

Impact of the COVID-19 pandemic on pediatric emergency department utilization for head injuries

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ABSTRACT

Head injuries are a leading cause of death and disability in children, accounting for numerous emergency department (ED) visits. It is unclear how the COVID-19 pandemic has influenced healthcare utilization for pediatric head injuries. We hypothesize that the proportion of ED visits attributable to head injury and severity will increase during the COVID-19 era. Retrospective study using electronic health record data to compare proportion and severity of head injury for children 0–21 years of age from three urban mid-Atlantic EDs in the pre-COVID-19 era (March–June 2019) and COVID-19 era (March–June 2020). Controlling for confounders, logistic regression analyses assessed ORs of head injury outcomes. The χ^2 analyses identified differences in patient characteristics. The proportion of head injury visits within the ED population significantly increased during the COVID-19 era (adjusted OR (aOR)=1.2, 95% CI 1.1 to 1.4). Proportion of visits requiring hospitalization for head injury increased by more than twofold in the COVID-19 era (aOR=2.3, 95% CI 1.3 to 4.3). Use of head CT imaging did not significantly change in the COVID-19 era (aOR=1.0, 95% CI 0.7 to 1.6). The proportion of ED visits and hospitalizations for head injury increased during the COVID-19 era. This could be due to changes in the level of supervision and risk exposures in the home that occurred during the pandemic, as well as differences in postinjury care, level of awareness regarding injury severity, and threshold for seeking care, all of which may have influenced pediatric healthcare utilization for head injuries.

INTRODUCTION

Head injuries are the leading cause of death and disability among children in the USA,^{1,2} accounting for nearly 400,000 emergency department (ED) visits annually.^{3–5} Head injuries occur when there is trauma to the scalp, skull, or brain, leading to clinical manifestations which include concussion, contusion, hematoma, and skull fractures.⁶

The COVID-19 pandemic has created a unique challenge in daily living. With school and daycare closures, children began spending a greater time at home, a common location for injuries. Head injuries are one of the most

Significance of this study

What is already known about this subject?

- ⇒ Head injuries are a leading cause of death and disability in children, accounting for a substantial number of emergency department (ED) visits.
- ⇒ In children, the home is a common location for head injuries.
- ⇒ With the COVID-19 pandemic, children are spending a substantially greater time in the home, which potentially increases risk for acquiring head injury.

What are the new findings?

- ⇒ This study of the Johns Hopkins Pediatric Emergency Health System reveals increases in the proportion of head injury visits and hospitalizations among the pediatric ED population during the COVID-19 era.
- ⇒ This increase may reflect changes in supervision and risk exposures in the home that occurred during the COVID-19 era, as well as the threshold for seeking care and healthcare utilization.

How might these results change the focus of research or clinical practice?

- ⇒ Assessing ED utilization for head injuries allows us to better understand how the COVID-19 pandemic continues to affect pediatric healthcare utilization and shape injury mechanisms.
- ⇒ Postinjury care, level of awareness and knowledge regarding injury severity, as well as threshold for seeking care, are all important factors that may become affected by the pandemic and can subsequently influence head injury epidemiology.
- ⇒ A further understanding of these factors is needed to develop head injury prevention strategies to reduce injuries in children.

common forms of injury in the home, especially in children younger than 4 years of age.⁷ Fall-related head injuries are especially common in infants due to their proportionally larger head sizes relative to their bodies in comparison to adults.⁸ In fact, limited available studies have

observed substantial increases in the severity of injuries during the COVID-19 pandemic.^{9 10}

Understanding changes in head injury patterns and utilization of pediatric ED services for head injuries has not been studied and is crucial for targeting public health interventions. Children are at a developmental stage in their life when the occurrence of head injury, although seemingly minor at first, may cause long-term neurological damage and disability to the developing brain if not recognized and/or treated in a timely manner. Specifically, head injury can potentially lead to a loss of function in the muscle, speech, hearing, and taste depending on the area of the brain involved, and such severely impacted children may require lifelong medical and rehabilitative treatment.¹¹

For this reason, we undertook this study to specifically explore the impact of the COVID-19 pandemic on the epidemiology of head injury within the pediatric ED population during the early months of the pandemic. We hypothesize that the proportion of ED visits attributable to head injury and severity of those injuries will increase in the COVID-19 era, with control for potential confounders.

MATERIALS AND METHODS

Design and sample

This is a retrospective secondary data analysis comparing the proportion of ED visits for head injury and severity of those injuries between the pre-COVID-19 era (March 1, 2019–June 30, 2019) and COVID-19 era (March 1, 2020–June 30, 2020) in pediatric patients who were evaluated at three Baltimore-area ED facilities—two community-based hospitals (PED 1 and PED 2) and a designated level 1 pediatric trauma center (PED 3). The primary outcomes of the study included the presence of medically attended head injury, head injury-associated hospital admission, and presence of head CT imaging. Inclusion criteria were age between 0 and 21 years of age, having an ED visit during the specified time periods, and having all specified variables (race, ethnicity, sex, age, ED disposition, ED orders) available in the medical chart. Any patient with missing data for any of the variables was excluded from the analysis. There were 1045 patients (5.2%) excluded from the pre-COVID-19 period and 540 patients (5.9%) excluded from the COVID-19 period. The proportion of patients excluded from each time period are roughly equal, and so the effect on the analysis was proportional for each time period. The Strengthening the Reporting of Observational Studies in Epidemiology cross-sectional/reporting guidelines were used.

Data source

Data were retrieved from the Precision Medicine Analytics (PMAP) Data Commons platform, which pulls data from a variety of sources including Epic medical records and other local database sources.¹²

Patients with head injury were identified by using International Classification of Diseases 10th Revision (ICD-10) final diagnostic codes between S00 and S09. Data extraction included chief complaint, arrival time, ED disposition, ICD-10 final diagnostic codes, CT imaging orders placed and sociodemographic characteristics including race, ethnicity, age and sex (online supplemental appendix). As a proxy of

socioeconomic status (SES), Area Deprivation Index (ADI) ranks were collected based on zip codes at the census block level.¹³ This index has been adapted and validated by the University of Wisconsin-Madison research team.¹³ The ADI incorporates factors including income, education, employment, and housing quality to provide national percentile rankings of neighborhoods by socioeconomic disadvantage for any particular region.¹³ The national ADI rank ranges from 1 (least disadvantaged/highest SES) to 100 (most disadvantaged/lowest SES); we divided the numerical ranks into four groups (1–25, 26–50, 51–75, 76–100). Data were categorized into eras depending on when the ED visit occurred: pre-COVID-19 era versus COVID-19 era. Race was determined by self-report of the patient/family and includes the following options: black, white, Asian, American Indian/Pacific Islander, Native Hawaiian and other. ED disposition was classified as ‘hospital admitted’ or ‘discharged’. Identification of patients with a head CT was done by searching for ‘CT HEAD’ under the orders list.

Data analysis

Data were extracted from the PMAP database and entered in Microsoft Excel for Mac 2021 and were analyzed by using StataIC V.16.1. Severity of head injury was measured by two metrics: ED disposition (admitted vs discharged) and head CT (obtained vs not obtained). ED disposition and head CT were dichotomized in order to quantify severity. Only patients that were coded as ‘discharged’ or ‘admitted’ in the dataset were included in the analysis. Patients coded as ‘transferred to another facility’ were excluded. There were 686 patients (2.3%) who were transferred to another facility and were excluded from the analysis. Age was dichotomized to <2 years of age and ≥2 years of age, based on clinical guidelines for management of head injury that differentiate for these age ranges.^{14 15} Visit level was the unit of analysis in this study and it was possible that a patient could have been included more than once for different ED visits. Comparisons between children with medically attended head injuries in the COVID-19 era with those in the pre-COVID-19 era were made using descriptive statistics, χ^2 tests, and t-tests.

Logistic regression was used to test for associations between each exposure of interest (race and era) with each head injury outcome measure of interest (presence of medically attended head injury, head injury-associated hospitalization, and head CT use). All regression models included all ED visits and included the following variables: era, race, ethnicity, sex, and age group. Presenting hospital was included as an additional variable in the models that assessed for head injury and head CT use, however this was not included in the hospitalization model since the threshold for hospital admission varied between the community hospitals and the academic trauma center. Therefore, hospitalization was assessed by a subgroup analysis only among patients presenting to the academic trauma center (PED 3). The addition of an interaction term between race and era was included in all models to assess whether presence in the COVID-19 era modifies the association between race and head injury outcomes. Therefore, race was assigned as a binary variable and in all regression models, only patients who were of either black or white race were included. In

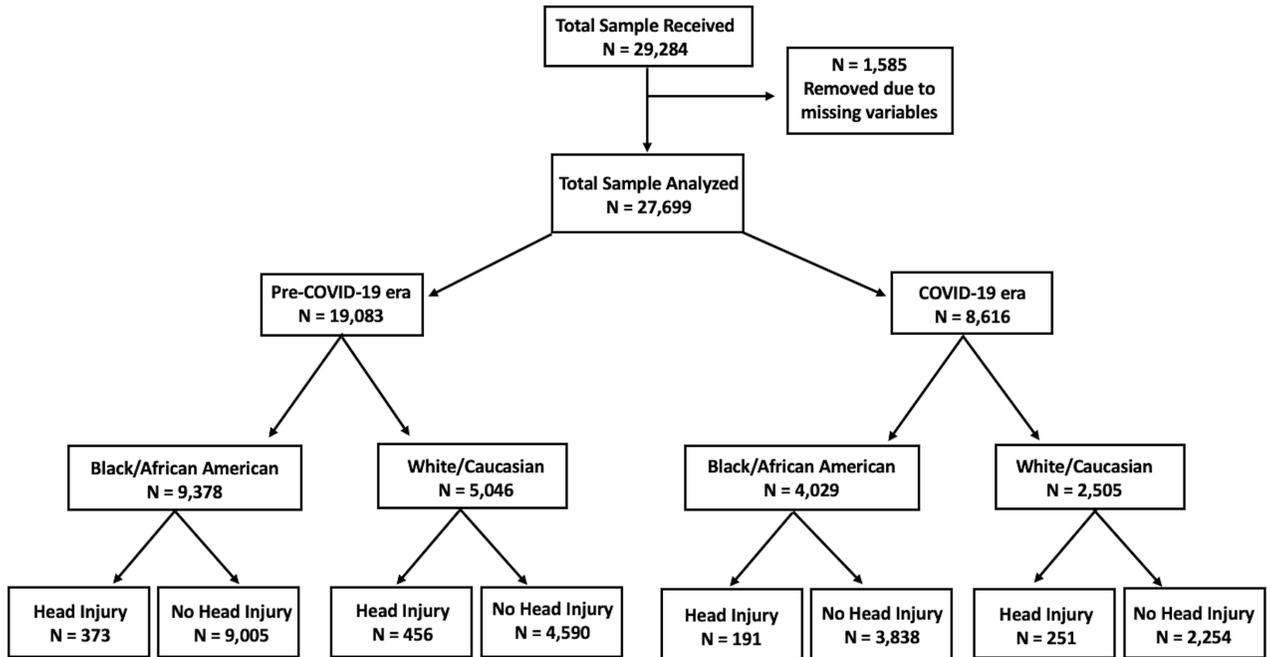


Figure 1 Study participants flow chart. This displays the study participant flow chart which shows how participants were divided up. Participants were divided up by the time period they were evaluated in and for presence of head injury.

the head injury model, the outcome was coded as ‘1’ if the patient had a head injury diagnosis (ICD-10: S00–S09). In the hospitalization model, the outcome was coded as ‘1’ if the patient had a head injury diagnosis and was admitted to the hospital. In the head CT model, the outcome was coded as ‘1’ if the patient had a head injury diagnosis and received a head CT. The heterogeneity of effects method was used in which the ORs of medically attended head injury, head injury-associated hospital admission, and head CT use were compared between the two racial groups across time periods.

RESULTS

There were 27,699 patient encounters included in the analysis (figure 1) with 19,083 ED visits (68.9%) in the pre-COVID-19 era and 8616 ED visits (31.1%) in the COVID-19 era. Characteristics of the study population for each respective time period are summarized in table 1. Overall demographic and patient characteristics were similar between the two time periods. However, during the COVID-19 era there was a decline in the proportion of blacks visiting the ED (pre-COVID-19: 49.1%, COVID-19: 46.8%; $p < 0.001$), whereas a significant increase was observed in whites (pre-COVID-19: 26.4%, COVID-19: 29.1%; $p < 0.001$). There was also a significant increase in the proportion of ED visits for head injury (pre-COVID-19: 5.5%, COVID-19: 6.4%; $p = 0.004$) in the COVID-19 era.

Multivariable estimates shown in table 2 include all patients who were evaluated at an ED during the specified time periods. Era was a significant risk factor for presenting with a head injury, even after controlling for differences in sociodemographic characteristics including ethnicity, sex, age group, and SES level (ie, ADI rank). The absolute number of head injuries decreased during the COVID-19 era, but the proportion of head injuries within the ED

population increased (adjusted OR (aOR)=1.2, 95% CI 1.1 to 1.4). Black patients represented a lower proportion of head injury visits than white patients (aOR=0.5, 95% CI 0.4 to 0.6). Male sex (aOR=1.6, 95% CI 1.4 to 1.8) and age 2 years and older (aOR=1.6, 95% CI 1.4 to 1.9) were positively associated with medically attended head injury, whereas Hispanic ethnicity (aOR=0.5, 95% CI 0.3 to 0.7) was negatively associated with medically attended head injury. There was no significant interaction term between era and race, suggesting that time period did not affect differentially the likelihood of a medically attended head injury across the two racial groups.

Multivariable estimates shown in table 3 include all patients who were evaluated at an ED during the specified time periods and assess for changes in head injury severity indicated by hospitalization and head CT use. Since the threshold for hospital admission varies in community hospitals (PED 1 and PED 2) compared with the main academic hospital (PED 3), a subgroup analysis was performed to assess for hospital admission. Among patients evaluated in PED 3, the proportion of visits requiring hospitalization for head injury was found to be more than twofold higher in the COVID-19 era (aOR=2.3, 95% CI 1.3 to 4.3). Use of head CT imaging did not significantly change in the COVID-19 era (aOR=1.04, 95% CI 0.7 to 1.6). Black patients represented a lower proportion of ED visits resulting in head injury-associated hospitalization compared with white patients (aOR=0.4, 95% CI 0.2 to 0.9), and subsequently a lower proportion received head CT imaging compared with white patients (aOR=0.4, 95% CI 0.2 to 0.6), adjusting for era, sex, age group, and SES level. The age group 2 years and older also had a significant negative association with hospitalization (aOR=0.3, 95% CI 0.2 to 0.6), suggesting that head injury severity was lower in this age group. Presenting hospital was also significantly

Table 1 Characteristics of patients seen in emergency department, by era

Characteristics	Pre-COVID-19 era N=19,083	COVID-19 era N=8616	P value*
Overall, no (%)	19,083 (68.9)	8616 (31.1)	<0.001
Sex, no (%)			
Male	9960 (51.2)	4426 (51.4)	0.20
Female	9123 (47.8)	4190 (48.6)	
Age, no (%)			
<2	4359 (22.8)	2041 (23.7)	0.12
≥2	14,724 (77.2)	6575 (76.3)	
Mean (SD)	7.10 (5.86)	7.38 (6.10)	<0.001
Race, no (%)			
White	5046 (26.4)	2505 (29.1)	<0.001
Black	9378 (49.1)	4029 (46.8)	
Asian	882 (4.6)	380 (4.4)	
American Indian/Pacific Islander	36 (0.2)	18 (0.2)	
Native Hawaiian	20 (0.1)	8 (0.1)	
Other	3721 (19.5)	1676 (19.5)	
Ethnicity, no (%)			
Non-Hispanic	15,869 (83.2)	7196 (83.5)	0.46
Hispanic	3214 (16.8)	1420 (16.5)	
National ADI rank			
1–25 (highest SES)	5392 (28.3)	2592 (30.1)	0.001
26–50	4766 (25.0)	2124 (24.7)	
51–75	4219 (22.1)	1932 (22.4)	
76–100 (lowest SES)	4706 (24.7)	1968 (22.8)	
Hospital, no (%)			
PED 1	3137 (16.4)	1269 (14.7)	<0.001
PED 2	5398 (28.3)	2196 (25.5)	
PED 3	10548 (55.3)	5151 (59.8)	
Overall hospital admission, no (%)	1471 (7.7)	992 (11.5)	<0.001
Presence of head injury, no (%)	1058 (5.5)	553 (6.4)	0.004

For categorical variables, proportions are compared with χ^2 tests.
*For continuous variables, means are compared with t-tests.
ADI, Area Deprivation Index; SES, socioeconomic status.

associated with head CT use, in which head CT scans were ordered twice as much in community hospitals (PED 1 and PED 2) (aOR=2.2, 95% CI 1.4 to 3.4) compared with the major trauma hospital (PED 3). There were no significant interaction terms between race and era for either of the severity outcomes, indicating that time period did not affect differentially the likelihood of hospital admission nor head CT use across the two racial groups.

DISCUSSION

Our study found that the number of total ED visits dropped during the COVID-19 era, however the proportion of ED visits for head injury increased during that time. Black patients represented a lower proportion compared with white patients among those with head injury. Head injury severity increased during the COVID-19 era.

Our study found that the proportion of ED visits due to head injury and hospitalization significantly increased from the pre-COVID-19 to the COVID-19 era in the pediatric

Table 2 Multivariate logistic regression analyses demonstrating associations with medically attended head injury

Factors	Adjusted OR*	95% CI	P value
Era			
Pre-COVID-19 (2019)	(ref)		
COVID-19 (2020)	1.19	1.06 to 1.35	0.004
Race			
White	(ref)		
Black	0.49	0.43 to 0.56	<0.001
Interaction: race×era	1.07	0.84 to 1.36	0.60
Black patients in pre-COVID-19 era	0.48	0.41 to 0.56	<0.001
Black patients in COVID-19 era	0.51	0.42 to 0.63	<0.001
National ADI rank			
1–25 (highest SES)	(ref)		
26–50	0.82	0.70 to 0.96	0.01
51–75	0.88	0.74 to 1.05	0.15
76–100 (lowest SES)	0.83	0.69 to 1.00	0.06
Sex			
Female	(ref)		
Male	1.58	1.40 to 1.78	0.001
Age			
<2	(ref)		
≥2	1.61	1.37 to 1.88	<0.001
Ethnicity			
Non-Hispanic	(ref)		
Hispanic	0.49	0.33 to 0.74	0.001
Presenting hospital			
Academic hospital (PED 3)	(ref)		
Community hospital (PED 1 and 2)	1.48	1.30 to 1.67	<0.001

*Adjusted for race, ADI rank, sex, age group, ethnicity, and presenting hospital.
ADI, Area Deprivation Index; SES, socioeconomic status.

patient ED visit population, although the total number of ED visits substantially dropped during the COVID-19 era. In contrast, the opposite trend has been documented in adults as there have been decreases in the proportion of head injury admissions during the pandemic period.⁹ In adults, most head injuries occur by motor vehicle accidents occurring outside the home.¹⁶ Whereas in children, head injuries are most commonly due to falls occurring in the home.¹⁶ It is possible that with stay-at-home orders and lockdown measures which increase the time that children spend at home, children may be getting disproportionately affected due to a higher risk of head injury in the home.

Interestingly, our study also found that black patients represented a lower proportion of head injury visits compared with white patients. A fewer proportion of black patients also required hospitalization and head CT imaging compared with white patients, even after accounting for SES level. Although the exact mechanism as to why these racial differences exist is unclear, several reasons have been hypothesized. First, these differences could reflect differences in sustaining head injury due to varying levels of supervision and risk exposures in the home,¹⁷ as well as other factors (such as parental education level, parental occupation and income level, differences in parental monitoring

Table 3 Multivariate logistic regression analyses demonstrating associations with head injury-associated hospitalization and head CT use

Factors	Hospitalization*			Head CT		
	Adjusted OR†	95% CI	P value	Adjusted OR‡	95% CI	P value
Era						
Pre-COVID-19 (2019)	(ref)			(ref)		
COVID-19 (2020)	2.33	1.25 to 4.34	0.008	1.04	0.67 to 1.61	0.87
Race						
White	(ref)			(ref)		
Black	0.42	0.20 to 0.87	0.02	0.39	0.24 to 0.63	<0.001
Interaction: race×era	1.29	0.37 to 4.50	0.69	0.79	0.30 to 2.07	0.64
Black patients in pre-COVID-19 era	0.36	0.13 to 1.0	0.05	0.42	0.24 to 0.72	0.002
Black patients in COVID-19 era	0.47	0.19 to 1.16	0.10	0.33	0.14 to 0.76	0.009
National ADI rank						
1–25 (highest SES)	(ref)			(ref)		
26–50	1.04	0.47 to 2.32	0.92	0.81	0.49 to 1.35	0.42
51–75	0.80	0.31 to 2.09	0.65	0.36	0.17 to 0.77	0.009
76–100 (lowest SES)	0.48	0.16 to 1.49	0.20	0.55	0.26 to 1.19	0.13
Sex						
Female	(ref)			(ref)		
Male	1.38	0.73 to 2.59	0.32	1.06	0.70 to 1.59	0.16
Age						
<2	(ref)			(ref)		
≥2	0.30	0.16 to 0.56	<0.001	1.14	0.68 to 1.91	0.63
Ethnicity						
Non-Hispanic	(ref)			(ref)		
Hispanic	N/A§	N/A	N/A	0.24	0.03 to 1.76	0.16
Presenting hospital						
Academic hospital (PED 3)	N/A¶	N/A	N/A	(ref)		
Community hospital (PED 1 and 2)				2.16	1.38 to 3.38	0.001

*Hospitalization was assessed by a subgroup analysis among patients presenting to PED 3 only.
†Adjusted for race, sex, and age group.
‡Adjusted for race, ADI rank, sex, age group, ethnicity, and presenting hospital.
§Ethnicity was not included in the model because there were no patients in the Hispanic group with a head injury-associated hospitalization.
¶Presenting hospital was not applicable since the model only consists of patients evaluated at PED 3.
ADI, Area Deprivation Index; N/A, not available; SES, socioeconomic status.

and caregiver styles¹⁸) that have been shown to influence the collective home environment.¹⁹ Second, since this study measured medically attended head injuries (ie, ED visits), these findings could reflect differences in healthcare access and/or utilization.²⁰ In addition, factors such as sign and symptom recognition as well as differences in the level of concern about head injuries can vary between racial groups and influence the threshold for seeking medical care.²¹

We explored changes between the two time periods where we found a significant decrease in ED utilization during the COVID-19 era. While we cannot dogmatically speak to the cause of this, it is likely that children were less likely to come into the ED for evaluation during the COVID-19 era due to fear of the virus, isolation measures that were imposed early in the pandemic, and safety concerns, all of which could have contributed to the decrease in total visits and the observed decline. Other reasons include that threshold for seeking medical care was likely to be higher, as well as changes in injury prevalence due to changes in activity patterns resulting in head injury (ie, less sports, school closures, less motor vehicle driving) may have likely occurred as well. We also found a significant decrease in ED

utilization among blacks from the pre-COVID-19 era to the COVID-19 era, a trend not observed in whites. While drops in the overall number of ED visits in the COVID-19 era have been greatly documented,^{17,22} this differential drop between racial groups highlights the possible barriers to healthcare access in black populations. Blacks are more likely to lack health insurance coverage.^{23,24} In addition, it has been well reported throughout the pandemic that blacks were at a higher risk for severe and fatal COVID-19 infections, and this could have contributed to decreased ED utilization and a higher threshold to seeking care, given concerns about COVID-19 exposure.²⁵

It was interesting to find differences in head injury outcomes by age group. Our study found that the likelihood of presenting to the ED with a head injury was higher in children 2 years of age and older, however head injury severity was higher in children younger than 2 years of age. This has been extensively documented where severe head trauma such as skull fracture and intracranial injury are more likely to be present among children younger than 2 years, whereas minor head injury is predominantly observed in children 2 years and older, due to differing levels of risk exposure.⁵

We also observed that head CT use was substantially higher in the community-based hospitals in comparison to the pediatric trauma center, potentially reflecting differences in the severity of head injury cases presenting to these facilities. This is contrary to what was expected since management of severe head injury cases is usually directed to trauma centers, when feasible.²⁶ However, another possible reason could be hospital-based differences in ordering head CTs for children. Many clinicians receive guidance about the need to obtain head CTs using PECARN guidelines, which is a clinical validation tool to assess head injury severity and the subsequent need for head CT scans in children,¹⁴ but subjectivity and varying degrees of how they are followed between hospitals have been shown.²⁷ Many studies have documented higher rates of obtained head CTs for children with minor head injuries at community hospitals in comparison to academic centers,^{28 29} which may reflect clinicians' level of comfort and experience in diagnosing minor head trauma in children and use of adult-specific decision tools for pediatric patients.³⁰ It would be interesting to further explore the effects that differential adherence to these guidelines can have on overall head CT use between different hospitals, particularly since head CT imaging is used as a major indicator for head injury severity and predictor of future outcomes.³¹

This study has several limitations. First, our study only assessed medically attended head injury which may underestimate the true prevalence during the pandemic period. There are also many factors that influence medical-seeking behavior including parental educational level, parental perceptions in seriousness of injury,³² insurance status, place of residence, and overall trust in the healthcare system. Another limitation was that we were unable to assess circumstances surrounding injury, as these were not in-depth medical chart reviews that often provide important clinical details regarding on how the injury was acquired and the use of any safety measures. Additionally, recognizing that the year of 2020 was dynamic, we may see different results depending on the time period being assessed in the year. Although in our study we did not find a significant interaction between era and race, the era was limited to the early part of the pandemic. It is possible that use of a longer window of time may also impact these results. Finally, our study was limited to hospitals that are situated in more urban environments, mainly within and surrounding Baltimore city, which could limit generalizability to other areas. To address these limitations, future research should assess different time periods throughout the year to see how head injury trends fluctuate in the presence of a pandemic. Seasonal patterns may have an effect as well since children are more likely to remain outdoors during the summer months, thus influencing injury mechanisms. Newer data are becoming available as the COVID-19 pandemic is aggressively being monitored, providing avenues to further injury research.

CONCLUSION

A decline in the total number of ED visits was observed in the COVID-19 era, however the proportion of ED

visits for head injury increased during this time in our pediatric study population. Black patients represented a fewer proportion compared with white patients among those with head injury, and this difference was not affected by the pandemic. The increase in the proportion of head injuries and hospitalization during the COVID-19 era may reflect changes in supervision and risk exposures in the home that occurred during the COVID-19 era. Postinjury care, level of awareness and knowledge regarding injury severity, as well as threshold for seeking care, may have also been influenced during the pandemic. Intervention efforts should be targeted to further understand how the pandemic continues to influence the collective home environment to shape pediatric healthcare utilization for head injuries.

Contributors SS conceptualized and designed the study, acquired, analyzed, and interpreted the data, drafted the manuscript, critically revised the manuscript for intellectual content, performed the statistical analysis, and provided overall study supervision. SS accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. ACG, and EMMcD conceptualized and designed the study, acquired, analyzed, and interpreted the data, critically revised the manuscript for intellectual content, provided administrative, technical, and material support for the study, and provided overall study supervision. LMR conceptualized and designed the study, acquired, analyzed, and interpreted the data, drafted the manuscript, critically revised the manuscript for intellectual content, performed the statistical analysis, provided administrative, technical, and material support for the study, and provided overall study supervision. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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