account for correlations within health systems and cases of multiple encounters per patient. A "base model" was constructed on baseline variables including age at encounter, sex, race, payor, number of chronic conditions, and obesity. A "full model" was constructed using variables from the "base model" in addition to congenital and chronic conditions under test of hypothesis. An omnibus test was performed to determine whether congenital anomalies or chronic diagnoses were significant at an alpha of 0.05. Analyses were conducted using Spark and R, including the "ordinal" package for cumulative link mixed models.[20–22]

RESULTS

In total, there were 927,805 pediatric patient encounters with COVID-19 from March 2020 to February 2022. The unmatched cohort comprised 846,758 (91.2%) patients who were asymptomatic or had mild COVID-19, 60,299 (6.5%) patients who experienced moderate COVID-19, and 20,748 (2.2%) patients who experienced severe COVID-19 symptoms. The matched cohort comprised 85,649 (80.0%) patients who were asymptomatic or had mild COVID-19; 14,317 (13.4%) patients with moderate COVID-19; and 7014 (6.6%) patients with severe COVID-19. Refer to Table 1 for summary statistics on the matched cohort and to the supplemental material for summary statistics on the full/unmatched data. (Table 2)

A likelihood ratio (omnibus) test, between the full and base models, suggested that congenital anomalies were significantly associated with the severity of COVID-19 ($p < 0.001$). Congenital anomalies observed (in decreasing magnitude of odds ratios) were: circulatory disorders, with 284% increase in odds of more severe COVID-19 (OR, 3.84; 95% CI, 3.63–4.06); cleft lip/palate, with 187% increase in odds of more severe COVID-19 (OR, 2.87; 95% CI, 2.48–3.32); other classes of digestive system disorders, with 162% increase in odds of more severe COVID-19 (OR, 2.62; 95% CI, 2.42–2.84); respiratory disorders, with 124% increase in odds of more severe COVID-19 (OR, 2.24; 95% CI, 2.04–2.46); neurologic disorders, with 115% increase in odds of more severe COVID-19 (OR, 2.15; 95% CI, 1.99–2.32); musculoskeletal developmental disorders, with 68% increase in odds of more severe COVID-19 (OR, 1.68; 95% CI, 1.58–1.77); chromosomal abnormalities, with 54% increase in odds of more severe COVID-19 (OR, 1.54; 95% CI, 1.43–1.66); genitourinary disorders, with 31% increase in odds of more severe COVID-19 (OR, 1.31; 95% CI, 1.22–1.41); other classes of congenital anomalies, with 23% increase in odds of more severe COVID-19 (OR, 1.23; 95% CI, 1.15–1.32); eye, ear, face, and neck disorders, with 16% increase in odds of more severe COVID-19 (OR, 1.16; 95% CI, 1.03–1.31). A graphical manifestation of the effect of these congenital anomalies on odds of more severe COVID-19 is displayed in Fig. 1.

DISCUSSION

Congenital circulatory conditions have been shown to be associated with poor COVID-19 outcomes.[8–10,23–26] There is,

Table 1. Summary statistics by COVID-19 severity.

Variables	COVID-19 severity		
	Mild ($n = 85,649$)	**Moderate ($n = 14,317$)**	**Severe ($n = 7014$)**
Age (median, IQR)	2 (0, 9)	4 (1, 12)	2 (0, 11)
Sex			
Female	37,075 (43%)	5871 (41%)	2964 (42%)
Male	48,502 (57%)	8436 (59%)	4048 (58%)
Unknown	72 (<0.1%)	10 (<0.1%)	2 (<0.1%)
Race			
White	52,872 (62%)	9397 (66%)	4283 (61%)
American Indian/Alaska Native	487 (0.6%)	90 (0.6%)	33 (0.5%)
Asian or Pacific Islander	1680 (2.0%)	349 (2.4%)	161 (2.3%)
Black or African American	15,583 (18%)	2059 (14%)	1202 (17%)
Mixed racial group	772 (0.9%)	156 (1.1%)	28 (0.4%)
Other racial group	9337 (11%)	1399 (9.8%)	714 (10%)
Unknown racial group	4918 (5.7%)	867 (6.1%)	593 (8.5%)
Payor			
Commercial	22,046 (26%)	5089 (36%)	2219 (32%)
Governmental	28,295 (33%)	4576 (32%)	2057 (29%)
Other or unknown	34,359 (40%)	4531 (32%)	2685 (38%)
Self-Pay	949 (1.1%)	121 (0.8%)	53 (0.8%)
Encounter type			
Admitted for observation	8140 (9.5%)	3137 (22%)	317 (4.5%)
Emergency	47,577 (56%)	1067 (7.5%)	171 (2.4%)
Inpatient	16,690 (19%)	10,053 (70%)	6526 (93%)
Urgent care encounter	13,242 (15%)	60 (0.4%)	0 (0%)
Obesity	9128 (11%)	1979 (14%)	860 (12%)
Non-congenital chronic conditions (Median, IQR)	0 (0, 1)	1 (0, 2)	1 (0, 2)
Congenital anomalies by body system			
Neurologic	3946 (4.6%)	1449 (10%)	968 (14%)
Eye, ear, face, and neck	2253 (2.6%)	440 (3.1%)	324 (4.6%)
Circulatory	9013 (11%)	2702 (19%)	2676 (38%)
Respiratory	2366 (2.8%)	814 (5.7%)	710 (10%)
Cleft lip/palate	801 (0.9%)	369 (2.6%)	223 (3.2%)
Other digestive systems	3413 (4.0%)	1350 (9.4%)	660 (9.4%)
Genitourinary	6179 (7.2%)	1359 (9.5%)	658 (9.4%)
Musculoskeletal	10,685 (12%)	2471 (17%)	1338 (19%)
Other congenital anomalies	6038 (7.0%)	1450 (10%)	968 (14%)
Chromosomal	4917 (5.7%)	1350 (9.4%)	984 (14%)
Medications			
Remdesivir	62 (<0.1%)	145 (1.0%)	184 (2.6%)
COVID-19 convalescent plasma	3 (<0.1%)	6 (<0.1%)	3 (<0.1%)
Dexamethasone	6591 (7.7%)	5337 (37%)	3095 (44%)
Heparin	799 (0.9%)	1209 (8.4%)	2234 (31.9%)
Immunoglobin therapy	236 (0.3%)	85 (0.6%)	113 (1.6%)
Methylprednisolone	728 (0.8%)	888 (6.2%)	1,207 (17%)
Rituximab	50 (<0.1%)	36 (0.3%)	9 (0.1%)
Tocilizumab	16 (<0.1%)	16 (0.1%)	31 (0.4%)
Aspirin	810 (0.9%)	735 (5.1%)	899 (13%)
Lopinavir/ritonavir	0 (0%)	1 (<0.1%)	0 (0%)

Table 2. Cumulative link mixed-effects model for congenital anomalies.

Variables	Odds ratios	*p* value
Congenital anomalies		
Circulatory	3.84 (3.63, 4.06)	<0.001
Cleft lip/palate	2.87 (2.48, 3.32)	<0.001
Other digestive systems	2.62 (2.42, 2.84)	<0.001
Respiratory	2.24 (2.04, 2.46)	<0.001
Neurologic	2.15 (1.99, 2.32)	<0.001
Musculoskeletal	1.68 (1.58, 1.77)	<0.001
Chromosomal	1.54 (1.43, 1.66)	<0.001
Genitourinary	1.32 (1.22, 1.41)	<0.001
Other congenital anomalies	1.23 (1.15, 1.32)	<0.001
Congenital anomalies of the eye, ear, face and neck	1.16 (1.03, 1.31)	0.01
Variables controlled for[a]		
Age (years)	1.02 (1.02, 1.03)	<0.001
Sex (Reference, Female)		
Male	1.17 (1.13, 1.22)	<0.001
Other/unknown	0.93 (0.44, 1.94)	0.84
Race (Reference, White)		
American Indian or Alaska Native	0.94 (0.72, 1.23)	0.65
Asian or Pacific Islander	1.06 (0.93, 1.21)	0.37
Black or African American	0.75 (0.70, 0.79)	<0.001
Mixed racial group	0.76 (0.62, 0.95)	0.01
Other racial group	0.77 (0.71, 0.83)	<0.001
Unknown racial group	1.06 (0.98, 1.16)	0.15
Payor (Reference, Commercial)		
Governmental	0.78 (0.73, 0.82)	<0.001
Other/unknown	0.64 (0.61, 0.68)	<0.001
Self-pay	0.70 (0.58, 0.86)	0.001
Obesity	1.21 (1.14, 1.29)	<0.001
Number of other chronic conditions	1.26 (1.25, 1.28)	<0.001

[a]These variables also made up the base model. Omnibus test was between the base model and a full model containing all variables in this table. Statistical significance was assessed using the likelihood ratio test *p* value of the omnibus test.

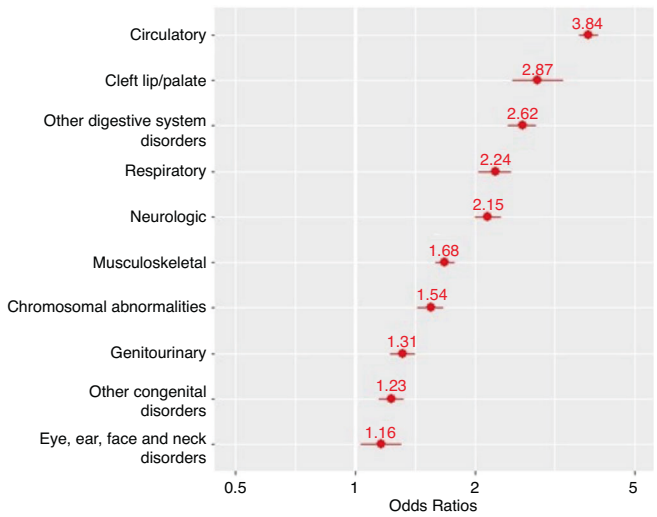

Fig. 1 Association between congenital anomalies and COVID-19 severity.

however, a dearth of studies and information on COVID-19 severity among patients with other congenital anomalies. The aim of this study was a comprehensive assessment and comparison of predispositions to severe COVID-19 due to congenital anomalies. Considering the large number of individual congenital anomalies, we grouped these conditions by the organ/body systems affected for feasibility and as a guide for investigations into single/specific congenital anomalies. Our findings indicate that all types of congenital anomalies were associated with more severe COVID-19 outcomes in this large pediatric patient cohort, compared to patients without anomalies. We also demonstrated that congenital circulatory conditions (congenital heart defects) conferred a higher risk of severe COVID-19 than any other category of congenital anomaly in this population (as already shown in prior studies[8]), which validates continued focus on SARS-CoV-2 infection prevention and mitigation among patients with congenital circulatory conditions. However, our findings of increased risk for severe COVID-19 in the setting of all types of anomalies indicates a need to extend this prevention and treatment focus to patients with any type of anomaly to prevent severe COVID-19 infection.

Circulatory disorders were closely followed by congenital digestive defects such as cleft lip/palate or malformations of internal digestive organs, in terms of the increased in odds of more severe COVID-19. Previous studies have established a relationship

between malnutrition and severe COVID-19.[27,28] The increased risk of severe COVID-19 in children with congenital digestive conditions may be partly explained by malnutrition attributable to the congenital digestive conditions.

Respiratory and neurologic manifestations of COVID-19 have been clearly established.[29–38] Cough (56%), rhinorrhea (20%), sore throat (18%), and shortness of breath (12%) are the most common respiratory manifestations of COVID-19 in pediatric patients (Hoang 2020).[39] The most common neurological manifestations of COVID-19 in children are seizures or status epilepticus (children <5 years old) and anosmia (children >13 years old).[40] Congenital respiratory anomalies such as congenital pulmonary airway malformation and sequestrations are most often unilateral and do not have a significant effect upon pulmonary mechanics unless very large. Pulmonary hypoplasia is most often observed in the setting of cardiac anomalies or congenital diaphragmatic hernia. However, congenital respiratory anomalies were shown in our data to be associated with a higher risk of severe COVID-19. Our search of the literature on this topic was limited by a paucity of published data on respiratory anomalies and COVID-19 outcomes in pediatric and adult patients. In addition, patients with preexisting/chronic respiratory or neurologic conditions have been shown to have poor COVID-19 outcomes.[8] Consequently, preexisting congenital defects in these systems are likely to result in more severe COVID-19 outcomes, and our findings confirmed this.

All other congenital anomalies, including those affecting the musculoskeletal and genitourinary systems and chromosomal abnormalities, were associated with significant increases in the odds of more severe COVID-19. This implies that there may be additional physiologic burdens from congenital defects that predispose these patients to worse COVID-19 outcomes. The increased odds of more severe COVID-19 among children with congenital anomalies follows a similar pattern to respiratory syncytial virus (RSV) infection. Incomplete development and malformations of critical organs are associated with worse RSV outcomes as well.[41–45] Further studies are needed to clarify the causal pathways between congenital anomalies and increased risk of severe COVID-19.[46] It is important to note that patients with congenital anomalies may be at higher risk for additional comorbid/chronic conditions that have been associated with higher risk of severe outcomes of COVID-19. Consequently, we accounted for related conditions already known to be associated with severe outcomes.[47–50]

Prior research has demonstrated that children with CHD are at higher risk for severe respiratory infections than non-CHD patients due to physiological factors such as: increased pulmonary blood flow; increased pulmonary venous pressures related to poor ventricular function, leading to pulmonary edema, and therefore decreased functional residual capacity; and higher predisposition to hypoxia due to ventilation-perfusion mismatch and/or the anatomical nature of the CHD.[51,52] Both adults and children with COVID-19 infections and CHD have been shown to have longer length of stay and more complications than patients without CHD, while children with CHD have been shown to have higher mortality as well.[53] Our current study findings are in line with these prior studies and others.

This study had several limitations. Data related to the severity of underlying congenital defects was not available and may be a source of bias. Data on diagnoses in the database was limited to information from 2015. Consequently, only children diagnosed or treated for a congenital defect from 2015 were captured as having a history of such defects, leading to the exclusion of those with conditions that resolved prior to 2015. Cases of the multisystem inflammatory syndrome in children (MIS-C) were not excluded due to late introduction of the corresponding diagnosis code and complexity of the corresponding definition. Inpatient deaths in this cohort were assumed to be due to COVID-19 because it was not possible to determine which deaths were due to other causes. Data on clinic visits and children infected at home were not captured, and results are therefore conditional on seeking hospital or emergency department care and are thus limited to the more severely ill children. The health systems considered included all census regions of the US, but local outbreaks may have been masked at the census region level. The use of demographic variables for matching and modeling was to reduce associated bias and may not generalize to the entire pediatric population. Studies dedicated to assessing related impacts may be required to provide more robust estimates of their effects. Lastly, SARS-CoV-2 variants were not captured in the database, and there may be other unmeasured confounders with temporal dependence that arose as the pandemic evolved. To reduce bias due to these unmeasured confounders, we matched patients on month of encounter. Furthermore, as part of de-identification procedures, all dates were consistently shifted by 35 days at most in either direction. Consequently, months of SARS-CoV-2 infection used for matching were within one month of each other if not exact.

CONCLUSION

All congenital anomalies examined in this study were found to be associated with increased COVID-19 severity in pediatric patients in the US. The results presented in this study highlight the necessity for more studies into specific anomalies and for pediatric health care professionals to offer timely intervention and care to pediatric patients with both congenital anomalies and SARS-CoV-2 infection.

DATA AVAILABILITY

The data that support the findings of this study are available from Oracle® Health but restrictions apply to the availability of these data, which were used under a data use agreement for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Oracle® Health.

REFERENCES

1. World Health Organization. Birth defects. https://www.who.int/news-room/fact-sheets/detail/birth-defects (2022).
2. World Health Organization. Congenital anomalies. https://www.who.int/health-topics/congenital-anomalies (2022).
3. Center for Disease Control and Prevention, C. & others. Update on overall prevalence of major birth defects–Atlanta, Georgia, 1978–2005. *MMWR Morb. Mortal. Wkly Rep.* **57**, 1–5 (2008).
4. Murphy, S. L., Kochanek, K. D., Xu, J. & Arias, E. Mortality in the United States, 2020. *NCHS Data Brief*.
5. CDC. Infant Mortality. *Centers for Disease Control and Prevention* https://www.cdc.gov/reproductivehealth/maternalinfanthealth/infantmortality.htm (2022).
6. Mai, C. T. et al. National population-based estimates for major birth defects, 2010–2014. *Birth Defects Res.* **111**, 1420–1435 (2019).
7. El-Chouli, M. et al. Time trends in simple congenital heart disease over 39 years: A Danish nationwide study. *J. Am. Heart Assoc.* **10**, e020375 (2021).
8. Ehwerhemuepha, L. et al. Association of congenital and acquired cardiovascular conditions with COVID-19 severity among pediatric patients in the US. *JAMA Netw. Open* **5**, e2211967–e2211967 (2022).
9. Giordano, R. & Cantinotti, M. Congenital heart disease in the era of COVID-19 pandemic. *Gen. Thorac. Cardiovasc Surg.* **69**, 172–174 (2021).
10. Sabatino, J. et al. COVID-19 and congenital heart disease: results from a nationwide survey. *J. Clin. Med.* **9**, 1774 (2020).
11. Delahoy, M. J. Hospitalizations associated with COVID-19 among children and adolescents—COVID-NET, 14 States, March 1, 2020–August 14, 2021. *MMWR Morb. Mortal. Wkly Rep.* **70**, 1255–1260 (2021).
12. AAP. Children and COVID-19: State-Level Data Report. *American Academy of Pediatrics* https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/ (2021).
13. Ehwerhemuepha, L. et al. Cerner real-world data (CRWD) - A de-identified multicenter electronic health records database. *Data Brief.* **42**, 108120 (2022).

14. Ehwerhemuepha, L. et al. HealtheDataLab - a cloud computing solution for data science and advanced analytics in healthcare with application to predicting multi-center pediatric readmissions. *BMC Med Inf. Decis. Mak.* **20**, 1–12 (2020).
15. ICD10data.com. Other congenital malformations. *Congenital malformations, deformations and chromosomal abnormalities* https://www.icd10data.com/ICD10CM/Codes/Q00-Q99/Q80-Q89 (2022).
16. Feudtner, C., Feinstein, J. A., Zhong, W., Hall, M. & Dai, D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr.* **14**, 199 (2014).
17. Berlin, D. A., Gulick, R. M. & Martinez, F. J. Severe Covid-19. *N. Engl. J. Med.* **383**, 2451–2460 (2020).
18. Preston, L. E. et al. Characteristics and disease severity of US children and adolescents diagnosed with COVID-19. *JAMA Netw. Open* **4**, e215298–e215298 (2021).
19. Austin, P. C. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm. Stat.* **10**, 150–161 (2011).
20. Christensen, R. H. B. ordinal—Regression Models for Ordinal Data. Preprint at (2019).
21. Spark, A. Apache Spark: Lightning-fast cluster computing. http://spark.apache.org (2016).
22. R Core Team. R: A Language and Environment for Statistical Computing. Preprint at https://www.R-project.org/ (2022).
23. Haiduc, A. A. et al. COVID-19 and congenital heart disease: an insight of pathophysiology and associated risks. *Cardiol. Young-.* **31**, 233–240 (2021).
24. Hromić-Jahjefendić, A. et al. Associations and disease–disease interactions of COVID-19 with congenital and genetic disorders: A comprehensive review. *Viruses* **14**, 910 (2022).
25. Khan, M. S. I. et al. Risk of congenital birth defects during COVID-19 pandemic: Draw attention to the physicians and policymakers. *J. Glob. Health* **10**, 020378 (2020).
26. Rodriguez, Z. et al. COVID-19 convalescent plasma clears SARS-CoV-2 refractory to remdesivir in an infant with congenital heart disease. *Blood Adv.* **4**, 4278 (2020).
27. Kurtz, A. et al. Long-term effects of malnutrition on severity of COVID-19. *Sci. Rep.* **11**, 14974 (2021).
28. Bedock, D. et al. Prevalence and severity of malnutrition in hospitalized COVID-19 patients. *Clin. Nutr. ESPEN* **40**, 214–219 (2020).
29. Nordvig, A. S. et al. Potential neurologic manifestations of COVID-19. *Neurol. Clin. Pract.* **11**, e135–e146 (2021).
30. Schirinzi, T., Landi, D. & Liguori, C. COVID-19: Dealing with a potential risk factor for chronic neurological disorders. *J. Neurol.* **268**, 1171–1178 (2021).
31. Lin, J. E. et al. Neurological issues in children with COVID-19. *Neurosci. Lett.* **743**, 135567 (2021).
32. Nuzzo, D. & Picone, P. Potential neurological effects of severe COVID-19 infection. *Neurosci. Res.* **158**, 1–5 (2020).
33. Abdel-Mannan, O. et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol.* **77**, 1440–1445 (2020).
34. Mahalakshmi, A. M. et al. Does COVID-19 contribute to development of neurological disease? *Immun. Inflamm. Dis.* **9**, 48–58 (2021).
35. Chou, S. H.-Y. et al. Global incidence of neurological manifestations among patients hospitalized with COVID-19—A report for the GCS-NeuroCOVID consortium and the ENERGY consortium. *JAMA Netw. Open* **4**, e2112131–e2112131 (2021).
36. Koralnik, I. J. & Tyler, K. L. COVID-19: A global threat to the nervous system. *Ann. Neurol.* **88**, 1–11 (2020).
37. Bodro, M., Compta, Y. & Sanchez-Valle, R. Presentations and mechanisms of CNS disorders related to COVID-19. *Neurol.-Neuroimmunol. Neuroinflamm.* **8**, e923 (2021).
38. Beaud, V. et al. Pattern of cognitive deficits in severe COVID-19. *J. Neurol. Neurosurg. Psychiatry* **92**, 567–568 (2021).
39. Hoang, A. et al. COVID-19 in 7780 pediatric patients: A systematic review. *EClinicalMedicine* **24**, 100433 (2020).
40. LaRovere, K. L. et al. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. *JAMA Neurol.* **78**, 536–547 (2021).
41. Vartiainen, P. et al. Risk factors for severe respiratory syncytial virus infection during the first year of life: development and validation of a clinical prediction model. *Lancet Digit Health* **5**, e821–e830 (2023).
42. Meberg, A. & Bruu, A.-L. Respiratory syncytial virus infections in congenital heart defects–hospitalizations and costs. *Acta Paediatr.* **95**, 404–406 (2006).
43. Kristensen, K., Hjuler, T., Ravn, H., Simões, E.A. & Stensballe, L.G. Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. *Clin. Infect. Dis.* **54**, 810–817 (2012).
44. Jama-Alol, K. A., Moore, H. C., Jacoby, P., Bower, C. & Lehmann, D. Morbidity due to acute lower respiratory infection in children with birth defects: A total population-based linked data study. *BMC Pediatr.* **14**, 1–7 (2014).
45. Welliver, R. C. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. *J. Pediatr.* **143**, 112–117 (2003).
46. Corsello, G. & Giuffrè, M. Congenital malformations. *J. Matern.-Fetal Neonatal Med.* **25**, 25–29 (2012).
47. Pinto, N. M. et al. Obesity is a common comorbidity in children with congenital and acquired heart disease. *Pediatrics* **120**, e1157–e1164 (2007).
48. Ferguson, R. L. Medical and congenital comorbidities associated with spinal deformities in the immature spine. *JBJS* **89**, 34–41 (2007).
49. Engelfriet, P. et al. The spectrum of adult congenital heart disease in Europe: Morbidity and mortality in a 5 year follow-up period: The Euro Heart Survey on adult congenital heart disease. *Eur. Heart J.* **26**, 2325–2333 (2005).
50. Vanamo, K., Rintala, R. J., Lindahl, H. & Louhimo, I. Long-term gastrointestinal morbidity in patients with congenital diaphragmatic defects. *J. Pediatr. Surg.* **31**, 551–554 (1996).
51. Geskey, J. M. & Cyran, S. E. Managing the morbidity associated with respiratory viral infections in children with congenital heart disease. *Int. J. Pediatr.* **2012**, 646780 (2012). & others.
52. Cabalka, A. K. Physiologic risk factors for respiratory viral infections and immunoprophylaxis for respiratory syncytial virus in young children with congenital heart disease. *Pediatr. Infect. Dis. J.* **23**, S41–S45 (2004).
53. Strah, D. D. et al. Worse hospital outcomes for children and adults with COVID-19 and congenital heart disease. *Pediatr. Cardiol.* **43**, 541–546 (2022).

AUTHOR CONTRIBUTIONS

L.F.G. conceptualized and designed the study, drafted the initial manuscript, and critically reviewed and revised the manuscript. L.E. conceptualized and designed the study, conducted statistical analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript. P.T.Y., Y.G., and S.A. critically reviewed and revised the manuscript. A.M., K.G., M.C., and M.S. assisted with statistical analyses, and critically reviewed and revised the manuscript.

FUNDING

A.M., K.G., M.C., and M.S. roles in the research reported in this publication were supported by the National Institute of Allergy And Infectious Diseases of the National Institutes of Health (NIH; R25AI170491). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The other authors received no additional funding. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

This retrospective cohort study was approved by the Children's Hospital of Orange County Institutional Review Board (IRB #2008107). All patient information was deidentified and patient consent was not required.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-024-03076-9.

Correspondence and requests for materials should be addressed to Laura F. Goodman.