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Original Article (Pages: 18700-18711)

Investigating the Frequency of Coagulation Abnormality in Hospitalized Children with Covid19: A Cross-Sectional Study

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Abstract

Background: Based on the findings of previous studies, patients with severe Covid-19 have a much greater occurrence of coagulation abnormalities. Additionally, individuals who get this novel virus are susceptible to developing disseminated intravascular coagulation. The present study aimed to investigate the frequency of coagulation disorders in children with covid-19 who were hospitalized in Bandar Abbas Children's Hospital during 2020-2021.

Methods: This study was done retrospectively. The medical records of all children were checked with a definite diagnosis of Covid-19, based on positive PCR results. Age, gender and comorbidity status were obtained from the medical records of the patients. In addition, white blood cell count, blood platelet count, hemoglobin concentration, CRP, PT, PTT, INR, D-dimer and fibrinogen were checked. Data was analyzed using SPSS 22 software with a significance threshold of 0.05.

Results: In this study 20.63% had coagulation abnormalities. The groups with and without coagulation disease exhibited a significant difference in the proportions of neutrophils and lymphocytes. Specifically, the coagulation disorder group had elevated levels of neutrophils and reduced levels of lymphocytes (P= 0.043, P= 0.041, respectively). The average D-dimer level and age in the group with coagulation disorder was significantly greater than those in the group without coagulation problem (P= 0.000, P=0.045).

Conclusion: According to the findings of this research, 20.63% of children who were definitively diagnosed with covid-19 had coagulation abnormalities. Only the alterations in D-dimer, lymphocyte, and neutrophil levels were shown to be substantially associated with coagulation disorders in this investigation. Specifically, in the group with coagulation disorders, there was an elevation in neutrophil count and a decrease in lymphocyte count.

Key Words: Children, Coagulation Disorder, Covid-19, D-Dimer.

* Please cite this article as: Karimi Rouzbahani A, Tahmasebi Ghorabi S, Mohammadian M, Mohammad Zadeh M, Goudarzi Z, Mallahi M, Molavi MA. Investigating the Frequency of Coagulation Abnormality in Hospitalized Children with Covid19: A Cross-Sectional Study. J Ped Perspect 2024; 12 (04):18700-18711. DOI: **10.22038/ijp.2024.79640.5451**

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Received date: Feb.30,2024; Accepted date: Apr.21,2024

1- INTRODUCTION

Covid-19 is a highly transmissible and communicable illness that first presents as an acute respiratory infection. The illness is caused by SARS-CoV-2 virus, a member of the coronavirus family, which has swiftly disseminated globally. This illness has been officially designated an epidemic by the World Health Organization (1, 2). As of mid-October 2020, global reports indicated almost 50 million cases of infection and one million fatalities. (3) The primary mode of transmission for this virus is by respiratory droplets and contact with both symptomatic and asymptomatic individuals. This method of transmission is particularly significant in the spread of the virus from asymptomatic patients to others, particularly children. Furthermore, the genetic material of SARS-CoV-2, namely its RNA, has been detected in the excrement of some individuals, indicating the potential for transmission by the oral ingestion of fecal matter (5, 4). The predominant manifestations of Covid-19 include fever, dry cough, sore throat, myalgia, weariness ; and children often exhibit less severe symptoms (7, 6). Children who are infected may not exhibit any symptoms or may only have moderate symptoms like coughing, fever, and nasal congestion. Furthermore, children have shown a higher prevalence of gastrointestinal symptoms, including diarrhea, nausea, vomiting, and abdominal pain, compared to adults (8). Severe instances have shown the occurrence of acute respiratory distress syndrome (ARDS), characterized by lung failure or a severe coagulation issue resulting from uncontrolled inflammation (9).

Thrombotic consequences are a significant concern in individuals diagnosed with COVID-19 (10). The Corona virus 2019 (COVID-19) is often linked to increased blood clotting and the spread of blood clotting throughout the body, known as Disseminated Intravascular Coagulation (DIC). The heightened coagulability is evident via the development of progressive lung and renal illness, Pulmonary Embolism (PE), Venous Thrombotic Events (VTE), and stroke (11).

Preliminary findings on the impact of the COVID-19 pandemic indicate that a significant proportion of infected individuals have thrombocytopenia (36.2%) and potentially high levels of D-dimer (46.4%). The percentage is considerably greater in individuals with severe COVID-19 disease (57.7% and 59.6%, respectively) (12).

Recent investigations indicate that individuals who get this virus are susceptible to disseminated intravascular coagulation (DIC) (13, 14). Elevated levels of D-dimer and fibrin degradation products, as well as increased prothrombin time, are linked to a worse prognosis in individuals affected by the new coronavirus. Tang et al. found that 80% of the whole sample, namely 15 out of 21 individuals, who met the international diagnostic criteria for thrombosis and hemostasis, experienced mortality (14). A meta-analysis undertaken by Lippi et al. revealed a significant reduction in platelet count among afflicted individuals, with thrombocytopenia being five times more prevalent (15). Studies have shown that some individuals, particularly children, may have an inflammatory condition known as MIS-C (Multisystem Inflammatory Syndrome in Children) in connection with SARSCoV-2. This illness often occurs several weeks after infection. This scenario is accompanied by a diverse array of cardiovascular problems, including arrhythmia, coronary artery aneurysm, myocarditis, and abrupt cardiogenic shock (3, 16). The present study aimed to investigate the frequency

of coagulation disorders in children with COVID-19 who were admitted to Bandar Abbas Children's Hospital during 2020-2021. This research is particularly significant due to the limited existing information on coagulation disorders in children with COVID-19, both globally and specifically in Iran.

2 MATERIALS AND METHODS

2.1. Design and participants

The present study was a descriptive-analytical study of retrospective type, conducted on all children admitted to Bandar Abbas Children's Hospital with a confirmed diagnosis of COVID-19 during 2020-2021.

2-1-1. Sampling method and sample size

In this study, the census sampling method was used; in this way, the files of all children infected with covid-19 who were admitted to the hospital during one year were reviewed and the patients who met the conditions to be included in the study were included in the study.

2-1-2. Inclusion and Exclusion criteria

The inclusion criteria included children under the age of 18, afflicted with COVID-19 based on the results of RT-PCR and lung CT scan. The exclusion criteria were Incompleteness of file information and/or the unwillingness of parents of patients to complete incomplete information. Also children with hematological diseases, tuberculosis, malignancies, and those on anticoagulation drugs were excluded from the study.

2-2. Data collection instruments

The data collection tools included patients' files. Basic and clinical information for all patients was recorded in the checklist prepared by the researcher. Primary information included age, sex, while clinical information included Comorbidities, symptoms of covid-19 and the results of the patients' tests.

2-3. Procedure

After obtaining ethical approval from the Ethics Committee of Hormozgan University of Medical Sciences and necessary coordination with the hospital's security and management, the researcher proceeded to collect data. A number of 135 cases of hospitalized children with covid-19 were examined, 9 patients were excluded because they did not meet the conditions for entering the study, and a total of 126 patients were included in the study. Information including age, gender, underlying diseases, covid-19 symptoms, WBC and RBC count, Neutrophils, lymphocytes, blood platelet count, hemoglobin concentration, CRP, PT, PTT, INR, D-dimer and fibrinogen was collected from the patient files and in the checklist prepared by the researcher. Finally, the collected data were analyzed by a statistical expert using SPSS 22 software to perform the necessary data analysis and assess the relationships between variables.

2-4. Data analysis

Statistical analysis was performed using SPSS 22. Qualitative variables were shown as frequency and percentage, and quantitative variables were shown as mean and standard deviation. Quantitative variables were tested using Kolmogorov–Smirnov test or histogram for normal distribution. For quantitative variables, Mann–Whitney and independent t-tests were performed. For qualitative data, Fisher's exact test was used. P-values of <0.05 were considered as statistically significant.

3- RESULTS

This study examined the files of 126 hospitalized children with Covid-19. The research participants had an average age

of 55.22±29.91 months (1-168 months), with 63 (48.50%) being girls and 63 (48.50%) being boys. Among the examined children, 89 (70.63%) were ˗<5 years old (60 months) and 37 (29.37%) were >5 years old (60 months).

The findings indicated that 26 individuals (20.63%) had coagulation abnormalities, while 28 patients (22.22%) had at least one associated disease, allergic pathology accounted for the highest percentage with 11.11%. Among the symptoms of Covid-19, fever was the most common one (94.44%). Respiratory symptoms were dominated by cough (79.36, 46.3%) and runny nose (71.42%). Gastrointestinal symptoms were less common and included vomiting and diarrhea (23.80% and 35.71%). Headache was the least observed symptom in patients with 19.84%. Furthermore, there were no instances of bleeding or thrombotic problems seen in any of the patients. **Table 1** displays further demographic/clinical data of the patients.

Table-1: Frequency distribution and percentage of basic and clinical information of the patients

Variable	Category	Frequency	Percent (%)
gender	Male	63	48.50
	Female	63	48.50
Age (Months)	˗<60	89	70.63
	>60	37	29.73
Symptoms	Fever	119	94.44
	Appetite loss	78	61.90
	Runny nose	90	71.42
	Cough	100	79.36
	Sore throat	85	67.46
	Vomiting	30	23.80
	Diarrhea	45	35.71
	Weakness	63	50
	Shortness of breath	58	46.03
	Headache	25	19.84
Comorbidities	Allergic pathology	14	11.11
	Nutritional disorders	5	3.96
	Thyroid diseases	2	1.58
	Digestive system diseases	3	2.38
	Kidney problems	2	1.58
	Nervous system diseases	1	0.79
	Heart diseases	1	0.79
Coagulation disorder	Yes	26	20.63
	No	100	79.37

The results of **Table 2** showed that the highest mean in the studied patients was related to D-dimer with 779.07±1894.44. Also, Fibrinogen with an average of 331.70±68.35 was reported in patients. The lowest average was related to INR (1.10±0.17). More information is given in **Table 2**.

The fibrinogen factor was assessed in 10 instances, with 6 instances showing impairment. The D-dimer factor was analyzed in a total of 77 instances, with

20 cases showing impairment and 57 cases having a normal D-dimer factor. PT, PTT, and INR variables were assessed in 26 patients, with 3 cases showing abnormal results. Platelet factor showed thrombocytopenia in 10 instances and thrombocytosis in 23 instances. Additionally, the study revealed that the majority of individuals (74 individuals) did not have any coagulation condition or underlying illness. On the other hand, 22 individuals had a coagulation disorder but did not have any underlying disease. 24 individuals had no coagulation condition but presented an underlying illness, whereas the fewest number of individuals had both a coagulation issue and an underlying disease. The data analysis revealed that there is no statistically significant difference in relation to the underlying ailment.

Table-2: Mean and standard deviation of the laboratory findings of the patients

Variable	Mean	Standard deviation	Minimum	Maximum
Age (Month)	55.22	29.91	1	168
WBC count	9.12	4.53	2	23
RBC	4.34	0.69	2	6
Neutrophils (percentage)	59.18	21.21	6	94
lymphocytes (percentage)	33.65	20.36	3	79
Hemoglobin (g/dl)	10.35	1.66	6	15
Platelet count	287.74	150.90	5	959
CRP (mg/l)	34.67	52.50	1	383
PT	13.44	1.63	12	19
PTT	30/34	8.96	7	57
INR	1.10	0.17	1	2
D-dimer(ng/ml)	779.07	1894.44	0	10000
Fibrinogen(ml/dl)	331.70	68.35	230	443

Based on the outcomes of the Kolmogorov-Smirnov test, a separate t-test was conducted to compare the levels of hemoglobin, while a Mann-Whitney test was used to evaluate the other variables between the two groups, one with a coagulation disease and the other without. As shown in **Table 3,** there is no notable disparity in WBC count, RBC count, hemoglobin concentration, platelet count, CRP levels, PT, PTT, and INR between patients with and without coagulation problems (P>0.05).

In patients with coagulation disorders, the average age was higher than that in patients who did not have coagulation disorders, and the results of Mann-Whitney test showed that this relationship was statistically significant (65±19 vs. 52±63 months; P=0.045). The groups with and without coagulation exhibited a significant difference in the proportions of neutrophils and lymphocytes. Specifically, the group with coagulation disorder had elevated levels of neutrophils and reduced levels of lymphocytes (P= 0.043, P= 0.041; respectively). As anticipated, the mean D-dimer level in the group with coagulation disorder was significantly greater than that in the group without coagulation disorder (2228.17 vs. 110.26; P=0.000) (**Table3**).

Fisher's exact test was used to investigate the relationship between gender variables, co-morbidities and the presence or absence of coagulation disorders. The presence of bleeding disorders was reported more in girls than in boys; so that out of 26 patients with coagulation

disorders, 14 (11.11%) were girls and 12 (9.52%) were boys. Fisher's exact test showed that there was no statistically significant difference between gender and the presence or absence of coagulation disorders (P=0.660). The presence of bleeding disorders was more reported in children who did not have concomitant diseases; so that out of 26 patients with coagulation disorders, 22 (17.46%) had no comorbidities and only 4 (3.17%) had comorbidities. Fisher's exact test showed that there was no statistically significant difference between comorbidities and the presence or absence of coagulation disorders.

Table-3: The relationship between laboratory results and coagulation disorders

Variable	Coagulation disorder		P-value
	No (100 people) Mean ± SD	Yes (26 people) Mean ± SD	
age (month)	52.63+27.80	65.19+35.81	0.045
WBC count	9.08+4.65	9.25+4.13	0.689
Hemoglobin (g/dl)	10.38+1.62	10.24+1.86	0.644
RBC	4.32+0.67	4.41+0.78	0.748
Neutrophils (percentage)	57.39+20.25	65.93+23.73	0.043
lymphocytes (percentage)	35.12+19.47	28.30+22.91	0.041
Platelet count	299.38+154.26	244.76+131.66	0.080
CRP (mg/l)	27.79+37.94	58.63+82.58	0.071
PT	13.58+1.84	13.27+1.42	0.980
PTT	30.36+11.30	30.32+5.62	0.820
INR	1.11+0.20	1.09+0.13	0.781
D-dimer(ng/ml)	110.26+340.49	2228.17+2871.13	0.000
Fibrinogen(ml/dl)	276.50+65.76	359.14+57.28	0.222

4- DISCUSSION

The present research included the examination of 126 children admitted to Bandar Abbas Children's Hospital and had a confirmed diagnosis of Covid-19, which was determined by a positive RT-PCR test. According to the findings, 20.63% of children who were definitively diagnosed with covid-19 had coagulation disorder. This conclusion is consistent with the findings published by Borrello et al., where 13.8% (3) of children had coagulation abnormalities, and with the research conducted by Ponti et al. (17), where 36.6% of children with covid-19 had coagulation disorders. In contrast to our research, Noni et al. (18) reported that over 90% of children with covid-19 had coagulation abnormalities, with just 3% (7 patients) experiencing severe coagulation issues. A retrospective study compared the coagulation status and clinical characteristics of patients with SARS-CoV-2-induced severe pneumonia (COVID-19 group) and patients with non-SARS-CoV-2-induced severe pneumonia (non-COVID-19 group). It was observed that coagulation disorders usually accompanied severe COVID-19. Therefore, the researchers suggested that higher levels of D-dimer could help decision making on the initiation of anticoagulation therapy (19).

One possible explanation for the statistical discrepancy is that the research was carried out at a highly specialized medical facility for children, where even little alterations in platelet markers such as PT, PTT, INR, and D-dimer are seen as indicators of coagulation problems.

The research findings indicated that over 70% of patients with coagulation disorders were below the age of 5 years. However, there was an equal distribution of coagulation disorders across both sexes. Furthermore, there was no statistically significant association between age and the presence of coagulation disorders (P>0.05). Moreover, there was statistically significant association between age and the presence of coagulation disorders (P>0.05). Research done on children with Covid-19 revealed that around 56% of the patients who had coagulation abnormalities were boys in the preschool age group, namely under the age of 7 (20). The platelet count in the majority of our examined patients fell within the normal range. However, 20% of the patients exhibited platelet counts beyond the normal range, and these cases were associated with coagulation disorders and thrombocytopenia. There was no statistically significant difference seen between patients with coagulation disorder and those without coagulation disease (P>0.05). Consistent with the findings of Shi et al. (1), 7.3% of the patients had platelet problems, although our investigation did not find a statistically significant association between platelet disorders and the condition (P=0.2). In the study by Boyarchuk et al., the number of platelets was reported to be normal in most patients (86.8%). No significant difference was found between the median of platelet levels and coagulation profile indicators between the groups with long COVID and those who had recovered (22).

Also, unlike our study, the retrospective studies of Ponti et al. (17) and Yang et al. (23), on coagulation disorders in affected patients, found a strong correlation between coagulation disorders and platelets (P< 0.05). Ponti's research revealed that 36% of patients diagnosed with covid-19 saw a reduction in platelet count, particularly those with severe cases of the illness who had thrombocytopenia as a result of coagulation abnormalities. The absence of variable assessment in all patients contributes to the disparity between this research and the other studies including the present investigation.

A meta-analysis by Lippi et al. found that COVID-19 patients had significantly lower platelet counts. Severe COVID-29 patients had a five-fold higher risk of thrombocytopenia than normal patients (9). In Aliasgarzade's study, the average platelet count was 200.15 ± 82.85, and there was no statistically significant difference between the two groups who died and survived in terms of the number of platelets (P=0.87) (15, 24).

Platelet count is a straightforward and affordable biomarker that is easily accessible. It is also linked to the severity of sickness and the likelihood of death in the ICU, regardless of other factors. Platelet count serves as a promising biomarker for Covid-19, since new studies indicate a considerable decrease in platelet count among Covid-19 patients. Furthermore, this reduction is more pronounced in individuals who have succumbed to the disease compared to those who have survived (25, 26).

Reduced platelet counts in Covid-19 patients are linked to a higher likelihood of severe illness and death. Additionally, low platelet counts might serve as a sign of deteriorating clinical condition while hospitalized. A separate study team discovered that individuals suffering from severe pneumonia induced by SARS-CoV2 had a more significant reduction in platelet levels compared to those with pneumonia produced by non-SARS-CoV2 (15, 27).

Patients who had a notable elevation in platelet count and a greater Platelet-to-Lymphocyte Ratio (PLR) following therapy had a prolonged duration of hospitalization. The presence of injured lung tissue and pulmonary endothelial cells may trigger the activation of platelets in the lungs, resulting in the creation of pathogen accumulations. This process ultimately leads to an increase in platelet consumption (28, 29).

The majority of individuals in our research had coagulation parameters within the normal range. Approximately 20% of patients had alterations in D-dimer, a crucial coagulation factor, whereas fewer than 5% of patients showed changes in fibrinogen, another significant coagulation component. Approximately 15% of patients had abnormal values for PT, PTT, and INR. The rise in D-dimer levels among patients was statistically significant ($P<0.05$), although the increases in other coagulation factors, such as fibrinogen, were not statistically significant ($P>0.05$).

The research conducted by Noni et al. (18) examined coagulation problems in children with covid-19. The results showed that among patients with coagulation disorders, 36% had PT disorder, 28% had PTT and INR disorder, 84% had elevated D-Dimer levels, and 8.5% had abnormal Fibrinogen levels. In contrast to our investigation, there was a significant correlation seen between all coagulation factors and coagulation disorders ($P<0.05$). In the study of Aliasgarzade et al., significant differences were found between the surviving and deceased patients in D-dimer, LDH, PT, and INR levels ($P < 0.05$). This is consistent with our study in terms of the significance of the D-dimer variable (24).

Kander's research (30) corroborated the results of our investigation on coagulation problems in individuals with Covid-19. Among the patients in this study, particularly those with severe forms of the condition, 10% exhibited abnormalities in fibrinogen levels, while 90% showed abnormalities in D-Dimer levels. Approximately 20% of the patients had problems in the three coagulation biomarkers: PT, PTT, and INR. This research found a significant correlation between fibrinogen and D-Dimer levels and coagulation problems ($P<0.05$). Although by increasing focus on these two criteria, patients heighten the likelihood of developing internal thrombosis and DIC in comparison to other options. The findings of this research do not align with the outcomes of our investigation. In another study done in France by Helms et al. (31) about coagulation abnormalities, similar to our own investigation, it was shown that over 90% of patients exhibited the presence of D-Dimer factor. In addition, platelets and coagulation factors deviated from the normal range in only 19% of individuals. Notably, there was a substantial rise in coagulation factors among patients with a specific form of severe illness ($P<0.05$), which contradicted the results of our research.

In a study conducted in New York, USA (20), it was observed that out of the children hospitalized with Covid-19, only 27 children experienced coagulation disorders. Among these children, 7 (25%) had complications related to venous thrombosis and abnormalities in the Fibrinogen and D-Dimer factors. In contrast to our investigation, this particular study discovered a significant correlation between coagulation factors and coagulation abnormalities in Covid-19 patients ($P<0.05$). The presence of an underlying illness in some children accounts for this phenomenon, albeit the reason remains unidentified in certain instances. Out of the whole sample of children, 8 individuals (38%) received anticoagulant treatment. It is important to

highlight that only 16 children had signs of the severe form of the condition, but other children with moderate to mild forms also experienced coagulation disorders. In a n investigation conducted by researchers in Italy, over a span of 8 months, it was found that only 13.8% of the patients had coagulation factor abnormalities. Furthermore, all cases showed elevated levels of D-dimer and PT. The research found that 16.6% of patients had mortality due to coagulation problems, which were often accompanied by underlying diseases. Additionally, all coagulation factors were compromised in these individuals (3). The findings of this investigation were congruent with the outcomes of our study.

Our research found that around 3.2. % of individuals with coagulation abnormalities had a comorbid condition. Aligned with our research in Europe (18), a study has been undertaken to assess and handle coagulation abnormalities in pediatric patients with Covid-19. It demonstrates that among infants affected by Covid-19 and exhibiting mild to moderate coagulation problems, 12% of cases had moderate coagulation disorders, while 64% had severe coagulation disorders, both of which were associated with an underlying medical condition. Consistent with the research conducted by Mitchell et al. (20), over 70% of the patients (all of whom died) had coagulation problems. Similarly, in the investigations conducted by Zanza et al. (32) and Giannis et al. (10), more than half of the patients had underlying illnesses in addition to coagulation disorders. According to the results of the mentioned studies, consistent with our review, the presence of an underlying disease raises the likelihood of coagulation disorders. However, unlike those studies, this study did not find a significant association between the history of underlying disease and coagulation disorders (P>0.05).

Two prospective studies including children (without pre-existing medical conditions) who were hospitalized for Covid-19 and MIS-C did not document any instances of thrombosis and embolism problems. In addition, a retrospective analysis of children (without pre-existing medical conditions) diagnosed with Covid-19, which investigated the occurrence of abnormal medical tests during admission and at the time of hospital release, did not observe any instances of thrombosis or embolism problems. Recent research has shown that individuals with a pre-existing medical condition are more prone to experiencing vascular problems associated with coagulation abnormalities (20, 33, 34). According to the presented ideas, Covid-19 illness triggers an upsurge in the activity of inflammatory proteins and cytokines, resulting in the broad release of plasminogen. This release damages endothelial cells due to inflammation. Activators have the potential to ultimately enhance the likelihood of developing coagulation problems. In individuals with certain underlying medical conditions, particularly systemic disorders, this process is heightened due to the underlying factors and the increased likelihood of intravascular blood clot formation in connection with Covid-19 infection (35, 36).

The majority (about 60%) of patients with coagulation problems in our research had an elevation in C-Reactive Protein (CRP) levels in line with their clinical progression. These findings were consistent with the studies conducted by Zenzav et al. (32) on pediatric patient problems. They found that individuals with coagulation problems had an elevation in CRP levels. Elevated biomarkers may be indicative of acute circumstances and the crucial stage of the

illness, particularly in the setting of weakened vascular systems and coagulation processes that lead to significant damage in essential organs. The primary biomarkers associated with Covid-19 are CRP, ESR, Ferritin, and Procalcitonin, which are also involved in immunological response.

5- CONCLUSION

The findings of the current investigation revealed a prevalence rate of 20% for coagulation abnormalities among hospitalized children who have received a confirmed diagnosis of covid-19. A strong correlation was observed between the alterations in D-dimer, lymphocyte, and neutrophil levels and the presence of coagulation disorders. Specifically, individuals with coagulation disorders exhibited elevated neutrophil counts and decreased lymphocyte counts. Additionally, as anticipated, the average D-dimer level was higher in the group with coagulation disorders compared to the group without coagulation disorders. Knowledge and research on coagulation problems associated with covid-19 are continuously growing. The occurrence of thrombotic or thromboembolic events in children with COVID-19 and MIS-C seems to be few. However, when compared to other patients, the prevalence of these illnesses is elevated in individuals with Covid-19. Consequently, it is necessary to gather and revise thorough and exhaustive instructions. However, similar to adults, it is important to address the incidence of hemorrhagic consequences and the need for suitable and cost-effective therapies in children with COVID-19 or MIS-C infection, particularly those with underlying health conditions that increase the risk of blood clotting events.

5-1. Limitations of the study

A significant disadvantage of this research was the presence of a flaw in the data file and the retrospective design, which hindered the possibility of conducting further investigations on the treatment and the impact of anticoagulant medication on afflicted individuals. Furthermore, the perplexity and flaws in the data resulted in the exclusion of the samples from the research.

6- ACKNOWLEDGEMENTS

This material is extracted from the thesis of the professional medical doctor programme, which has been accepted by Hormozgan University of Medical Sciences with the ID IR.HUMS.REC.1400.220. The authors would like to extend their appreciation to the university's research vice-chancellor, the hospital staff, and the study participants for their valuable contributions to this research.

7- CONFLICT OF INTEREST

None.

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