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# Clinical and Laboratory Manifestation of Gastrointestinal Involvement in MIS-C: A Single-Center Observational Study

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**Abstract:** Background: Digestive symptoms and gastrointestinal issues in children with coronavirus 2019 disease (COVID-19) and Multisystem Inflammatory Syndrome in Children (MIS-C) are commonly reported in pediatric studies from different countries. Our retrospective observational study aimed to summarize the main digestive symptoms and objective data on gastrointestinal involvement in children with MIS-C. Methods: We present the clinical, laboratory, and imaging data of 51 children with MIS-C hospitalized in a single center from 25 November 2020 to 24 April 2021, focusing on gastrointestinal involvement. Results: A total of 46/51 children (90.2%) reported at least one abdominal symptom (abdominal pain (86%, N = 44), vomiting, nausea, diarrhea), predominantly at presentation. Most children were older than 5 years (N = 40, 78%), predominated by the male sex (N = 37, 72.5%), and with a mean age of 8.82 ± 4.16 years. We found a tendency for lymphopenia, neutrophilia, and higher levels of CRP, d-dimer, and ferritin in MIS-C patients with abdominal pain (R-squared 0.188, F-statistic vs. constant model: 11.9, $p$-value = 0.00122, 20% explanation of variation with $p = 0.001$). We found a statistically significant linear relationship (regression) between neutrophile percentage (NEU%) and hospital stay and a tendency for elevated transaminases to be more frequent in older children (27.3% under 5 years and 65% over 5 years; $p = 0.0583$). We found no significant associations between digestive symptoms and age or the predominant SARS-CoV-2 variant. Conclusions: Most of our MIS-C patients presented with abdominal pain, usually along with other GI symptoms, which could be applied in clinical practice to MIS-C in children visiting the emergency room with abdominal pain and evidence of recent COVID-19 contact or infection. Further information from larger cohorts of MIS-C patients is needed to better understand the epidemiology of gastrointestinal involvement in these patients.

**Keywords:** Multisystem Inflammatory Syndrome in Children (MIS-C); SARS-CoV-2; COVID-19; children; gastrointestinal involvement; abdominal pain; gastrointestinal symptom; vomiting; diarrhea; lymphopenia; laboratory markers

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## 1. Introduction

Studies on coronavirus disease 2019 (COVID-19) in children continue to provide predominantly controversial data. Usually, SARS-CoV-2 infection in children causes mild

symptoms and runs a benign course [1]. However, adults and children with SARS-CoV-2 infection usually have typical respiratory symptoms that could turn into respiratory failure [2,3]. Moreover, gastrointestinal issues in patients with COVID-19 are also frequent, including nausea, diarrhea, vomiting, anorexia, and abdominal pain [4]. These symptoms could also be attributed to gastrointestinal mucosal involvement during COVID-19 [5]. In addition, an alteration of laboratory parameters of liver enzymes and liver morphology has been observed [1,4,6].

Moreover, the excretion of SARS-CoV-2 in feces in children lasts significantly longer than in adults [7,8]. Therefore, we can assume that this elongated excretion may play an additional role in the gastrointestinal impairment of children with COVID-19.

Until recently, COVID-19 was reported to be uncomplicated in children [9,10]. However, a few months after the worldwide spread of SARS-CoV-2, it became clear that some children infected with COVID-19 can become seriously ill and develop a critical condition called Multisystem Inflammatory Syndrome in Children (MIS-C) [11]. The MIS-C definition is already well described. The diagnostic criteria include clinical, laboratory, and other data: fever above 38.0 °C for more than 1–3 days; systemic inflammation signs; several organ impairment; hypotension and shock; coagulopathy; elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, IL-6, procalcitonin, fibrinogen, ferritin, and lactic acid dehydrogenase (LDH); decreased albumin neutrophilia and lymphopenia; etc. [12–14].

Children who develop MIS-C have inflammation in specific organs and tissues such as the lungs, heart, kidneys, blood vessels, digestive system, brain, eyes and, skin. In addition, many immunological alterations and features have also been described [15].

The factors that predispose and cause MIS-C are still unknown. Therefore, diagnosing and studying the drivers of the syndrome's pathological process and organ tropism can help clarify the cause and the appropriate treatment. Recently, we demonstrated that the liver could also be involved in MIS-C which presents with typical laboratory and instrumental findings, such as elevated transaminases, hypoalbuminemia, ascites, hepatosplenomegaly, abdominal pain, diarrhea, etc. [6]. In addition, we recently demonstrated some typical abdominal and thoracic imaging features in children with MIS-C that could be useful for diagnosing and following these pediatric patients [16].

Since pediatric studies from different countries show that digestive system symptoms and gastrointestinal issues in children with MIS-C are common, we also conducted such analyses in our cohort of confirmed pediatric patients with MIS-C to evaluate the leading gastrointestinal symptoms. Our retrospective observational study aimed to summarize the main digestive symptoms and laboratory markers indicating gastrointestinal organ involvement in children with MIS-C. Additionally, we analyzed the prevalence of liver and pancreas injuries and their relationship to clinically emerged gastrointestinal symptoms.

## 2. Materials and Methods

### *2.1. Study Subjects*

We present the clinical, laboratory, and imaging outcomes in 51 children with confirmed MIS-C from a single center, enrolled in the period 25 November 2020–24 April 2021. Most children were older than 5 years (N = 40, 78%) and predominantly male (N = 37, 72.5%). The mean age of the MIS-C cohort was 8.82 ± 4.16 years.

In all included cases, the clinical and laboratory constellation covers the criteria for MIS-C, which were adopted as an inclusion criterion. In one case, a 16-year-old boy initially presented with symptoms of severe COVID-19, followed by a clinical and laboratory picture of MIS-C. It covered all of the CDC criteria for an MIS-C case [17] definition with multisystem involvement, in addition to a single positive SARS-CoV-2 rapid antigen test.

The inclusion criteria for the participants in the study were as follows:

1. Age under 18, fever > 38.0 °C for ≥24 h (or subjective fever lasting ≥24 h), laboratory-confirmed inflammation (assessed by elevated CRP, erythrocyte sedimentation rate

(ESR), fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6, higher neutrophils, low lymphocytes, and low albumin) and multisystem (>2) organ involvement;
2. Exclusion of other diagnoses;
3. Confirmed recent or current infection with SARS-CoV-2 (RT-PCR, antigen, or serological tests) or epidemiological data for exposure to the virus four weeks ago.

All the included children had a negative nasopharyngeal rapid antigen test (except one, already described) and anti-SARS-CoV-2 seropositivity. Additionally, in several cases, family member contact with a confirmed positive COVID-19 test was reported in the last two months before enrolment, supporting possible past SARS-CoV-2 infection. Twenty-six children underwent nasopharyngeal PCR with an initial negative result. However, a repeated PCR in two children during the hospitalization showed a positive result.

To evaluate any age-related differences in the clinical and laboratory signs of gastrointestinal (GI) involvement, we defined two age subgroups—under and over 5 years old. This cut-off was chosen based on the similarities between MIS-C and Kawasaki disease (KD), particularly the KD-like phenotype of MIS-C described in previous studies [18]. The second division into subgroups was defined clinically according to the main GI symptom—with and without abdominal pain.

### *2.2. Epidemiology and Clinical Methods*

All the enrolled children were hospitalized in the Pediatric Department of the leading emergency hospital in Sofia, Bulgaria. At admission, the enrolled children underwent a complete physical examination. The most prominent clinical symptoms at admission were abdominal pain and fever. Furthermore, pediatric surgeons evaluated all children who presented with moderate and severe digestive symptoms (abdominal pain, vomiting, nausea, diarrhea) during the first physical exam and the hospital stay. In addition, at admission, a complete medical history was taken for all children, including concomitant conditions and confirmed or suspected COVID-19 in the previous two months or close family contact with a confirmed COVID-19 case.

### *2.3. Laboratory Methods*

- General laboratory evaluation

The general laboratory evaluation included the following blood tests: complete blood count, erythrocytes sedimentation rates, inflammatory markers (C-reactive protein (CRP), procalcitonin (PCT)), ferritin, AST (aspartate aminotransferase, SGOT), ALT (SGPT, alanine aminotransferase), GGT (gamma-glutamyl transferase), LDH (lactate dehydrogenase), ALP (phosphatase, alkaline), total serum proteins and albumin, total and direct bilirubin, coagulation (INR (International Normalized Ratio), PT (Prothrombin Time), d-dimer, and fibrinogen). The observed biochemical indexes were interpreted according to age and sex. The upper limit of the normal (ULN) and lower limit of normal (LLN) comply with the pediatric reference values [19].

For better analysis of the gastrointestinal involvement, we defined the following laboratory variables:

- Liver—the laboratory signs of liver involvement were separately assessed by investigating the markers for hepatocellular injury (hepatocytolysis) (ALT and/or AST more than the ULN lab reference value), cholestasis (ALP, GGT, and/or total, direct bilirubin more than the ULN) and impaired synthetic liver function (albumin and total protein less than LLN, coagulation);
- Pancreas—serum amylase and lipase levels. The pancreatic enzymes were analyzed in a small number of patients when clinically indicated.

Additionally, we used the following term, established previously [6]:

- Liver injury—ALT and/or AST over the ULN and ALP, GGT, and bilirubin over ULN.

When cardiac involvement was clinically suspected, CPK (creatine phosphokinase), CK-MB fraction (creatine kinase-MB fraction) and troponin I testing were performed. When

indicated, echocardiography by an experienced pediatric cardiologist was conducted (see Imaging Tests section).

- Serological and immunological tests

In fifty children, serological evaluation of anti-SARS-CoV-2 antibodies with different methods was performed; quantitative total IgM and IgG in 14 children, and qualitative IgG titer in the other 36, expressed as S/CO and AU/mL and after 27 March 2021 as widely accepted BAU/mL. In addition, interleukin-6 (IL-6) was evaluated in 32 children. A certified immunological laboratory performed the serological anti-SARS evaluation and IL-6 assessment (Elecsys, Roche diagnostics).

- Microbiological and virological tests

All children underwent a nasopharyngeal rapid antigen test at admission, and 26 children were tested by RT-PCR. However, the PCR testing did not provide SARS-CoV-2 genotyping. In addition, routine microbiology testing (oropharyngeal, nasal swab, hemoculture, urine culture) was performed in all cases and for those with GIT complaints, feces/anal secretion was also assessed. However, fecal virological tests were not taken due to technical and financial limitations, outside of the few children who initially had positive results from SARS-CoV-2 PCR. When indicated (in seven cases), rapid nasopharyngeal influenza A and B tests and EBV-VCA—IgM/IgG were performed to exclude an alternative diagnosis.

- Imaging tests

All children except one underwent at least one abdominal ultrasound (US) examination, computer tomography (CT) of abdomen and pelvis (N = 19) or chest (N = 14), and conventional X-ray of the chest (N = 22) or abdomen (N = 10). All the imaging examinations were performed and analyzed by certified radiologists specialized in pediatric pathology. The abdominal US were performed with a convex and linear probe. The linear probe was used to observe the superficial structures including the mesenterial lymph nodes. Both convex and linear probes were used for abdominal ultrasound imaging. The linear probe provided a detailed view of superficial structures like the mesenteric lymph nodes. Additionally, 24 h vital sign monitoring and ECG (electrocardiography) records were performed, and when indicated, echocardiography by an experienced pediatric cardiologist was conducted (N = 38).

To evaluate the imaging findings (the abdominal US and/or CT, when applicable) and their correlations with clinical symptoms and laboratory markers, we defined the following imaging phenotypes: serositis (CT and or US data for ascites), mesenteric lymphadenitis, enteritis/enterocolitis, hepatosplenomegaly, gallbladder involvement (CT and or US data for gallbladder wall thickness, intraluminal sludge, increased luminal distention), and pancreas involvement.

### *2.4. Statistical Methods and Analysis*

We used Excel for descriptive statistics and the open-source platform Octave for data preparation and modeling with multinomial logistic regression, paired *t*-testing, and linear regression models. We used logistic regression for binary variables or variables with discrete values like 1, 2, 3, etc., for classification when they are dependent on other variables with discrete values or continuous measurements. We checked for correlations for the multinomial regression; no principal component analysis was necessary.

### *2.5. Ethics*

The study was conducted following the Declaration of Helsinki. The study design and protocol (No 123-20/23.12.2020) were approved by the Ethics Committee of the University Hospital "N. I. Pirogov." All parents signed informed consent to include their children in the study. All children older than 12 years signed informed consent on their own before participating in the study, in addition to the signed consent from their parents.

## 3. Results

### *3.1. Demographic and Epidemiological Characteristics*

In our cohort, children over 5 years predominated (N = 40, 78%) with a statistically significant difference (chi-square test $p = 2.94$). In 46 children (90.2%), at least one abdominal symptom (abdominal pain, vomiting, nausea, diarrhea) was reported, predominantly at presentation. Thirty-eight children (74.5%) had severe abdominal pain with clinical suspicions of acute abdomen; in ten (20%), the symptoms mimicked acute appendicitis. Seven children underwent surgical intervention—five laparotomies with appendectomy and two thoracenteses for treating pleural effusion. We observed the following comorbidities in the children: allergic rhinitis, mild bronchial asthma, cerebral palsy and epilepsy, and drug allergies.

Almost half of the children (N = 23, 45%) presented with respiratory symptoms (in 20 of them not at admission but during the hospital stay)—cough, chest pain, and different degrees of respiratory distress. Clinical, laboratory, imaging, and functional evidence for heart involvement was objectified in half of the children (N = 26, 51%). Four children (three with myocarditis rapidly progressing to cardiovascular shock and one with severe acute renal failure) during the first 48 h after hospitalization were transferred to the Pediatric Intensive Care Unit (PICU) or Pediatric Cardiac Intensive Care Unit (PCICU). The patients were administered fluid therapy, antibiotics, corticosteroids, anticoagulants (low-molecular-weight heparin, acetylsalicylic acid (ASA)), gastroprotectors, spasmolytics, intravenous immunoglobulin G (IVIG), oxygen therapy, innotropics, and diuretics.

All cases recovered and were discharged with clinical and laboratory improvement and in good general condition. No fatal cases were registered at the hospital.

The baseline demographic characteristics and laboratory data of the MIS-C patients in the main group are listed in Table 1. We did not find a significant difference in the two sub-groups separated according to the abdominal pain (Supplementary Table S1).

**Table 1.** Baseline demographic characteristics and laboratory data.

| **Laboratory Test** | | **Main Group N = 51 Mean ± SD and/or Number of Patients Tested (%)** |
|---|---|---|
| Mean age | | 8.82 ± 4.16 |
| Number of male patients | | 37 (72.5) |
| Positive epidemiology history (contact with COVID-19) * | | 15 (29.4) |
| Positive history of COVID-19 symptoms * | | 21 (41.1%) |
| Comorbidities | | 14 (27.5%) |
| Digestive symptoms | Vomiting | 26 (51%) |
| | Diarrhea | 23 (45%) |
| | Any | 37 (72.5%) |
| Absolute leucocytes count | | 13.18 ± 6.84 (51) |
| Absolute lymphocyte count | | 1.46 ± 1.20 (51) |
| Absolute neutrophil count | | 10.81 ± 5.88 (51) |
| Neutrophile percentage | | 82.58 ± 9.29 (51) |
| Platelet count | | 259.74 ± 153.29 (51) |
| CRP initial, mg/dL | | 19.91 ± 12.70 (51) |
| CRP follow-up, mg/dL | | 11.77 ± 7.69 (51) |

**Table 1.** *Cont.*

| Laboratory Test | Main Group N = 51 Mean ± SD and/or Number of Patients Tested (%) |
|---|---|
| PCT, ng/mL | 8.48 ± 13.02 (51) |
| Ferritin, ng/mL | 552.02 ± 370.77 (33) |
| IL-6, ng/mL | 117.52 ± 138.80 (32) |
| D-dimer, ng/mL | 2234.82 ± 1962.17 (43) |
| Fibrinogen, g/L | 5.26 ± 1.65 (44) |
| ASAT, IU/mL | 89.00 ± 173.44 (46) |
| ALAT, IU/mL | 67.13 ± 99.66 (46) |
| GGT, IU/mL | 67.78 ± 83.01 (37) |
| ALP, IU/mL | 132.16 ± 57.67 (31) |
| LDH, U/L | 359.50 ± 187.03 (45) |
| Total bilirubin, umol/L | 17.30 ± 22.24 (41) |
| Direct bilirubin, umol/L | 8.04 ± 14.83 (41) |
| Total protein, g/L | 60.63 ± 9.89 (41) |
| Albumin, g/L | 33.93 ± 7.32 (49) |
| Amylase, U/L | 47.88 ± 26.64 (22) |
| Lipase, U/L | 65.56 ± 98.74 (12) |
| Abdominal ultrasound (US) at admission (number of patients tested) | |
| US mesenteric lymphadenitis | 22 (47) |
| US ascites | 32 (47) |
| US gallbladder | 5 (49) |
| US enteritis/enterocolitis | 3 (44) |

* at the past two months prior the admission SD—standard deviation, CRP—C-reactive protein, PCT—procalcitonin, IL-6—interleukin 6, ASAT—aspartate aminotransferase, ALAT—alanine transaminase, LDH—lactate dehydrogenase, US—ultrasound.

We found a tendency for lymphopenia, neutrophilia, and higher CRP, D-dimer, and ferritin in the abdominal pain group, which could become significant with a larger dataset (Supplementary Table S1).

### *3.2. Digestive Symptoms*

A total of 46/51 children (90.2%) reported at least one abdominal symptom (abdominal pain, vomiting, nausea, diarrhea), predominantly at presentation. The most common GI symptoms were abdominal pain (n = 44, 86.2%), diarrhea, and vomiting. Unstable loose stools with or without increased visible mucus (usually mild), was the most prominent dyspeptic symptom following abdominal pain (N = 23, 45.1%). Less frequent was vomiting (N = 10, 19.6%) and a more severe symptom in two patients was mild hematemesis (Table 2).

Using the chi-square test, we found no significant differences between age groups (under and above 5 years old) when comparing digestive symptoms. However, regarding the severe abdominal pain resembling acute abdomen syndrome, we found a borderline significance ($p$ = 0.09)—the tendency showed that children over 5 years old were more likely to develop acute abdomen.

**Table 2.** Main digestive symptoms in the two age groups (>5 and ≤5 years old).

| Digestive Symptoms | Children ≤ 5 Years Old N = 11 | Children > 5 Years Old N = 40 | All Children N = 51 | *p* |
|---|---|---|---|---|
| Diarrhea and/or vomiting, N (%) | 7 (63.63%) | 30 (75%) | 37 (72.54%) | n.s. |
| Abdominal pain, N (%) | 8 (72.72%) | 36 (90%) | 44 (86.20%) | n.s. |
| Acute abdomen, N (%) | 1 (9.09%) | 11 (27.5%) | 12 (23.53%) | 0.09 |
| Diarrhea, N (%) | 6 (54.54%) | 17 (42.5%) | 23 (45.1%) | n.s. |
| Vomiting, N (%) | 5 (45.45%) | 21 (52.5%) | 26 (50.98%) | n.s. |
| Icterus, N (%) | 0 (0%) | 3 (7.5%) | 3 (5.88%) | n.s. |

n.s.—not significant (>0.05).

We observed a high incidence of severe abdominal pain in our cohort (N = 12, 23.53%). In half of the severe abdominal pain group, four boys and two girls, all older than 5 (5–11 years old, mean age 9), laparotomy with appendectomy was performed. None of the children had severe intestinal obstruction or intussusception, a typical surgical condition characterized by acute abdomen in the age group under 5. There was no statistical difference in digestive symptoms when comparing boys and girls.

Looking into positive epidemiology history and positive COVID symptoms, we found the following. Dividing children into ≤5 years old and >5 years old groups, the correlation coefficient between epidemiology history and COVID-19 symptoms was 0.15 for >5 years old but 1 for ≤5 years old. In contrast, in the older children with MIS-C, SARS-CoV-2 infection was usually asymptomatic and they only initially showed symptoms of MIS-C. Additionally, for children ≤5, there was a 0.57 correlation between positive epidemiology and diarrhea (or vomiting), but only -0.29 for the age group >5 years (negative, meaning less likely to have diarrhea if they had previous contact with an infected person).

### *3.3. Other Findings in MIS-C Children*

Regarding liver involvement and hepatocytolysis, we divided the liver involvement indices into four categories—hepato-cytolysis (elevated AST and/or ALT > ULN), cholestasis (elevated GGT/ALP > ULN and or elevated total/direct bilirubin), impaired synthetic liver function (total serum protein and albumin levels < LLN), and impaired coagulation (elevated INR and or prothrombin time s/%). When comparing hepato-cytolysis in the two age groups (under and over five years old), we found an increased incidence of elevated transaminases in older children (27.3% under 5 and 65% older than five years). The difference was on the verge of significance ($p = 0.0583$). However, according to sex (23 of 37 boys had cytolysis and 6 out of 14 girls), there was no significant difference in liver cytolysis laboratory markers in boys and girls ($p = 0.35$).

Laboratory evidence for cholestasis was equally observed in boys and girls without significant difference (68% in boys and 71% in girls, $p = 0.95$). Cholestasis was primarily mild with mean GGT, mean ALP, mean total BN, and direct BN, without significant differences between the two age groups. Considering synthetic liver function, serum albumin was below the LLN in all tested children.

We also defined pathological coagulation findings as elevated INR > ULN and or PT (prothrombin time) expressed as time (seconds) or percentage (%). In 46 children, coagulation was assessed at least once during the hospitalization. Twenty-one (45%) had elevated INR and/or PT (sec/%). In addition, we found a strong statistically significant relationship between hepatocytolysis (ASAT and/or ALAT > ULN) and impaired coagulation (INR and/or PT (sec/%) > ULN) (Supplementary Figure S1). This logistic regression showed us hepatocytolysis increases the probability of inadequate coagulation.

Regarding pancreatic function, we found the following observations. Lipase serum levels were evaluated in 12 children (19 boys and 3 girls) and amylase levels were measured in 22 children (11 boys and 1 girl). The decision for conducting these tests was predominantly clinical—the patients showed severe abdominal pain and severe dyspeptic symptoms. Most of the tested children were older than 5 years old (mean age 9.25 years). One child

under 5 had an amylase test, and two had a lipase test. The mean lipase serum level was 65.45 U/mL. Two children out of the 12 tested had elevated lipase levels—a 10-year-old boy with 161 U/mL and a four-year-old boy with 345 U/mL. The sex differences between 11 boys and one girl were not statistically significant out of a sample of 37 boys and 14 girls ($p = 0.1845$). Still, it was possible this may become significant with larger datasets. Here, the potential significance would mean that it is much more likely to record elevated lipase levels in boys.

The mean amylase serum level was 47.89 U/mL without a significant difference between boys and girls (46.67 U/mL vs. 48.08 IU/mL, respectively). Twenty children with assessed amylase had low serum proteins (albumin and total protein); two patients did not present with hypoalbuminemia. The mean amylase level in the first group was 49.92 IU/mL and 27.5 IU/mL. In a more extensive patient sample, we could expect a correlation between hypoproteinemia in patients with MIS-C and elevated pancreatic enzymes.

Using logistic regression analysis, we could not prove a meaningful relationship between CRP and PCT as markers of hyperinflammation, laboratory markers for cholestasis, and the serum levels of pancreatic enzymes.

### *3.4. Imaging Phenotypes*

#### 3.4.1. Pancreas Involvement

In 17 patients, we looked for correlations between the CT data for pancreas involvement and hepatocytolysis, cholestasis, and impaired coagulation. In two, we found imaging data for pancreatic edema. We did not find any significant correlations between the tested variables and clinical value.

#### 3.4.2. Hepatosplenomegaly

The correlation between the CT data for hepatosplenomegaly and hepatocytolysis was low (0.34) without a statistically significant logistic relationship ($p = 0.9999$).

#### 3.4.3. Gallbladder Involvement

The CT and US data for gallbladder involvement demonstrated a very low and negative correlation of $-0.1307$, which indicates the independence of the two screening methods. In addition, when using the CT data for gallbladder involvement, no statistically significant relationships are found with hepatocytolysis, cholestasis, and impaired hemostasis. When using the US investigation, which is a more indicative method for detecting gallbladder wall thickness, intraluminal sludge, and increased luminal distention, we found no correlation or logistic relationship between US-observed gallbladder involvement and hepatocytolysis, cholestasis, and impaired coagulation.

## 4. Discussion

In April 2020, the UK National Health Service alerted medical specialists of some cases of children infected with SARS-CoV-2 who developed a critical condition called MIS-C [11,20]. More subsequent reports from the USA and other European countries have also identified cases of this hyperinflammatory syndrome with multisystem involvement in children. In addition, these patients had laboratory-confirmed previous or current SARS-CoV-2 infection by RT-PCR or serological tests [21–24]. Currently, it is known that MIS-C is a potentially life-threatening condition that can occur 2–6 weeks after COVID-19 in previously healthy children. The condition is characterized by inflammation in multiple organs and altered laboratory markers.

MIS-C has concomitant gastrointestinal symptoms and can even resemble inflammatory bowel disease. About 25% of children with an acute SARS-CoV-2 infection and almost 90% with MIS-C develop symptoms such as diarrhea, abdominal pain, nausea, or vomiting [25]. There was a high incidence of severe abdominal pain in our cohort. However, this observation is promising for a larger sample size (there were only 11 children $\leq 5$ years old in our study). Here, the results could be influenced by the specific profile of the Pediatric

team in our center. In half of the severe abdominal pain group, four boys and two girls, all older than 5 (5–11 years old, mean age 9), laparotomy with appendectomy was performed.

One of the first published datasets from the United Kingdom provided information on eight patients with GI symptoms [22]. The same symptoms were observed in 6 out of 10 children in Italy [24]. In the USA, a cohort of 44 patients under 21 years old with MIS-C was examined, and GI symptoms were a presenting symptom in 84.1% of cases [26]. At the end of August 2021, there were more than 4400 reported MIS-C patients in the United States [27]. However, there is a lack of an assessment of cases worldwide because many of them have not been reported because they have not been identified. One study covered 614 children from 34 countries, including low- and middle-income countries [28]. Using government surveillance data for MIS-C cases in seven regions of the United States, the incidence of MIS-C was estimated at approximately 3 per 10,000 individuals under 21 years [29].

Abrams et al. published a systematic review of 1470 MIS-C patient records (440 from PubMed, 734 from Embase, 65 from medRxiv and bioRxiv, and 231 from subsequent citations) [30]. Eight published studies involving a total of 440 patients were examined in detail. They were selected according to specific criteria established by the UK Royal College of Paediatrics and Child Health, the USA Centers for Disease Control and Prevention [31], and the WHO [32]. Patients with MIS-C usually present with fever and gastrointestinal, cardiovascular, and mucocutaneous manifestations. In contrast, respiratory manifestations are the most commonly observed manifestations of COVID-19 but were not seen in all patients with MIS-C. All reported studies show highly elevated levels of laboratory markers of inflammation, suggesting that hyperinflammation is a primary feature of MIS-C [30]. About 50–59% of MIS-C patients in all studies were males younger than 20 years which corresponds with our results [29]. We also observed elevated inflammatory markers in our MIS-C group of patients.

GI symptoms are the most common clinical manifestations of MIS-C in about 87% of children [30]. As we demonstrated, a similar percentage of MIS-C patients presented with GI symptoms, especially abdominal pain. Abdominal pain, diarrhea, and vomiting were the most common. In some children, the abdominal pain could manifest as an acute abdomen, as we observed. Other conditions related to MIS-C are liver and pancreatic involvement in children. They have been poorly investigated thus far, but more and more data are being collected to clarify these conditions [33]. When we analyzed our group of patients with MIS-C to determine the prevalence of liver and pancreas injuries and their relationship to clinical outcomes, we found a tendency for hepatocytolysis, assessed by elevated transaminases. This observation showed a tendency to be more frequent in older children. However, according to gender, there was no significant difference in laboratory markers of liver cytolysis and in cholestasis data between boys and girls.

We compared these data with those obtained in Giannattasio A. et al.'s study conducted on 55 patients with MIS-C. Their study showed that over half of the patients developed liver disorders before or after hospitalization [34]. In this study, 16 of 55 participants showed evidence of liver injury, and 5 had increased total serum lipase levels. In addition, 10 patients developed a liver injury in the hospital, and another 19 had elevated pancreatic enzyme levels. Moreover, the incidence of elevated transaminases was significantly higher in older children. These data are consistent with our work.

Prolonged hospital stays were associated with pancreatic injury in patients. This finding was statistically significant ($p = 0.004$). However, this could be related to the pancreatic injury requiring more intensive treatment, but it also could be only an observation without causality. Our data showed a delay between symptom onset and hospital admission. The mean delay was 5.33 days $\pm$ 6.92, consistent with Giannattasio's data for the lag between the first symptoms and hospital admission. The liver injury began earlier, before the increase in pancreatic enzymes. Liver and pancreatic involvement often accompany MIS-C, but in most cases, these problems are mild and usually resolved without complications. None of the patients developed acute liver failure.

Among the patients with pancreatic involvement (based on lipase serum levels), we did not obtain a statistical significance between genders because there were more boys in the group. However, regarding amylase levels, we found that the distribution was more uniform between the age and gender groups, and there were no significant differences between the two groups regarding inflammatory parameters.

Interestingly, children who developed acute liver involvement during COVID-19 were under three years old, while liver injury occurred more frequently in older children diagnosed with MIS-C [35]. This is consistent with the works of Perez et al. and Giannattasio et al. [34,36]. These studies demonstrated that liver involvement was more common in older patients with MIS-C. In MIS-C, liver injury may be related to a massive release of pro-inflammatory cytokines, including IL-18 [37–40]. The functional disturbances in these patients resemble liver involvement in adults with severe COVID-19 [41]. There is no clear indication that pancreatic enzyme elevation is associated with MIS-C. There may be various reasons as dysfunction in the reticuloendothelial system, mesenteric disturbances, or elevated amylase and lipase serum levels occur due to diarrhea [42,43]. Our results on pancreas and liver function in MIS-C patients may prove redundant if the results are confirmed in larger cohorts. However, given the uncertain circumstances that have yet to be elucidated, we suggest that full liver and pancreas tests be included in the ongoing assessment of MIS-C from the beginning. In addition, MIS-C patients also need close observation during their hospital stay to detect early liver and pancreatic damage. Further information from larger cohorts of MIS-C patients is required better to understand the pathophysiology of the liver and pancreatic involvement.

In COVID-19, there are reports of high amylase levels and subsequent renal damage, which is not typically seen in MIS-C patients [44]. If the results of these studies are confirmed in large patient populations, there is likely a direct relationship between liver and pancreatic injury and MIS-C.

Nevertheless, the fact that the correlation coefficient between epidemiology history and COVID-19 symptoms was 0.15 for >5 years old but 1 for $\leq$5 years old represents a 100% correlation between having a positive epidemiology history and a positive history of COVID symptoms in the younger age group. This observation could mean that children under five years of age who have been in contact with a sick person in the family are more likely to have symptomatic COVID-19 infections.

Taking into account all the gathered information for MIS-C and its unpredictive onset, one can assume that MIS-C should be prevented. However, the frequency of MIS-C may change as more of the population is vaccinated, and vaccination of children aged 5 to 12 with approved vaccines has begun. The vaccination coverage in children is still far from that in adults, so all this information will be beneficial to prevent the development of the syndrome or its milder course [45].

The strengths of our study are that we provided epidemiological and clinical data on the frequency and rate of GI involvement for children with MIS-C in a single Bulgarian center. In addition, although our study presented single-center research, we gathered a considerable proportion of all the MIS-C cases in our country. Therefore, our data could be valuable as representative information for GI involvement in MIS-C at a national level, in Europe and worldwide. Moreover, we are starting to create an official national MIS-C registry to obtain all cases in the country and to have a large database. This database would be used for more extensive analyses.

However, our research has some limitations. The study is monocentric, so our group of patients was limited. Some of our results that did not reach statistical significance require further confirmation in a larger population. Additionally, the use of CT for assessing the pancreas and bile duct involvement in MIS-C patients was under hospital recommendations and guidelines; therefore, we could not perform MRI for all MIS-C cases. We agree that MRI is safer and more sensitive for imaging the bile ducts or intestines and that CT should not be overused in children.

## 5. Conclusions

We observed that GI symptoms, such as abdominal pain, vomiting, and diarrhea, were frequent in our MIS-C patients—almost 90% of diagnosed cases exhibited GI involvement. Additionally, most cases did not develop severe or fatal complications. Although we did not find correlations between the morphological changes (CT and US) in the liver and pancreas and the laboratory evidence of organ involvement, we found a tendency for elevated transaminases to occur more often in older children without a sex predilection.

Taking into account that the majority of our MIS-C patients presented with leading abdominal pain and other GI symptoms, this could be employed in clinical practice. We must keep MIS-C in mind for children visiting the emergency room with abdominal pain and evidence of recent COVID-19 contact or active infection.

Further information from larger cohorts of MIS-C patients is needed to better understand the epidemiology of gastrointestinal involvement in these patients and to provide supporting information to healthcare staff practitioners in emergency and primary care.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/gastroent14020017/s1, Table S1. Baseline demographic characteristics and laboratory data—subgroup abdominal and without abdominal pain, Figure S1. Logistic regression for the dependence of hemostasis on hepatocytolisys.

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**Informed Consent Statement:** All parents signed informed consent to include their children in the study. All children older than 12 years signed additional informed consent on their own.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author. The data are not publicly available due to restrictions, e.g., privacy or ethics.

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