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**THE IMPACT OF SARS-COV-2 INFECTION ON
CHILDREN
DOCTORAL THESIS SUMMARY**

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Table of contents

| | |
|---|-----------|
| Introduction | 1 |
| I General part | 5 |
| 1. Current state of knowledge | 5 |
| 1.1. SARS-CoV-2 Infection | 5 |
| 1.1.1. Epidemiology of SARS-CoV-2 Infection..... | 5 |
| 1.1.1.1. Global Epidemiological Context | 5 |
| 1.1.1.2 Local Epidemiological Context..... | 5 |
| 1.1.2. Epidemiological Characteristics of SARS-CoV-2 Infection in the Pediatric Population | 6 |
| 1.2. Virology of SARS-CoV-2 | 7 |
| 1.2.1. Molecular Architecture of the SARS-CoV-2 Virus | 8 |
| 1.2.2. Transmission Pathway. Virus Variants..... | 8 |
| 1.3. Variation of Clinical-Biological Patterns..... | 10 |
| 1.3.1. Clinical Spectrum of Manifestations, from Asymptomatic to Severe Forms | 10 |
| 1.3.2. Clinical Particularities of the Infection in the Pediatric Population | 11 |
| 1.3.3. Risk Factors Associated with Severe Forms of the Disease in Children | 12 |
| 1.4. Relevant Laboratory and Imaging Investigations in the Diagnosis and Monitoring of Acute Infection | 13 |
| 1.5. Diagnostic Criteria - Classification of Disease Forms | 14 |
| 1.6. Current Approaches in the Treatment of COVID-19 in Children | 15 |
| 2. Multisystem Inflammatory Syndrome in Children (PIMS-C/MIS-C) Associated with SARS-CoV-2 | 17 |

| | |
|---|-----------|
| 2.1. Epidemiology: Incidence in the Pediatric Population, Statistical Characteristics | 17 |
| 2.2. Pathogenic Mechanisms Involved in PIMS-C/MIS-C and Differences from Other Inflammatory Syndromes..... | 17 |
| 2.2.1. Mechanisms Involved in the Occurrence of Cardiac Lesions | 20 |
| 2.3. Clinical Presentation: Symptoms, Severity, and Variability of Manifestations | 22 |
| 2.4. Paraclinical Investigations | 24 |
| 2.5. Diagnostic Criteria, Positive Diagnosis | 27 |
| 2.5.1. Case Definitions | 27 |
| 2.5.2. Spectrum of PIMS - Classification into Phenotypes | 27 |
| 2.6. Principles of PIMS-C/MIS-C Treatment | 28 |
| 2.7. Short and Long-term Impact of SARS-CoV-2 Infection in Children | 30 |
| II. Personal Contributions | 32 |
| 3. Working Hypothesis and General Objectives | 32 |
| 3.1. Working Hypotheses | 32 |
| 3.2. General Objectives | 33 |
| 4. General Research Methodology | 34 |
| 4.1. Study Plan | 34 |
| 4.1.1. Inclusion and Exclusion Criteria | 34 |
| 4.1.1.1. Inclusion Criteria for Patients with Acute SARS-CoV-2 Infection | 34 |
| 4.1.1.2. Inclusion Criteria for Patients Diagnosed with PIMS-C/MIS-C | 35 |

| | |
|---|----|
| 4.1.1.3. Exclusion Criteria for the SARS-CoV-2 Patient Group | 36 |
| 4.1.1.4. Exclusion Criteria for the PIMS-C/MIS-C Patient Group | 36 |
| 4.1.2. Patient Evaluation | 36 |
| 4.2. Ethics Committee Approval | 38 |
| 4.3. Informed Consent | 38 |
| 4.4. Statistical Analysis | 38 |
| 4.5. Study Limitations | 38 |
| 5. Evolution Trend of SARS-CoV-2 Infection and Its Impact on the Pediatric Population from 01.03.2020 to 31.12.2021 | 40 |
| 5.1. Study Group Covid 19 - Acute SARS-CoV-2 Infection | 41 |
| 5.1.1. Demographic and Epidemiological Data: Age, Gender, and Origin of Patients | 41 |
| 5.1.2. Anamnestic-Clinical Data. Clinical Spectrum of Manifestations - Characteristics of the SARS-CoV-2 Group Based on Presentation Modalities | 44 |
| 5.1.3. Classification of Covid 19 Disease Forms: Clinical Spectrum of Manifestations, from Asymptomatic to Severe Forms | 48 |
| 5.1.4. Paraclinical Characteristics of the SARS-CoV-2 Patient Group | 50 |
| 5.1.4.1. Complete Blood Count with Leukocyte Formula | 50 |
| 5.1.4.2. Evaluation of the Non-Specific Inflammatory Syndrome in the SARS-CoV-2 Group | 53 |
| 5.1.4.3. Evaluation of Biochemical Data to Determine the Degree of Multiorgan Damage in the SARS-CoV-2 Group | 54 |

| | |
|--|-----|
| 5.1.4.4. Importance of Evaluating Paraclinical Parameters in Severe Disease Forms in the SARS-CoV-2 Patient Group | 54 |
| 5.1.4.5. Imaging Investigation Results in the SARS-CoV-2 Patient Group | 58 |
| 6. Analysis of PIMS-C/MIS-C Group Results | 60 |
| 6.1. Demographic and Epidemiological Data | 60 |
| 6.2. Hospitalization Duration | 61 |
| 6.3. Anamnestic-Clinical Data | 62 |
| 6.4. Presentation Modalities | 63 |
| 6.5. PIMS-C/MIS-C Phenotypes | 68 |
| 6.6. Statistical Analysis of Anamnestic-Clinical Data | 68 |
| 6.7. Paraclinical Investigations | 71 |
| 6.8. Treatment Used in the PIMS-C/MIS-C Patient Group | 96 |
| 7. Hematological Predictive Parameters for Severe Forms of COVID 19 and PIMS-C/MIS-C | 98 |
| 8. Conclusions | 102 |
| ANNEX 1 – Anamnestic-Clinical Evaluation in PIMS-C/MIS-C | 105 |
| ANNEX 2 - Staged Investigational Proposal in PIMS-C/MIS-C | 106 |
| ANNEX 3 – Diagnostic Criteria for PIMS-C/MIS-C | 108 |
| ANNEX 4 – Data Collection Form | 110 |
| ANNEX 5 – Study Scheme | 112 |
| ANNEX 6 – Informed Consent | 113 |
| Bibliography | 124 |

Introduction

The SARS-CoV-2 infection has posed a significant challenge to humanity since December 2019, rapidly becoming a global public health issue. In light of the considerable impact that the SARS-CoV-2 infection has had on the population, the interest shown by the medical and scientific community in understanding and decoding the "secrets" of this devastating pathogen is fully justified.

From the analysis of international and national epidemiological data, a significant difference is evident between the pediatric and adult populations in terms of infection rates, transmission methods, and clinical manifestations. The low incidence of the disease among the pediatric population, as well as the different disease patterns observed in this age group, are subjects of high interest for current and future research. There are still many unanswered questions, but it is certain that this is most likely the result of a combination of factors.

The impact of SARS-CoV-2 infection among children needs to be monitored long-term, with increasing attention being drawn to a condition characterized by a severe multisystem inflammatory syndrome associated with SARS-CoV-2 exposure - post-COVID-19 Multisystem Inflammatory Syndrome (PIMS/MIS-C). From the data obtained so far, PIMS appears to be not so much the result of the acute disease but rather an inappropriate hyperimmune response to a previous SARS-CoV-2 infection/exposure, thus a post-infectious complication necessitating the inclusion of this entity in the differential diagnosis of the febrile child.

In this context, the main objective of this paper is to evaluate the impact of SARS-CoV-2 infection on the pediatric population, both concerning the acute disease (COVID-19) and the long-term consequences of the infection, paying particular attention to the appearance of post-COVID-19 Multisystem Inflammatory Syndrome (PIMS/MIS-C). The study also aims to establish correlations between potential risk factors and the occurrence of severe forms of the disease, as well as to evaluate possible temporal correlations during the early waves of the COVID-19 pandemic. Considering these aspects, the current doctoral research also aims to identify new parameters for paraclinical evaluation of the evolution and correlation of these with the degree of multi-organ involvement: the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR). Additionally, the study aims to establish the utility of some parameters with limited historical use in pediatric practice but demonstrated importance in adults for

evaluating cardiovascular involvement in the context of SARS-CoV-2 infection (NT-proBNP, Troponin), aiming to establish reliable reference values for the pediatric population.

The paper is structured into two parts: the general theoretical part and the special part, which includes personal contributions.

The General Part includes 2 chapters:

- **Chapter 1** covers notions about the SARS-CoV-2 virus infection, including data on the epidemiology of the infection, its global epidemiological impact, as well as the situation in Romania, highlighting the epidemiological particularities of the infection in the pediatric population. Additionally, this chapter discusses the molecular architecture of the SARS-CoV-2 virus and the clinical spectrum of acute infection manifestations, with a focus on the clinical features of the disease in children. A synthesis of the main risk factors for severe forms of the disease in children is provided, along with diagnostic criteria and therapeutic approaches as mentioned in recent specialized literature.

- **Chapter 2** addresses the main post-infectious complication associated with the SARS-CoV-2 virus, namely the post-COVID-19 Multisystem Inflammatory Syndrome (PIMS/MIS-C). This chapter includes a synthesis of the main epidemiological notions related to this newly described entity in the specialized literature, as well as the pathophysiological mechanisms involved. Considering the importance of cardiovascular involvement in the evolution of PIMS-C/MIS-C, a concise analysis of the mechanisms leading to cardiac lesions is presented. The chapter also offers an overview of the clinical picture of the disease, detailing the PIMS-C/MIS-C spectrum, the paraclinical evaluation recommended in current guidelines for this pathology, and the diagnostic criteria formulated internationally to date. The chapter concludes with a synthesis of the treatment principles for PIMS-C/MIS-C.

- **The final part of Chapter 2** provides a comprehensive overview of the impact that the SARS-CoV-2 virus infection has had on the pediatric population, both in the short term and concerning long-term complications (PIMS-C/MIS-C).

The Special Part includes the observational, descriptive, longitudinal study, which included 372 patients aged 0-18 years enrolled at the "Dr. Victor Gomoiu" Children's Clinical Hospital between 01.03.2020 and 31.12.2021, with a diagnosis of acute SARS-CoV-2 virus infection, respectively **Post-COVID-19 Multisystem Inflammatory Syndrome (PIMS)**. In this part of the thesis, the information has been structured into 6 chapters.

- **Chapter 3** – Research Hypothesis and General Objectives
- **Chapter 4** – General Research Methodology
- **Chapter 5** – Trend of SARS-CoV-2 Infection Evolution and Its Impact on the Pediatric Population from 01.03.2020 to 31.12.2021
- **Chapter 6** – Analysis of Results in the PIMS-C/MIS-C Group
- **Chapter 7** – Hematological Predictive Parameters for Severe Forms of COVID-19 and PIMS-C/MIS-C
- **Chapter 8** – Conclusions

1. Research Hypothesis and General Objectives

Although humanity seems to have overcome the COVID-19 pandemic that began in 2019, there are still numerous unanswered questions regarding SARS-CoV-2 infection, especially about its impact on the pediatric population.

While adults were severely affected by SARS-CoV-2 infection from the beginning, the pediatric population initially seemed protected, with the early pandemic characterized by a low incidence of infection among children and the appearance of mild or moderate forms of the disease in them. The true risks posed by SARS-CoV-2 infection to the pediatric population only began to become apparent in April 2020. More than a month after the pandemic was declared, the National Health Service in the UK raised an alarm, indicating a possible correlation between the significant number of cases of children with manifestations similar to Kawasaki disease and possible complications of SARS-CoV-2 infection.

In this context, the main objective of this work is to evaluate the impact of SARS-CoV-2 infection on the pediatric population, both in terms of the acute disease (COVID-19) and the long-term consequences of the infection. The work pays special attention to the appearance of post-COVID-19 Multisystem Inflammatory Syndrome (PIMS/MIS-C). We analyzed both the immediate consequences of the acute infection and the long-term complications, in the context where more and more studies emphasize the long-term effects of this infection. These include the appearance of Multisystem Inflammatory Syndrome long after the acute episode and cardiac involvement both during the acute episode and within PIMS/MIS-C. Additionally, the study aims to establish correlations between potential risk factors and the occurrence of severe forms of the disease, as well as to identify possible temporal correlations in the early waves of the COVID-19 pandemic.

The main objectives of the project are:

- Establishing the incidence of acute SARS-CoV-2 infection among children and relating it to the temporal phases of the pandemic.
- Defining possible clinical patterns of acute SARS-CoV-2 infection, categorizing the severity forms.
- Identifying risk factors for severe forms of the disease.
- Determining the incidence of PIMS/MIS-C and categorizing clinical forms of the disease.

- Establishing the severity degree, identifying risk factors for severe forms, and correlating paraclinical data (hematological, biochemical, immunological) with the degree of multi-organ involvement both in acute infection and in PIMS-C cases.

- Identifying new parameters (easily obtainable) for paraclinical evaluation of disease progression and correlating them with the degree of multi-organ involvement: NLR (Neutrophil-Lymphocyte Ratio), PLR (Platelet-Lymphocyte Ratio).

- Evaluating the utility of parameters with limited historical use in pediatric practice, but demonstrated importance in adults, for assessing cardiovascular involvement in the context of SARS-CoV-2 infection: NT-proBNP, Troponin. Assessing the possibility of establishing reliable reference values for the pediatric population using "cut-off" values for adults as well as data from extensive population studies in specialized literature.

- Comparing the epidemiological, clinical, paraclinical, and treatment characteristics of PIMS-C/MIS-C phenotypes, with an emphasis on clinical or subclinical cardiovascular involvement, to identify common elements that impact therapeutic approaches.

As a secondary objective, this work aims to draw attention to the serious short- and long-term consequences of SARS-CoV-2 infection, initially considered to have a mild course in children, emphasizing again the role of prevention in limiting the spread of this virus.

2. Research Methodology. Materials and Methods

I conducted an observational, descriptive, longitudinal study that included 372 patients aged 0-18 years enrolled from the Dr. Victor Gomoiu Children's Clinical Hospital during the period from 01.03.2020 to 31.12.2021, diagnosed with acute SARS-CoV-2 infection or post-COVID-19 Multisystem Inflammatory Syndrome (PIMS-C).

Study Plan: 372 patients were enrolled and divided into 2 groups:

- A group of patients diagnosed with acute SARS-CoV-2 infection, n=311
- A group of patients diagnosed with PIMS-C/MIS-C, n=61*

*In the group of patients diagnosed with PIMS-C/MIS-C, patients were categorized based on the presentation phenotype: non-Kawasaki forms (undifferentiated inflammatory syndrome, shock-like form), Kawasaki-like form.

Inclusion Criteria for the Study:

Inclusion Criteria for Patients with Acute SARS-CoV-2 Infection:

- Patient age: 0-18 years
- Admission to Dr. Victor Gomoiu Children's Clinical Hospital during one of the analyzed temporal stages
- Positive RT-PCR test from nasopharyngeal swab.

*Evaluation and categorization of cases into clinical patterns were performed using the suspect/confirmed case definition established by the National Institute of Public Health (INSP) and transmitted through the National Center for Surveillance and Control of Communicable Diseases (CNSCBT), as well as the recommendations of international guidelines and protocols.

Inclusion Criteria for Patients with a Diagnosis of PIMS-C/MIS-C:

- Patient age: 0-18 years
- Admission to Dr. Victor Gomoiu Children's Clinical Hospital, Bucharest, during the period from 31.03 to 31.12.2020
- Presence of fever for at least 72 hours at the time of presentation
- Evidence of single or multiple organ involvement detected by the reasons for admission and elements obtained from clinical and paraclinical examination:

Gastrointestinal: Abdominal pain, diarrhea, vomiting, acute abdomen, jaundice, altered liver function

Cardiovascular: Hypotension, shock, oliguria, myocardial dysfunction (cardiac marker, echocardiographic evaluation), pericardial effusion, coronary involvement

Cutaneomucosal: Conjunctivitis, eyelid edema/erythema, rash, enanthem/mucositis

Neurological: Headache, confusion, myalgias, meningismus

Renal: Oliguria, edema, nitrogen retention

Respiratory: Cough, odynophagia, respiratory failure, hypoxemia, pleurisy

Hematological: Lymphadenopathy, changes in complete blood count, coagulopathy

- Evidence of inflammatory syndrome: measurement of inflammatory markers (CRP, ESR, Procalcitonin, Fibrinogen, Ferritin)
- Exclusion of other possible diagnoses: no other microbiological evidence
- Association with SARS-CoV-2 infection/exposure (SARS-CoV-2 IgG serology)

The inclusion criteria for the studied group were based on international guidelines for the diagnosis of PIMS-C developed by WHO/CDC, as well as the application of the Management Protocol for Pediatric Multisystem Inflammatory Syndrome post-Covid ed.1, developed and approved within the Dr. Victor Gomoiu Children's Clinical Hospital.

Exclusion Criteria for the SARS-CoV-2 Patient Group:

- Negative result of the SARS-CoV-2 RT-PCR test, even if the rapid antigen test was positive
- Patients with positive SARS-CoV-2 RT-PCR/rapid antigen test but within the first 90 days of being diagnosed with an acute COVID-19 infection

Exclusion Criteria for the PIMS-C/MIS-C Patient Group:

- Establishment of an alternative diagnosis for the multisystem inflammatory syndrome, without epidemiological or paraclinical connection to SARS-CoV-2 infection
- Failure to meet the diagnostic criteria according to the internal diagnostic and treatment protocol of the Dr. Victor Gomoiu Children's Clinical Hospital
- Patients with underlying cardiac conditions (congenital heart defects, hypertension)
- Patients known to have congenital or acquired immunodeficiencies

- Children known to have genetic conditions that associate cardiovascular changes (Klinefelter, Marfan)
- Patients undergoing immunosuppressive or substitution therapy (Gammanorm)
- Patients known to have autoimmune conditions or hemato-oncological diseases

To achieve the proposed objectives, the patients were evaluated as follows:

The initial evaluation was common for both groups and included:

- Verification of inclusion and exclusion criteria
- General characteristics: age, sex, race, residence, contact information, epidemiological context (contact history)
- Medical and surgical history of pre-existing conditions; for the group of patients diagnosed with PIMS, the time interval from acute infection was evaluated
- Clinical examination: pediatric evaluation, interdisciplinary consultations depending on the specific symptoms
- Paraclinical evaluation: collection at the time of enrollment of complete blood count with leukocyte formula, CRP, cardiopulmonary X-ray (for those with respiratory manifestations)

For the group of patients diagnosed with PIMS-C/MIS-C, evaluation was performed at the time of enrollment in the study and subsequently at 48-72 hours after admission, and at the time of discharge, in accordance with the internal protocol applied in the clinic.

The study was presented and approved by the Ethics Committee of Dr. Victor Gomoiu Children's Clinical Hospital, meeting the necessary criteria for conducting the research according to current regulations, and developed in accordance with the Declaration of Helsinki. All subjects included in the study had an Informed Consent signed by a parent or guardian.

Statistical Analysis: The statistical analysis was performed using IBM SPSS Statistics 20. For descriptive analysis, percentages, frequencies, means, standard error of the means, standard deviation, medians, and IQR were calculated. To detect positive associations between categorical variables, the Chi-Square test, Likelihood ratio, Fisher's Exact Test, and Phi coefficient were used. For continuous variables, the normality of the data distribution was tested. To detect significant correlations between numerical variables, the Spearman test was used. For inter-variable analysis, the following tests were used: parametric ANOVA and non-parametric: Kruskal-Wallis and Mann-Whitney. For measuring biochemical parameters, the Friedman

ANOVA test was used, and statistical significance correction was made using the post-hoc Bonferroni test and the Wilcoxon test.

3. Summary of Study Results

As a result of the research conducted over the 2-year period and after comparing the obtained results with data from similar studies in the international literature, I will summarize the important results of the thesis.

The study analyzed the evolution of SARS-CoV-2 during the first 5 pandemic waves, identifying clinical patterns that were later correlated with the circulating variants of the SARS-CoV-2 virus, highlighting certain particularities consistent with the specialized literature.

The obtained results highlighted the evolution of SARS-CoV-2 infection in the pediatric population during the first 2 years of the pandemic, noting a significant increase in pediatric cases during the circulation period of the Delta variant (October 2020), with a subsequent increase in the incidence of PIMS-C/MIS-C following the emergence of this variant. Similar to the panoramic perspective offered by the meta-analysis conducted by Kemiri et al., this study also highlighted the evolution of epidemiological data of SARS-CoV-2 infection before and after the emergence of the Delta B.1.617.2 and Omicron B.1.1.529 variants. Thus, a significant increase in pediatric cases was observed during the circulation period of the Delta variant (October 2020), along with an increase in the incidence of PIMS-C/MIS-C following the emergence of this variant.

Regarding the trend of SARS-CoV-2 infection evolution, the study results mention the first case diagnosed with PIMS-C/MIS-C in the clinic in September 2020, approximately one month after the increase in the number of cases diagnosed with SARS-CoV-2 infection.

3.1 Epidemiological Data in the Two Analyzed Groups

Regarding the epidemiological data, the study results mention the distribution by sex of the patients, consistent with CDC data and other studies, with a predominance of the male sex in both analyzed groups (57.6% in the SARS-CoV-2 group and 60.7% in the PIMS-C/MIS-C group) [1, 2]. These results underline once again the potential increased susceptibility of the male sex to acute SARS-CoV-2 infection. In the SARS-CoV-2 group, a statistically significant difference was observed between biological sex and patient age, whereas in the PIMS-C/MIS-C group, young age is considered to be a potential protective factor against severe forms of the disease.

Relating this information to the severity of the forms detected in the patients included in the study, it can be concluded that younger age could represent a favorable prognostic factor for patients with PIMS-C/MIS-C, as mentioned by some studies [3].

3.2 Clinical Spectrum of Manifestations in the Two Analyzed Groups. Correlations with Severity Factors

When analyzing the symptomatology reported by the patients included in the study, we aimed to establish the clinical particularities in order to classify them into different degrees of severity and forms of the disease.

A particular feature of the clinical evolution of SARS-CoV-2 infection in children is the presence of digestive manifestations (abdominal pain, vomiting, diarrhea). The presence of digestive manifestations, especially the appearance of diarrhea, is an important topic for future research, particularly since the persistence of the SARS-CoV-2 virus in feces for an extended period has been demonstrated, raising questions about the fecal-oral transmission route [4, 5].

Cardiovascular involvement secondary to SARS-CoV-2 infection is one of the most studied aspects of the infection in adults and is considered a factor of increased severity. In children, however, cardiac manifestations are very rarely encountered in the clinical picture of the acute infection. Nevertheless, they represent an extremely important subject in the analysis of long-term consequences, especially in the evolution of PIMS-C/MIS-C. [6,7]. In the enrolled SARS-CoV-2 patient group, cardiovascular involvement was observed in varying degrees in only 1.5% of the patients, while in the PIMS-C/MIS-C group, cardiovascular involvement was detected in 14.8% of the patients. These results correlate with the data in the literature, particularly with the observations from the study conducted by Valverde et al., which mentions that cardiovascular involvement in children is more likely the result of the cytokine storm (arising in the context of PIMS-C/MIS-C) rather than the direct action of the virus on the myocardium during the acute infection period [7,8]. However, the results should be interpreted with caution, given that one of the main limitations of the conducted study is that in the SARS-CoV-2 group, during the early period of the pandemic, patients were enrolled who were later transferred to infectious disease clinics and could not be monitored dynamically.

By evaluating the clinical profiles of the patients included in the PIMS-C/MIS-C study group, it was found that 58 (96.6%) of them could be classified into one of the three main phenotypes of the condition (Kawasaki-like, Shock-like, and Non-specific); however, in 3

patients (3.34%), the clinical profile did not allow classification into any of the three categories, as they exhibited a particular form characterized by the association of fever with digestive manifestations, but without other data overlapping with the three classic phenotypes.

Thus, the PIMS-C/MIS-C study group was divided into two subgroups based on the presence of criteria for classification into the Kawasaki-like form: 45.9% presented the Kawasaki-like form, and 54.09% the non-Kawasaki-like form. This separate evaluation into subgroups was decided because, from the beginning, PIMS-C/MIS-C was considered a condition overlapping the characteristics of Kawasaki disease [9].

3.3 **Paraclinical Characteristics of the Patients Included in the Study**

To outline the **hematological and immunological profile** of patients diagnosed with acute SARS-CoV-2 infection as well as those with PIMS-C/MIS-C, this study followed the sequential investigation recommended by international protocols and the Diagnostic and Treatment Protocol of the Clinic where the research was conducted. Thus, in addition to evaluating known paraclinical parameters as potential predictors for severe forms, special attention was given to determining new hematological markers that are easy to obtain but have been limited in use in pediatric pathology until now.

Hematological parameters such as the Neutrophil-Lymphocyte Ratio (NLR) and the Platelet-Lymphocyte Ratio (PLR), which are easily obtained through a complete blood count, are often used in the diagnosis and subsequent prognosis evaluation of inflammatory or infectious conditions [10,11].

Following the analysis of the study groups, it was observed that the mentioned biochemical parameters were significantly associated with severe forms of COVID-19, and in the PIMS-C/MIS-C group, they were correlated with several severity factors.

In the PIMS-C/MIS-C group, a statistically significant correlation between CRP value at admission and NLR value was noted, suggesting that this hematological marker could be used to evaluate inflammation. A statistically significant decrease in NLR values, consistent with changes in other inflammatory markers (NT-proBNP, IL-6), was also observed in the PIMS-C/MIS-C group during hospitalization, indicating its potential utility in monitoring favorable evolution.

Regarding the NLR and PLR ratios in the patients evaluated in this study, higher median NLR values but lower PLR values were observed in patients with the Kawasaki-like phenotype

compared to those with other forms of PIMS-C/MIS-C. In the Kawasaki-like phenotype subgroup, significantly higher NLR values ($p=.017$) were found compared to other disease phenotypes, contradicting the results of Rekhman et al., which mention similar values regardless of the presence of cutaneomucosal changes [12].

Considering that PIMS-C/MIS-C is by definition a hyperinflammatory status and the pathophysiology of both acute infection and especially PIMS-C/MIS-C centers around the cytokine storm and immune response, special attention was given to analyzing biological inflammatory markers in patients included in both study groups. Analyzing the values obtained in the PIMS-C/MIS-C group for the main inflammatory markers, a good correlation between CRP and IL-6 values was observed, suggesting a direct proportional relationship, although this correlation was not statistically significant. Additionally, a statistically significant correlation was noted between CRP values at admission and NT-ProBNP and NLR values (both being significantly positively associated with increased IL-6). A statistically significant decrease in NLR values, consistent with changes in other inflammatory markers (NT-proBNP, IL-6), was also observed in the PIMS-C/MIS-C group during hospitalization, indicating its potential utility in monitoring favorable evolution.

An increasing number of studies have reported the characteristics of cardiac markers in patients with PIMS-C/MIS-C [8,13]. Some investigations suggested that patients who develop severe forms of the disease have very high NT-proBNP values from the onset. NT-proBNP is a promising biomarker for detecting cardiac dysfunction in conditions where heart failure and inflammation coexist [8,14].

Since reference values for children are significantly age-dependent, age-adjusted Z-log-NT-proBNP values were calculated according to Palm et al.'s recommendations, and Z-log > 1.96 was considered elevated NT-proBNP. All patients in the PIMS-C/MIS-C group had Z-log-NT-proBNP > 1.96 . For statistical analysis, very high NT-proBNP was defined as Z-log-NT-proBNP > 4 (double the average values for age).

Based on the observations of this doctoral study, NT-proBNP appears to be a promising biomarker for initial screening and monitoring of myocardial dysfunction in the acute phase, where Z-log-NT-proBNP > 4 may be more indicative of concerning echocardiographic findings associated with disease severity. Therefore, I consider that using age-adjusted NT-proBNP

values could help identify children at risk of severe MIS-C and cardiac involvement, providing uniformity in research studies using NT-proBNP.

3.4 Therapeutic Approach

Regarding the therapeutic approach for the patients in the analyzed groups, I mention that this evaluation only targeted the PIMS-C/MIS-C group. Being an observational study, I monitored the response to the instituted treatment, paying special attention to the forms that required immunomodulatory therapy. By dynamically correlating the evolution of hematological and immunological parameters during hospitalization, a rapid good response was observed in most cases, with fever and symptoms remitting within 24-48 hours of initiating IVIG therapy. It was observed that myocardial involvement seems to recover rapidly and with almost complete normalization of cardiac function a few days after immunomodulatory therapy and administration of cardiovascular support, which further supports the previous findings. Thus, early identification of cardiac dysfunction is crucial to promptly start treatment modalities and prevent cardiovascular complications.

I note that in the PIMS-C/MIS-C group, of the 61 included patients, 5 developed forms refractory to immunomodulatory therapy, requiring repeated administration of IV immunoglobulin, and one of these patients developed hemolytic anemia with cold agglutinins upon administration of the second dose, requiring transfer to a Hematology clinic.

4. Conclusions

1. The change in the pattern of involvement of the pediatric population can be considered the main characteristic of the first 2 years of the COVID-19 pandemic. Thus, a significant increase in pediatric cases was observed during the circulation period of the Delta variant (October 2020), along with a subsequent increase in the incidence of PIMS-C/MIS-C following the emergence of this variant.

2. A difference related to the age of the patients was noted in relation to the temporal cluster. (page in the paper where this is found) Thus, after the first months of the pandemic, there was an increase in the number of acute SARS-CoV-2 infection cases in children older than 13 months, and especially a significant increase in incidence in the school-aged and adolescent groups.

3. The gender distribution of the patients shows a predominance of males in both analyzed groups (57.6% in the SARS-CoV-2 group and 60.7% in the PIMS-C/MIS-C group), highlighting

a statistically significant difference in the SARS-CoV-2 group between biological sex and patient age ($p=.045$).

4. Males were found to be more susceptible to acute infection, especially at younger ages, while older age was identified as a higher risk factor for the occurrence of PIMS-C/MIS-C in males. In the PIMS-C/MIS-C group, a statistically significant difference ($p=.017$) was observed between the biological sex of the patients and their age, with an increase in the degree of involvement correlating with older age in males compared to females.

5. In the PIMS-C/MIS-C patient group, the median age was 63.69 months, with a median of 45 months. Relating this information to the severity of the forms detected in the patients included in the study, it can be concluded that younger age could represent a favorable prognostic factor for patients with PIMS-C/MIS-C (significant association $p<.001$ between the age of the included patients and the degree of multi-organ involvement: the younger the age, the less likely multi-organ involvement is, with younger ages more likely to be diagnosed with incomplete forms of PIMS-C/MIS-C).

6. A particular feature of the clinical evolution of SARS-CoV-2 infection in children is the presence of digestive manifestations (abdominal pain, vomiting, diarrhea).

7. Patients with severe COVID-19 are more likely to present neurological impairments compared to those with milder forms. However, the strength of this association is weak ($\Phi = 0.179$), indicating that while there is a connection, it is not very strong.

8. Cardiac manifestations are very rarely encountered in the clinical picture of acute infection in children.

9. The data obtained in the SARS-CoV-2 group indicate that NLR, PLR, CRP, D-dimers, and Ferritin were significantly associated with severe forms of COVID-19.

10. The presence of lymphopenia in COVID-19 patients has also been shown to be not only pathognomonic but also a potential risk factor for severe forms of the disease.

11. There is a good correlation between CRP and IL-6 values, suggesting a direct proportional relationship, which may imply the use of CRP as a substitute inflammatory marker for IL-6 when this determination is not possible.

12. The statistically significant decrease in NLR values, consistent with changes in other inflammatory markers (NT-proBNP, IL-6), in the PIMS-C/MIS-C group during hospitalization can be interpreted as a useful factor in monitoring favorable evolution.

13. PCT does not certify the bacterial origin of the inflammatory syndrome but rather offers a useful tool in assessing the severity of the systemic inflammatory syndrome. Thus, the results obtained highlight a statistically significant correlation between CRP and PCT values at admission, in the absence of arguments for bacterial sepsis.

14. The lack of reactive thrombocytosis in a significant number of patients in the PIMS-C/MIS-C group can be considered a useful factor in making the differential diagnosis with Kawasaki disease, including in the subgroup of patients with Kawasaki-like phenotype.

15. In the Kawasaki-like phenotype subgroup, significantly higher NLR values ($p=.017$) were found compared to other disease phenotypes, leading to the conclusion that the presence of cutaneomucosal manifestations can be considered a risk factor for severe forms.

16. Based on the observations, NT-proBNP appears to be a promising biomarker for initial screening and monitoring of myocardial dysfunction in the acute phase, where $Z\text{-log-NT-proBNP} > 4$ may be more indicative of concerning echocardiographic findings associated with disease severity. Therefore, I consider that using age-adjusted NT-proBNP values could help identify children at risk of severe MIS-C and cardiac involvement.

17. In the SARS-CoV-2 group, common findings on chest X-rays in children with COVID-19 pneumonia include "ground-glass" opacities and consolidations distributed bilaterally, peripherally, and subpleurally. CT thoracic changes in children with COVID-19 are similar to those observed in adults. Halo sign consolidations were observed in patients with severe forms of the disease. Pleural effusion was detected in an insignificant number of cases in the SARS-CoV-2 group.

18. The findings of this doctoral research indicate that although children have remained consistently less affected compared to adults, new facets of the infection have been identified among the pediatric population. High-quality longitudinal studies with well-defined health outcomes and valid control groups are needed to understand and quantify the direct and indirect impact of the COVID-19 pandemic on children and adolescents and to provide appropriate medical care and counseling services.

Personal Contributions

Through this research, I approached the impact of SARS-CoV-2 infection on pediatric patients in a multidisciplinary manner, aiming to identify new parameters for paraclinical evaluation of the evolution and correlate them with the degree of multi-organ involvement.

In light of the obtained results, it can be concluded that the change in the pattern of involvement of the pediatric population can be considered the main characteristic of the first 2 years of the COVID-19 pandemic.

The originality of the current study lies in the attention given to identifying new hematological parameters, which are easy to obtain and could be used as risk factors for severe evolution, both in acute infection and in the evolution of PIMS-C/MIS-C. Thus, parameters such as the Neutrophil-Lymphocyte Ratio (NLR) and the Platelet-Lymphocyte Ratio (PLR) can be used to evaluate the prognosis of inflammatory conditions in children, including SARS-CoV-2 infection or PIMS-C/MIS-C.

Additionally, a novel element is the use of age-adjusted NT-proBNP values (Z-log-NT-proBNP) as a parameter to identify children at risk of severe MIS-C and cardiac involvement. NT-proBNP appears to be a promising biomarker for initial screening and monitoring of myocardial dysfunction in the acute phase, and Z-log-NT-proBNP > 4 may be more specific for concerning echocardiographic findings associated with disease severity.

Study Limitations

The current study was subject to several limitations, and the obtained results should be interpreted with caution, as they do not reflect the general population but only patients admitted to Dr. Victor Gomoiu Children's Clinical Hospital. It should also be noted that the research was conducted during the "discovery" period of both the acute disease and especially PIMS-C/MIS-C, which meant insufficient data and variable case approaches depending on periodic changes in guidelines. Therefore, there is a discrepancy within the SARS-CoV-2 group regarding the uniformity of case approaches in the early period of the pandemic compared to 2021.

Regarding the establishment of the hematological and immunological profile of the analyzed patients, an important impediment was the limited use in routine pediatric practice of certain markers that proved essential in monitoring patients in the PIMS-C/MIS-C group. Thus, changes in parameters such as IL-6, NT-proBNP, Troponin, and D-Dimers, which are not widely used in pediatric pathology, proved difficult to interpret due to the lack of conclusive data on their variations in other pediatric conditions and in the general population.

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