

Anesthesia complications in COVID-19 positive pediatric patients: Results from a rapid literature review and meta-analysis

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Abstract

Children are less likely to experience severe COVID-19-related complications compared to adults; they are still an understudied, vulnerable population. Given the unique challenges posed by COVID-19 in pediatric patients, effective perioperative management is essential to mitigate potential complications and ensure safe anesthesia practices. In this manuscript, the objective was to produce a systematic literature review with meta-analysis to increase the understanding of current research to help guide anesthesiologists in perioperative management. Our analysis of the literature identifies respiratory complications as a primary concern for patients undergoing anesthesia while infected with COVID-19. Three databases were searched and screened for reviews and there were 939 combined articles found. These databases are large collections of published scientific articles which were sorted through using keywords which allowed us to find and analyze these articles. After the databases were screened, there were a number of articles which worked within our criteria which were looking for pediatric anesthesia patients during the beginning of the pandemic and their complications. The odds ratio was calculated for each paper to generate an overall combined effect size, heterogeneity, and publication bias. After screening and removing duplicates, 10 articles were included for further review, and 6 were eligible for meta-analysis. Their combined effect size was 3.71 (CI 2.45, 7.24, $p = 0.05$), heterogeneity $I^2=0.76$, and funnel plot for publication bias demonstrated right skew. Our results show there is a statistically significant increase in modest COVID-19 complications in pediatric patients from anesthesia. These modest complications include respiratory events, use of vasopressors, cardiac, SIRS, and unplanned escalations of care. Clinically insignificant results may have been missed due to publication bias in our study. While we found statistically significant results showing an increase in pediatric complications, it is possible that clinically insignificant results could add even more to this topic, so we concluded that larger, more robust, studies need to be conducted.

Keywords: COVID-19, pediatrics, critical care, anesthesia

1. Introduction

It has been more than three years since the first case of SARS-CoV-2 infection, also known as COVID-19, was first reported in the United States in 2020. Since then, the medical community has learned a great deal about the virus and the impact that it has on many aspects of human health, including how it affects children. Children are an at-risk population with unique physiological characteristics, while studies have shown that children are less likely to experience severe COVID-19-related complications compared to adults it is worth investigating further. (1) COVID-19 can have a significant impact on the respiratory system including airway inflammation and impaired lung function, which can complicate ventilation and oxygenation. These challenges pose heightened risks during anesthesia, as patients may require careful monitoring and additional support to maintain airway stability and ensure safe outcomes. An estimated 3.9 million surgeries are performed on children each year in the United States alone. (2) The medical community's understanding of COVID-19 infection is constantly evolving, mirroring the ongoing evolution of the virus itself; as we learn more, other areas of medicine, including pediatric anesthesia, must also adapt to address emerging concerns. A comprehensive understanding of perioperative management, anesthetic response, and postoperative recovery in children affected by COVID-19 is imperative to guide physician decision-making and optimize patient care. This review will focus on literature published from 2021 to 2023 in an effort to provide a more complete perspective of the intricate relationship between COVID-19 infection and anesthesia complications in children.

2. Methods

This study, as a systematic review and meta-analysis, is exempt from the University of Toledo's Institutional Review Board.

Literature search and screening

Two investigators under the guidance of a clinical librarian searched the databases of PubMed, Cochrane Library, and EMBASE. Articles were searched up till the retrieval date of February 10, 2023. The search terms for PubMed were: ("sars-cov-2"[MeSH] OR covid 19[All fields] OR covid19[All fields] OR "sars-cov-2"[All Fields] OR "covid-19"[MeSH] OR "covid-19"[All Fields]) AND

("anaesthesia"[All Fields] OR "anesthesia"[MeSH] OR "anesthesia"[All Fields] OR "anaesthesias"[All Fields] OR "anesthesias"[All Fields]) AND ("paediatrics"[All Fields] OR "pediatrics"[MeSH] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]). Results were stored in Endnote and uploaded to Rayyan for screening. (3)

Inclusion and exclusion criteria were defined by all investigators before the screening. Our purpose was to investigate the intra-postoperative complications relating to anesthesia in pediatric patients positive for COVID-19. Our exclusion criteria include papers that did not report anesthetic complications, articles lacking separate data on pediatric and COVID-19 patients, studies published before 2021, consensus statements, case reports, other review papers, and articles not published in English.

Three investigators were involved in independently screening articles to reduce the probability of missed articles from fatigue or oversight error. The third reviewer was also used as a tiebreaker if two reviewers disagreed. All articles tagged "maybe" or "conflict" by the program were discussed as full text by the group to further identify qualifying studies.

Bias Assessment and Quality of Evidence

To assess certainty in our included retrospective observational studies, the Newcastle Ottawa Quality Assessment was performed. (4) Selection, comparability, and outcome were analyzed for each study to assess the certainty of evidence. Each assessment category generated a score using the Newcastle assessment. That score was used to stratify each study as poor, fair, or good evidence quality.

Data Extraction and Meta-Analysis

Data was extracted by two investigators and validated by a third. Data was extracted in the form of a standardized table that included study design, population characteristics, primary outcomes, and event rates. Articles included for review were analyzed for thematic analysis. Articles that compared COVID-19-positive patients with matched COVID-negative patients were included in the meta-analysis to find the odds of anesthesia complications. Anesthesia complications used in our analysis included respiratory events and overall anesthetic complications.

Meta-analysis was conducted through Meta-Essentials. (5) Heterogeneity was assessed via the I² test, with statistically significant I² greater than 50%. Odds ratios of dichotomous data and their 95% confidence intervals were used to assess the

data for effect size and subgroup analysis. A funnel plot was created using inverse variance as the weighing method and log odds ratios in a fixed effect model for publication bias. The trim and fill method was used to adjust for publication bias. Sensitivity analysis was used to evaluate the robustness of the studies and their conclusion to clinical practice.

3. Results

Study Selection

Rayyan was used for study screening and selection. After our database search, 939 articles were found, and after removing duplicates, we had 820 articles. 778 records were excluded by our three independent screeners, and 46 records were assessed as a group for further determination. From these 46 records, we as a team excluded 36 records due to reasons such as lack of relevant data, insufficient focus on anesthetic complications, or failure to meet our inclusion criteria. 10 records were included in our review, and 6 of the 10 had control groups that allowed them to participate in our meta-analysis. Our flowchart of the process can be visualized in Figure 1.

Population characteristics

A total of 9965 patients were included in our review, 929 of which were COVID-19-positive. The sample sizes ranged from 73 to 7896. Average ages were reported in 5 articles, with the overall average age of participants of 7.2 years with a range of ages from <1 year to 18 years. Studies were a mix of case-control, cohort, and chart review studies. All studies were retrospective.

Risk of bias and quality of evidence

We used the Newcastle Ottawa Quality Assessment to assess for certainty of our evidence. Three studies in our review did not have a comparable control group in their studies, resulting in an evaluation grade of poor. Individual results can be seen in Table 1.

Overall Anesthesia Complications

Six studies were included for the meta-analysis of anesthesia complications in COVID-19-positive patients compared to control groups. Studies were removed from meta-analysis if they did not have a COVID-negative group for comparison or if they did not list data for complications resulting from anesthesia. Heterogeneity for included articles was $I^2=0.76$. Complications in the meta-analysis included use of vasopressors, cardiac issues, SIRS, unplanned escalations of care, and respiratory complications

such as laryngospasm, bronchospasm, hypoxemia, unexpected respiratory support, ARDS, and pneumonia. Individual results of the study are seen in Table 2, and odds ratios were generated from events in each group.

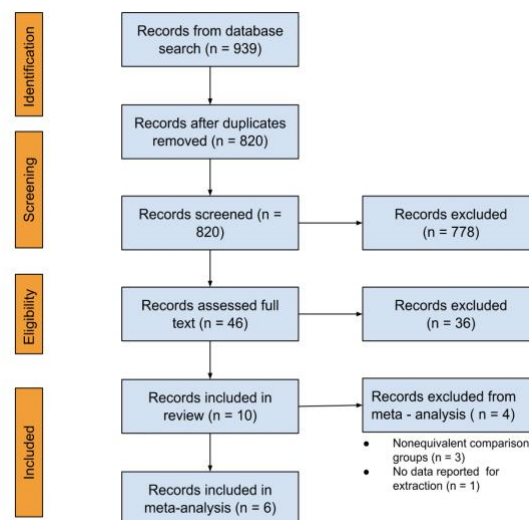


Figure 1. Flow of review and inclusion/exclusion process: Our search criteria yielded 939 results from the database search, and after the removal of duplicates 820 results remained. Based on inclusionary criteria, 778 results were removed when evaluated by our reviewers based on title, year published, and abstract screening. The full text of the remaining 46 results were read by our reviewers and screened- with 36 results being excluded due to incomplete fulfillment of our inclusionary criteria. Of the 10 remaining, 4 were removed as they could not be incorporated into our meta analysis due to either a lack of control groups or a lack of data.

Results of the combined effect size are presented in a forest plot in Figure 2. The combined effect size is 3.71 (CI 2.45, 7.24), suggesting pediatric patients with COVID-19 have higher odds for anesthesia complications. A funnel plot seen in Figure 3 was generated for publication bias and suggested bias toward data that gave a large effect size.

Table 1. Results of studies included in our literature review: 10 studies were found that met inclusionary criteria. Of these, 6 were found to have control groups present that compared complications of anesthesia to COVID positive patients.

Study Name	Study Groups	Sample Size	Method	Data Collection Dates	Evidence Quality
Complications associated with paediatric airway management during the COVID-19 pandemic: an international, multicentre, observational study ⁽⁶⁾	+ Vs -	7896	Cohort	4/3/2020 - 11/01/2020	Good
Anesthetic outcomes in pediatric patients with COVID-19: A matched cohort study ⁽⁷⁾	+ Vs -	105	Case-control	01/3/2020 - 09/24/2020	Good
Postoperative respiratory complications in SARS-CoV-2 positive pediatric patients across 20 United States hospitals: A Cohort Study ⁽⁸⁾	Symptomatic Vs Asymptomatic	266	Cohort	03/13/2020 - 10/31/2020	Good
Perioperative Management for Emergency Surgery in Pediatric Patients with COVID-19: Retrospective Observational Study ⁽⁹⁾	+ Vs -	73	Cohort	05/1/2020 - 12/31/2020	Poor
Urgent Neurosurgical Interventions in the COVID-19-Positive Pediatric Population ⁽¹⁰⁾	+	8	Chart Review	03/2020 - 10/2021	Poor
General Anesthesia for Pediatric Radiation Therapy in the Era of COVID-19 ⁽¹¹⁾	+	78	Observational	03/1/2020 - 01/29/2021	Poor
Postanesthesia complications in pediatric patients with previous SARS-CoV-2 infection: A cohort study ⁽¹²⁾	+ Vs -	341	Cohort	01/03/2020 - 10/07/2020	Good
Coronavirus disease 2019 convalescent children: outcomes after congenital heart surgery ⁽¹³⁾	+ Vs -	1109	Cohort	10/2020 - 06/2021	Good
Surgical outcomes in children with perioperative SARS-CoV-2 diagnosis ⁽¹⁴⁾	+ Vs -	291	Cohort	03/1/2020 - 06/30/2021	Good
Anesthetic Complications Associated With Severe Acute Respiratory Syndrome Coronavirus 2 in Pediatric Patients ⁽¹⁵⁾	+ Vs -	150	Cohort	04/28/2020 - 09/30/2020	Good

Table 2. Results of studies included in meta-analysis: Each of the 6 selected studies is depicted in this table. The breakdown includes the number of events for both the COVID positive and control groups, their associated odds ratio, and the outcome measured.

Article	Author, year	Study Name	Covid + events	Covid - events	Odds Ratio	Outcome Studied
Complications associated with paediatric airway management during the COVID-19 pandemic: an international, multicentre, observational study	MB Peterson et al 2022 ⁽⁶⁾	A	24/329	214/7567	2.7	Hypoxemia during airway management
Anesthetic outcomes in pediatric patients with COVID-19: A matched cohort study	Cronin J et al 2021 ⁽⁷⁾	B	9/35	1/70	24.15	Postanesthesia complications 30 days after procedure
Postanesthesia complications in pediatric patients with previous SARS-CoV-2 infection: A cohort study	Geng-Ramos et al 2023 ⁽¹²⁾	C	9/34	15/255	5.76	Postanesthesia complications 30 days after procedure
Anesthetic Complications Associated With Severe Acute Respiratory Syndrome Coronavirus 2 in Pediatric Patients	Saynhalath R et al 2021 ⁽¹⁵⁾	D	6/51	1/99	13.07	Respiratory complications, interop and 7 days after procedure
Coronavirus disease 2019 convalescent children: outcomes after congenital heart surgery	Joshi S et al 2021 ⁽¹³⁾	E	25/348	323/780	1.08	Re-intubation rates
Surgical outcomes in children with perioperative SARS-CoV-2 diagnosis	Nielson C et al 2022 ⁽¹⁴⁾	F	4/73	3/218	4.15	Respiratory complications postop

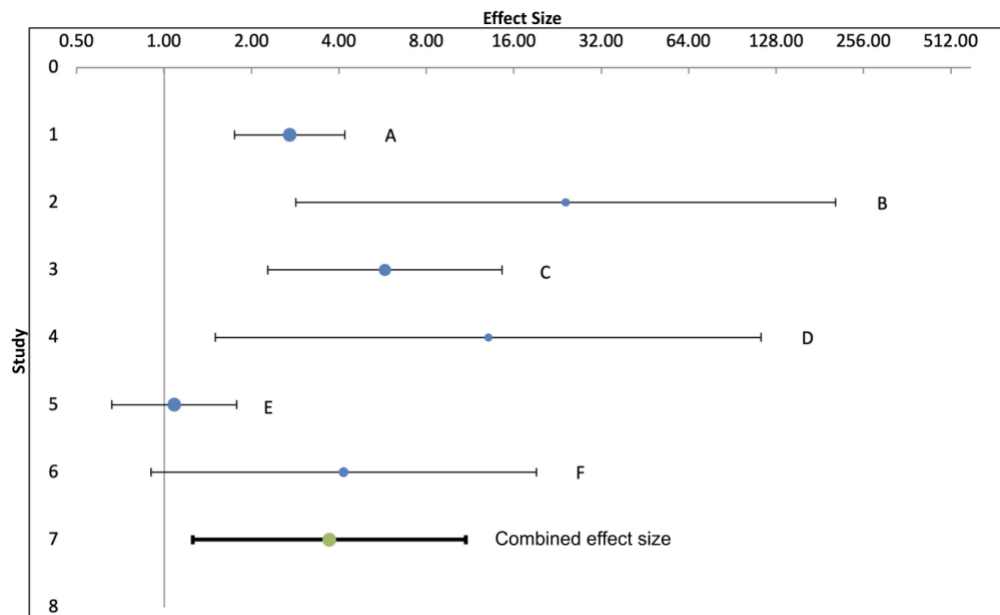


Figure 2. Combined effect size: The odds ratio of each study was plotted, and the combined overall effect size with all participants combined was shown in study 7. When combined there is an odds ratio of 3.71 demonstrating that COVID patients had higher rate of anesthetic complications.

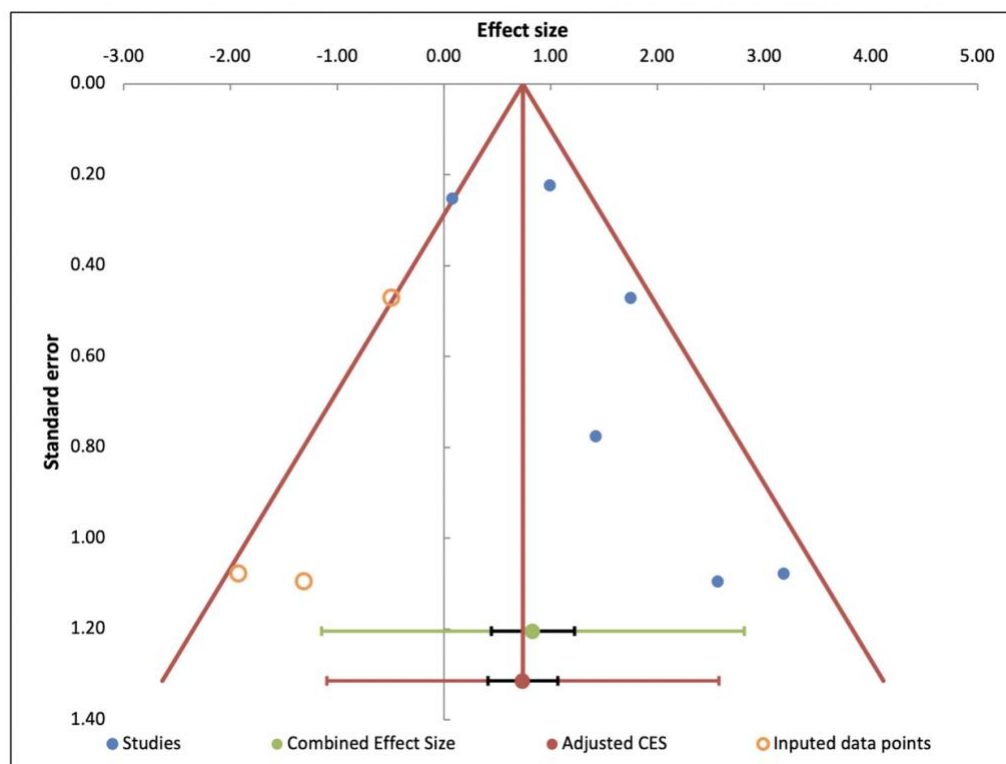


Figure 3. Funnel plot demonstrating publication bias: Inputted data points (orange circles) were placed to account for potentially missing studies due to bias. The combined effect size shown depicts the effect amongst the studies included within this review. The adjusted CES, depicted by the red dot and line, represented the effect size when potential publication bias is accounted for. The funnel demonstrates an asymmetric appearance indicating that there is a bias towards larger effect sizes.

4. Discussion

Our review focuses on the intricate relationship between COVID-19 infection and post-anesthesia complications in pediatric patients, focusing exclusively on articles written after 2021 in order to obtain a more comprehensive view of recent findings in regard to the infection. The analyses performed encompassed several factors, including patient demographics, surgical characteristics, symptomatology, and the spectrum of postoperative complications, shedding new light on the nuanced nature of this relationship.

Heterogeneity in Risk Factors and Patient Characteristics

A recurring theme in the reviewed literature is the lack of agreement regarding the identification of consistent, specific risk factors that contribute to post-anesthesia complications in pediatric patients infected with COVID-19. Despite investigation, current data is notably inconclusive concerning how American Society of Anesthesiology (ASA) physical status classification, age group, and type of surgery could serve as reliable predictors of increased risk. This further underscores the complexity of the interplay between COVID-19 infection and post-anesthesia outcomes in the pediatric population. Additionally, while it is evident that symptomatic patients are more prone to experiencing complications following anesthesia administration compared to age-matched asymptomatic individuals, there remains considerable uncertainty about how symptomatology alters a patient's risk.

Respiratory Complications and COVID-19 Infection

Our analysis of the literature highlights respiratory complications as a central concern for patients receiving anesthesia while also being infected with COVID-19.

Studies by Cronin et al. (7), Joshi et al. (13), and Nielson et al. (14), all suggest an elevated risk of mild respiratory events, including hypoxemia, in Covid-19-positive groups, with additional studies proposing a positive association similar to those observed with other viral upper respiratory infections (15). Additionally, qualitative analysis highlights minimal differences in respiratory outcomes between asymptomatic and symptomatic Covid-19-positive patients (15). This information could potentially be leveraged to inform clinical practice and further enhance the management of non-urgent pediatric surgical cases in asymptomatic COVID-19-positive patients.

Roles of Surgical Factors and Perioperative Management

The association between COVID-19 infection and post-anesthesia complications is further complicated by the addition of surgery. Geng-Ramos et al. (12) note the heightened risk of all-cause complications for COVID-19-positive patients within the first week following surgery. Additionally, this same study also identified an increased risk for cardiac-related complications for up to 42 days following anesthesia administration in this same population. Furthermore, this study suggested that there could be some benefit to using perioperative echocardiography for risk stratification and reduction in the context of pediatric COVID-19-positive patients (12). Moreover, while ASA status—the American Society of Anesthesiologists classification system used to assess a patient's risk for anesthesia-related complications—and surgical emergency status appear to exert influence on the relationship between COVID-19 infection and post-anesthesia complications, there is no clear consensus on exactly how this relationship is affected. We submit that a multifaceted, and perhaps multi-specialty, approach is warranted for accurate risk assessment and mitigation in the COVID-19-positive pediatric population.

Holistic Assessment of Complications

Our review and analysis of the data indicate a statistically significant increase in the odds of experiencing post-anesthesia complications when comparing pediatric patients with active COVID-19 infection to their healthy peers. While the calculated odds ratio of 3.71 ($p = 0.05$) suggests a heightened risk, it is important to note that observed complications were largely modest in severity. Across all studies analyzed for this review, none reported fatalities that were directly associated with anesthesia and COVID-19 infection. The rightward skewness of the publication bias funnel plot shown above suggests a tendency to publish reports focusing on COVID-19 complications in pediatric patients, indicating an inclination to emphasize severe cases while underreporting cases with minimal experienced complications. This publication bias might result in an overestimation of the true risk of COVID-19 complications in the context of pediatric anesthesia administration.

Implications for Clinical Practice and Areas of Future Research

The findings of this review provide insight into the complex relationship between COVID-19 infection and post-anesthesia complications in

pediatric patients. However, it also clearly highlights that substantial knowledge gaps persist, necessitating further research to clarify the heterogeneity of risk factors, the physiologic mechanisms underlying complications, as well as the efficacy of perioperative interventions. These insights have practical implications for clinical decision-making and perioperative management in the context of COVID-19, emphasizing the importance of individualized approaches tailored to patient characteristics and risk profiles.

Included articles in our review collected data before the COVID-19 vaccine was approved for pediatric patients. Areas for future study include comparing vaccinated COVID-19 pediatric cases versus unvaccinated and COVID-19-negative patients. Furthermore, as time has passed more viral strains have emerged. Our studies were taken from multi centers with a large majority not reporting specific strains which is something which could be expanded upon in future reviews.

Our review has modest results but can be helpful to guide clinical management to determine optimal surgical timing in regard to post-anesthesia complications. Perioperative management can be optimized by screening pediatric patients for COVID-19 as well as COVID-19-related complications. These steps can be taken to reduce the rate of adverse events during anesthetic administration, as well as during the post-anesthesia period.

Limitations

We noted several limitations in our review, including small study sizes, lack of generalizability to the broader population, publication bias, and unintentional errors. One of the main limitations of this review is the number of studies included. Our focus was specifically on outcomes for pediatric patients, which presented a unique challenge. Many studies identified during our review included pediatric patients but often combined them with adult patients in their cohorts, without age stratification. As a result, we had to exclude these studies based on our inclusion criteria, which specified that only studies focused solely on pediatric outcomes could be considered. This criterion significantly reduced the number of viable studies. The articles that we accepted into our review all contain small population sizes and many are single-center studies. This makes their results difficult to generalize to the larger pediatric population of the United States. However, these studies included a strictly pediatric population and concentrated on anesthetic complications. Due to the specific focus

of this review and the inclusion criteria, these studies were accepted because they met our requirements. Further limitations include the ever-present potential for publication bias as studies identifying complications associated with COVID-19 infection are more likely to be pursued and published. Finally, there is the possibility of committing unintentional errors due to user inexperience or fatigue.

Moreover, even studies that concentrated on pediatric complications frequently lacked control groups, making them ineligible for inclusion in our meta-analysis. The requirement to include only studies published after 2021 further complicated our search, as many relevant preliminary findings were published prior to this date, particularly during the early stages of the pandemic.

Given more time, there should be more studies looking at the specific complications of CoVid-19 within pediatric patients which would allow a larger analysis to be done and provide more substantial conclusions. In addition, future meta-analysis should strive to include more multi-center studies as well as pediatric patients of all demographics to allow more generalizability. Finally, more meta-analysis of this topic would lower the likelihood of user inexperience or fatigue due to a larger amount of people inputting ideas and prevention of fatigue to affect one group only.

5. Conclusion

Pediatric patients who test positive for COVID-19 infections are at increased risk for anesthesia complications; however, the adverse effects are moderate and may be overreported. The complications that were noted include the need for vasopressors, cardiac issues, SIRS, unplanned escalations of care, and respiratory complications such as laryngospasm, bronchospasm, hypoxemia, unexpected respiratory support, ARDS, and pneumonia. While our review presents modest findings, it offers valuable insights for guiding clinical management in determining the optimal timing for surgeries concerning post-anesthesia complications. Enhancing perioperative management through the screening of pediatric patients for COVID-19 can help minimize the risk of adverse events both during anesthesia and in the post-anesthesia period. In light of new variants and increased vaccine status, further research needs to be conducted to increase the validity and generalizability of our study.

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