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Original Paper

ACUTE APPENDICITIS IN PAEDIATRIC PATIENTS WITH DELTA AND OMICRON VARIANTS OF SARS-COV-2: CASE SERIES

Arnis Eņģelis[1,3,#], Liene Smane[2,4], Astra Zviedre[1,3], Anda Ķīvīte-Urtāne[7], Timurs Zurmutai[1,5], Jana Pavāre[2,4], Jurijs Bormotovs[5,6], Mohit Kakar[1,3], and Aigars Pētersons[1,3]

[1] Department of Paediatric Surgery, Rīga Stradiņš University, 45 Vienības Av., Rīga, LV-1004, LATVIA

[2] Department of Paediatrics, Rīga Stradiņš University, 45 Vienības Av., Rīga, LV-1004, LATVIA

[3] Department of Paediatric Surgery, Children's Clinical University Hospital, 45 Vienības Av., Rīga, LV-1004, LATVIA

[4] Department of Paediatrics, Children's Clinical University Hospital, 45 Vienības Av., Rīga, LV-1004, LATVIA

[5] Department of Doctoral Studies, Rīga Stradiņš University, 16 Dzirciema Str., Rīga, LV-1007, LATVIA

[6] Department of Anaesthesiology & Intensive Care, Children's Clinical University Hospital, 45 Vienības Av., Rīga, LV-1004, LATVIA

[7] Department of Public Health and Epidemiology, Institute of Public Health, Rīga Stradiņš University, 9 Kronvalda Blvd., Rīga, LV-1010, LATVIA

[#] Corresponding author, Arnis.Engelis@rsu.lv

Contributed by Aigars Pētersons

COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is generally milder in children. Acute appendicitis (AA) is a common diagnosis in children, but greater understanding is needed for more adjusted treatment of these patients when in conjunction with acute COVID-19 infection. We provide a retrospective case series study of comparison of patients with AA and positive SARS-CoV-2 Delta (B.1.671.2) and Omicron (B.1.1.529) variants. There were 16 paediatric patients admitted to a tertiary hospital with suspected acute appendicitis and COVID-19. Compared with the Delta variant (B.1.617.2), children infected with Omicron variant (B.1.1.529) of SARS-CoV-2 infection were more likely to have fever (p = 0.04) and pain migration to the right lower quadrant (RLQ) (p = 0.02). Further studies are needed to characterise the differences between SARS-CoV-2 variants (Delta vs Omicron) in cases of acute appendicitis in children.

Keywords: *coronavirus disease 2019, abdominal surgery, children, viral.*

INTRODUCTION

After the coronavirus disease 2019 (COVID-19) pandemic, more data is becoming available regarding the combination of previously known diseases with COVID-19 infection (Baloch *et al*., 2020). COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is generally milder in children (Yasuhara *et al*., 2020). The majority of paediatric infections are asymptomatic or manifest as upper respiratory tract infection or mild pneumonia; however, an increasing number of studies report that a variety of gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, and abdominal pain as well as some atypical findings can also be found in paediatric patients (Pan *et al*., 2020; Racko *et al*, 2021; Howard-Jones *et al.*, 2022). A review by Pousa *et al*. found that non-pulmonary gastrointestinal manifestation is most common in paediatric patients with COVID-19, causing new diagnostic and treatment challenges to medical staff, especially while differentiating surgical and non-surgical abdominal conditions (Pousa *et al*., 2021).

Puoti *et al*. (2021) proposed pathophysiologic mechanisms of gastrointestinal symptoms associated with COVID-19 and included acute appendicitis (AA) as one of the manifes-

tations of SARS-CoV-2 infection in children (Abdalhadi *et al.*, 2020; Puoti *et al.*, 2021). SARS-CoV-2 RNA has been found in stool samples from infected individuals, and its viral receptor, angiotensin-converting enzyme 2 (ACE2), is known to be overexpressed in the gut mucosa. It has been reported that viral infections can cause AA via several mechanisms, including lymphoid hyperplasia, which induces appendix ulcerations, leading to bacterial infection. An association has been found between SARS-CoV-2 infection and AA, and it was discovered that an atypical histological COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is generally milder in children.

There is a rising number of reports of children with both positive COVID-19 and AA, but the amount of data is still insufficient. Literature largely consists of case reports and small case series (Acevedo *et al.*, 2021; Meyer *et al.*, 2021; Nurnaningsih *et al.*, 2022).

In our addition to the data pool, we provide a retrospective case series study of comparison of patients with AA and positive SARS-CoV-2 Delta (B.1.671.2) and Omicron (B.1.1.529) variants. Given the lack of individual strain testing, variants were determined by date of positive testing and prevalent population strain on the particular date.

MATERIALS AND METHODS

This study was designed as a retrospective case series study, and all patients had a positive Delta (B.1.617.2) or Omicron variant (B.1.1.529) of SARS-CoV-2 infection and AA. Between March 2020 and March 2022, a total of sixteen children aged 3–17 years old with the Delta or Omicron variant of SARS-CoV-2 infection and AA were admitted to the Children's Clinical University Hospital (CCUH) in Rīga, Latvia. All children who presented with abdominal pain during the pandemic were tested for COVID-19. Diagnoses of acute complicated or uncomplicated appendicitis were established using CCUH guidelines, and were treated surgically or non-surgically, according to CCUH guidelines. Non-surgical treatment of AA in children is applied only for uncomplicated cases while surgical treatment is used only for patients with complicated appendicitis and for those who have a failure of non-surgical treatment due to acute appendicitis. According to the diagnostic and treatment algorithm of AA at CCUH the criteria for uncomplicated AA are an Alvarado score ≥ 7, CRP cut of values 8.4 mg/l or IL-6 cut of value 36.2 pg/ml and signs of appendicitis in an ultrasound. The criteria for complicated AA are Alvarado score ≥ 7, CRP cut of values > 8.4 mg/l or IL-6 cut of value > 36.2 pg/ml, signs of appendicitis in an ultrasound and peritoneal irritation symptoms (Zviedre *et al.*, 2019).

Clinical and laboratory data from all paediatric patients admitted with Delta (B.1.617.2) or Omicron variant (B.1.1.529) of SARS-CoV-2 infection at the hospital were retrospectively assessed using electronic medical records. Patients with multisystem inflammatory syndrome in children (MIS-C) were excluded from the study.

Statistical data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM SPSS Corp.). Statistical significance was evaluated at the level of $p < 0.05$. Differences in clinical and laboratory findings between study groups representing SARS-CoV-2 variants of interest were evaluated using the Chi-Square or Fisher's Exact test in the case of categorical variables or Mann-Whitney U test in the case of continuous variables.

RESULTS

A total of sixteen paediatric patients were admitted to a tertiary hospital with suspected acute appendicitis and COVID-19. Patients were 3–17 years old (mean age 10.73 ± 4.3 SD), of whom eight were male. Tables 1 and 2 provide an overview of patient demographics, a clinical and treatment overview, as well as a summary of laboratory findings. All patients were European and had tested positive for SARS-CoV-2, but none of them developed respiratory symptoms. Six patients were infected with the Delta coronavirus variant (B.1.617.2) and ten with the Omicron variant (B.1.1.529). Ten patients had complicated appendicitis (according to intraoperative macroscopic or pathology finding) and five had acute uncomplicated appendicitis. In one case, ovarian apoplexy with chronic appendicitis was diagnosed. Eleven of sixteen patients had operative treatment, and appendicitis was confirmed by a pathology examination. All patients presented the primary symptom of right lower abdominal pain, while fourteen patients had nausea or vomiting, and only five patients had diarrhoea. Thirteen study patients had a documented fever > 38.0 °C for ≥ 24 h at the time of presentation. Compared with the Delta variant (B.1.617.2), children infected with the Omicron variant (B.1.1.529) of SARS-CoV-2 infection were more likely to have fever ($p = 0.04$) and pain migration to the right lower quadrant (RLQ) ($p = 0.02$). A summary of clinical characteristics is shown in Figure 1.

Out of the 16 patients, 68.75% (n = 11) had Alvarado scores of 7 or less and 31.25% (n = 5) had Alvarado scores greater than 7. Ultrasound was performed in 13 patients as first imaging. Among the complicated appendicitis patients, seven were perforated appendicitis, one was macroscopically gangrenous (s. destructive), one — phlegmonous, and one was phlegmonous appendicitis with fibrine patches (the last two cases were gangrenous (s. destructive) according to the pathology report). There were no statistically significant differences between laboratory tests. A summary of laboratory findings is shown in Figure 2.

Length of stay of the patients was 3–11 days (median days 5 ± 2 SD). There were no admissions to an intensive care unit among patients with acute appendicitis and COVID-19. All patients recovered and were discharged.

Table 1. Demographic features, clinical and treatment overview of AA patients

Case No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age (years)	15	14	15	12	16	5	3	17	13	8	9	10	11	6	7	8
Sex	M	M	F	F	F	F	M	M	M	M	M	F	F	F	M	F
Diagnosis (incl. COVID-19)	AcA	AcA	AcA	AcA	Ovarian apoplexy, chronic appendicitis	AnA	AcA	AnA	AnA	AcA	AnA	AcA	AnA	AcA	AcA	AcA
Symptoms before surgery (d)	2	1	3	1	2	N/A	2	3	1	1	2	3	1	3	1	4
Severe illness	No	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes	No	Yes	No	No
Fever	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abdominal pain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nausea or vomiting	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Diarrhea	No	Yes	No	No	No	No	Yes	No	Yes	No	Yes	No	No	No	No	Yes
Lack of appetite	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pain migration to RLQ	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No	No	No
Local tenderness in RLQ	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Local resistance in RLQ	No	No	No	No	Yes	No	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes
Alvarado score	8	9	7	7	7	7	7	7	6	9	5	7	5	8	8	6
ICU admission	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Antibiotics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hospital stay duration, d	5	7	9	11	4	5	6	4	4	5	3	7	4	5	4	4

F, female; M, male; AcA, acute complicated appendicitis; AnA, acute non-complicated appendicitis; RLQ, right lower quadran

Table 2. Summary of laboratory findings

Case No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age (years)	15	14	15	12	16	5	3	17	13	8	9	10	11	6	7	8
Sex	M	M	F	F	F	F	M	M	M	M	M	F	F	F	M	F
Hemoglobin, g/dl	N/A	12.4	11.6	10	12.9	13.2	11.6	15.2	14.2	13.5	13.1	11.8	12.5	11.6	13.3	12.2
CRP, mg/l	13.4	25.25	1.07	2.57	0.4	7.58	42.18	0.6	35.77	9.57	3.24	76.87	5.3	48.7	6.97	32.67
IL-6, pg/ml	NP	13.8	67.2	243	6.28	23.2	NP	50.1	NP	NP	47.0	NP	11.3	NP	16.1	90.2
White blood count, $\times 10^3$/mkl	9.38	10.17	15.65	14.84	10.17	9.8	14.73	13.92	9.76	15.42	9.98	6.81	5.62	13.7	17.75	9.61
Neutrophil, $\times 10^3$/mkl	8.05	9.12	13.89	11.80	5.65	7.58	12.74	11.66	8.24	11.51	6.49	5.83	3.8	8.48	14.83	6.83
Lymphocite, $\times 10^3$/mkl	N/A	0.65	0.94	1.35	3.26	1.25	1.33	1.4	0.58	2.70	2.73	0.35	1.20	3.60	0.67	1.45
Platelets, $\times 10^3$/mkl	165	188	281	240	262	236.00	312	251	258	384	213	153	228	338	329	150
Blood culture	NP	NP	NP	NP	Neg	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
PCR	NP	NP	NP	NP	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	NP
Serology	Pos	Pos	NP	Pos	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	Pos
Antigen test	NP	NP	Pos	Pos	NP	NP	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Neg
Prior 4 weeks exposure	Unk	Unk	Unk	Pos	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
Vaccination status	V-	V-	V-	V-	V-	V-	V-	V+	V-	V-	V-	V-	V-	V-	V-	V-
MIS-C	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

CRP, C-reactive protein; F, female; M, male; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction; Il-6, Interleukin 6; NP, not performed; Pos, positive; Neg, negative; V+vaccinated; V-not vaccinated; Unk, unknown

DISCUSSION

COVID-19-associated AA occurs in children. It can affect both girls and boys. Almost all the patients described herein presented with abdominal pain and complaints of various other typical symptoms, such as fever, nausea, and vomiting. None of the patients presented any respiratory symptoms. The diagnosis of SARS-CoV-2 infection in the patients reported herein was confirmed by sending nasopharyngeal samples for RT-PCR analysis or quantitative immunochemical tests for antibody serology, or an express antigen test for COVID-19. During the early stages of the pandemic, the number of paediatric cases were low. The true incidence of SARS-CoV-2 or COVID-19 infection of children in the world at that time was explained by 65% of asymptomatic cases in children and not enough testing facilities (Alsohime *et al*., 2020). Between March 2020 and March 2022, the case series of 16 children with AA and COVID-19 ranging from 3 to 17 years old in Latvia was also not large. Only six patients were infected with the

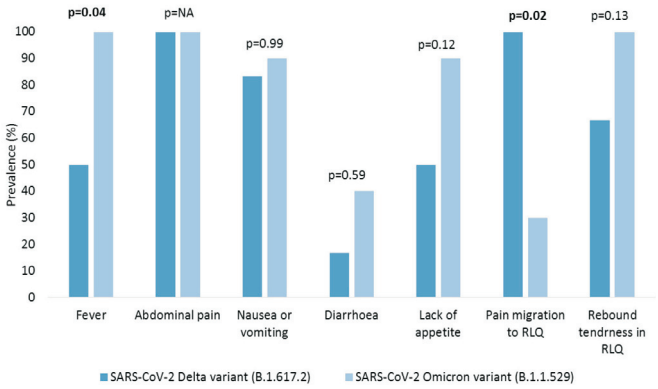

Fig. 1. Clinical characteristics of patients with Delta (n = 6) and Omicron (n = 10) variant of SARS-CoV-2 infection.

Delta variant (B.1.617.2). As the COVID-19 pandemic progressed, the relative proportion of paediatric cases increased. Indeed, with the emergence of the Omicron variant in late 2021, as it was also in Latvia, ten children were infected with this variant (B.1.1.529) (Karim *et al*., 2021).

The Delta (B.1.617.2) variant was first reported in India in October 2020 and was more transmissible and had higher viral load in infected samples (Alsohime *et al*., 2020). The Omicron variant (B.1.1.529) was first identified in Botswana in November 2021 and was the most highly mutated strain and even more contagious (Tian *et al*., 2021). The clinical picture of COVID-19 in children ≤ 9 years of age most commonly presents with fever (46%) while older children 10–19 years of age are more likely to have a cough (41%) and fever (35%) (Alsohime *et al*., 2020). Analysis of 48.2% cases the Omicron variant showed a significantly larger association with the development of croup in paediatric patients compared to the Delta variant (Tian *et al*., 2022). In our study of patients with AA and COVID-19 variants, children infected with Omicron variant and AA were more likely to have fever compared to the Delta variant. The significant difference of clinical presentation between COVID-19 variants in our study may be caused by appendix comorbidity. There was pain migration to the right lower quadrant (RLQ) significantly more frequently in patients infected with the Omicron variant compared to the

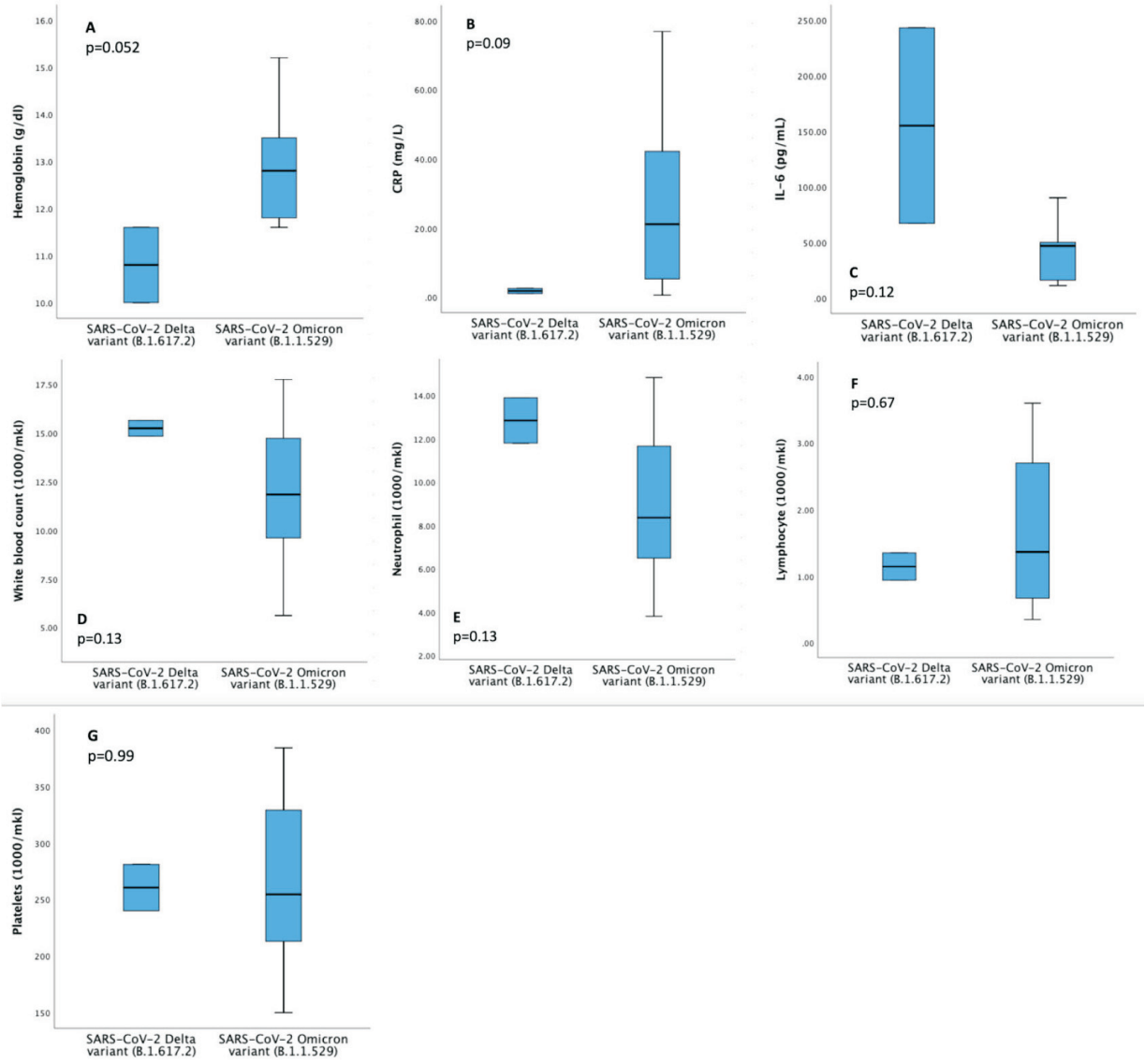

Fig. 2. Laboratory markers of patients with Delta (n = 6) and Omicron (n = 10) variant of SARS-CoV-2 infection.

Delta variant. These are new data from that in previous publications, which generally describe the overall effect of COVID-19 on AA and its treatment.

There is no novelty about which of the SARS-CoV-19 variants (Delta or Omicron) has more of an impact on AA diagnosis and treatment. Studies from Australia, France, Israel, Italy, Spain, the UK, and the US described the influence of the pandemic on appendicitis cases in children. Overall, the mean change of appendicitis cases revealed an increase of 13.4% compared to the period before the onset of COVID-19 (Kohler *et al*., 2021; Tunç *et al*., 2022). In our study sixteen children with symptomatic SARS-CoV-19 and AA, ten patients had complicated AA and five had uncomplicated AA. One patient had right ovarian apoplexy and appendix with lymphocyte infiltration and was full-blooded, according to the pathology report.

According to the literature, a trend was seen towards more complicated AA during the pandemic, but this effect was without statistical significance. Some paediatric studies examined the effect of COVID-19 on symptom duration until presentation in hospital in children (Kohler *et al*., 2021; Montalva *et al*., 2020). The duration of symptoms was from 51.5 to more than 72 h before seeking medical help during the pandemic (Bada-Bosch *et al*., 2021). Our study showed that the duration of symptoms was 48 h for patients with AA and either SARS-CoV-19 variant. Epidemiological investigation showed that the incubation period (time between infection and illness onset) after infection with the Delta and Omicron variant was 2–3 days (Tian *et al*., 2021). According to the noted incubation period for children infected with the Delta or Omicron variant and the median duration of symptoms for children with AA and one of the SARS-CoV-2 variants in our study, symptomatic COVID-19 infection could occur two days later than the onset of the clinical presentation of AA. The severity of COVID-19 is mainly related to hosting factors, especially cellular immune responses in patients.

Treatment of AA during the COVID-19 pandemic slightly depended on the management strategy of each hospital. There was a tendency for children to more likely receive antibiotic treatment instead of appendectomy for AA during the pandemic. Gerall *et al*. (2020) conducted a retrospective review of a total of 89 patients, where 41 patients were treated for appendicitis from 1 March to 31 May 2019 (non-pandemic) and 48 were treated during the same time period in 2020 (pandemic) in New York City. It was concluded that patients treated during the pandemic had higher rates of non-operative treatment (25.0% vs 7.3%, $p = 0.044$) requiring increased antibiotic use rather than surgical treatment. Compared with our study results and the local CCUH diagnostic and treatment guidelines for AA, we did not find that conservative treatment of AA would be greater than surgical treatment for patients with or without SARS-CoV-2. According to our protocol, patients with uncomplicated AA received conservative treatment, while patients with complicated AA received surgical treatment (Fisher *et al*., 2021). Observing ten Omicron cases and six Delta cases, 50% of Omicron cases and 84% of Delta cases underwent laparoscopic appendectomy. We hypothesise that children who receive surgical treatment with AA and positive SARS-CoV-2 infection could be with the complicated AA and Delta variant. Our study also confirmed that COVID-19 patients infected with Delta have a higher risk of hospitalisation, ICU admission, and mortality (Funk *et al*., 2021). The current gold standard treatment is an appendectomy in the majority of cases performed laparoscopically. Overall, successful treatment was reported in 73.4% of patients treated with antibiotics and 97.4% of patients who received an appendectomy, respectively (Kohler *et al*., 2021). During the COVID-19 pandemic, SARS-CoV-2 variants emerged and spread worldwide. Further studies are needed to characterise the differences between SARS-CoV-2 variants (Delta vs Omicron) and acute appendicitis in children.

The common clinical picture, including abdominal pain, anorexia, nausea, vomiting, rebound tenderness, and leukocytosis with neutrophilia, in both patient groups did not differ much from the typical clinics of AA in children (Zviedre *et al*., 2019). The Alvarado score in all patients was between 5 and 9. Diarrhoea, being not common in typical AA clinics, was present in five children. We did not find any serious pulmonary symptoms in either patient group.

Regarding the most popular general issue discussed about paediatric appendicitis during the COVID-19 pandemics, we found that 62.5% of cases were with complicated appendicitis, while it typically occurs almost three times less, depending on the study year.

The comparably small differences in our results between both groups can be explained by the small patient number in each group. A larger, maybe multicentre, dataset would contribute more significantly to this analysis. This study is clinically relevant as it highlights potential variant-specific symptoms that could improve early diagnosis and management of acute appendicitis (AA) in the context of changing SARS-CoV-2.

Additionally, such research can improve protocols for monitoring inflammation markers and conducting timely imaging studies, helping clinicians avoid misdiagnosis or delays. Future research based on this study's findings could lead to refined guidelines, emphasising the importance of variant awareness in AA management, particularly as new SARS-CoV-2 variants continue to emerge.

Our study also faced limitations. Firstly, our patient group was small, but we tried to include all AA cases that occurred during the COVID-19 pandemic. The sample size limitation also increased by dividing the patients into two cohorts: six patients with Delta and 10 with the Omicron variant. This affected statistical results and made it more difficult to explain the difference in pain migration to TLQ. Nevertheless, we considered it important to publish our results. Secondly, there was an absence of certainty about the variants given the lack of individual sequencing data, and

there were no pathology results in non-operated patients. Despite the study's limitations, we believe that our contribution to research is considerable, and that our data may be used for further studies. Thirdly, given the lack of individual strain testing, variants were determined by date of positive testing and prevalent population strain on the particular date. The factors described and analysed between COVID-19 cohorts are not compared to a control group of acute appendicitis prior to COVID-19.

CONCLUSIONS

Patients with acute appendicitis and SARS-CoV-2 Omicron variant infection were more likely to present with fever and pain migrating to the right lower quadrant than those with the Delta variant. These findings suggest possible variant-specific differences in clinical presentation. Further research is necessary to better understand how SARS-CoV-2 variants like Delta and Omicron may differently influence the symptoms and progression of acute appendicitis in paediatric patients.

ETHICS

This study was approved by the Children's Clinical University Hospital, Rīga, Latvia. Every patient, along with their parents, who was admitted to the CCUH for treatment, signed an agreement with the hospital in their first language (approval No. 6-1/07/35).

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available upon request to the corresponding author.

AUTHOR CONTRIBUTIONS

AE, AZ, AP, LS, and JP conceptualised the study. TZ, AZ, and MK collected data. AK-U performed statistical analyses. All authors contributed to the article and approved the submitted version.

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AKŪTS APENDICĪTS BĒRNIEM AR SARS-COV-2 INFEKCIJAS *DELTA* UN *OMIKRON* VARIANTIEM: GADĪJUMU SĒRIJA.

Covid-19, ko izraisa smagā akūtā respiratorā sindroma koronavīruss 2 (SARS-CoV-2), bērniem parasti ir vieglāks. Akūts apendicīts (AA) ir izplatīta diagnoze bērniem, tāpēc ir nepieciešama lielāka izpratne par šo pacientu ārstēšanu saistībā ar akūtu Covid-19 infekciju. Mēs piedāvājam retrospektīvu klīnisko gadījumu sērijas izpēti pacientiem ar AA un pozitīvu SARS-CoV-2 infekcijas *Delta* (B.1.671.2) un *Omicron* (B.1.1.529) variantu salīdzinājumu. Vienā terciārajā slimnīcā ar aizdomām par akūtu apendicītu un apstiprinātu Covid-19 infekciju tika hospitalizēti 16 bērni. Salīdzinot ar Delta variantu (B.1.617.2), bērniem, kuri bija inficēti ar SARS-CoV-2 infekcijas Omicron variantu (B.1.1.529), biežāk bija drudzis (p = 0,04) un sāpju migrācija uz vēdera labo apakšējo kvadrantu (p = 0,02). Nepieciešami turpmāki pētījumi, lai raksturotu atšķirības starp SARS-CoV-2 infekcijas *Delta* un *Omicron* variantiem kombinācijā ar AA bērniem.