D-DIMER AND ITS CLINICAL ASSOCIATION IN HOSPITALIZED CHILDREN WITH COVID-19 IN MEDAN, SUMATERA UTARA

THESIS

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UNIVERSITAS MUHAMMADIYAH SUMATERA UTARA

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D-DIMER AND ITS CLINICAL ASSOCIATION

IN HOSPITALIZED CHILDREN WITH COVID-19

IN MEDAN, SUMATERA UTARA

This Thesis Is Submitted as One of the Requirements to Obtain A Bachelor's Degree in Medicine

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STATEMENT OF ORIGINALITY

I, the undersigned, hereby declare that this thesis is my own work, and all sources, both quoted and referenced, have been stated correctly.

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Therefore, I make this statement to be used as it should be.

Medan, 16 December 2021

Basrah Bee Binte Shaik Hussain

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FOREWORD

I praise Allah SWT's for His guidance. I was able to complete this thesis with the title "D-dimer and its Clinical Correlation to Multisystem Inflammatory Syndrome in Children (MIS-C) with COVID-19"

Alhamdulillah, throughout the completion of this thesis, I am fully aware that I had a great deal of guidance and aid from numerous parties during the preparation and execution of this thesis. I pray that the knowledge, patience, and fortitude gifted to me by those individuals who are involved, can be turned into good deeds in this life and the hereafter. The purpose of this paper is to fulfil one of the prerequisites in obtaining a medical degree at Universitas Muhammadiyah Sumatera Utara (UMSU).

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Lastly, I pray that Allah SWT is pleased and repays all the kindness of all those who have aided me throughout this journey. May this thesis be beneficial to the advancement of science.

Medan, 16 December 2021

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APPROVAL OF PUBLICATION
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As a member of the academic community of Universitas Muhammadiyah Sumatera Utara, I, the undersigned:

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ABSTRAK

Pendahuluan: Pengetahuan saat ini menunjukkan bahwa anak yang terinfeksi COVID-19 memiliki daya tahan yang tinggi dan presentasi dengan gejala klinis yang ringan. Namun, pada Mei 2020 MIS-C, Sindrom Peradangan Multisistem pada Anak-anak telah dilaporkan sebagai penyakit anak berbahaya yang sementara terkait dengan COVID-19. D-dimer telah terbukti terkait dengan COVID-19 yang parah dan kritis, tetapi sedikit yang diketahui tentang karakteristik klinis yang dominan dan hasil laboratorium pada anak-anak di Indonesia, khususnya Medan, Sumatera. **Tujuan:** Penelitian ini bertujuan untuk mengevaluasi D-dimer dan hubungan klinisnya dengan MIS-C dengan COVID-19 di RS Bunda Thamrin dari tahun 2020 hingga 2021. **Metode:** Penelitian ini merupakan penelitian deskriptif analitik dengan desain potong lintang (*Cross sectional*). Parameter klinis dan laboratorium dari rekam medis anak terkonfirmasi COVID-19 yang dirawat di RS Bunda Thamrin dianalisis. 154 kasus dimasukkan dalam penelitian ini. Variabel kategorik dibandingkan dengan menggunakan Uji Chi-square. **Hasil:** Sebagian besar kasus COVID-19 terjadi pada pasien anak usia > 5 tahun (64,3%) diikuti oleh anak usia < 5 tahun (35,7%). Usia rata-rata adalah 8,8 $\pm$ 5,83 tahun dengan dominasi pada pasien laki-laki (56,5%). Gejala umum yang muncul meliputi manifestasi pernapasan seperti batuk (76,0%), rinore (51,3%) dan demam (39,0%). Ada hubungan antara D-dimer dengan karakteristik klinis p=0,042 ($p<0,05$) dan D-dimer dengan hasil laboratorium p=0,000 pada CRP, neutrofil dan limfosit dan p=0,011 pada trombosit ($p<0,05$). 1 pasien diduga mengalami MIS-C di RS Bunda Thamrin Medan. **Kesimpulan:** D-dimer dapat menjadi penanda awal yang berguna untuk memprediksi manifestasi COVID-19 yang parah seperti MIS-C.

Kata kunci: MIS-C, SARS-CoV-2, COVID-19, D-dimer

ABSTRACT

Introduction: *Current knowledge indicates that children infected with COVID-19 are highly resilient and present with mild clinical symptoms. However, in May 2020 MIS-C, a Multisystem Inflammatory Syndrome in Children have been reported to be a dangerous childhood disease temporarily associated with COVID-19. D-dimer has been shown to be associated with severe and critical COVID-19, but little is known about the dominant clinical characteristics and laboratory results in Indonesian children, particularly Medan, Sumatra.* ***Objective:*** *This study aims to evaluate D-dimer and its clinical relationship to MIS-C with COVID-19 at RS Bunda Thamrin from the year 2020 to 2021.* ***Methods:*** *This research is a descriptive analytical study with a cross-sectional design. Clinical and laboratory parameters from medical records of confirmed COVID-19 children admitted to RS Bunda Thamrin were analyzed. 154 cases were included in this study. Categorical variables were compared using the Chi-square Test.* ***Results:*** *Majority of COVID-19 cases occur in pediatric patients aged > 5 years (64.3%) followed by children aged < 5 years (35.7%). The median age is 8.8 + 5.83 years with a predominance in male patients (56.5%). Common presenting symptoms include respiratory manifestations such as cough (76.0%), rhinorrhoea (51.3%) and fever (39.0%). There is an association between D-dimer and the clinical characteristics p=0.042 (p<0.05) and D-dimer with laboratory results p=0.000 in CRP, neutrophils and lymphocytes and p=0.011 in thrombocytes (p<0.05).1 patient is suspected to have MIS-C in RS Bunda Thamrin Medan.* ***Conclusion:*** *D-dimer could be an early useful marker for predicting severe COVID-19 manifestations such as MIS-C.*

Keywords: *MIS-C, SARS-CoV-2, COVID-19, D-dimer*

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
SARS-CoV 2	Severe Acute Respiratory Syndrome – 2
CDC	Centre for Disease Control
WHO	World Health Organization
IDAI	Indonesia Paediatrician Society
LMIC	Lower Middle-Income Country
KD	Kawasaki Disease
PICU	Pediatric Intensive Care Unit
ACE2	Angiotensin-Converting Enzyme 2
TMPRSS2	Transmembrane Protease Serine Protease 2
RAS	Renin Angiotensin System
DC	Dendritic Cell
PRR	Pattern Recognition Receptors
CRS	Cytokine Release Syndrome (CRS)
IL-6 AMP	IL-6 Amplifier
MAS	Macrophage Activation Syndrome (MAS)
IVIG	Intravenous Immunoglobulin
WBC	While Blood Cell Count
ALC	Absolute lymphocyte Count
ANC	Absolute neutrophil count
PLT	Platelet Count
CRP	C-reactive protein
PCT	Procalcitonin
LDH	Lactate dehydrogenase
ESR	Erythrocyte sedimentation rate
DVT	Deep Vein Thrombosis
PE	Pulmonary Embolism
DIC	Disseminated intravascular coagulation

LIST OF ATTACHMENT

CHAPTER 1
INTRODUCTION

1.1 Background

The end of 2019 challenged the world with an epidemic of a novel coronavirus (SARS-CoV-2) first observed in Wuhan, China.[1] The Chinese Center for Disease Control (CDC) reported in February 2020 that of the first 72,000 cases, only 2% were children.[2] The World Health Organisation (WHO) later declared the viral outbreak a pandemic, on March 11, 2020. And as of Aug 23, 2020 a total of almost 23 057 288 COVID-19 patients including 800 906 deaths have been confirmed by the WHO.[3]

In December 2020, the Indonesia Paediatrician Society (IDAI) reported 77 254 confirmed pediatric cases of COVID-19 and noted 542 deaths (2.7%) which is 2.5% more than the mortality rate reported in the United States (0.2%).[4] Between March 2 and August 2020 in Indonesia, five provinces contributed over 60% out of a total of 111 450 confirmed COVID-19 cases. They are, West Java, DKI Jakarta, Central Java, South Sulawesi and West Java.[3] Children made up 8.71% of the cases while the death mortality was reported to be 2.03 % for 0-5 year old, and 0.82% for 6-18 year olds. This is concerning as Indonesia comes second to India as a Lower Middle-Income Country (LMIC) that has suffered the highest number of confirmed COVID-19 cases.[5] Indonesia is also the fourth most populous country with a population of up to 274 million people.

Current knowledge indicates that children with COVID- 19 are reported to be asymptomatic or present with mild clinical symptoms such as fever, cough or gastrointestinal symptoms.[1] However, on May 14, 2020 the United States CDC released a health advisory reporting MIS-C, a systemic inflammatory syndrome with overlapping features of Kawasaki disease (KD).[6] The United Kingdom also reports similar findings where eight children with Kawasaki-like disease symptoms were admitted to the Pediatric Intensive Care Unit (PICU).[7] Although most children experience a milder course of infection, there is a concern for an inflammatory cascade in pediatric patients.

In Bandung, RSUP Hassan Sadikin reported a fatal course of MIS-C coinfected with dengue.[7] While in Jakarta, RS Dr. Cipto Mangunkusumo reported one patient meeting the criteria of MIS-C.[8] This warrants the need for more detailed analysis of the clinical presentation and outcome of COVID-19 in pediatric patients, as little is known about the prevalence and characteristics of fatal COVID-19 cases in Indonesia.

Laboratory findings of pediatric patients with COVID-19, showed that increased D-dimer, fibrinogen, procalcitonin, C-reactive protein, ferritin levels and low oxygen saturation were associated with severe disease and mortality.[9] Recent literature suggests that D-dimer can be a reliable predictor of thrombotic state identification and COVID-19 outcome. Rostami *et al*., suggests that examining coagulation tests from the start of the diagnosis can be useful for monitoring the disease and delivering effective management.[10]

From the background above, the researcher wants to explore the relationship between D-dimer and clinical manifestation of Multisystemic Inflammatory Syndrome in Children with COVID-19 at RS Bunda Thamrin Medan from the year 2020 to 2021.

1.2 Research Problem

The research problem formulated in this study is, is there a relationship between D-dimer and clinical manifestation of Multisystemic Inflammatory Syndrome in Children with COVID-19 in RS Bunda Thamrin from the year 2020 to 2021?

1.3 Hypothesis

There is no association between D-dimer and clinical manifestation of Multisystemic Inflammatory Syndrome in Children with COVID-19 in RS Bunda Thamrin from the year 2020 to 2021.

1.4 Aim of Study

1.4.1 General Aim

This study aims to evaluate D-dimer and its clinical relationship to Multisystem Inflammatory Syndrome in Children with COVID-19 at RS Bunda Thamrin from the year 2020 to 2021.

1.4.2 Specific Aim

a. To assess the demographic data (age and gender) in pediatric patients with COVID-19 at RS Bunda Thamrin Medan in the year 2020 to 2021.
b. To evaluate other clinical presentation of COVID-19 in pediatric patients with COVID-19 at RS Bunda Thamrin Medan in the year 2020 to 2021.
c. To evaluate other laboratory markers (CRP, neutrophil, lymphocyte, and thrombocyte) in pediatric patients with COVID-19 cases at RS Bunda Thamrin Medan in the year 2020 to 2021.

1.5 Benefit of Study

1.5.1 For Researcher

a. To assess the significance of D-dimer in screening, diagnosing, and managing MIS-C.
b. To gain an insight into the role of other laboratory tests in screening, diagnosing, and managing MIS-C.
c. To apply statistical knowledge into research to develop evidence-based practice in the field of pediatric medicine.

1.5.2 For Subject / Reader

a. To add insight and increase awareness of the reader, on D-dimer and its significance in MIS-C.

1.5.3 For Institution

a. To add input onto the topic of D-dimer and MIS-C in pediatric medicine and act as additional reference material in further studies.

CHAPTER 2
LITERATURE REVIEW

2.1 COVID-19

2.1.1 Definition

COVID-19 is a disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses of ~30 kb.[11] Coronaviruses have four subfamilies. They are alpha, beta, gamma and delta coronaviruses based on their genomic structures. Alpha and beta coronaviruses only infect mammals. COVID-19 is closely related to beta coronaviruses which is also known as bat-coronavirus.[12] It is similar to outbreaks of SARS-CoV in 2002-2003 and Middle Respiratory Syndrome (MERS) Coronavirus in 2021.

2.1.2 Epidemiology

Even though children have a lower prevalence of COVID-19 than adults, the number of pediatric cases in Indonesia has been quickly growing.[13] In a study by Aisyah *et.al.*, the five provinces with the highest number of COVID-19 confirmed cases that contributed over 60% of national cases, include West Java, DKI Jakarta, Central Java, South Sulawesi and West Java.[3] Between March 2 and August 2020, out of a total of 111 450 confirmed COVID-19 cases in Indonesia, 8.71% were children. The death mortality was reported to be 2.03 % for 0-5year old, 0.82% for 6-18year olds. This was higher than the 0-0.2% mortality rate in USA and the Indonesian Pediatrician Society (IDAI) who reported 0.9% of death among children aged 0-5 years and 1.8% of death among children aged 6-18 years.[4]

Table 2.1 National Demographic of COVID-19 in Indonesia[3]

Characteristics	Confirmed		Recovered		Death	
	(n) / %		(n) / %		(n) / %	
0–5year old	2,507	2.25	1 723	68.73	51	2.03
6-18year old	7,197	6.46	5 169	71.82	59	0.82

2.1.3 Etiology

COVID-19 is caused by the novel coronavirus SARC-CoV2. Its genetic sequence was found to be more than 80% identical to SARS-CoV and 50% similar to MERS. The virion's diameter ranges between 50 to 200 nanometres. Spike (S) protein, envelope I protein, membrane (M) protein, and nucleocapsid (N) protein are the four known structural proteins. The S protein has three segments on the envelope that form a crown-like shape, which is where the family name comes from: corona which is Latin for crown.[12]

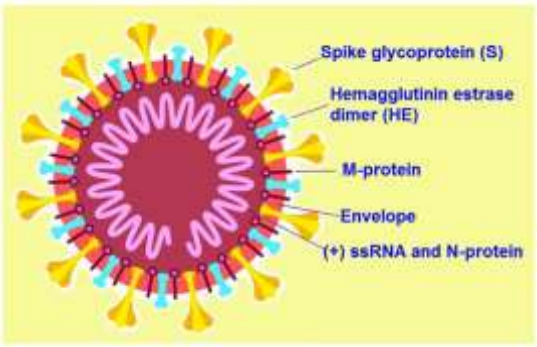

Image 1. Typical Structure of SARS-CoV2[12]

2.1.4 Pathogenesis

Attachment, penetration, biosynthesis, maturity, and release are the five phases in a virus's life cycle within the host. According to research, SAR-Cov-2 enters the body through the binding of the Viral S protein. This S protein has two functional subunits: an N-terminal (S1) domain for receptor binding and a C-terminal (S2) domain for viral-cell membrane fusion. The functional receptor for SARS-Cov-2 has been identified as human Angiotensin-Converting Enzyme 2 (ACE2) on epithelial cells. Epithelial cells that express ACE2 make up one-third of lung cells. It is a Type I transmembrane glycoprotein found in the mucosal epithelium of the nose, mouth, and lungs. It's also found in the endothelial cells of blood vessels, heart, liver, renal tubules, and gastrointestinal system among other cells and tissues.[14]

Following SARS-CoV-2 attachment to the host protein, cellular proteases such as Transmembrane Protease Serine Protease 2 (TMPRSS2), cathepsin L, and furin cleave the S protein to facilitate viral entry into the respiratory tract via endocytosis. SARS-CoV uncoats itself, releasing viral contents inside the host cell, viral RNA enters the nucleus for replication, and new viruses get released from the cell. This virus then proceeds to travel down the airway and into the lungs' alveolar epithelial cells.

In the Renin Angiotensin System (RAS), ACE2 acts as a negative regulator of ACE. ACE2 converts Angiotensinogen II to Angiotensinogen (1-7). Angiotensinogen (1-7) promotes vasodilation and has anti-inflammatory properties, unlike Angiotensinogen II, which induces vasoconstriction and inflammation. When SARC-CoV-2 binds to ACE2 receptors, the enzyme ACE2 is unable to carry out its usual activity. Resulting in increased local Angiotensinogen II that causes inflammation, damages the lining of blood vessels, and cause tissue damage.[12]

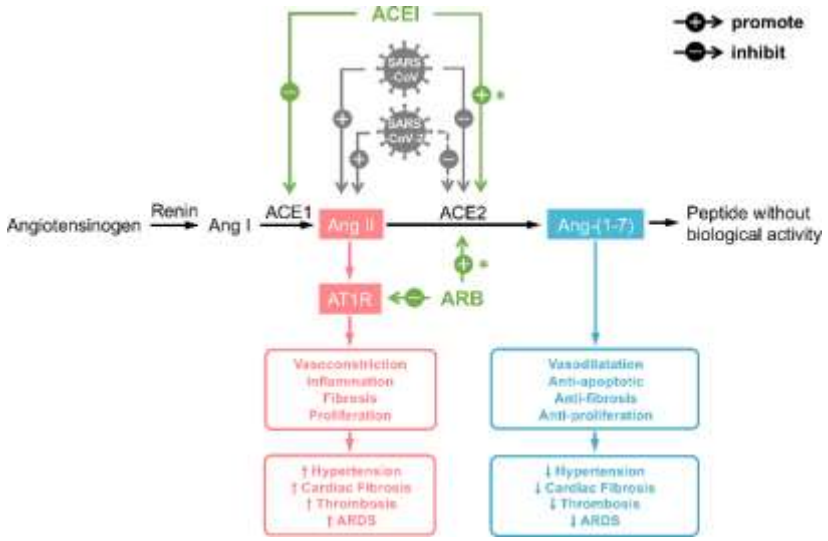

Image 2. Pathogenesis of COVID-19[15]

2.1.5 Host Response

Clinico-immunological progression suggests that COVID-19 can be divided into 3 phases:

a. Phase 1

This phase is known as the first immune defense-based protective phase.[16] Marked by flu-like illness with high viral load. During the first week of symptoms, hight titres of SARS-CoV 2 can be found in the nasopharyngeal and endotracheal tract. Patients in this stage have mild symptoms because of the immune system's attempt to eradicate the virus by inflammation. This process is mediated by the Innate immunity, which includes epithelial cells, alveolar macrophages, and dendritic cells (DC). When viral antigens engage toll-like receptors as pattern recognition receptors (PRR) in those cells, they generate inflammatory cytokines and chemokines, which attract additional immune cells, resulting in extensive lung inflammation.

Additionally, the virus infected lung epithelial cells generate IL-8, a neutrophil chemoattractant. The virus-infected apoptotic cells are phagocytized by DCs and macrophages and then transported to the draining lymph nodes, where they deliver viral antigens to T cells. B cells are activated by CD4 + T cells, which results in the generation of virus-specific antibodies. CD8 + T cells, on the other hand, destroy virally infected cells.[11] Hence, vistal airway damage is common in early lung injury.

b. Phase 2

Phase 2 is known as the second inflammation-driven damaging phase,[16] marked by decreasing viral titres but hyperinflammatory response that leads to lung and end-organ injury. High levels of IL-2, IL-6, IL-7, IL-10, TNF-2 α, G-CSF, MCP-1, and MIP-1 α are seen in hospitalized individuals with severe COVID-19. This suggests that severe COVID-19 is a Cytokine Release Syndrome (CRS), a condition brought on by cytokine storm. Infected patients with SARS-CoV in Phase 2 have severe symptoms that can lead to respiratory failure. This occurs approximately 4-7 days since the onset of symptoms occur.

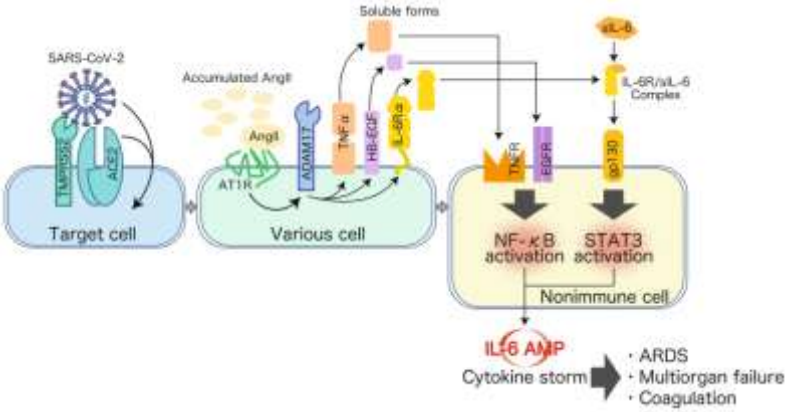

Image 3. Hyperinflammatory Pathogenesis of COVID-19[17]

Most notably, IL-6 in the blood is observed to be greater in non-survivors than in survivors, which can inhibit normal T cell activation and trigger the activation of NF-kB pathway. The NF-kB pathway can also be activated by increased blood levels of free Angiotensinogen II owing to reduced ACE2-mediated degradation when SARS-CoV-2 occupies ACE2. Known as the anti-inflammatory circuit, the hyperactivation of NF-kB in IL-6 Amplifier (IL-6 AMP) may result in fatal symptoms such as ARDS, severe pneumonia, multiorgan failure, and coagulation.[17] Patients also exhibit multiorgan failure with coagulation abnormalities evidenced by low platelet count and an increased D-dimer which is associated with poor prognosis. The presence of thrombosis and pulmonary embolism in the lungs, lower limbs, hands, brain, heart, liver, and kidneys also indicates significant endothelial damage.

Among severe COVID-19 cases in children, a phenomenon known as MIS-C develops during the late-post infectious phase, comparable to what is described in adults, as cytokine storm.[18] A hyperimmune response occurs for unknown causes as evidenced by the fact that children with MIS-C have higher SARS-CoV 2 spike IgG titre than those with severe COVID-19, suggesting that MIS-C is related to immune dysregulation that appears after an acute infection. Other possibilities include Macrophage Activation Syndrome (MAS) and CRS.[19]

c. Phase 3

This phase is known as the recovery phase. Most children recover following initial short flu-like illness without progressing to critical phase.[20] In a study by Dhochak *et.al*., it is hypothesized that children have a milder and faster recovery than adults because adult lungs (alveolar type II cells) gradually have impaired regenerative potential while children have a good regenerative capacity.[20] Other hypothesis include the possibility that epithelial cells in children, may express fewer or differently shaped ACE2 proteins leading to lower morbidity rate.[21] However, increasing studies are noting that children with symptomatic or asymptomatic COVID-19 are experiencing long-term effects many months after the initial infection termed "Long COVID" syndrome similar to adults. Symptoms include fatigue, muscle and joint pain, headache, dyspnoea, heart palpitations, and gastrointestinal complaints but research has been scarce.[22]

2.1.6 Diagnosis of COVID-19 and MIS-C

2.1.6.1 Clinical Manifestation of COVID-19 and MIC-S

When compared to adults, children with COVID-19 have been found to be asymptomatic or have mild clinical symptoms. Fever, cough, rhinorrhoea, sore throat, sputum production, diarrhea, and vomiting are all common mild symptoms.[23] Children under 7 years old present with fever, diarrhea and vomiting whereas cough was more common in older children.[6] Dyspnea and cyanosis are common in severe pediatric cases, which can progress to ARDS, septic shock, refractory metabolic acidosis and coagulation dysfunction.[24]

When it comes to severe cases, clinicians originally struggled to distinguish between MIS-C and KD. Patients with MIS-C, like those with KD, have a prolonged fever and mucocutaneous symptoms and elevated inflammatory markers.[25] MIS-C, unlike KD, affects older children ($\geq$5 years old), whereas KD affects youngsters as young as 1.5 years old. The main clinical classification for diagnosis of MIS-C is summarized in Table 2.1.

Table 2.1. Main Clinical Manifestation for MIS-C[18]

Organ System	**Reported Prevalence**	**Main Symptoms**
Gastrointestinal	82-87	Diarrhea, vomiting, abdominal pain
Mucocutaneous	69-73	Skin rash, conjunctivitis
Cardiovascular	71-100	Myocardial dysfunction, vasogenic shock, myocardial infarction, coronary artery dilation or aneurysm, arrhythmia
Respiratory	14-47	Upper respiratory tract infection, shortness of breath, pneumonia, ARDS
Neurologic	22-55	Headache, dysarthria, dysphagia, meningism, cerebellar ataxia, global proximal muscle weakness, reduced reflexes
Renal	3-38	Acute insufficiency

2.1.6.2 Case Definition of COVID-19 and MIS-C

According to *Panduan Tatalaksana COVID-19* (PDPI, PERKI, PAPDI, PERDATIN, IDAI) or Panduan 5OP (*Lima Organisasi Profesi*).[26] A suspected case is defined as a case that meets: one clinical criteria and one epidemiological criteria summarized in Table 2.2. The diagnostic criterion for MIS-C by WHO and CDC is summarized in Table 2.3.

Table 2.2. Case Definition of COVID-19[26]

Clinical Criteria:

1. Acute fever (≥ 380 C)/history of fever* and cough OR
2. There are 3 or more of the following acute symptoms/signs: fever/history of fever*, cough, fatigue, headache, myalgia, sore throat, coryza/cold/ nasal congestion*, shortness of breath, anorexia/nausea/vomiting*, diarrhea, loss of consciousness

Epidemiological Criteria:

1. In the last 14 days before the onset of symptoms, patient has a history of living or working in a high-risk place of transmission OR
2. In the last 14 days before the onset of symptoms, patient had a history of living or traveling in the country/region Indonesia reported having local transmission OR
3. In the last 14 days prior to symptoms, patient has a history of working in health service facilities, both in providing services medical, and non-monitoring of cases and contacts OR
4. Someone with Severe Acute Respiratory Illness OR
5. 5. A person who is asymptomatic who does not meet the epidemiological criteria with a positive SARS CoV-2 rapid antigen result.

A confirmed case is defined as a case that meets any of the following criteria:

a. A person with a positive RT-PCR result
b. A person with a positive SARS-CoV-2 rapid antigen result AND
   meet the criteria for the definition of a probable case OR
   suspect case (criteria A or B)
c. A person without symptoms (asymptomatic) with rapid results SARS-CoV-2 antigen positive AND have a history of close contact with a probable case OR confirmed.
d. Confirmation cases are divided into 2:
    a. Confirmed cases with symptoms (symptomatic)
    b. Confirmed cases asymptomatic (asymptomatic)

Table 2.3. WHO and CDC diagnostic criteria for MIS-C [18]

Characteristic	**WHO** **All 6 criteria must be met**	**CDC** **All 4 criteria must be met**
1. Age	< 19 years	< 21 years
2. Fever	≥ 3 days	> 38 °C (100.4 °F) for 24 h
3. Inflammation	Increased levels of CRP, ESR, procalcitonin	At least one of these laboratory results: increased levels of CRP, erythrocyte sedimentation, procalcitonin IL-6, fibrinogen, D-dimer, ferritin, LDH, neutrophils; reduced albumin and low lymphocytes
4. SARS-CoV 2 infection	SARS-CoV-2 positivity at swab testing or serology, otherwise, exposure to a probable COVID-19 case	SARS-CoV-2 positivity at swab testing or serology, otherwise exposure to a probable COVID-19 case
5. Exclusion of other Diagnosis	No other diagnosis	-
6. Organ Dysfunction	At least two of the following organs in failure: circulation, heart, coagulation, gastrointestinal, skin, respiratory	-

2.1.6.3 Classification of COVID-19 and MIS-C

The classification of COVID-19 according to *Panduan 5OP* is summarized in Table 2.4.[26] Clinicians have also created a spectrum of severity for diagnosis, to categorize the variation in presentation of MIS-C summarized in Table 2.5.

Table 2.4. Clinical Classification of COVID-19 [26]

No.	Clinical Classification
1.	**Asymptomatic** Testing positive for SARS-CoV-2, but without clinical symptoms or abnormal chest imaging findings.
2.	**Mild** With only fever, cough, pharyngeal pain, nasal congestion, fatigue, headache, myalgia, or discomfort, etc., and without signs of pneumonia by chest imaging or sepsis.
3.	**Moderate** With or without fever, with respiratory symptoms such as cough; and chest imaging indicating changes of viral pneumonia, but not reaching the criteria of severe pneumonia.
4.	**Severe** a. Tachypnea: ≥60 times/min (<2 months), ≥50 times/ min (2–12 months), ≥40 times/min (1–5 years), ≥30 times/min (>5 years) (after ruling out the effects of fever and crying) b. Oxygen saturation < 93% under a resting state c. Dyspnea: assisted breathing (moans, nasal flaring, and three concave sign), cyanosis, intermittent apnea d. Disturbance of consciousness: somnolence, coma, or convulsion e. Food refusal or feeding difficulty, with signs of dehydration. f. Pulmonary high-resolution CT (HRCT) examination showing bilateral or multi-lobe infiltrates, rapid progression of disease in a short period or with pleural effusion.
5.	**Critical** a. Patient with Acute Respiratory Distress Syndrome (ARDS) b. Sepsis AND Septic shock

Table 2.5. Current Subtypes of MIS-C[19]

Subtype	**Patient Demographics**	**Symptoms / Signs**	**Serology Test**
MIS-C without KD	No specific demographic data identified	a. Cardiovascular & gastrointestinal involvement b. More likely to have shock, cardiac dysfunction. c. Markedly elevated CRP and ferritin	Almost all patients in this group had a positive serology (with or without positive PCR test)
MIS-C Overlapping with Severe Acute COVID-19	a. Higher mortality rate than other two subgroups b. Age of patients tends to be older than those with KD like features. c. These patients tend to have higher comorbidities	Respiratory involvement (Cough, SOB, Pneumonia, ARDS)	Most patients had a positive PCR test without seropositivity

Continuation of Table 2.5

MIC-S Overlapping with KD	Children were younger in this group compared to the other two groups	a. Rash and mucocutaneous involvement b. Less common to have shock or myocardial dysfunction	a. Approximately 2/3 of patients had positive SARS-CoV-2 serology and a negative PCR test. b. Approximately 1/3 of patients were positive for both PCR test and serology

2.1.6.4 Diagnostic Evaluation of MIS-C

The American College of Rheumatology (ACR) published a clinical guideline for MIS-C associated with SARS-CoV-2 and hyperinflammation in paediatrics with COVID-19. The diagnostic evaluation of MIS-C consists of two tiers; (1) screening and (2) evaluation to reduce over testing and prevent unnecessary use of resources;[27]

a. Tier 1 diagnostic approach

This tier is recommended in patients without life-threatening manifestations and proceed to Tier 2 only if laboratory results from Tier 1 is concerning. It includes laboratory studies that are easily obtained in most clinical facilities such as, complete blood count with differential, complete metabolic panel, erythrocyte sedimentation rate (ESR), CRP and testing for SARS-CoV-2 by PCR or serology. To enter Tier 2 of testing, patients should have elevated ESR and/or CRP and a least 1 other suggestive laboratory feature, lymphopenia, neutrophilia, thrombocytopenia, hyponatremia, or hypoalbuminemia.

b. Tier 2 diagnostic approach

Tier 2 encompasses more complex testing for children with abnormal vital signs, physical examination findings that are concerning and significantly elevated levels of inflammation markers or cardiac involvement requiring hospitalization. Electrocardiogram and echocardiogram are done in this stage. Further assessment for systemic inflammation which includes D-dimer, ferritin, procalcitonin, Lactate dehydrogenase (LDH) and cytokine panels should be completed.

2.1.7 Management

Treatment for mild COVID-19 instances in children includes both general and supportive care. Isolation (for a maximum of 10 days after the beginning of symptoms and 3 days without symptoms), bed rest, and appropriate calorie, water, and vitamin consumption are all examples of supportive treatment. Vital signs, electrolyte balance, and oxygen saturation are also monitored. Routine blood, urine, and serial chest imaging should be provided when facilities are available. When a patient's temperature rises above 38.5°C, antipyretic medicines are prescribed. Non-invasive oxygen treatment, such as a high-flow nasal cannula and continuous positive airway pressure are also given for severe and critical cases in pediatric patients who develop symptoms of ARDS.

Antimicrobials like antibiotics should be administered only in individuals who have a secondary bacterial infection or coinfection. Empiric wide spectrum antibiotics, such as Azithromycin and Levofloxacin, might be administered based on clinical suspicion. However, collecting specimens to confirm the pathogenic etiology is preferable. According to studies, there are no effective antiviral medicines available for children with COVID-19. Antivirals should not be used for treatment or prophylaxis in COVID-19, according to the current WHO interim guideline, unless clinical trials are conducted. According to other research, it might be evaluated on a case-by-case basis. Oseltamivir, Favipiravir, and Remdesivir are examples of antivirals administered to patients with COVID-19.[26]

Immune modulating drugs, such as corticosteroids, are crucial in mediating immune mediated lung damage in the critical phase. Corticosteroids like Dexamethasone suppress lung inflammation, reduce immunological response,

and increase pathogen clearance, when a Cytokine Storm occurs. In other cases, they are also given in children with COVID-19 who has exacerbation of asthma, septic shock, ARDS, toxic symptoms, encephalitis or hemophagocytic syndrome. Other treatments include Intravenous Immunoglobulin (IVIG) and plasmapheresis, which seek to neutralize inflammatory cytokines, strengthen endothelium membranes, and reduce the state of inflammation when cytokine storm has occurred.[28]

2.2 Laboratory Findings in COVID-19 progression

COVID-19 relies heavily on laboratory tests. It is used to detect infected individuals who may be asymptomatic, to objectively measure disease severity, and to make decisions as well as plan for patient care. Tests requested for COVID-19 are summarized in Table 2.6.

Table 2.6 Abnormal Biomarkers in COVID-19 with severe systemic disease[29]

Haematological Biomarkers		Biochemical Biomarkers		Coagulation Biomarkers	Inflammatory Biomarkers	Potential New Biomarkers	
↑	↓	↑	↓	↑	↑	↑	↓
WBC Count	Lymphocyte Count	ALT	Albumin	PT	ESR	Hcy	Ang (1-7)
Neutrophil Count	Platelet Count	AST		D-dimer	CRP	Ang II	Ang (1-9)
	Eosinophil Count	Total bilirubin			Serum ferritin	NLR	Alamandine
	T cell count	BUN			PCT	MLR	
	B cell count	CL			IL-2		
	NK cell count	LDH			IL-6		
		Myoglobin			1L-8		
		CK-MB			IL-10		
		Cardiac					
		Troponin I					
		Creatinine					

a. Hematologic biomarkers

Hematologic tests used to stratify COVID-19 include WBC, ALC, ANC, neutrophil-lymphocyte ratio (NLR), platelet count, eosinophil count and haemoglobin. Severe cases of COVID-19 tend to have lower ALC and PLT, higher ANC and higher NLRs as well as increased WBC.[30]

b. Biochemical biomarkers

Biochemical tests include LDH, cardiac (CK, cardiac troponin), liver (ALT, AST) and renal function (BUN, creatinine) markers.[29] Recent clinical practice suggests that the identifying IL-6, LDH, and transaminases in addition to

routine laboratory tests, is useful for identifying high risk patients and those who might potentially benefit from anti-IL-6 immunotherapy.

c. Inflammatory biomarkers

Inflammatory biomarkers include ESR, CRP, ferritin, PCT and Interleukins. Increased ESR and CRP has been associated with disease development and early predictor for severe COVID-19. IL-6 and ferritin are reported to be significantly increased in non-survivors vs. survivors. PCT also known as pro-peptide of calcitonin is a mediator of inflammation, produced by C-cells of the thyroid glands. In severe infection, PCT may be excessively synthesized as a result of endotoxins and/or cytokines by extra-thyroid tissues such as liver, pancreas, kidney, lung, intestine and within leukocytes. PCT values are more discriminative than WBC and CRP in distinguishing a bacterial infection from other inflammatory process. PCT value remains within reference ranges or moderately increased, in systemic inflammatory response non-infectious stimuli or viral infection such as non-complicated COVID-19. In pediatric cases, an elevated PCT has been reported to reflect bacterial co-infection in the lower respiratory tract.[29]

d. Coagulation biomarkers

Abnormal coagulation markers are associated with poor prognosis Specifically D-dimer is commonly elevated in non-survivor patients. It is a unique marker of fibrin degeneration.[13] Presence of D-dimer in blood shows that blood clotting has started. It is used as a marker in diagnosing Deep vein thrombosis (DVT), pulmonary embolism (PE), and disseminated intravascular coagulation (DIC). D-dimer values of 1.5 g/ml are used to predict venous thromboembolism. While increased D-dimer levels (3-4 times) is associated with high mortality as it indicates activation of blood clotting factors because of sepsis, cytokine storm and impending multiple organ failure.[31]

e. Physiology of D-dimer formation

After a clot has formed, the fibrinolytic system breaks down the crossed-linked fibrin mesh. Fibrin degradation product (FDP) and D-dimer are two clot breakdown products produced by this mechanism. Three enzymes are involved in this process: thrombin, factor XIIIa, and plasmin. Thrombin converts fibrinogen

to fibrin in secondary hemostasis. Factor XIII (fibrin stabilizing factor) is activated into factor XIIIa when thrombin binds to fibrin. Its job is to covalently crosslink fibrin forming a fibrin meshwork that is stable. Plasmin cleaves stable fibrin meshwork at locations (bonds between lysine and glutamine residues) during fibrinolysis, resulting in FDPs. FDPs come in a wide range of molecular weights, including D-dimer and fragment E complex.[10]

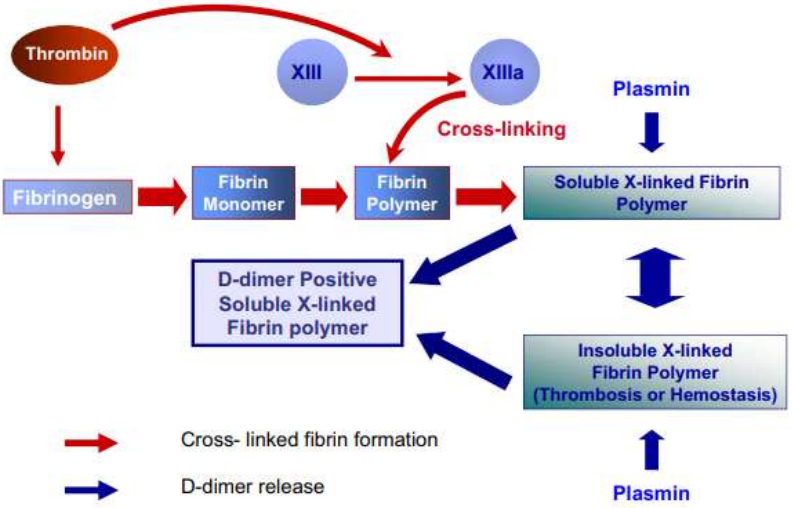

Image 4. D-dimer formation[13]

In conclusion, D-dimer monitoring will be an important tool in clinical practice for detecting severe COVID-19 cases as well as MIS-C in pediatric patients. According to studies, examining coagulation tests from the beginning of the diagnosis can be helpful to guide therapy and evaluate prognosis.[32] This is why, the author wants to investigate D-dimer's relationship with clinical manifestation of COVID-19 in pediatric patients.

2.3 Theoretical Framework

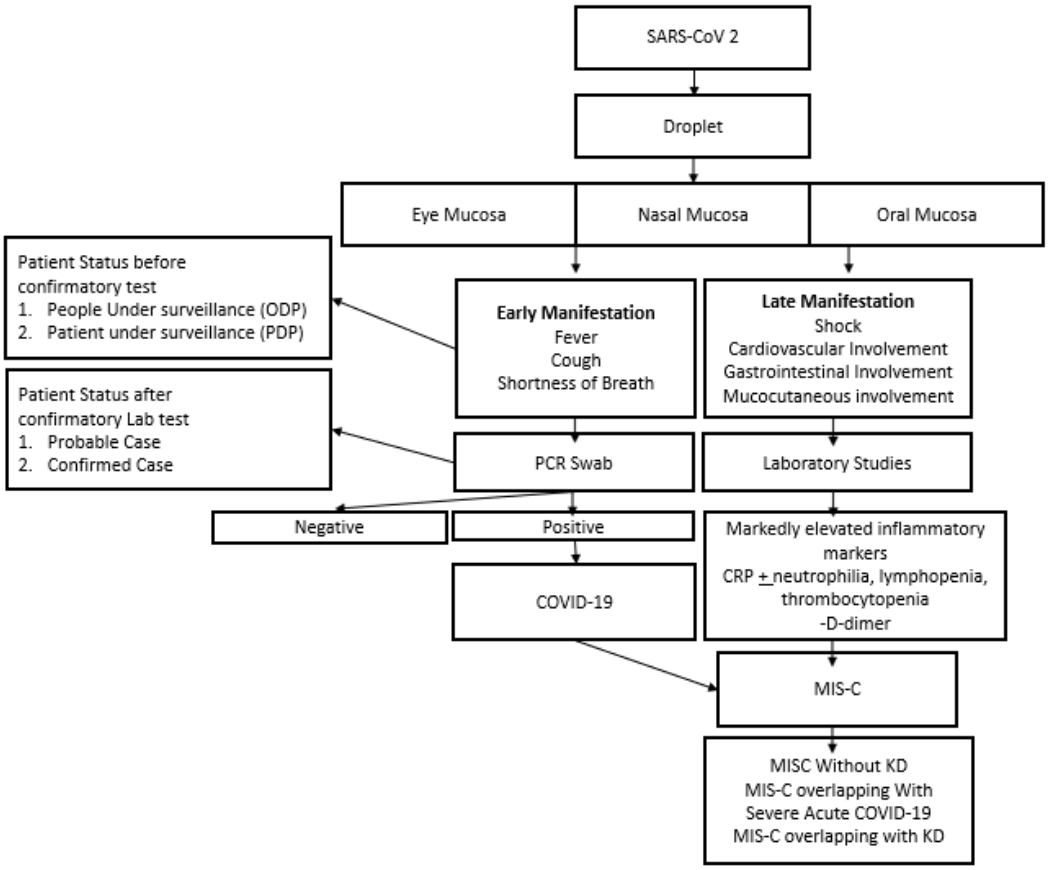

Image 5. Theoretical Framework

2.4 Conceptual Framework

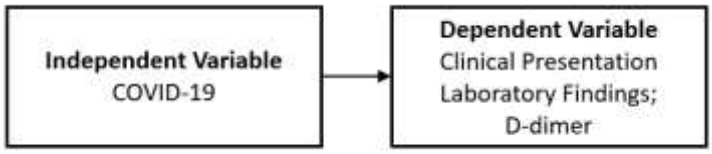

Image 6. Conceptual Framework

CHAPTER 3
METHODOLOGY

3.1 Operational Definition

Table 3.1 Operational Definition

Variable	Operational Definition	Instrument	Results	Scale
Dependent Clinical Manifestation	Display or disclosure of characteristic signs or symptoms of an illness.	Medical Records	1. Respiratory: Cough, SOB, Pneumonia 2. Gastrointestinal: Diarrhea, Vomiting, Abdominal pain 3. Mucocutaneous: Skin rash, Conjunctivitis 4. Cardiovascular: Myocardial dysfunction, Vasogenic shock, Myocardial infarction, Coronary artery dilation or aneurysm, Arrhythmia 4. Neurological: Headache, altered mental status, seizures	Nominal

Continuation of Table 3.1

Dependent Laboratory Examination, D-dimer	D-dimer is a fibrin degradation product (FDP) a small protein fragment present in blood after a blood clot has been degraded by the process, fibrinolysis	Medical Records	1.Normal < 500 ng/dL 2.Elevated > 500 ng/dL	Nominal
Independent COVID-19	Disease caused by SARS-CoV2 tested by swab PCR or serology	Medical Records	1.Positive 2.Negative	Nominal
MIS-C	Multisystemic Inflammatory Syndrome in children diagnosed according to CDC criteria	Medical Records	1. MIS-C without KD 2. MIS-C Overlapping with Severe Acute COVID-19 3. MIS-C Overlapping with KD	Nominal
Age	The length of time that a person has lived, or a thing has existed	Medical Record	1.< 5 years old 2.> 5 years old	Nominal
Sex	The category in which humans are divided into based on their reproductive functions	Medical Record	1.Male 2.Female	Nominal

Continuation of Table 3.1

Laboratory Examination, Neutrophil, Lymphocyte, CRP, Thrombocyte	Neutrophil, Lymphocyte, and platelet count is a haematological marker. While CRP is an inflammatory marker used to objectively measure disease severity	Medical Records	1. Normal < 5 Years: Neutrophil: 25-60% Lymphocyte: 25-50% Thrombocyte: 181,000-521,000 /uL > 5 Years: Neutrophil: 50-70% Lymphocyte:25-50% Thrombocyte: 181,000-521,000 / uL CRP: <5 mg/L 2. Elevated / Reduced	Nominal

3.2 Research Design

This research is a descriptive analytical study with a cross-sectional design where data is only collected once to assess D-dimer levels and its relationship to clinical manifestation of pediatric patients with COVID-19 in RS Bunda Thamrin Medan.

3.3 Time and Place

3.3.1 Time of Study

This study will be done carried out from May 2021 to Dec 2021

Table 3.2 Timeline

Activity	Month							
	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Title Submission								
Literature Study								
Proposal preparation								
Proposal Seminar								
Data collection								

3.3.2 Place of Study

This study will be done in RS Bunda Thamrin, Medan

3.4 Research Population and Sample

3.4.1 Population

The population of this study will be children (1 month – 18 years) who were diagnosed with Covid-19 in RS Bunda Thamrin Medan from April 2020 to March 2021.

3.4.2 Sample

The sample of this study involves paediatric patients (<5 years old) diagnosed with COVID-19 in RS Bunda Thamrin that fulfils the inclusion criteria throughout the study period from April 2020 to March 2021.

Below, is the Minimum sample size formula, calculated using the Slovin's formula:

a. For children <5 years old:

$$n = \frac{Z^2.p.q}{d^2} = \frac{Z^2.p.(1-p)}{d^2}$$

$$n = \frac{2^2.0{,}025\ .0{,}898}{0{,}05^2}$$

$$n = \frac{0{,}089}{0{,}0025} = 35{,}92 \approx 36\ sample$$

b. For children > 5 years old:

$$n = \frac{Z^2.p.q}{d^2} = \frac{Z^2.p.(1-p)}{d^2}$$

$$n = \frac{2^2.0{,}065\ .0{,}935}{0{,}05^2}$$

$$n = \frac{0{,}2431}{0{,}0025} = 97.24 \approx 98\ sample$$

Explanation:

n= Minimum number of samples required

Z= Degree of trust

p= Proportion of children affected by COVID-19

q= 1-p

d= Limit error or absolute precision

From the data above, the minimum sample size calculated is 36 for children < 5 years and 98 for children >5 years old.

The sample criteria used in this study are:

a. Inclusion Criteria

1. Pediatric patients aged 1 month – 18 years where the child has been diagnosed with COVID-19 and is being treated in RS Bunda Thamrin Medan

2. Pediatric patients aged 1 month – 18 years confirmed to have COVID-19 by PCR swab test

3. Pediatric patients who had undergone laboratory examinations, including D-dimer

b. Exclusion Criteria

1. Pediatric patients aged 1-18 years with incomplete medical record

3.5 Data collection Technique

Data collection will be carried out using secondary data obtained from the results of medical records in RS Bunda Thamrin Medan, data will then be collected for data analysis. The sample will be obtained by taking data from medical records of patients who meet the inclusion criteria from RS Bunda Thamrin Medan. Data will be recorded according to the variable to be studied including comorbidities and chronic diseases present in the pediatric patient.

3.6 Data Processing and Analysis Technique

3.6.1 Data Processing

a. Editing

   Checking the name and completeness of patient identification in the medical records.

b. Coding

   Allocating a certain code or number in the data to make it easier for tabulation and analysis.

c. Data Entry

   Entering data into a computer program.

d. Cleaning

   Re-checking the data that has been entered to find out if there are any errors or not.

e. Tabulation

   To compile and present data that has been coded and totalled in the form of tables or graphs.

3.6.2 Data Analysis

In this study, data processing will be carried out with the help of a computer, using the Statistical Program for Social Science (SPSS). Data from this study will be analysed using univariate and bivariate methods.

Univariate analysis is carried out to see the general description and distribution of independent variables and dependent variables studied. This study has categoric variables which will be analysed in terms of frequency and percentage and presented in the form of tables.

Bivariate analysis of data is used to see the association between the dependent and independent variables studied. If the data is normally distributed, Chi-Square (X^2) test will be used. If the data is not normally distributed, Fisher test will be used. Results will be considered significant when $p<0.05$.[33]

3.7 Research Flow

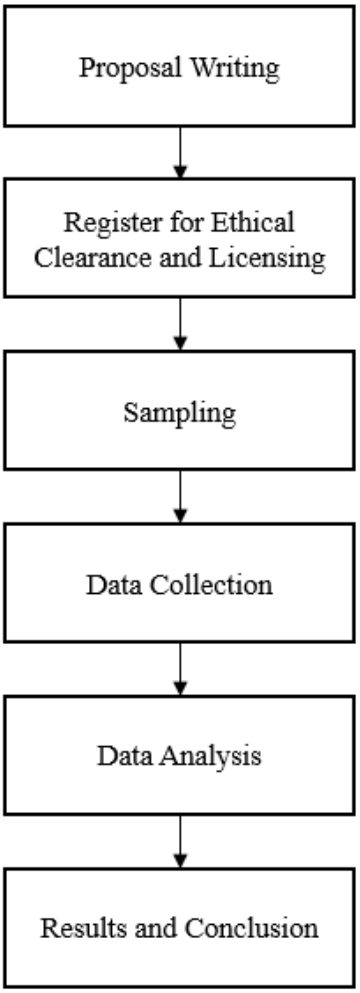

Image 7. Research flow

CHAPTER 4

RESULT AND DISCUSSION

4.1 Research Result

4.1.1 Univariate Analysis

This research was carried out in RS Bunda Thamrin, Medan, from May to December 2021. There were 154 patients in this study's sample. Medical records of patients who met the inclusion criteria were used to collect data. The study was carried out after obtaining an approval from the Ethics Commission with the Number: 654/KEPK/FKUMSU/ 2021.

4.1.1.1 Demographic Data of Pediatric Patients with COVID-19 Based on Age in RS Bunda Thamrin, Medan

The following are the results of age-based demographic data on pediatric COVID-19 patients at RS Bunda Thamrin in Medan:

Table 4.1 Demographic Data of Patients Based on Age

Age Group	N	%
< 5 Years	55	35.7
> 5 Years	99	64.3
Total	**154**	**100**

Based on table 4.1, the results show that majority of COVID-19 cases occur in pediatric patients aged > 5 years with 99 individuals (64.3%) followed by children aged < 5 years with 55 individuals (35.7%).

4.1.1.2 Demographic Data of pediatric patients with COVID-19 Based on Gender in RS Bunda Thamrin, Medan

The following are the results of gender-based demographic data of pediatric COVID-19 patients at RS Bunda Thamrin in Medan:

Table 4.2 Demographic Data of Patients Based on Gender

Age Group	Male		Female	
	N	%	N	%
< 5 Years	28	18.2	27	17.5
> 5 Years	59	38.3	40	26.0
Total	**87**	**56.5**	**67**	**43.5**

According to table 4.2, the majority of pediatric patients with COVID-19 at RS Bunda Thamrin were male children with 87 individuals (56.5%) of which 59 individuals (38.3.%) were aged > 5 years and 28 individuals were aged < 5 years. COVID-19 were found in 67 female children (43.5%) of which, 40 individuals (26.0%) were aged > 5 years, and 27 individuals (17.5%) were aged < 5 years.

4.1.1.3 Distribution of Clinical Presenting Features of Pediatric Patients with COVID-19 in Bunda Thamrin, Medan

The following are the results of the distribution of presenting features of pediatric COVID-19 patients at RS Bunda Thamrin in Medan:

Table 4.3 Distribution of Presenting Features of Pediatric Patients

Clinical Presenting Features	**< 5 years old (n=55)**	**>5 years old (n=99)**	**Total (n=154)**
Age	2 ± 1.4	12.3 (5.10-18.0)	8.8 ± 5.82
Fever	42 (76.4%)	80 (80.8%)	60 (39.0%)
Duration of fever (d)	2 (1-7)	2 (1-14)	
Nausea / Vomiting	7 (13.0 %)	10 (10.1%)	17 (11.0%)
Diarrhea	18 (32.7 %)	4 (4.0%)	22 (14.3%)
Rash	0	0	0
Conjunctivitis	0	0	0
Cough	38 (69.1%)	79 (79.8%)	117 (76.0%)
Rhinorrhoea	23 (41.8%)	56 (56.6%)	79 (51.3%)
Dyspnea	1 (1.8%)	11 (11.1%)	12 (7.8%)
Anosmia	1 (1.8%)	16 (16.2%)	17 (11.0%)
Headache	1 (1.8%)	19 (19.2%)	20 (12.9%)
Duration of Symptoms before admission, (d)	3.5 (0-11)	4 (0-15)	3.84 (0-14)

Data are n (%), median ± SD or mean (min-max)

Based on the table 4.3, clinical presentation that often appear in pediatric patients with COVID-19 in patients aged < 5 years and > 5 years were fever. 42

individuals (76.4%) aged of < 5 years and 80 individuals (80.8%) aged > 5 years had fever. Cough was present in 38 individuals (69.1%) aged <5 years and 79 individuals (79.8%) aged > 5 years. Rhinorrhoea was present in 23 individuals (41.8%) aged < 5 years and 56 individuals (56.6%) aged > 5 years. Diarrhea is present in 18 individuals (32.7%) aged < 5 years and 4 individuals (4.0%) aged > 5 years. Nausea / Vomiting was present in 7 individuals (13.0%) aged < 5 years and 10 individuals (10.1%) aged > 5 years. Headache was present in 1 individual (1.8%) and 19 individuals (19.2%) aged > 5 years. Anosmia was present in 1 individual (1.8%) aged < 5 years and 16 individuals (16.2%) aged > 5 years. Dyspnea was present in 1 individual (1.8%) aged < 5 years and 11 individuals (11.1%) aged > 5 years.

4.1.1.4 Laboratory Test Result of Pediatric Patients with COVID-19 based on CRP Levels in RS Bunda Thamrin

The following are the laboratory test findings of pediatric patients with COVID-19 at RS Bunda Thamrin based on CRP levels:

Table 4.4 Laboratory Test Result of Patients based on CRP Levels

CRP	< 5 Years	> 5 Years	Total	
			N	%
Normal	49	82	131	85.1
Elevated	6	17	23	14.9

According to table 4.7, pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal CRP levels which is found in 131 individuals (85.1%) while CRP levels were elevated in 23 individuals (14.9%).

4.1.1.5 Laboratory Test Result of Pediatric Patients with COVID-19 based on Neutrophil Count in RS Bunda Thamrin

The following are the laboratory test findings of pediatric patients with COVID-19 at RS Bunda Thamrin based on Neutrophil count:

Table 4.5 Laboratory Test Result of Patients based on Neutrophil Count

Neutrophil	< 5 Years	> 5 Years	Total	
			N	%
Neutropenia	29	41	70	45.4
Normal	25	51	76	49.4
Neutrophilia	1	7	8	5.1

According to table 4.5, pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal Neutrophil count which is found in 76 individuals (49.4%) followed by Neutropenia in 70 individuals (45.5%) and Neutrophilia in 8 individuals (5.1%).

4.1.1.6 Laboratory Test Result of Pediatric Patients with COVID-19 based on Lymphocyte count in RS Bunda Thamrin

The following are the laboratory test findings of pediatric patients with COVID-19 at RS Bunda Thamrin based on Lymphocyte count:

Table 4.6 Laboratory Test Result of Patients based on Lymphocyte Count

Lymphocyte	**< 5 Years**	**> 5 Years**	**Total**	
			N	%
Lymphocytopenia	2	9	11	7.1
Normal	16	58	74	48.1
Lymphocytosis	37	32	69	44.8

According to table 4.6, pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal lymphocyte count which is found in 74 individuals (48.1%) followed by lymphocytosis in 69 individuals (44.8%) and lymphocytopenia in 11 individuals (7.1%).

4.1.1.7 Laboratory Test Result of Pediatric Patients with COVID-19 based on Thrombocyte count in RS Bunda Thamrin

The following are the laboratory test findings of pediatric patients with COVID-19 at RS Bunda Thamrin based on Thrombocyte count:

Table 4.7 Laboratory Test Result of Patients based on Thrombocyte Count

Thrombocyte	**< 5 Years**	**> 5 Years**	**Total**	
			N	%
Thrombocytopenia	5	6	11	7.1
Normal	45	92	137	89.0
Thrombocytosis	5	1	6	3.9

According to table 4.7, pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal thrombocyte count which is found in 137 individuals (89%) followed by thrombocytopenia in 11 individuals (7.1%) and thrombocytosis in 6 individuals (3.9%).

4.1.1.8 Laboratory Test Result of Pediatric Patients with COVID-19 based on D-dimer levels in RS Bunda Thamrin

The following are the laboratory test findings of pediatric patients with COVID-19 at RS Bunda Thamrin based on D-dimer:

Table 4.8 Laboratory Test Result of Patients based on D-dimer levels

D-dimer	< 5 Years	> 5 Years	Total	
			N	%
Normal	43	91	134	87
Elevated	12	8	20	13

According to table 4.8, pediatric patients at RS Bunda Thamrin with confirmed COVID-19 commonly present with normal D-dimer levels which is found in 134 individuals (87%) while D-dimer levels were elevated in 20 individuals (13%).

4.1.1.9 Distribution of MIS-C Diagnostic Evaluation based on ACR Clinical Guideline

The following are the distribution of MIS-C diagnostic evaluation of laboratory tests in pediatric patients with COVID-19 at RS Bunda Thamrin based on D-dimer:

Table 4.9 MIS-C Diagnostic Evaluation based on ACR Clinical Guideline

Laboratory Result	Age	
	< 5 years	> 5 years
Tier 1 Diagnostic Test		
Elevated CRP	6	17
Elevated CRP and Neutrophilia	0	4
Elevated CRP and Lymphopenia	0	3
Elevated CRP and Thrombocytopenia	0	2
Tier 2 Diagnostic Test		
Elevated Tier 1 diagnostic tests and D-dimer	0	2
Met CDC MIS-C diagnostic criteria	0	1

Based on table 4.9, out of 23 pediatric patients with elevated CRP levels, 9 individuals had elevation of CRP and at least one other inflammatory marker in the Tier 1 Diagnostic test based on the MIS-C Clinical Guideline by American

College of Rheumatology. Out of the 9 individuals, only 2 had elevated Tier 1 diagnostic tests and elevated D-dimer. Out of the 2 pediatric patients, only 1 individual is suspected to have MIS-C based on the CDC criteria.

4.1.2 Bivariate Analysis

4.1.2.1 Chi-square Test between D-dimer and Clinical Presentation of Pediatric Patients with COVID-19 at RS Bunda Thamrin

The following is the bivariate analysis of D-dimer and clinical presentation of pediatric patients with COVID-19 using Chi-square test:

Table 4.10 Chi-square Test between D-dimer and Clinical Presentation

Clinical Presentation	D-Dimer		p
	Normal	Elevated	
Fever	52	8	0.042
Nausea / Vomiting	17	0	
Diarrhea	21	1	
Cough	113	5	
Rhinorrhoea	79	0	
Dyspnea	10	2	
Anosmia	16	1	
Headache	17	3	

Based on the results above, the correlation analysis of D-dimer with clinical presentations of patients with COVID-19, the results were p = 0.42 (*p <0.05*), which indicates that there is a relationship between the value of D-Dimer and clinical presentation of pediatric patients with COVID-19 at RS Bunda Thamrin.

4.1.2.2 Chi-square Test between D-dimer and Laboratory Biomarkers of Pediatric Patients with COVID-19 at RS Bunda Thamrin

The following is the bivariate analysis of D-dimer and Laboratory Biomarkers of pediatric patients with COVID-19 using Chi-square test:

Table 4.11 Chi-square Test between D-dimer and Laboratory Biomarkers

Laboratory Biomarkers	D-Dimer		P Value
	Normal	Elevated	
CRP			
• Normal	131	0	0.000
• Elevated	3	20	
Neutrophil			
• Neutropenia	58	11	0.000
• Normal	75	1	
• Neutrophilia	0	8	
Lymphocyte			
• Lymphocytopenia	0	11	0.000
• Normal	74	0	
• Lymphocytosis	60	9	
Thrombocyte			
• Thrombocytopenia	0	11	0.011
• Normal	128	9	
• Thrombocytosis	6	0	

Based on the table above, the results of the correlation analysis of D-dimer and Laboratory Biomarkers; CRP, neutrophils and lymphocytes each obtained a value of p = 0.000 ($p < 0.05$), and the value of the analysis test on platelets with d-dimer obtained a value of p = 0.011 ($p<0.05$), it indicates that there is a correlation of D-dimer values to the increase and decrease of laboratory biomarker values in pediatric patients with COVID-19 at Bunda Thamrin Hospital Medan.

4.2 Discussion

Based on data obtained from medical records of pediatric patients from RS Bunda Thamrin from the period 2020-2021, 154 patients met the inclusion criteria. Data was obtained in the form of age, gender, clinical presenting features, and laboratory test results. Majority of COVID-19 cases occur in pediatric patients aged > 5 years with 99 individuals (64.3%) followed by children aged < 5 years with 55 individuals (35.7%). The median age is 8.8 $\pm$ 5.83 years. Majority of the patients were male children with 87 individuals (56.5%) of which, 59 individuals (38.3.%) were aged > 5 years and 28 individuals were aged < 5 years.

This result is in line with the findings of Hee et al., who noted that MIS-C equally affected children with a median age of 8.6 years and affected slightly more boys than girls.[34] Lawrensia et al., noted that MIS-C predominantly affects children with older age groups around 9–15 years.[35] While Hoste et al., noted a median age of at least 8.4 years with a predominance of male patients in 586/716 cohort patients. However, the author concludes that while early reports suggested that males were overrepresented, MIS-C has yet to establish a significant gender predilection.[36]

In relation to age, Dhochak et al., postulated that the expression of ACE-2 receptor which is the primary target for SARS-CoV-2, decreases with age and younger children, less frequently have risk factors such as co-morbidities, smoking, and obesity.[20] In relation to male predilection, Lipsky et al., cited a few reasons such as (1) males express more ACE2 in their lungs and heart than females. (2) Females have a stronger natural immune response because they have two X chromosomes which contains several important genes related to immunity and immune regulation such as the gene coding for Toll-like receptor 7 (TLR7) which helps control the innate immune response by recognizing single-stranded RNA of viral origin, like an RNA coronavirus and contributes to the faster clearing of SARS-CoV-2. (3) The female sex hormone estrogen may be protective as it activates the immune system.[37]

Based on the data obtained from this study, the most common presenting symptom include respiratory manifestations such as cough (76.0%), rhinorrhoea (51.3%), fever (39.0%), headache (12.0%), diarrhea (11.0%), nausea/vomiting (11%), anosmia (11%) and dyspnea (7.8%). It is worth noting however, that these are common mild symptoms of COVID-19.[23]

Whereas in MIS-C, the most common presentation is persistent fever along with gastrointestinal and mucocutaneous features.[38] The prominent difference in symptoms between MIS-C and COVID-19 was that skin rash and gastrointestinal symptoms were more common in MIS-C, whereas respiratory symptoms were more common in COVID-19.[34] Al-Qahtani et al., also mentioned that while MIS-C resembles severe COVID-19, a general rule is that respiratory manifestations such as breathlessness, coughing, increased oxygen demand and progressive lung consolidation do not occur in MIS-C.[39] Ozsurekci et al., reported that elevated CRP and conjunctivitis was 100% accurate in differentiating between severe COVID-19 and MIS-C.[39] Although 14.9% of patients in this study, was reported to have elevated CRP, no signs of conjunctivitis was reported. But the author believes that 1 patient is suspected to have MIS-C and met the CDC diagnostic criteria. It is worth noting however, that there are other diagnostic criteria for MIS-C from WHO, RCPCH as well as KDCA. Despite the definitions having common elements, they substantially differ in other criteria. For instance, in CDC's definition, laboratory tests from which abnormal results could diagnose MIS-C is much more numerous than WHO's definition. Whereas the case definition by RCPCH seems less strict in requiring evidence of multiorgan involvement and SARS-CoV-2 infection. Given the different criteria to define MIS-C, a wide spectrum of clinical signs and symptoms, there could be more than 1 children suspected to have MIS-C in this study. It is hoped that a unified terminology and diagnostic criteria would be established soon.[38]

The differences seen in the clinical presentation in this study, could be due to genetic susceptibility and geographical regions. Lee et al., from New York stated that only 5.5% of MIS-C occurs in Asian persons with majority of cases occurring among Black (34.4%), Hispanic (29.8%) and White (12.8%) children.[40]

Li et al., from South Korea postulated another reasons which include (1) different prevalence rate of COVID-19. Korea has an infection rate of around 0.07% which is lower than main European cities where infection rate reaches up to 9%. Since children's cases account for less than 2% of all cases all over the world, the association between COVID-19 and MIS-C might be found only when the prevalence rate is high.[41] In Indonesia however, infection rate of COVID-19 reaches up to 8.71% in children in March 2 and August 2020 and yet MIS-C is rarely reported.[5]

In relation to geographical reason, Kaushik et al., reported GI and conjunctival manifestations were seen most commonly in children from the United States, while rash was commonly reported in cases from India, and cardiovascular involvement was most commonly seen in studies from Europe.[34,42] In conclusion, no patients were clinically diagnosed with MIS-C in RS Bunda Thamrin. This could partly be due to the hospital being a secondary hospital where more severe cases of COVID-19 would be referred to tertiary hospital. And the lack of Tier 2 complex testing for children as recommended by the clinical guideline by The American College of Rheumatology.[27] Cardiac manifestations of MIS-C were unexplored in this study.

In terms of Laboratory features, CRP is an early marker of infection and inflammation produced by the liver.[29] It works by binding to phocholine expressed highly on the surface of cells damaged by SARS-CoV-2. It activates the classical pathway of the immune system and modulate phagocytic activity to clear microbes and damaged cells.[43] Based on this study, pediatric patients at RS Bunda Thamrin with COVID-19 most commonly present with normal CRP levels which is found in 131 individuals (85.1%) while CRP levels were elevated in 23 individuals (14.9%).

Why majority of individuals present with normal CRP levels could be explained by the fact that CRP levels rises rapidly within 6 to 8 hours, peaks in 48 hours from the disease onset and decreases when the inflammatory stages end.[43] Patients in this study could have presented to the hospital later, when CRP concentration is already decreasing. As for only a small percentage of individuals present with elevated CRP levels, Zhang et al., noted that CRP levels were only

significantly different between patients with mild or markedly elevated D-dimer levels 1-3 days after ICU admission.[44] While Poudel et al., noted that CRP showed statistical elevation among deceased cases with high D-dimer values.[45] No patients in RS Bunda Thamrin in this study was admitted to the ICU or were deceased.

Neutrophils serve as first responders to many infections. Studies suggest that neutrophils enhance antiviral defense by interacting with other immune cell populations, virus internalization and killing mechanism, cytokines release.[46] In terms of neutrophil counts, this study shows that pediatric patients at RS Bunda Thamrin commonly present with normal neutrophil count which is found in 76 individuals (49.4%) followed by neutropenia in 70 individuals (45.5%) and neutrophilia in only 8 individuals (5.1%).

Why neutropenia is found in individuals could be explained by Mank et al., who cited that there have been cases of neutropenia seen in acute COVID-19 usually related to immunosuppression. It is a common haematological finding and has a variety of etiology such as medications, malignancy, and infection but no association with SARS-CoV-2 has been clearly described in recent publications.[47] On the other hand, Liu et al., noted that ICU cases of pediatric patients with COVID-19 is more likely to present with neutrophilia due to the activation of neutrophils to generate immune response to fight COVID-19 virus which subsequently contributes to cytokine storm.[48]

The lymphocyte count has been cited to be an important parameter to directly discriminate between COVID-19 patients with and without severe disease. Although lymphopenia had been known to be a marker of severe COVID-19 disease in adults.[49] Studies show that the most common abnormalities detected in children with COVID-19 were lymphocytosis.[50] This is in line with the results of this study where pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal lymphocyte count which is found in 74 individuals (48.1%) followed by lymphocytosis in 69 individuals (44.8%) and lymphocytopenia in 11 individuals (7.1%).

The proposed mechanism was that lymphocytes express ACE2 receptors on their surface, enabling SARS-CoV-2 to directly infect lymphocytes. The

systemic increase in cytokines and inflammatory mediators hence, resulted in marked lymphocytic apoptosis. Kosmeri et al., postulated that lesser children present with lymphopenia due to their immature immune system or the less severe manifestation of COVID-19 in children.[50] On the other hand, Zhao et al., noted that lymphocytes were found to be prone to decrease continually and severely in ICU and dead patients.[51] It could be concluded that in children, age and clinical severity may have an impact of lymphocytes.

Thrombocytopenia has been associated with respiratory deterioration in children. Studies found that lung is a reservoir for resident megakaryocytes and hematopoietic progenitor cells.[48] It is often encountered in critically ill patients and those admitted to the pediatric ICU.[51] This is in line with the results of this study where pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal thrombocyte count which is found in 137 individuals (89%) followed by thrombocytopenia in 11 individuals (7.1%) and thrombocytosis in 6 individuals (3.9%).

Liu et al., postulated that thrombocytopenia could be caused by damage to the lungs. COVID-19 affects the primary site of terminal platelet production which accounts for about 50% of total platelet production. On top of that, SARS-CoV-2 also damages endothelial cells leading to abnormal coagulation, platelet activation and aggregation reducing the number of thrombocytes.[42]

In terms of Chi-square analysis, this study found that there is an association between D-dimer and clinical presentations of pediatric patients at RS Bunda Thamrin with COVID-19, with p = 0.042 ($p < 0.05$). Zhao et al., studied the association of D-dimer to 36 demographic characteristics and found that age, gender, blood pressure and dyspnea were positively correlated with D-dimer.[51] Similarly, Ozen et al., found that D-dimer values were positively correlated with age, length of stay and lung involvement.[52]

There is also an association between D-dimer and laboratory biomarkers such as CRP, neutrophils, and lymphocytes with p = 0.000 ($p < 0.05$), and thrombocytes with p = 0.011 ($p < 0.05$). It can be concluded that there is a relationship between D-Dimer values to the rise and fall of laboratory biomarker values in pediatric patients with COVID-19 at RS Bunda Thamrin. Zhao et al.,

analysed 62 laboratory tests and 32 of them were significantly associated with D-dimer; CRP p=0.01, neutrophilia p = <0.020, lymphopenia p = <0.001, thrombocytopenia p = <0.009.[51] While Ozen et al., found that D-dimer was positively correlated with fibrinogen, neutrophil count and negatively correlated with lymphocyte count.[52]

D-dimer is a specific biomarker that interacts with other coagulation molecules, inflammatory cytokines, and markers for organ/tissue injury. Studies show that D-dimer could serve as an independent predictor of fatality, severity and potentially serve as a marker for daily monitoring of thrombolytic therapy[51]. This study showed that elevated D-dimer is associated with a broad-spectrum of immune responses to SARS-CoV-2 infection, such as acute phase protein (CRP) and inflammation indicators (neutrophil, lymphocyte). These associations may support the concept that high circulating cytokines and hyperfibrinolysis may be functionally correlated.[51]

Viremia and cytokine storm syndrome causes a rise in pro-inflammatory cytokines (IL-2, IL-6, IL-8, IL-17, TNF-α) which lead to upregulation of tissue factor expression on the endothelial cells, resulting in an increased pro-coagulant state.[51] IL6 and other proinflammatory cytokines/chemokines, steroids, and miRNAs upregulate the fibrinogen synthesis up to 10-fold during the acute phase of injury and infection.[53] In COVID-19 a hypercoagulable state is followed by hyperfibrinolysis. Physiologically, hyperfibrinolytic homeostasis maintains vascular patency and normal organ function.[51] Fibrinogen is turned over to fibrin monomers by thrombin and cleaved by plasmin into FDP and D-dimers by fibrinogenolysis.

Extremely elevated D-dimer seems to be the consequence of hyperfibrinolysis predominately in the pulmonary capillaries and other organs. D-dimer can be a good marker of multi-organ damage because soluble fibrin is synthesized in the liver, bone marrow, brain, lung, and gastrointestinal epithelium. It can be distributed to plasma, interstitial fluid and platelets and lymph.[50] Patients with critical forms of the disease have additional complications including acute kidney injury, acute cardiac injury, congestive heart failure, all of which can increase the levels of D-dimer.[52]

4.3 Research Limitation

The author realizes that several limitations might have influenced the results obtained in this study.

1. A major limitation of this study is selection bias because of its retrospective nature. Only patients admitted to the hospital were included, which meant that patients with COVID-19, who were not admitted according to hospital guidelines, were not included in the study. Some otherwise eligible cases had to be excluded due to incomplete laboratory tests and medical records, specifically D-dimer on admission.
2. Since the data in this study was obtained from laboratory tests conducted in RS Bunda Thamrin, Medan with their own laboratories, kits, measurement, and normal values of laboratory results, it could cause potential measurement bias when compared with data from existing literatures.

CHAPTER 5

CONCLUSION AND SUGGESTION

5.1 Conclusion

In conclusion, Majority of COVID-19 cases in pediatric patients occur in pediatric patients aged > 5 years with a male predominance. The most common presenting symptom of COVID-19 in pediatric patients at RS Bunda Thamrin include respiratory manifestations such as cough, rhinorrhoea, fever, headache, diarrhea, nausea/vomiting, anosmia, and dyspnea. Majority of COVID-19 pediatric patients at RS Bunda Thamrin have normal CRP, neutrophil, lymphocyte, thrombocyte, and D-dimer levels indicating mild disease progression. D-dimer was associated with clinical presentations of pediatric patients with COVID-19 at RS Bunda Thamrin with p = 0.042 ($p < 0.05$) and was associated with CRP, neutrophils, lymphocytes with p value = 0.000 ($p < 0.05$), and thrombocytes, p value = 0.011 ($p < 0.05$), in pediatric patients at RS Bunda Thamrin indicating a relationship with the increase and decrease of laboratory biomarker values. D-dimer could be inter-regulated by a spectrum of clinical variables. The clinical relevance of elevated D-dimer may be multifaceted. Studies conclude that D-dimer can be used to predict severity, prognosis, and outcome of critically ill patients with COVID-19. It is hoped that D-dimer could be a useful marker for predicting severe COVID-19 in children such as MIS-C.

5.2 Suggestion

Suggestions by the author based on the results and conclusions are:

1. Further research is needed to explore cardiac manifestations of pediatric patients with COVID-19.
2. Further research is needed to analyse other laboratory tests that meets the diagnostic criteria of MIS-C.
3. Further assess the strength of the association between D-dimer and clinical manifestations of COVID-19 cases in terms of demographic, clinical presentation laboratory test results and outcome should be assessed using contingency coefficient test.

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Attachment 1. Ethical Clearance

UMSU

KOMISI ETIK PENELITIAN KESEHATAN
HEALTH RESEARCH ETHICS COMITTEE
FAKULTAS KEDOKTERAN UNIVERSITAS MUHAMMADIYAH SUMATERA UTARA
FACULTY OF MEDICINE UNIVERSITY OF MUHAMMADIYAH SUMATERA UTARA

KETERANGAN LOLOS KAJI ETIK
DESCRIPTION OF ETHICAL APPROVAL
"ETHICAL APPROVAL"
No : 654KEPK/FKUMSU/2021

Protokol penelitian yang diusulkan oleh :
The Research protocol proposed by

Peneliti Utama
Principal In Investigator : Basrah Bee Binte Shaik Hussain

Nama Institusi
Name of the Instutution : Fakultas Kedokteran Universitas Muhammadiyah Sumatera Utara
Faculty of Medicine University of Muhammadiyah Sumatera Utara

Dengan Judul
Tittle

"D-DIMER DAN KORELASI KLINIS MULTISYSTEM INFLAMMATORY SYNDROME PADA ANAK (*MIS-C*) DENGAN COVID-19 "

"D-DIMER AND ITS CLINICAL CORRELATION TO MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) WITH COVID-19 "

Dinyatakan layak etik sesuai 7 (tujuh) Standar WHO 2011, yaitu 1) Nilai Sosial, 2) Nilai ilmiah
3) Pemerataan Beban dan Manfaat, 4) Resiko, 5) Bujukan / Eksploitasi, 6) Kerahasiaan dan Privacy, dan
7) Persetujuan Setelah Penjelasan,yang merujuk pada Pedoman CIOMS 2016.Hal ini seperti yang ditunjukkan oleh terpenuhinya indikator setiap standar.

Declarated to be ethically appropriate in accordance to 7 (seven) WHO 2011 Standards,1)Social Values,2)Scentific Values,3)Equitable Assesment and Benefits,4)Risks,5)Persuasion / Exploitation,6) Confidentiality and Privacy,and 7)Informed Consent,refering to the 2016 CIOMS Guadelines.This is as indicated by the fulfillment of the indicator of each standard

Pernyataan Laik Etik ini berlaku selama kurun waktu tanggal 09 Oktober 2021 sampai dengan tanggal 09 Oktober 2022
The declaration of ethics applies during the periode October 09,2021 until October 09, 2022

Medan, 09 Oktober 2021
Ketua

Dr.dr Nurfadly,MKT

Attachment 2. Research Permit

MAJELIS PENDIDIKAN TINGGI
UNIVERSITAS MUHAMMADIYAH SUMATERA UTARA
FAKULTAS KEDOKTERAN
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Nomor : 1423/II.3-AU/UMSU-08/A/2021
Lamp. : -
Hal : **Mohon Izin Penelitian**

Medan, 06 Rabi'ul Awal 1443 H
13 Oktober 2021 M

Kepada : Yth. **Direktur RS Bunda Thamrin**
di
Tempat

Assalamu'alaikum Wr. Wb.

Dengan hormat, dalam rangka penyusunan Skripsi mahasiswa Fakultas Kedokteran Universitas Muhammadiyah Sumatera Utara (FK UMSU) Medan, maka kami mohon bantuan Bapak/Ibu untuk memberikan informasi, data dan fasilitas seperlunya kepada mahasiswa kami yang akan mengadakan penelitian sebagai berikut :

N a m a : Basrah Bee Binte Shaik Hussain
NPM : 1808260058
Semester : VII (Tujuh)
Fakultas : Kedokteran
Jurusan : Pendidikan Dokter
Judul : D-Dimer And Its Clinical Correlation To Multisystem Inflammatory Syndrome In Children (MIS-C) With Covid-19

Demikianlah hal ini kami sampaikan, atas kerjasama yang baik kami ucapkan terima kasih. Semoga amal kebaikan kita diridhai oleh Allah SWT. Amin.

Wassalamu'alaikum Wr. Wb

Hormat kami,
An. Dekan
Wakil Dekan I,

dr. Siti Masliana Siregar, Sp.THT-KL(K)
NIDN : 0106098201

Tembusan :
1. Wakil Rektor I UMSU
2. Ketua Skripsi FK UMSU
3. Pertinggal

Attachment 3. Results of Data Analysis

Attachment 3. Documentation

Attachment 4. Data Analysis

Normality Test

Case Processing Summary

		Cases					
		Valid		Missing		Total	
	D-Dimer	N	Percent	N	Percent	N	Percent
Neutrophil	Normal	134	100.0%	0	0.0%	134	100.0%
	Elevated	20	100.0%	0	0.0%	20	100.0%
Lymphocyte	Normal	134	100.0%	0	0.0%	134	100.0%
	Elevated	20	100.0%	0	0.0%	20	100.0%
Thrombocyte	Normal	134	100.0%	0	0.0%	134	100.0%
	Elevated	20	100.0%	0	0.0%	20	100.0%
CRP	Normal	134	100.0%	0	0.0%	134	100.0%
	Elevated	20	100.0%	0	0.0%	20	100.0%
Clinical Presentation	Normal	134	100.0%	0	0.0%	134	100.0%
	Elevated	20	100.0%	0	0.0%	20	100.0%

Test of Normality[b,c,d,e]

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	D-Dimer	Statistic	df	Sig.	Statistic	df	Sig.
Neutrophil	Normal	.339	134	.061	.710	134	.172
	Elevated	.509	20	.121	.433	20	.078
Lymphocyte	Normal	.314	134	.077	.758	134	.321
Thrombocyte	Normal	.460	134	.133	.483	134	.441
CRP	Normal	.538	134	.111	.131	134	.122
Clinical Presentation	Normal	.283	134	.214	.774	134	.088

a. Lilliefors Significance Correction

b. Lymphocyte is constant when D-Dimer = Elevated. It has been omitted.

c. Thrombocyte is constant when D-Dimer = Elevated. It has been omitted.

d. CRP is constant when D-Dimer = Elevated. It has been omitted.

e. Clinical Manifestation is constant when D-Dimer = Elevated. It has been omitted.

Clinical Presentation

Clinical Presentation * D-Dimer 2 Crosstabulation

Count

		D-Dimer 2		
		Normal	Elevated	Total
Clinical Presentation	Fever	52	8	60
	Nausea / Vomiting	17	0	17
	Diarrhea	21	1	22
	Cough	113	5	118
	Rhinorrhoea	79	0	79
	Dyspnea	10	2	12
	Anosmia	16	1	17
	Headache	17	3	20
Total		329	20	345

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	14.112[a]	7	.042
Likelihood Ratio	15.263	7	.033
Linear-by-Linear Association	.680	1	.409
N of Valid Cases	345		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is .56.

CRP

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
CRP * D-Dimer	154	100.0%	0	0.0%	154	100.0%

CRP * D-Dimer Cross-Tabulation

Count

		D-Dimer		
		Normal	Elevated	Total
CRP	Normal	131	0	131
	Elevated	3	20	23
Total		134	20	154

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	130.915[a]	1	.000		
Continuity Correction[b]	123.333	1	.000		
Likelihood Ratio	101.119	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	130.065	1	.000		
N of Valid Cases	154				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 2.99.

b. Computed only for a 2x2 table

Neutrophil

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Neutrophil * D-Dimer	154	100.0%	0	0.0%	154	100.0%

Neutrophil * D-Dimer Cross-Tabulation

Count

		D-Dimer		
		Normal	Elevated	Total
Neutrophil	Neutropenia	59	11	70
	Normal	75	1	76
	Neutrophilia	0	8	8
Total		134	20	154

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	20.621[a]	2	.000
Likelihood Ratio	27.553	2	.000
Linear-by-Linear Association	20.247	1	.000
N of Valid Cases	154		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 1.04.

Lymphocyte

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Lymphocyte * D-Dimer	154	100.0%	0	0.0%	154	100.0%

Lymphocyte * D-Dimer Cross-Tabulation

Count

		D-Dimer		
		Normal	Elevated	Total
Lymphocyte	Lymphocytopenia	0	11	11
	Normal	74	0	74
	Lymphocytosis	49	20	69
Total		134	20	154

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	28.315[a]	2	.000
Likelihood Ratio	35.852	2	.000
Linear-by-Linear Association	23.499	1	.000
N of Valid Cases	154		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 1.43.

Thrombocyte

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Thrombocyte * D-Dimer	154	100.0%	0	0.0%	154	100.0%

Thrombocyte * D-Dimer Cross-Tabulation

Count

		D-Dimer		
		Normal	Elevated	Total
Thrombocyte	Thrombocytopenia	0	11	11
	Normal	128	9	137
	Thrombocytosis	6	0	6
Total		134	20	154

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2.852[a]	2	.011
Likelihood Ratio	5.034	2	.001
Linear-by-Linear Association	.220	1	.003
N of Valid Cases	154		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is .78.

Attachment 6. Research Article

D-DIMER DAN ASOSIASI KLINIS PADA ANAK RAWAT INAP DENGAN COVID-19 DI MEDAN, SUMATERA UTARA

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ABSTRAK

Pendahuluan: Pengetahuan saat ini menunjukkan bahwa anak yang terinfeksi COVID-19 memiliki daya tahan yang tinggi dan presentasi dengan gejala klinis yang ringan. Namun, pada Mei 2020 MIS-C, Sindrom Peradangan Multisistem pada Anak-anak telah dilaporkan sebagai penyakit anak berbahaya yang sementara terkait dengan COVID-19. D-dimer telah terbukti terkait dengan COVID-19 yang parah dan kritis, tetapi sedikit yang diketahui tentang karakteristik klinis yang dominan dan hasil laboratorium pada anak-anak di Indonesia, khususnya Medan, Sumatera. **Tujuan:** Penelitian ini bertujuan untuk mengevaluasi D-dimer dan hubungan klinisnya dengan MIS-C dengan COVID-19 di RS Bunda Thamrin dari tahun 2020 hingga 2021. **Metode:** Penelitian ini merupakan penelitian deskriptif analitik dengan desain potong lintang (*Cross sectional*). Parameter klinis dan laboratorium dari rekam medis anak terkonfirmasi COVID-19 yang dirawat di RS Bunda Thamrin dianalisis. 154 kasus dimasukkan dalam penelitian ini. Variabel kategorik dibandingkan dengan menggunakan Uji Chi-square. **Hasil:** Sebagian besar kasus COVID-19 terjadi pada pasien anak usia > 5 tahun (64,3%) diikuti oleh anak usia < 5 tahun (35,7%). Usia rata-rata adalah 8,8 $\pm$ 5,83 tahun dengan dominasi pada pasien laki-laki (56,5%). Gejala umum yang muncul meliputi manifestasi pernapasan seperti batuk (76,0%), rinore (51,3%) dan demam (39,0%). Ada hubungan antara D-dimer dengan karakteristik klinis p=0,042 ($p<0,05$) dan D-dimer dengan hasil laboratorium p=0,000 pada CRP, neutrofil dan limfosit dan p=0,011 pada trombosit ($p<0,05$). 1 pasien diduga mengalami MIS-C di RS Bunda Thamrin Medan. **Kesimpulan:** D-dimer dapat menjadi penanda awal yang berguna untuk memprediksi manifestasi COVID-19 yang parah seperti MIS-C.

Kata kunci: MIS-C, SARS-CoV-2, COVID-19, D-dimer

D-DIMER AND ITS CLINICAL ASSOCIATION IN HOSPITALIZED CHILDREN WITH COVID-19 IN MEDAN, SUMATERA UTARA

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ABSTRACT

Introduction: *Current knowledge indicates that children infected with COVID- 19 are highly resilient and present with mild clinical symptoms. However, in May 2020 MIS-C, a Multisystem Inflammatory Syndrome in Children have been reported to be a dangerous childhood disease temporarily associated with COVID-19. D-dimer has been shown to be associated with severe and critical COVID-19, but little is known about the dominant clinical characteristics and laboratory results in Indonesian children, particularly Medan, Sumatra.* ***Objective:*** *This study aims to evaluate D-dimer and its clinical relationship to MIS-C with COVID-19 at RS Bunda Thamrin from the year 2020 to 2021.* ***Methods:*** *This research is a descriptive analytical study with a cross-sectional design. Clinical and laboratory parameters from medical records of confirmed COVID-19 children admitted to RS Bunda Thamrin were analyzed. 154 cases were included in this study. Categorical variables were compared using the Chi-square Test.* ***Results:*** *Majority of COVID-19 cases occur in pediatric patients aged > 5 years (64.3%) followed by children aged < 5 years (35.7%). The median age is 8.8 + 5.83 years with a predominance in male patients (56.5%). Common presenting symptoms include respiratory manifestations such as cough (76.0%), rhinorrhoea (51.3%) and fever (39.0%). There is an association between D-dimer and the clinical characteristics p=0.042 (p<0.05) and D-dimer with laboratory results p=0.000 in CRP, neutrophils and lymphocytes and p=0.011 in thrombocytes (p<0.05).1 patient is suspected to have MIS-C in RS Bunda Thamrin Medan.* ***Conclusion:*** *D-dimer could be an early useful marker for predicting severe COVID-19 manifestations such as MIS-C.*

Keywords: *MIS-C, SARS-CoV-2, COVID-19, D-dimer*

INTRODUCTION

The end of 2019 challenged the world with an epidemic of a novel coronavirus (SARS-CoV-2) first observed in Wuhan, China.[1] The Chinese Center for Disease Control (CDC) reported in February 2020 that of the first 72,000 cases, only 2% were children.[2] The World Health Organisation (WHO) later declared the viral outbreak a pandemic, on March 11, 2020. And as of Aug 23, 2020 a total of almost 23 057 288 COVID- 19 patients including 800 906 deaths have been confirmed by the WHO.[3]

In December 2020, the Indonesia Paediatrician Society (IDAI) reported 77 254 confirmed pediatric cases of COVID-19 and noted 542 deaths (2.7%) which is 2.5% more than the mortality rate reported in the United States (0.2%).[4] Between March 2 and August 2020 in Indonesia, five provinces contributed over 60% out of a total of 111 450 confirmed COVID-19 cases. They are, West Java, DKI Jakarta, Central Java, South Sulawesi and West Java.[3] Children made up 8.71% of the cases while the death mortality was reported to be 2.03 % for 0-5 year old, and 0.82% for 6-18 year olds. This is concerning as Indonesia comes second to India as a Lower Middle-Income Country (LMIC) that has suffered the highest number of confirmed COVID-19 cases.[5] Indonesia is also the fourth most populous country with a population of up to 274 million people.

Current knowledge indicates that children with COVID- 19 are reported to be asymptomatic or present with mild clinical symptoms such as fever, cough or gastrointestinal symptoms.[1] However, on May 14, 2020 the United States CDC released a health advisory reporting MIS-C, a systemic inflammatory syndrome with overlapping features of Kawasaki disease (KD).[6] The United Kingdom also reports similar findings where eight children with Kawasaki-like disease symptoms were admitted to the Pediatric Intensive Care Unit (PICU).[7] Although most children experience a milder course of infection, there is a concern for an inflammatory cascade in pediatric patients.

In Bandung, RSUP Hassan Sadikin reported a fatal course of MIS-C coinfected with dengue.[7] While in Jakarta, RS Dr. Cipto Mangunkusumo reported one patient meeting the criteria of MIS-C.[8] This warrants the need for more detailed analysis of the clinical presentation and outcome of COVID-19 in pediatric patients, as little is known about the prevalence and characteristics of fatal COVID-19 cases in Indonesia.

Laboratory findings of pediatric patients with COVID-19, showed that increased D-dimer, fibrinogen, procalcitonin, C-reactive protein, ferritin levels and low oxygen saturation were associated with severe disease and mortality.[9] Recent literature suggests that D-dimer can be a reliable predictor of thrombotic state identification and COVID-19 outcome. Rostami *et al*., suggests that examining coagulation tests from the start of the diagnosis can be useful for monitoring the disease and delivering effective management.[10]

From the background above, the researcher wants to explore the relationship between D-dimer and clinical manifestation of Multisystemic Inflammatory Syndrome in Children with COVID-19 at RS Bunda Thamrin Medan from the year 2020 to 2021.

METHOD

This research is a descriptive analytical study with a cross-sectional design. This study aims to evaluate D-dimer and its clinical relationship to MIS-C with COVID-19 at RS Bunda Thamrin. Data on clinical and laboratory parameters from medical records of confirmed COVID-19 children upon admission to RS Bunda Thamrin were analyzed. The inclusion criteria in this study is: 1. Pediatric patients aged 1 month – 18 years where the child has been diagnosed with COVID-19 and is being treated in RS Bunda Thamrin Medan. 2. Pediatric patients aged 1 month – 18 years confirmed to have COVID-19 by PCR swab test. 3. Pediatric patients who had undergone laboratory examinations, including D-dimer. The exclusion Criteria in this study is: 1. Pediatric patients aged 1-18 years with incomplete

medical record. Data was analyzed using univariate and bivariate methods with the help of the Statistical Program for Social Science (SPSS). Univariate analysis was studied to see the general description and distribution of independent and dependent variables studied. Bivariate analysis was studied to see the association between the dependent and independent variables studied. Categorical variables were analyzed using the Chi-square Test. Results were considered significant when $p<0.05$.

RESULT

This study was carried out in RS Bunda Thamrin, Medan, from May to December 2021. 154 cases were included in this study.

Table 1. Demographic Data of Patients Based on Age

Age Group	N	%
< 5 Years	55	35.7
> 5 Years	99	64.3
Total	**154**	**100**

The results from Table 1 show that majority of COVID-19 cases occur in pediatric patients aged > 5 years with 99 individuals (64.3%) followed by children aged < 5 years with 55 individuals (35.7%).

Table 2. Demographic Data of Patients Based on Gender

Age Group	Male		Female	
	N	%	N	%
< 5 Years	28	18.2	27	17.5
> 5 Years	59	38.3	40	26.0
Total	**87**	**56.5**	**67**	**43.5**

According to Table 2, most pediatric patients with COVID-19 at RS Bunda Thamrin were male children with 87 individuals (56.5%) of which 59 individuals (38.3.%) were aged > 5 years and 28 individuals were aged < 5 years. COVID-19 were found in 67 female children (43.5%) of which, 40 individuals (26.0%) were aged > 5 years, and 27 individuals (17.5%) were aged < 5 years.

Table 3. Distribution of Presenting Features of Pediatric Patients

Clinical Presenting Features	< 5 years old	>5 years old	Total
Age	2 ± 1.4	12.3 (5.10-18.0)	8.8 ± 5.82
Fever	42 (76.4%)	80 (80.8%)	60 (39.0%)
Nausea / Vomiting	7 (13.0 %)	10 (10.1%)	17 (11.0%)
Diarrhea	18 (32.7 %)	4 (4.0%)	22 (14.3%)
Rash	0	0	0
Conjunc-tivitis	0	0	0
Cough	38 (69.1%)	79 (79.8%)	117 (76.0%)
Rhinorr-hoea	23 (41.8%)	56 (56.6%)	79 (51.3%)
Dyspnea	1 (1.8%)	11 (11.1%)	12 (7.8%)
Anosmia	1 (1.8%)	16 (16.2%)	17 (11.0%)
Headache	1 (1.8%)	19 (19.2%)	20 (12.9%)

Based on the Table 3, clinical presentation that often appear in pediatric patients with COVID-19 in patients aged < 5 years and > 5 years were fever. 42 individuals (76.4%) aged of < 5 years and 80 individuals (80.8%) aged > 5 years had fever. Cough was present in 38 individuals (69.1%) aged <5 years and 79 individuals (79.8%) aged > 5 years. Rhinorrhoea was present in 23 individuals (41.8%) aged < 5 years and 56 individuals (56.6%) aged > 5 years. Diarrhea is present in 18 individuals (32.7%) aged < 5 years and 4 individuals (4.0%) aged > 5 years. Nausea / Vomiting was present in 7 individuals (13.0%) aged < 5 years and 10 individuals (10.1%) aged > 5 years. Headache was present in 1 individual (1.8%) and 19 individuals (19.2%) aged > 5 years. Anosmia was present in 1 individual (1.8%) aged < 5 years and 16 individuals (16.2%) aged > 5 years. Dyspnea was present in 1 individual (1.8%) aged < 5 years and 11 individuals (11.1%) aged > 5 years.

Table 4. Laboratory Test Result of Patients based on CRP Levels

CRP	< 5 Years	> 5 Years	Total	
			N	%
Normal	49	82	131	85.1
Elevated	6	17	23	14.9

According to Table 4, pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal CRP levels which is found in 131 individuals (85.1%) while CRP levels were elevated in 23 individuals (14.9%).

Table 5. Laboratory Test Result of Patients based on Neutrophil Count

Neutrophil	< 5 Years	> 5 Years	Total	
			N	%
Neutropenia	29	41	70	45.4
Normal	25	51	76	49.4
Neutrophilia	1	7	8	5.1

Referring to Table 5, pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal Neutrophil count which is found in 76 individuals (49.4%) followed by Neutropenia in 70 individuals (45.5%) and Neutrophilia in 8 individuals (5.1%).

Table 6. Laboratory Test Result of Patients based on Lymphocyte Count

Lymphocyte	< 5 Year	> 5 Year	Total	
			N	%
Lympho-cytopenia	2	9	11	7.1
Normal	16	58	74	48.1
Lympho-cytosis	37	32	69	44.8

According to Table 6, pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal lymphocyte count which is found in 74 individuals (48.1%) followed by lymphocytosis in 69 individuals (44.8%) and lymphocytopenia in 11 individuals (7.1%).

Table 7. Laboratory Test Result of Patients based on Thrombocyte Count

Thrombocyte	< 5 Year	> 5 Year	Total	
			N	%
Thrombo-cytopenia	5	6	11	7.1
Normal	45	92	137	89.0
Thrombo-cytosis	5	1	6	3.9

Based on Table 7, pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal thrombocyte count which is found in 137 individuals (89%) followed by thrombocytopenia in 11 individuals (7.1%) and thrombocytosis in 6 individuals (3.9%).

Table 8. Laboratory Test Result of Patients based on D-dimer levels

D-dimer	< 5 Years	> 5 Years	Total	
			N	%
Normal	43	91	134	87
Elevated	12	8	20	13

According to Table 8, pediatric patients at RS Bunda Thamrin with confirmed COVID-19 commonly present with normal D-dimer levels which is found in 134 individuals (87%) while D-dimer levels were elevated in 20 individuals (13%).

Table 9. MIS-C Diagnostic Evaluation based on ACR Clinical Guideline

Laboratory Result	Age	
	< 5 years	> 5 years
Tier 1 Diagnostic Test		
Elevated CRP	6	17
Elevated CRP and Neutrophilia	0	4
Elevated CRP and Lymphopenia	0	3
Elevated CRP and Thrombocytopenia	0	2
Tier 2 Diagnostic Test		
Elevated Tier 1 diagnostic tests and D-dimer	0	2
Met CDC MIS-C diagnostic criteria	0	1

Based on Table 9, out of 23 pediatric patients with elevated CRP levels, 9 individuals had elevation of CRP and at least one other inflammatory marker in the Tier 1 Diagnostic test based on the MIS-C Clinical Guideline by American College of Rheumatology. Out of the 9 individuals, only 2 had elevated Tier 1 diagnostic tests and elevated D-dimer. Out of the 2 pediatric patients, only 1 individual is suspected to have MIS-C based on the CDC criteria.

Table 10. Chi-square Test between D-dimer and Clinical Presentation

Clinical Presentation	D-Dimer		p
	Normal	Elevated	
Fever	52	8	0.042
Nausea / Vomiting	17	0	
Diarrhea	21	1	
Cough	113	5	
Rhinorrhoea	79	0	
Dyspnea	10	2	
Anosmia	16	1	
Headache	17	3	

Based on the results above, the correlation analysis of D-dimer with clinical presentations of patients with COVID-19, the results were p = 0.42 (*p <0.05*), which indicates that there is a relationship between the value of D-Dimer and clinical presentation of pediatric patients with COVID-19 at RS Bunda Thamrin.

Table 11. Chi-square Test between D-dimer and Laboratory Biomarkers

Laboratory Biomarkers	D-Dimer		P Value
	Normal	Elevated	
CRP			
Normal	131	0	0.000
Elevated	3	20	
Neutrophil			
Neutropenia	58	11	0.000
Normal	75	1	
Neutrophilia	0	8	
Lymphocyte			
Lympho-cytopenia	0	11	0.000
Normal	74	0	
Lympho-cytosis	60	9	
Thrombocyte			
Thrombo-cytopenia	0	11	0.011
Normal	128	9	
Thrombo-cytosis	6	0	

Based on the table above, the results of the correlation analysis of D-dimer and Laboratory Biomarkers; CRP, neutrophils and lymphocytes each obtained a value of p = 0.000 (*p <0.05*), and the value of the analysis test on platelets with d-dimer obtained a value of p = 0.011 (*p<0.05*), it indicates that there is a correlation of D-dimer values to the rise and fall of laboratory biomarker values.

DISCUSSION

Data was obtained in the form of age, gender, clinical presenting features, and laboratory test results. Majority of COVID-19 cases occur in pediatric patients aged > 5 years with 99 individuals (64.3%) followed by children aged < 5 years with 55 individuals (35.7%). The median age is 8.8 ± 5.83 years. Majority of the patients were male children with 87 individuals (56.5%) of which, 59 individuals (38.3.%) were aged > 5 years and 28 individuals were aged < 5 years.

This result is in line with the findings of Hee et al., who noted that MIS-C equally affected children with a median age of 8.6 years and affected slightly more boys than girls.[34] While Hoste et al., noted a median age of at least 8.4 years with a predominance of male patients in 586/716 cohort patients. The author concludes that while early reports suggested that males were overrepresented, MIS-C has yet to establish a significant gender predilection.[36]

In relation to age, Dhochak et al., postulated that the expression of ACE-2 receptor which is the primary target for SARS-CoV-2, decreases with age and younger children, less frequently have risk factors such as co-morbidities, smoking, and obesity.[20] In relation to male predilection, Lipsky et al., cited a few reasons such as (1) males express more ACE2 in their lungs and heart than females. (2) Females have a stronger natural immune response because they have two X chromosomes which contains several important genes related to immunity and immune regulation such as the gene coding for Toll-like receptor 7 (TLR7) which helps control the innate immune response by recognizing single-stranded RNA of viral origin, like an RNA coronavirus and contributes to the faster clearing of SARS-CoV-2. (3) The female sex hormone estrogen may be protective as it activates the immune system.[37]

The most common presenting symptom in this study include respiratory manifestations such as cough (76.0%), rhinorrhoea (51.3%), fever (39.0%), headache (12.0%), diarrhea (11.0%), nausea/vomiting (11%), anosmia (11%) and dyspnea (7.8%). However, these are common mild symptoms of COVID-19.[23]

Whereas in MIS-C, the most common presentation is persistent fever with gastrointestinal and mucocutaneous features.[38] The prominent difference in symptoms between MIS-C and COVID-19 was that skin rash and gastrointestinal symptoms were more common in MIS-C, whereas respiratory symptoms were more common in COVID-19.[34] Al-Qahtani et al., mentioned that while MIS-C resembles severe COVID-19, a general rule is that respiratory manifestations such as breathlessness, coughing, increased oxygen demand and progressive lung consolidation do not occur in MIS-C.[39] Ozsurekci et al., reported that elevated CRP and conjunctivitis was 100% accurate in differentiating between severe COVID-19 and MIS-C.[39] Although 14.9% of patients in this study, was reported to have elevated CRP, no signs of conjunctivitis was reported.

The author believes that 1 patient is suspected to have MIS-C and met the CDC diagnostic criteria. However, there are other diagnostic criteria for MIS-C from WHO, RCPCH as well as KDCA. Despite the definitions having common elements, they substantially differ in other criteria. For instance, in CDC's definition, laboratory tests from which abnormal results could diagnose MIS-C is more numerous than WHO's definition. Whereas the case definition by RCPCH seems less strict in requiring evidence of multiorgan involvement and SARS-CoV-2 infection. Given the different criteria to define MIS-C's wide spectrum of clinical signs and symptoms, there could be more than 1 children suspected to have MIS-C in this study.[38]

The differences seen in the clinical presentation, could be due to genetic susceptibility and geographical regions. Lee et al., from New York stated that only 5.5% of MIS-C occurs in Asian persons with majority of cases occurring among Black (34.4%), Hispanic (29.8%) and White (12.8%) children.[40] Li et al., from South

Korea postulated other reasons which include (1) different prevalence rate of COVID-19. Korea has an infection rate of around 0.07% which is lower than main European cities where infection rate reaches up to 9%. Since children's cases account for less than 2% of all cases all over the world, the association between COVID-19 and MIS-C might be found only when the prevalence rate is high.[41] In Indonesia however, infection rate of COVID-19 reaches up to 8.71% in children in March 2 and August 2020 and yet MIS-C is rarely reported.[5]

In relation to geographical reason, Kaushik et al., reported GI and conjunctival manifestations were seen most commonly in children from the United States, while rash was commonly reported in cases from India, and cardiovascular involvement was most commonly seen in studies from Europe.[34,42] In conclusion, no patients were clinically diagnosed with MIS-C in RS Bunda Thamrin. This could partly be due to the hospital being a secondary hospital where more severe cases of COVID-19 would be referred to tertiary hospital. And the lack of Tier 2 complex testing for children as recommended by the clinical guideline by The American College of Rheumatology.[27] Cardiac manifestations of MIS-C were unexplored in this study.

In terms of Laboratory features, CRP is an early marker of infection and inflammation produced by the liver.[29] It works by binding to phocholine expressed highly on the surface of cells damaged by SARS-CoV-2. It activates the classical pathway of the immune system and modulate phagocytic activity to clear microbes and damaged cells.[43] Based on this study, pediatric patients at RS Bunda Thamrin with COVID-19 most commonly present with normal CRP levels which is found in 131 individuals (85.1%) while CRP levels were elevated in 23 individuals (14.9%).

This could be explained by the fact that CRP levels rises rapidly within 6 to 8 hours, peaks in 48 hours from the disease onset and decreases when the inflammatory stages end.[43] Patients in this study could have presented to the hospital later, when CRP concentration is already decreasing. As for only a small percentage of individuals present with elevated CRP levels, Zhang et al., noted that CRP levels were only significantly different between patients with mild or markedly elevated D-dimer levels 1-3 days after ICU admission.[44] While Poudel et al., noted that CRP showed statistical elevation among deceased cases with high D-dimer values.[45] No patients in RS Bunda Thamrin in this study was admitted to the ICU or were deceased.

Neutrophils serve as first responders to many infections. Studies suggest that neutrophils enhance antiviral defense by interacting with other immune cell populations, virus internalization and killing mechanism, cytokines release.[46] In terms of neutrophil counts, this study shows that pediatric patients at RS Bunda Thamrin commonly present with normal neutrophil count which is found in 76 individuals (49.4%) followed by neutropenia in 70 individuals (45.5%) and neutrophilia in only 8 individuals (5.1%).

This could be explained by Mank et al., who cited that there have been cases of neutropenia seen in acute COVID-19 usually related to immunosuppression. It is a common haematological finding and has a variety of etiology such as medications, malignancy, and infection but no association with SARS-CoV-2 has been clearly described in recent publications.[47] Liu et al., noted that ICU cases of pediatric patients with COVID-19 is more likely to present with neutrophilia due to the activation of neutrophils to generate immune response to fight COVID-19 virus which subsequently contributes to cytokine storm.[48]

The lymphocyte count has been cited to be an important parameter to directly discriminate between COVID-19 patients with and without severe disease. Although lymphopenia had been known to be a marker of severe COVID-19 disease in adults.[49] Studies show that the most common abnormalities detected in children with COVID-19 were lymphocytosis.[50] This is in

line with the results of this study where pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal lymphocyte count which is found in 74 individuals (48.1%) followed by lymphocytosis in 69 individuals (44.8%) and lymphocytopenia in 11 individuals (7.1%).

The proposed mechanism was that lymphocytes express ACE2 receptors on their surface, enabling SARS-CoV-2 to directly infect lymphocytes. The systemic increase in cytokines and inflammatory mediators hence, resulted in marked lymphocytic apoptosis. Kosmeri et al., postulated that lesser children present with lymphopenia due to their immature immune system or the less severe manifestation of COVID-19 in children.[50] On the other hand, Zhao et al., noted that lymphocytes were found to be prone to decrease continually and severely in ICU and dead patients.[51] It could be concluded that in children, age and clinical severity may have an impact of lymphocytes.

Thrombocytopenia has been associated with respiratory deterioration in children. Studies found that lung is a reservoir for resident megakaryocytes and hematopoietic progenitor cells.[48] It is often encountered in critically ill patients and those admitted to the pediatric ICU.[51] This is in line with the results of this study where pediatric patients at RS Bunda Thamrin with COVID-19 commonly present with normal thrombocyte count which is found in 137 individuals (89%) followed by thrombocytopenia in 11 individuals (7.1%) and thrombocytosis in 6 individuals (3.9%).

Liu et al., postulated that thrombocytopenia could be caused by damage to the lungs. COVID-19 affects the primary site of terminal platelet production which accounts for about 50% of total platelet production. On top of that, SARS-CoV-2 also damages endothelial cells leading to abnormal coagulation, platelet activation and aggregation reducing the number of thrombocytes.[42]

In terms of Chi-square analysis, this study found that there is an association between D-dimer and clinical presentations of pediatric patients at RS Bunda Thamrin with COVID-19, with p = 0.042 (*p <0.05).* Zhao et al., studied the association of D-dimer to 36 demographic characteristics and found that age, gender, blood pressure and dyspnea were positively correlated with D-dimer.[51] Similarly, Ozen et al., found that D-dimer values were positively correlated with age, length of stay and lung involvement.[52]

There is also an association between D-dimer and laboratory biomarkers such as CRP, neutrophils, and lymphocytes with p = 0.000 (*p <0.05*), and thrombocytes with p = 0.011 (*p <0.05*). It can be concluded that there is a relationship between D-Dimer values to the rise and fall of laboratory biomarker values in pediatric patients with COVID-19 at RS Bunda Thamrin. Zhao et al., analysed 62 laboratory tests and 32 of them were significantly associated with D-dimer; CRP p=0.01, neutrophilia p = <0.020, lymphopenia p = <0.001, thrombocytopenia p = <0.009.[51] While Ozen et al., found that D-dimer was positively correlated with fibrinogen, neutrophil count and negatively correlated with lymphocyte count.[52]

D-dimer is a specific biomarker that interacts with other coagulation molecules, inflammatory cytokines, and markers for organ/tissue injury. Studies show that D-dimer could serve as an independent predictor of fatality, severity and potentially serve as a marker for daily monitoring of thrombolytic therapy[51]. This study showed that elevated D-dimer is associated with a broad-spectrum of immune responses to SARS-CoV-2 infection, such as acute phase protein (CRP) and inflammation indicators (neutrophil, lymphocyte). These associations may support the concept that high circulating cytokines and hyperfibrinolysis may be functionally correlated.[51]

Viremia and cytokine storm syndrome causes a rise in pro-inflammatory cytokines (IL-2, IL-6, IL-8, IL-17, TNF-α) which lead to upregulation of tissue factor expression on the endothelial cells, resulting in an increased pro-coagulant state.[51] IL6 and other proinflammatory cytokines/chemokines, steroids, and miRNAs upregulate the

fibrinogen synthesis up to 10-fold during the acute phase of injury and infection.[53] In COVID-19 a hypercoagulable state is followed by hyperfibrinolysis. Physiologically, hyperfibrinolytic homeostasis maintains vascular patency and normal organ function.[51] Fibrinogen is turned over to fibrin monomers by thrombin and cleaved by plasmin into FDP and D-dimers by fibrinogenolysis.

Extremely elevated D-dimer seems to be the consequence of hyperfibrinolysis predominately in the pulmonary capillaries and other organs. D-dimer can be a good marker of multi-organ damage because soluble fibrin is synthesized in the liver, bone marrow, brain, lung, and gastrointestinal epithelium. It can be distributed to plasma, interstitial fluid and platelets and lymph.[50] Patients with critical forms of the disease have additional complications including acute kidney injury, acute cardiac injury, congestive heart failure, all of which can increase the levels of D-dimer.[52]

CONCLUSION

In conclusion, majority of COVID-19 cases in pediatric patients occur in pediatric patients aged > 5 years with a male predominance. The most common presenting symptom of COVID-19 in pediatric patients at RS Bunda Thamrin include respiratory manifestations such as cough, rhinorrhoea, fever, headache, diarrhea, nausea/vomiting, anosmia, and dyspnea. Majority of COVID-19 pediatric patients at RS Bunda Thamrin have normal CRP, neutrophil, lymphocyte, thrombocyte, and D-dimer levels indicating mild disease progression. D-dimer was associated with clinical presentations of pediatric patients with COVID-19 at RS Bunda Thamrin with p = 0.042 ($p < 0.05$) and was associated with CRP, neutrophils, lymphocytes with p value = 0.000 ($p < 0.05$), and thrombocytes, p value = 0.011 ($p<0.05$), in pediatric patients at RS Bunda Thamrin indicating a relationship with the increase and decrease of laboratory biomarker values. D-dimer could be inter-regulated by a spectrum of clinical variables. The clinical relevance of elevated D-dimer may be multifaceted. Studies conclude that D-dimer can be used to predict severity, prognosis, and outcome of critically ill patients with COVID-19. It is hoped that D-dimer could also be a useful marker for predicting severe COVID-19 in children such as MIS-C.

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