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Title: Changes in Pediatric Intensive Care Unit Utilization and Clinical Trends during the Coronavirus Pandemic

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ABBREVIATIONS

COVID (Coronavirus disease 19)

ECMO (Extracorporeal membrane oxygenation)

LOS (Length of stay)

PICU (Pediatric Intensive Care Unit)

PIM2 (Pediatric Index of Mortality-2)

Q1 (Quarter 1)

Q2 (Quarter 2)

SMR (Standardized mortality rate)

U.S. (United States)

VPS (Virtual Pediatric Systems)

ABSTRACT

Background: Children have been less impacted by the Coronavirus disease 19 (COVID) pandemic, but its repercussions on pediatric illnesses may have been significant. We examined the indirect impact of the pandemic on a population of critically ill children in the United States.

Research Question: Were there significantly fewer critically ill children admitted to PICUs during the 2nd quarter of 2020, and were there significant changes in the types of diseases admitted?

Study Design and Methods: Retrospective observational cohort study using the Virtual Pediatric Systems (VPS, LLC) database. Participants were 160,295 children admitted to the Pediatric Intensive Care Unit (PICU) at 77 sites in the United States during quarters 1 (Q1) and 2 (Q2) of 2017-2019 (pre-COVID) and 2020 (COVID).

Results: The average number of admissions was similar between pre-COVID Q1 and COVID Q1, but decreased by 32% from pre-COVID Q2 to COVID Q2 (20,157 to 13,627 admissions/quarter). The largest decreases were in respiratory conditions, including asthma (1,327 subjects in pre-COVID Q2 [6.6% of patients] vs 241 subjects in COVID Q2 [1.8%]; p<0.001) and bronchiolitis (1,299 [6.5%] vs 121 [0.9%]; p<0.001). The percentage of trauma admissions increased, though the raw number of trauma admissions decreased. Admissions for diabetes mellitus and poisoning/ingestion also increased. In the multivariable model, illness severity-adjusted odds of ICU mortality for PICU patients during COVID Q2 increased compared to pre-COVID Q2 [OR 1.165; 95% CI 1.00, 1.357; p=0.049].

Interpretation: Pediatric critical illness admissions decreased substantially during the 2nd quarter of 2020, with significant changes in the types of diseases seen in PICUs in the United States. There was an increase in mortality in children admitted to the PICU during this period.

Take-Home Point

Study Question: Were there significantly fewer critically ill children admitted to PICUs during the 2nd quarter of 2020, and were there significant changes in the types of diseases admitted?
Results: During the second quarter of 2020, in the midst of the COVID pandemic, we observed a 32% decrease in PICU admissions (particularly infection-related respiratory conditions, with diabetes mellitus a notable outlier), a modest increase in severity of illness, and a 16.5% increase in the odds of mortality.
Interpretation: Pediatric critical illness admissions decreased substantially during the 2nd quarter of 2020, with significant changes in the types of diseases seen in PICUs in the United States.

Since first detected in the United States (U.S.) in January 2020, more than 500,000 American adults have died of coronavirus disease 2019 (COVID)[1-3]. Children have been less directly impacted by the disease, accounting for fewer than 5% of cases and rarely requiring hospitalization, developing critical illness, or dying from COVID[2,4-9]. However, the indirect impact of the COVID pandemic on children's overall health and on the development of critical illness is unclear.

During the first months of the pandemic, states issued stay-at-home orders, mandated masks, and closed schools in efforts to control the pandemic, with the federal government announcing nationwide restrictions on March 13, 2020. These public health efforts to mitigate the spread of the virus may have had both positive and negative effects on acute and chronic pediatric illnesses. Transmission of common viral infections and incidence of accidental trauma may have decreased due to these measures[10-13]. However, children's health may have been negatively impacted by reduced access to school-based nutritional and health services, postponement of elective surgical procedures, and delays in seeking care. Psychosocial stressors may have led to an increase in child abuse, intentional ingestions, and suicide attempts[2]. Severe infections, traumatic injuries, perioperative conditions, and acute exacerbations of chronic illnesses like asthma and diabetes are among the most common causes of admission to a Pediatric Intensive Care Unit (PICU), thus the epidemiology of pediatric critical illness was likely sensitive to the indirect effects of COVID.

We aim to examine the indirect impact of the COVID pandemic on children by comparing the epidemiology and outcomes of patients admitted to a large network of U.S. PICUs during the first months of the pandemic compared to the same months in previous years. We hypothesize that there would be significant fewer critically ill children admitted and significant changes in the types of diseases admitted to PICUs during the 2nd quarter of 2020.

METHODS

We conducted a retrospective observational cohort study using the Virtual Pediatric Systems database (VPS, LLC). VPS is a validated and quality-controlled clinical database dedicated to standardized outcome data sharing among PICUs. Data included in the database have an interrater reliability of greater than 95% and include patient-level variables for all admissions to the participating PICU. This study was reviewed by the Institutional Review Board of Connecticut Children's Medical Center and determined to be non-human subject research.

Creation of the study database

The VPS database was queried for children admitted to a U.S. PICU in either quarter 1 (Q1, January-March) or quarter 2 (Q2, April-June) of the years 2017-2020 in order to compare the pre-COVID (2017-2019) era to 2020. Only centers with complete 2020 data and at least one full year worth of pre-COVID data were included.

For this study, we abstracted demographics, primary diagnosis, Pediatric Index of Mortality-2 (PIM2) risk of mortality, interventions (e.g., mechanical ventilation by endotracheal tube or tracheostomy tube), patient type (scheduled vs. unscheduled admission; surgical vs. medical), PICU length of stay (LOS), and survival to PICU discharge[14]. Primary diagnosis was initially collected as the STAR code, VPS' proprietary diagnosis classification. The 2,153 individual STAR codes were organized into 73 primary diagnoses by combining related STAR codes (e.g. "asthma with status asthmaticus" and "asthma with acute exacerbation") using a system detailed in Supplemental File 1; seven authors (JZC, CKM, MCS, ATR, SLS, KER and CLC) reviewed the proposed categorization and disagreements were resolved by consensus.

Statistical analysis

For each center, baseline patient characteristics were calculated by summing data from 2017-2019 and dividing by the number of years of available data. These center-level averages were then summed together to create weighted average totals for "pre-COVID". Pre-COVID Q1 data were compared with Q1 data from 2020 (COVID Q1) and pre-COVID Q2 data were compared with Q2 data from 2020 (COVID Q2). Categorical variables were compared with the Chi-squared test and continuous variables were compared with Wilcoxon rank sum. The frequency of each primary diagnosis was compared between pre-COVID years and 2020 using the Chi-squared test with p values adjusted for multiple comparisons using the Bonferroni correction.

For each quarter, standardized mortality rate (SMR) was calculated by dividing the actual number of deaths by the number of deaths predicted using PIM2, which uniquely incorporates diagnoses into mortality risk prediction[14]. To compare the SMR for pre-COVID vs COVID for each quarter, a Z-test was performed to determine if the SMRs were significantly different from each other. SMRs were presented with 95% confidence intervals[15,16]. Finally, a multivariable logistic regression model for factors associated with mortality was created using variables chosen *a priori*: PIM2, age, race, medical vs. surgical, scheduled vs. unscheduled, and study year. Analyses were done using SAS/STAT software (v9.4; SAS Institute Inc, Cary, NC). Reported p-values less than 0.05 were deemed statistically significant, and were adjusted for multiple comparisons when appropriate, as described above. Data are shown as n (%) and median (IQR).

RESULTS

Demographics

In the first two quarters of 2017-2020, there were a total of 160,295 children admitted to the 77 participating PICUs, 69 of which had data for all three baseline years. The number of admissions in COVID Q1 was 1% less than in pre-COVID Q1 (22,895 vs. 23,197 admissions/quarter), but there was a 32% decrease in admissions in COVID Q2 compared to pre-COVID Q2 (13,627 vs. 20,157 admissions/quarter) (Table 1). Age, gender, race, and patient origin differed significantly between pre-COVID Q2 and COVID Q2 (Table 1 and Supplemental Table 1) and a higher fraction of COVID Q2 patients were surgical (30.5% vs. 29.0%, p=0.003). PIM2 scores were not significantly different between baseline and COVID Q1, but increased significantly from pre-COVID Q2 to COVID Q2.

Treatments and outcomes

Frequency of intubation was lower in pre-COVID Q1 compared to COVID Q1, but did not differ between pre-COVID Q2 and COVID Q2, though the raw number of children requiring intubation in Q2 decreased markedly from 4,191 (20.8% of subjects) to 2,920 (21.4%) (Table 1). Use of mechanical ventilation (including via tracheostomy) and extracorporeal membrane oxygenation (ECMO) did not change between baseline and 2020 for either Q1 or Q2. PICU LOS did not differ between baseline and COVID Q1, but was significantly shorter in COVID Q2 compared to pre-COVID Q2 (1.49 [0.88, 3.10] vs 1.63 [0.91, 3.60] days, p<0.001). Raw mortality rate did not differ between pre-COVID Q1 and COVID Q1, but was higher in COVID Q2 than baseline (2.6% vs. 2.1%, p=0.008). When adjusted for PIM2 score, the SMR did not differ between baseline pre-COVID Q1 and COVID Q1 (0.91 [0.86, 0.96] vs 0.89 [0.80, 0.97]; p=0.56) but when comparing pre-COVID Q2 and COVID Q2, the SMR was modestly higher in COVID Q2 although this was not significant (0.86 [0.81, 0.91] vs 0.94 [0.84, 1.04]; p=0.15) (Figure 1).

Diagnoses

Among the 73 primary diagnoses, the frequency differed significantly between pre-COVID Q1 and COVID Q1 in only five diagnoses (Figure 2A, Table 2, Supplemental Table 2). There were increases in influenza (2.0% vs 3.1%) and pneumonia (4.9% vs. 6.3%), and decreases in upper airway disease (0.6% vs 0.2%), respiratory tract anomalies (1.6% vs. 1.2%) and suicide (0.2% vs 0.1%; all $p<0.003$).

The frequency of 19 diagnoses differed significantly between pre-COVID Q2 and COVID Q2 (Figure 2B). The largest decreases in patient volume were observed in respiratory conditions, including asthma (1,327 subjects at baseline [6.6% of patients] vs 241 subjects in COVID Q2 [1.8%]; $p<0.0001$), bronchiolitis (1,299 [6.5%] vs 121 [0.9%]; $p<0.001$), pneumonia (1,027 [5.1%] vs 318 [2.3%], $p<0.001$), influenza (56 [0.3%] vs 3 [0.0%]; $p<0.001$), and respiratory failure/arrest (594 [3.0%] vs 280 [2.1%];$p<0.0001$). The frequency of brain trauma (4.2% vs 5.6%; $p<0.001$) and general trauma (2.6% vs 3.4%; $p<0.001$) increased while attempted suicide (0.2% vs. 0.1%; $p=0.02$) decreased in COVID Q2, though raw patient volumes decreased in all three diagnoses. Only five primary diagnoses had both a significant increase in frequency and an increase in raw patient volume, including diabetes mellitus (1,033 [5.1%] vs 1,276 [9.4%]; $p<0.001$), poisoning/ingestion (856 [4.3%] vs 946 [6.9%]; $p<0.001$), blood cancer (146 [0.7%] vs 158 [1.2%]; $p=0.003$), and neurologic/neurovascular disease (375 [1.9%] vs 411 [3.0%]; $p<00001$).

Factors associated with mortality

A multivariable logistic model was created to calculate odds ratio estimates for PICU mortality in Q1 and Q2 (Table 3). Mortality was not associated with study year using Q1 data. However, the odds ratio for mortality in COVID Q2 was 1.17 (95% CI; 1.0, 1.36; $p=0.047$) compared to pre-

COVID Q2 while controlling for PIM2, age, race and patient type. Non-white children and neonates also had increased odds of mortality.

DISCUSSION

Using quality-controlled data from 77 PICUs across the United States, we observed a 32% decrease in critically ill children admitted to the PICU in April-June of 2020 compared to the same time frame during the preceding three years, predominantly due to marked reductions in common infection-related respiratory conditions. Diabetes and poisoning/ingestion were notable outliers that increased both in frequency and patient volume. Mortality rate was higher in COVID Q2 compared to baseline, even after adjusting for demographics and the increase in illness severity at PICU admission, suggesting that the COVID pandemic negatively impacted children despite the low incidence of direct illness.

Our observed decrease in non-COVID patient volume is similar that of adult patients in New York City (38%)[17]. A larger relative decrease in admissions (59%) was reported from the medical services of a single tertiary children's hospital, though that study included general ward patients[13]. A decrease in PICU admissions was unsurprising given elective surgeries were deferred in many regions and the predictable effects of mask mandates and stay-at-home orders on transmission of pathogens that cause common PICU conditions (e.g., bronchiolitis and pneumonia). Observing that PICU medical and surgical admissions decrease by approximately 30% may help leaders prepare during future pandemics, and the disproportionate effects on specific diagnoses provide unique information about the causative factors underlying pediatric critical illnesses. For example, the marked reduction in critical asthma suggests that infections contribute substantially to severe exacerbations, though reduced allergen exposure and increased parental supervision may also have influenced this finding.

Diabetes mellitus was the primary diagnosis with the largest increase in raw patient volume, increasing by more than 200 admissions per quarter compared to the pre-COVID years in Q2. Similarly, in the United Kingdom, an increase in the proportion of patients with diabetic ketoacidosis was reported for March to April 2020 when compared to the previous two years[18,19]. Coronavirus disease 19 may contribute to the development of diabetes and/or ketoacidosis, since coronaviruses bind to angiotensin-converting enzyme 2 receptors that are expressed on multiple organs and tissues including pancreatic beta cells[19]. Alternatively, lack of access to school-based healthcare may account for a decrease in compliance with diabetes management. Future studies should endeavor to better understand if COVID infection increases the likelihood of diabetic ketoacidosis among children with diabetes or increases the chances that a child develops diabetes in the first place.

Financial stressors, school closures, social distancing, and sick family members may have a negative impact on the emotional wellbeing of children and their parents, but the changes in the epidemiology of trauma and self-harm in our cohort are unclear. The raw numbers of critically injured children decreased, but their relative frequency increased significantly, suggesting that traumatic injuries were less affected by the pandemic than other causes of PICU admission. Encouragingly, both the frequency and raw number of children requiring PICU care after attempting suicide decreased. Further study is needed to understand the relative contributions of intentional and accidental causes to the increase in observed poisonings.

Perhaps our most troubling findings were that severity of illness and raw mortality rates were higher in COVID Q2. The approximately 15% increase in mortality was statistically reliable in the logistic regression model, but the contributing factors are unclear and warrant additional exploration and external validation. Parents may have had a reluctance to bring children to medical facilities, as evidenced by decreases in rates of routine childhood vaccination and

Emergency Department visits during the pandemic, which could have led to delayed care and more severe illness at presentation[20]. Hospital systems were strained during Q2 of 2020 while dealing with the first pandemic in over a century. Care protocols changed frequently, supply shortages occurred, and healthcare workers dealt with unprecedented levels of stress; cardiac arrest in the PICU during COVID has been attributed to such factors[21-25]. All these factors may have potentially contributed to our findings.

There are several limitations to this study. First, this is an observational cohort study conducted through retrospective analysis of a large quality-benchmarking dataset. Database studies such as ours carry an inherent risk of inaccurate data entry. However, the VPS database uses strict quality control measures to reduce the likelihood of data entry errors, has low frequency of missing data and high interrater reliability, and has been used for many observational studies of pediatric critical illness[26,27]. Second, not all 77 centers had all three years of baseline data (four had 1 year and four had 2 years), but this was accounted for by averaging 2017-2019 data by center. Third, since we only included the 77 centers that contributed data to the VPS database during the periods of interest, our data may not be representative of all PICUs in the United States. However, we believe that by including multiple centers with diverse characteristics from every region of the country, our findings are likely generalizable beyond our sample and thus representative of the changes in PICU admissions throughout the country.

INTERPRETATION

During the second quarter of 2020, in the midst of the COVID pandemic, we observed a 32% decrease in PICU admissions (particularly infection-related respiratory conditions, with diabetes mellitus a notable outlier), a modest increase in severity of illness, and a 16.5% increase in the odds of mortality. Similar reductions in patient volume may be planned for when large-scale public health measures are next needed. The disproportionate impact on specific conditions

provides unique insight on the causative factors underlying pediatric critical illness and should be further investigated. Pending external validation, the observed increase in mortality risk warrants consideration to avoid indirect harms to children from this pandemic that predominantly affects adults.

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All authors conceptualized and designed the study. Drs. Zee-Cheng, Carroll, and McCluskey wrote the initial manuscript, edited and reviewed subsequent manuscripts, and prepared manuscripts for publication. Ms. Klein performed all formal data analysis and created tables and figures, and edited and reviewed manuscript drafts. Dr. Scanlon performed project administration, assisted with methodology, and edited and reviewed manuscript drafts. Dr. Rotta performed project administration, assisted with methodology, and edited and reviewed manuscript drafts. Dr. Shein curated and maintained data, developed initial methodology, and edited and reviewed manuscript drafts. Dr. Remy performed project administration, assisted with methodology, and edited and reviewed manuscript drafts. Dr. Pineda maintained data, assisted with methodology and data analysis, and edited and reviewed manuscript drafts.

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Table 1. Demographics and Treatments Received

	All Data[1] N=160,295	Pre-COVID Q1 Weighted Annual Averages[2] N=23,197	COVID Q1 N=22,895	*P* value*	Pre-COVID Q2 Weighted Annual Averages[2] N=20,157	COVID Q2 N=13,627	*P* value*
Age							
Neonate Birth to 29 days	5,444 (3.4%)	883 (3.8%)	788 (3.4%)	0.11	573 (2.8%)	512 (3.8%)	<0.0001
Infant 29 days to < 2 years	55,953 (34.9%)	9,011 (38.8%)	8,975 (39.2%)		6,254 (31.0%)	3,578 (26.3%)	
Child 2 years to < 6 years	31,630 (19.7%)	4,478 (19.3%)	4,459 (19.5%)		4,191 (20.8%)	2,369 (17.4%)	
Child 6 years to < 12 years	28,624 (17.9%)	3,851 (16.6%)	3,675 (16.1%)		3,904 (19.4%)	2,641 (19.4%)	
Adolescent 12 years to < 18 years	38,644 (24.1%)	4,976 (21.5%)	4,998 (21.8%)		5,235 (26.0%)	4,527 (33.2%)	
Weight, kg	15.9 (8.70, 39.20)	14.1 (8.0, 34.5)	14.0 (8.1, 35.0)	0.43	17.7 (9.6, 42.0)	22.4 (10.2, 51.3)	<0.0001
Female[3]	71,640 (44.7%)	10,362 (44.7%)	10,232 (44.7%)	0.96	8,987 (44.6%)	6,227 (45.7%)	0.043
Race White (vs. non-white)	63,119 (39.4%)	9,242 (39.8%)	8,728 (38.1%)	0.0002	7,916 (39.3%)	5,286 (38.8%)	0.37
Region							
Midwest	41,543 (25.9%)	5,930 (25.6%)	6,153 (26.9%)	0.0021	5,265 (26.1%)	3,564 (26.2%)	<0.0001
Northeast	9,826 (6.1%)	1,369 (5.9%)	1,227 (5.4%)		1,265 (6.3%)	698 (5.1%)	
South	40,361 (25.2%)	5,708 (24.6%)	5,603 (24.5%)		5,193 (25.7%)	3,765 (27.6%)	
West	68,565 (42.8%)	10,190 (43.9%)	9,912 (43.3%)		8,435 (41.9%)	5,600 (41.1%)	
PIM2 Median (25^{th}, 75^{th})	0.80 (0.20, 1.29)	0.78 (0.20, 1.21)	0.78 (0.20, 1.20)	0.94	0.83 (0.21, 1.44)	0.87 (0.31, 1.54)	<0.0001
Physical Length of Stay, days	1.74 (0.94, 3.77)	1.84 (0.96, 4.0)	1.83 (0.97, 3.9)	0.91	1.63 (0.91, 3.6)	1.49 (0.88, 3.1)	<0.0001
Unscheduled Patient Type	127,082 (79.3%)	18,942 (81.7%)	19,290 (84.3%)	<0.0001	15,412 (76.5%)	10,345 (75.9%)	0.25
Post-operative	41,192 (25.7%)	5,254 (22.7%)	4,676 (20.4%)	<0.0001	5,848 (29.0%)	4,157 (30.5%)	0.0032
Intubated	33,056 (20.6%)	4,739 (20.4%)	4,425 (19.3%)	0.0031	4,191 (20.8%)	2,920 (21.4%)	0.16
Mechanical Ventilation	39,841 (24.9%)	5,604 (24.2%)	5,365 (23.4%)	0.068	5,151 (25.6%)	3,470 (25.5%)	0.85
ECMO	993 (0.6%)	156 (0.7%)	143 (0.6%)	0.53	116 (0.6%)	76 (0.6%)	0.85
ICU Mortality	3,301 (2.1%)	442 (1.9%)	434 (1.9%)	0.95	429 (2.1%)	350 (2.6%)	0.0081

Data displayed as N (%) = frequency (column percentage), median (25^{th} percentile, 75^{th} percentile)

*P values for categorical data are based on the Chi-Squared Test while continuous variables are based on the Wilcoxon Signed-Rank test

1. Raw counts
2. Weighted averages weighted by the number of quarters the center submitted data (from 2017, 2018, and 2019), rounded to the nearest whole number
3. Two patients listed as 'Ambiguous' were treated as missing as they did not specify male or female, percentages are out of the total non-missing

Table 2: Diagnostic categories with significant changes between pre-COVID and COVID quarters. Frequencies calculated from total samples and for weighted averages, N rounded to nearest whole number. Full dataset in Supplemental Table 2.

	Pre-COVID Q1 n=23,197	**COVID Q1 n=22,895**	***P* value**	**Pre-COVID Q2 n=20,157**	**COVID Q2 n=13,627**	***P* value**
Asthma	1,299 (5.6%)	1,292 (5.6%)	>0.99	1,327 (6.6%)	241 (1.8%)	<0.0001
Blood Cancer	143 (0.6%)	147 (0.6%)	>0.99	146 (0.7%)	158 (1.2%)	0.003
Bronchiolitis	4,564 (19.7%)	4,707 (20.6%)	>0.99	1,299 (6.5%)	121 (0.9%)	<0.0001
Congenital Heart Disease	256 (1.1%)	249 (1.1%)	>0.99	278 (1.4%)	253 (1.9%)	0.037
Diabetes mellitus	1,072 (4.6%)	1,054 (4.6%)	>0.99	1,033 (5.1%)	1,276 (9.4%)	<0.0001
Electrolyte abnormality	189 (0.8%)	203 (0.9%)	>0.99	186 (0.9%)	183 (1.3%)	0.018
Head trauma	649 (2.8%)	645 (2.8%)	>0.99	853 (4.2%)	757 (5.6%)	<0.0001
Influenza	465 (2.0%)	717 (3.1%)	<0.0001	56 (0.3%)	3 (0.0%)	<0.0001
Neurologic / Neurovascular	328 (1.4%)	378 (1.7%)	>0.99	375 (1.9%)	411 (3.0%)	<0.0001
Newborn/Perinatal - All	13 (0.1%)	13 (0.1%)	>0.99	20 (0.1%)	34 (0.3%)	0.039
Other	347 (1.5%)	286 (1.3%)	>0.99	343 (1.7%)	338 (2.5%)	<0.0001
Pneumonia	1,137 (4.9%)	1,436 (6.3%)	<0.0001	1,027 (5.1%)	318 (2.3%)	<0.0001
Poisoning/ingestion	761 (3.3%)	867 (3.8%)	0.23	856 (4.3%)	946 (6.9%)	<0.0001
Respiratory - upper airway	129 (0.6%)	38 (0.2%)	<0.0001	127 (0.6%)	38 (0.3%)	0.0004
Respiratory failure/arrest (including ARDS)	651 (2.8%)	699 (3.1%)	>0.99	594 (3.0%)	280 (2.1%)	<0.0001
Respiratory tract anomalies	373 (1.6%)	264 (1.2%)	0.0022	440 (2.2%)	269 (2.0%)	>0.99
Sepsis	612 (2.6%)	639 (2.8%)	>0.99	573 (2.8%)	501 (3.7%)	0.0013
Suicide	53 (0.2%)	15 (0.1%)	0.0004	46 (0.2%)	9 (0.1%)	0.020
Non-head Trauma	417 (1.8%)	344 (1.5%)	0.97	520 (2.6%)	466 (3.4%)	0.0005
URI (includes croup, tracheitis, laryngitis)	438 (1.9%)	361 (1.6%)	0.77	3445 (1.7%)	139 (1.0%)	<0.0001

ARDS=Acute Respiratory Distress Syndrome; URI=upper respiratory infection

P values are resulting from 2x2 Chi-Squared tests and are adjusted for multiple comparisons using the Bonferroni adjustment. The Chi-Squared test is comparing each individual diagnosis to all other diagnoses, for example, pneumonia vs. all other non-pneumonia diagnoses.

Table 3: Multivariable Logistic Model Odds Ratio Estimates for ICU Mortality

Pre-COVID Q1 vs. COVID Q1

Effect	Odds Ratio Estimate	95% Wald Confidence Limits		*P* value
Adolescent (12 years to < 18 years) vs Infant (29 days to < 2 years)	1.42	1.22	1.66	<0.0001
Child (6 years to < 12 years) vs Infant (29 days to < 2 years)	1.28	1.08	1.52	0.0053
Child (2 years to < 6 years) vs Infant (29 days to < 2 years)	1.11	0.94	1.32	0.23
Neonate (Birth to 29 days) vs Infant (29 days to < 2 years)	2.25	1.78	2.83	<0.0001
Post-Operative (yes vs. no)	0.63	0.54	0.75	<0.0001
COVID Q1 vs Pre-COVID Q1	0.93	0.81	1.06	0.25
PIM2	1.11	1.10	1.11	<0.0001

n=88,176, AIC=11,884.46, AUC=0.86 (95% CI 0.85, 0.87)

Pre-COVID Q2 vs. COVID Q2

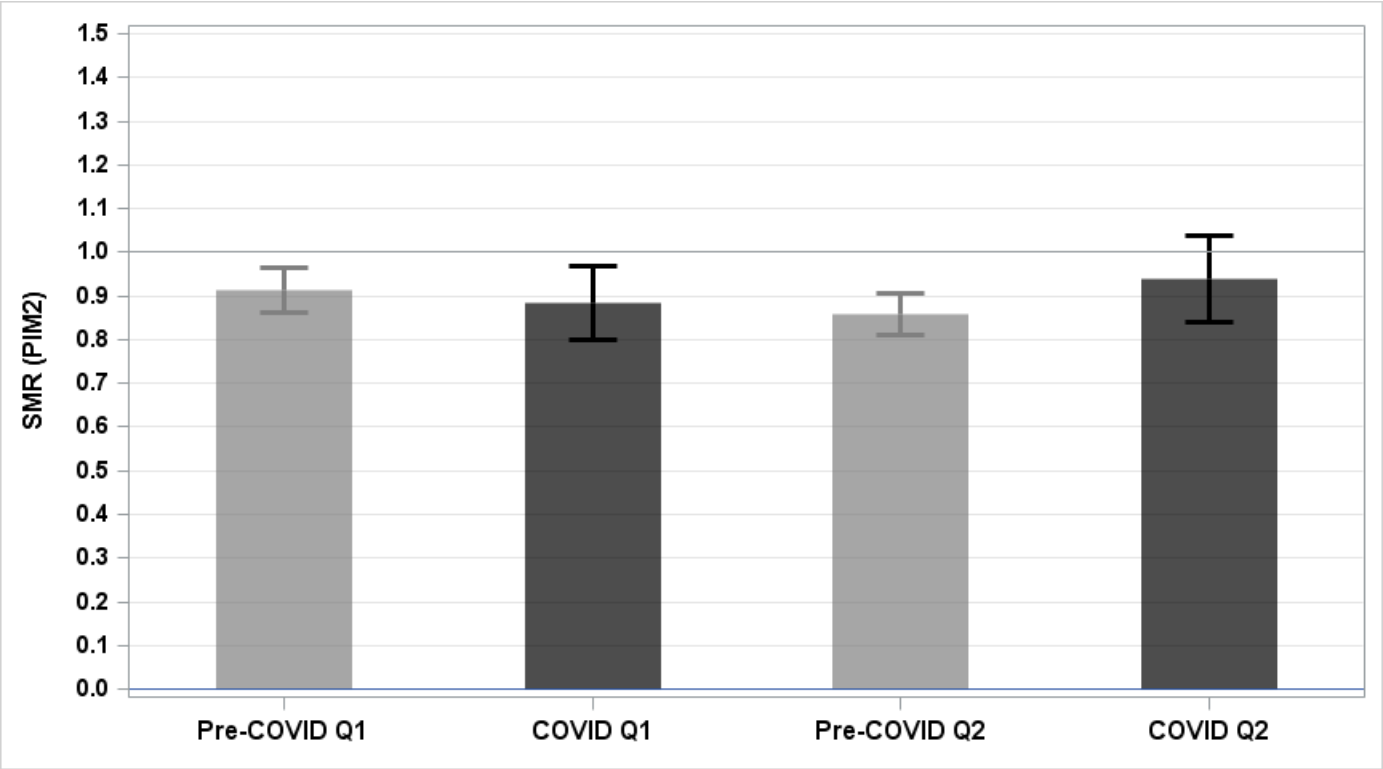
Effect	Odds Ratio Estimate	95% Wald Confidence Limits		*P* value
White vs. Non-white (race)	0.86	0.76	0.99	0.030
Adolescent (12 years to < 18 years) vs Infant (29 days to < 2 years)	0.92	0.78	1.09	0.33
Child (6 years to < 12 years) vs Infant (29 days to < 2 years)	1.04	0.87	1.25	0.64
Child (2 years to < 6 years) vs Infant (29 days to < 2 years)	0.86	0.72	1.04	.12
Neonate (Birth to 29 days) vs Infant (29 days to < 2 years)	1.84	1.41	2.39	<0.0001
Post-Operative (yes vs. no)	0.55	0.47	0.65	<0.0001
COVID Q2 vs Pre-COVID Q2	1.17	1.00	1.36	0.047
PIM2	1.11	1.10	1.11	<0.0001

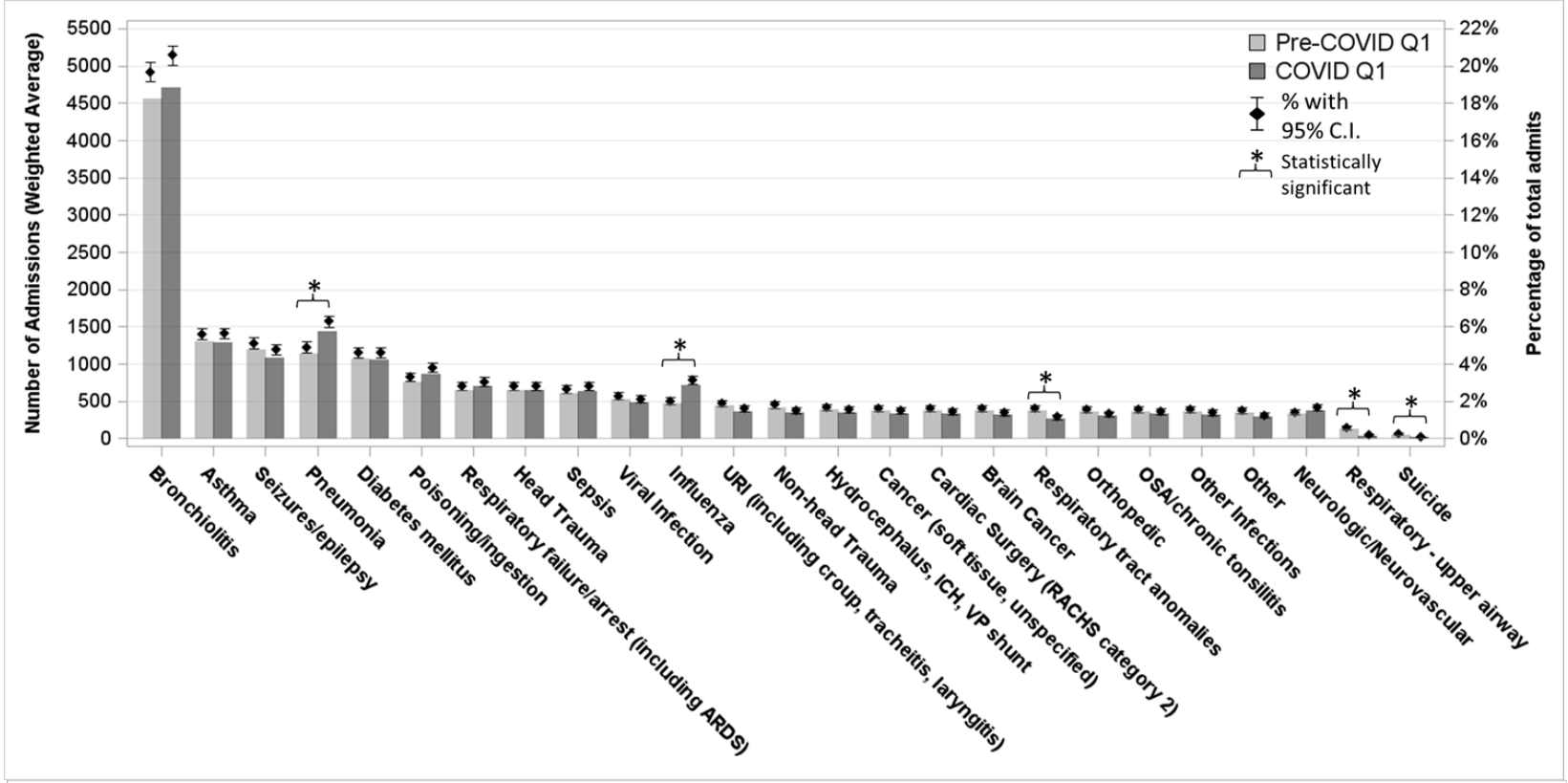
n=72,119, AIC=10,011.64, AUC=0.88 (95% CI 0.87, 0.89)

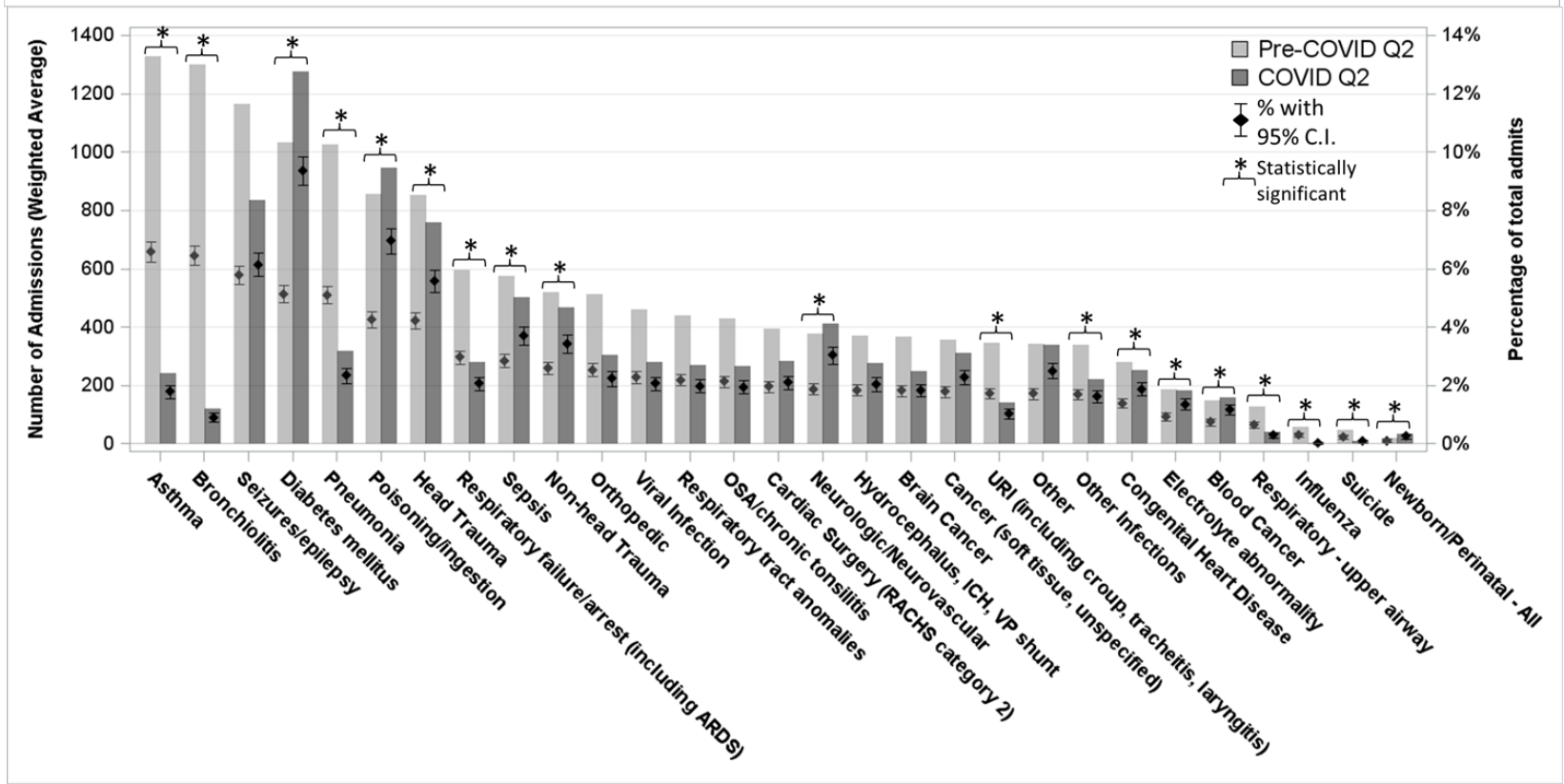
The rate of the missing values for variables in the multivariable regression model was 0% in both the Q1 and Q2 mortality models. There were 88,176 observations in Pre-Q1 + COVID-Q1 and all of them had complete data for the mortality model variables. The same was true for the Q2 model.

Figure 1. Standardized Mortality Ratios (SMR). Using PIM2 with 95% confidence intervals, reference line at 1 indicates the number of observed deaths is equal to the number of expected deaths.

Figure 2: Diagnostic categories in Q1 and Q2 pre-COVID (2017-2019) and during COVID (2020). For each diagnosis, the bars represent the weighted annual average of the number of children admitted to a participating ICU. The diamond and whiskers represent the percentage of admissions due to each diagnosis, which were compared between pre-COVID years and 2020 using the Chi-squared test with p values adjusted for multiple comparisons using the Bonferroni correction. Only diagnoses with ≥2500 admissions in entire dataset or statistically significant differences (Influenza, Respiratory upper airway, Suicide, Pneumonia, and Respiratory tract anomalies) are shown.


SMR (PIM2)
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Pre-COVID Q1
COVID Q1
Pre-COVID Q2
COVID Q2


Number of Admissions (Weighted Average)
Percentage of total admits
Pre-COVID Q1
COVID Q1
% with 95% C.I.
Statistically significant
Bronchiolitis
Asthma
Seizures/epilepsy
Pneumonia
Diabetes mellitus
Poisoning/ingestion
Respiratory failure/arrest (including ARDS)
Head Trauma
Sepsis
Viral Infection
Influenza
URI (including croup, tracheitis, laryngitis)
Non-head Trauma
Hydrocephalus, ICH, VP shunt
Cancer (soft tissue, unspecified)
Cardiac Surgery (RACHS category 2)
Brain Cancer
Respiratory tract anomalies
Orthopedic
OSA/chronic tonsillitis
Other Infections
Other
Neurologic/Neurovascular
Respiratory - upper airway
Suicide


Number of Admissions (Weighted Average)
Percentage of total admits
Pre-COVID Q2
COVID Q2
% with 95% C.I.
Statistically significant
Asthma
Bronchiolitis
Seizures/epilepsy
Diabetes mellitus
Pneumonia
Poisoning/ingestion
Head Trauma
Respiratory failure/arrest (including ARDS)
Sepsis
Non-head Trauma
Orthopedic
Viral Infection
Respiratory tract anomalies
OSA/chronic tonsillitis
Cardiac Surgery (RACHS category 2)
Neurologic/Neurovascular
Hydrocephalus, ICH, VP shunt
Brain Cancer
Cancer (soft tissue, unspecified)
URI (including croup, tracheitis, laryngitis)
Other
Other Infections
Congenital Heart Disease
Electrolyte abnormality
Blood Cancer
Respiratory - upper airway
Influenza
Suicide
Newborn/Perinatal - All