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PROFILE OF HEMOSTASIS PHYSICAL DISORDERS IN CONFIRMED COVID-19 PATIENTS TREATED IN THE ISOLATION ICU UDAYANA UNIVERSITY HOSPITAL

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ABSTRACT

COVID-19 is a highly transmissible disease caused by Coronaviruses. In some cases, coagulation disorders have been newly discovered as hemostasis disorders that occur due to a decrease in the patient's immune system. It's caused the patient to experience coagulopathy, endothelial dysfunction, and excessive platelet activation. This study aims to determine the characteristics of hemostasis disorders that occur in patients with confirmed COVID-19. A cross-sectional study was conducted at Udayana University Hospital on patients with confirmed COVID-19 who were treated in the Isolation ICU in 2020 to 2021. Patients with incomplete medical records and who did not undergo blood tests related to coagulation parameters such as PT, aPTT, INR, d-dimer, and platelet count on the first day were excluded from the subjects to be analyzed. The variables of age, gender, and comorbidities were analyzed to determine the demographic frequency of patients and to perform a cross-tabulation between the comorbidity variables and blood tests to describe the frequency of coagulation disorders. The results obtained from 169 patients showed the majority were male, and the age group was >60 years. In general, the values of aPTT and d-dimer increased in most patients, while the values of PT, INR, and platelet count were within normal limits. Patients with comorbidities of hypertension and type II diabetes mellitus also experienced the same thing, namely an increase in aPTT and d-dimer in most patients. These findings can help clinicians to prevent the worsening of conditions in patients with COVID-19 in the Isolation ICU.
Keywords: COVID-19., ICU., Coagulation Parameters.

INTRODUCTION

The world was shaken by the emergence of Coronavirus at the end of 2019, which is currently known as COVID-19. This virus is classified as an RNA virus in the Coronavirinae subfamily, Coronaviridae family and Nidovirales order. Coronaviruses are consist of four generations of CoV, namely Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus.[1] Transmission of SARS-CoV-2 can easily occur through contact between humans, either directly or indirectly, in various activities. Apart from that, it can spread through fomite transmission. Through this transmission, droplets will contaminate surfaces over a long period of time until they come into contact and infect humans. This is influenced by temperature, humidity and the type of surrounding surface.[2]

Epidemiology of COVID-19 cases based on WHO data dated on 10 February 2021, there were 106.321.987 cases with 2.323.282 deaths.[3] COVID-19 is diagnosed in several stages, namely history taking, physical examination and supporting examinations. Supporting examinations can include i-PCR, rapid tests, microorganism cultures, feces and urine examinations. Apart from that, diagnosis can be made by chemical blood tests in the form of blood gas analysis, electrolytes, liver function, kidney function and hematological examination.[4]

Coronavirus infection can cause symptoms according to the degree of severity. The main clinical symptoms of COVID-19 include fever, cough and difficulty breathing. Meanwhile, severe COVID-19 can cause several other symptoms such as a decreased immune system, metabolic acidosis, septic shock and bleeding due to physiological disorders hemostasis.[5]

Hemostasis is a process of stopping bleeding spontaneously from damaged blood vessels through blood vessel spasm, platelet adhesion and active involvement of coagulation factors. Impaired hemostasis function in COVID-19 sufferers can be detected through hematologic examination.[4] The examination consists of PT, aPTT, INR, D-dimer and platelets.[6]

Faal hemostasis disordered in COVID-19 patients can occur cause the patient's immune system is weakened due to inflammation, thus triggering a coagulopathy condition. The immune system is characterized by excessive cytokine

production, which predisposes to venous and arterial thromboembolism due to activation of the coagulation cascade caused by excessive inflammation, endothelial dysfunction, platelet activation, and blood flow stasis.[7]

Initially, COVID-19 was very rarely associated with abnormalities in the blood coagulation process until finally research in the Netherlands stated that thromboembolism in severe COVID-19 reached 31%. 27% of patients experienced venous thromboembolism and 3.7% of patients experienced arterial thrombosis.[8] Apart from that, research in China confirmed the existence cases of coagulation disorders, in 20 of 81 patients (25%) experienced venous thromboembolism and 8 of them has died.[9] The results of this research also stated that there were several abnormal parameter results in coagulation examinations in the form of PT, aPTT, INR, D-dimer and platelet count in severe COVID-19 patients with coagulation disorders.

Related to the problems revealed regarding the influence of COVID-19 on hemostasis function disorders. So the researchers wanted to know what the profile of hemostasis physiologic disorders was in the initial coagulation examination of COVID-19 patients treated in the Isolation ICU at Udayana University Hospital in 2020-2021. This study aims to determine whether there are hemostasis disorders that occur in COVID-19 patients, especially in patients with ICU Isolation care in Udayana University Hospital.

MATERIALS AND METHODS

This research is descriptive with a cross-sectional study design. This research aims to describe the profile of hemostasis physiology disorders that occur in COVID-19 patients treated at the Isolated ICU with data collection carried out based on a predetermined period from 2020-2021.

The target population for this study is patients who came to Udayana University Hospital, were confirmed to have COVID-19, and received treatment in the Isolation ICU at Udayana University Hospital in 2020-2021. The inclusion criteria for this study were patients who were confirmed to have COVID-19 in the Isolation ICU at Udayana University Hospital with complete medical record blood examination data and in accordance with the variables studied.

Data collection was carried out using the total sampling technique, which is by taking all of the medical record data from Udayana University Hospital. The study began in January 2023 and ended in August 2023, with a duration of 8 months, taking place in the medical record room of Udayana University Hospital.

The stages carried out in this research begin with research preparation such as making a proposal, asking permission from the ethics committee and preparing a formula for extracting data from medical records, while the research implementation stage consists of matching the data obtained with the inclusion criteria and exclusion criteria of the research.

The collected data will be processed and analyzed using univariate analysis to determine the frequency distribution and presentation of each variable studied. This research has received permission from the Udayana Ethics Committee with ethical clearance number: 218/UN14.2.2.VII.14/LT/2023.

The variables examined in this study were age, gender, comorbidities, main clinical symptoms, examination of coagulation parameters consist of PT, INR, D-dimer and platelet count. Comorbid variables were divided into 3 groups consisting of patients without comorbidities, one comorbid, two comorbid and more than two comorbidities.

RESULT

Table 1. Demographic Characteristics of Respondents

Demographic Characteristic	Frequency (n)	Percentage (%)
Gender		
Men	117	69.2%
Woman	52	30.8%
Total	169	100%
Age		
10-19 years	0	0%
20-29 years	7	4.1%
30-39 years	12	7.1%
40-49 years	24	14.2%
50-59 years	54	32%
>60 years	72	42.6%
Total	169	100%
Comorbid		
No Comorbid	64	37.9%
1 Comorbid	59	34.9%
2 Comorbid	37	21.9%
>2 Comorbid	9	5.3%
Total	**169**	**100%**

Based on table 1. The results of this study show that most COVID-19 patients were male about 117 people (69.2%). Looking at the age group, most of the patients were found to be in the age group >60 years, as much as 72 people (42.6%).

Based from the grouping of comorbidities, most patients were found to have no comorbidities about 64 people (37.9%) but this figure was not much different from patients who had 1 comorbid as much as 59 people (34.9%).

Table 2. Frequency Distribution Based on Comorbidity Distribution

Category	Frequency (%)
Hypertension	54 (32%)
Diabetes Mellitus Type II	52 (30.8%)
NSTEMI	9 (5.3%)
Coronary Artery Disease	8 (4.7%)
Asthma	8 (4.7%)
Chronic Kidney Disease	5 (3%)
Hypertensive Heart Disease	4 (2.4%)
Acute On Chronic Kidney Disase	4 (2.4%)
Immunologic Disorder	3 (1.8%)
Stroke non Hemorrhagic	3 (1.8%)
STEMI	3 (1.8%)
Neurological Disorder	2 (1.2%)
Acute Kidney Injury	2 (1.2%)
Chronic Heart Failure	2 (1.2%)
Dementia	1 (0.6%)
Uric Acid	1 (0.6%)
Infark Myocard	1 (0.6%)
Depression	1 (0.6%)

Based on table 2. It can be seen that the comorbid diseases of all patients were mostly hypertension with 54 people (32%) out of 169 people, followed by diabetes mellitus type II with 52 patients (30.8%) out of 169 people and other comorbid diseases did not show significant of numbers.

Table 3. Frequency Distribution Based on Main Clinical Symptoms

Category	Frequency (%)
Short of Breathness	131 (77.5%)
Fever	110 (65.1%)
Cough	109 (64.5%)
Malaise	36 (21.3%)
Anosmia	11 (6.5%)
Rhinorrhea	9 (5.3%)
Nausea	9 (5.3%)
Dispepsia	9 (5.3%)
Altered Mental Status	6 (3.6%)
Odinofagia	5 (3%)
Headache	5 (3%)
Anorexia	3 (2%)
Vomitus	2 (1.2%)
Diare	2 (1.2%)
Abdominal Pain	1 (0.6%)
Dizzy	1 (0.6%)
Vertigo	1 (0.6%)
Chest Pain	1 (0.6%)
Gatritis	1 (0.6%)
Melena	1 (0.6%)
Tetraparesis	1 (0.6%)
Heart Palpitations	1 (0.6%)
Dysuria	1 (0.6%)
Transaminitis	1 (0.6%)
Urine Retention	1 (0.6%)

Based on table 3 it is found that the main clinical symptoms seen from the overall data distribution of patients in this study mostly experienced shortness of breath, 131 people (77.5%) out of 169 people (100%), Followed by fever in 110 people (65.1%) out of 169 people (100%) and cough in 109 people (64.5%) out of 169 people (100%).

Table 4. Distribution of Coagulation Parameter Examination Results

Coagulation parameters	Frequency(n)	Percentage(%)
APTT		
Low	14	8.3%
Normal	65	38.5%
High	90	53.3%
PT		
Low	1	0.6%
Normal	93	55%
High	75	44.4%
INR		
Low	7	4.1%
Normal	137	81.1%
High	25	14.8%
D-Dimer		
Low	15	8.9%
High	154	91.9%
Platelet Count		
Low	43	25.4%
Normal	117	69.2%
High	9	5.3%
Total	**169**	**100%**

Based on table 4. Most patients were found to have an high values APTT in 90 people (53.3%). A number of patients were found to have normal APTT in 65 people (38.5%) and low values in 14 people (8.3%). Another coagulation examination, namely the PT value, was found to be normal in most patients as much as 93 people (55%). Meanwhile, a number of patients experienced an high values PT in 75 people (44.4%) and low values in 1 person (0.6%).

The INR value in most patients was found to be normal in 137 people (81.1%). Several patients were found with increased INR values in 25 people (14.8%) and decreased in 7 people (41.1%). Most patients were found with elevated D-dimer values in 154 people (91.9%) and normal values in 15 people (8.9%). Most patient were found to have platelet results in normal values in 117 people (69.2%), decreased in 43 people (25.4%) and increased in 9 people (53.3%).

Table 5. Results of Coagulation Parameters Based on Comorbidity of Hypertension and Diabetes Mellitus Type II

Coagulation Parameters	Without Hypertension (n=115)	Hypertension (n=54)	Without DM Type II (n=117)	DM Type II (n=52)
APTT				
Low	7 (6%)	7 (13%)	11 (9%)	3 (6%)
Normal	45 (39%)	20 (37%)	43 (37%)	22 (42%)
High	63 (55%)	27 (50%)	63 (54%)	27 (52%)
PT				
Low	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Normal	59 (51%)	34 (63%)	63 (54%)	30 (58%)
High	56 (49%)	19 (35%)	54 (46%)	21 (40%)
INR				
Low	2 (1%)	5 (9%)	6 (5%)	1 (2%)
Normal	95 (83%)	42 (78%)	96 (82%)	41 (79%)
High	18 (16%)	7 (13%)	15 (13%)	10 (19%)
Platelet Count				
Low	24 (21%)	19 (35%)	27 (23%)	16 (31%)
Normal	84 (73%)	33 (61%)	84 (72%)	33 (63%)
High	7 (6%)	2 (4%)	6 (5%)	3 (6%)
D-DIMER				
Low	11 (10%)	4 (7%)	14 (12%)	1 (2%)
High	104 (90%)	50 (93%)	103 (88%)	51 (98%)

Based on table 5. Most patient with hypertensive had an increased aPTT value of 27 people (50%) from 54 people (100%) and the D-dimer value in most patients with hypertension was also known to increase in 50 people (93%) from 54 people (100%).

Patients with Type II Diabetes Mellitus in this study found an increase aPTT values in 27 people (52%) out of 52 people (100%). D-dimer values, in patients with type II diabetes mellitus increased in 51 people (98%) out of 52 people (100%). Meanwhile, on PT, INR and platelet count examinations were still within the normal range for these two comorbidities as can be seen in the table.

DISCUSSION

Coagulation is a normal body mechanism called hemostasis. Hemostasis can be interpreted as the process of spontaneous stopping of blood by the body if there is bleeding. There are tests that must be carried out to diagnose coagulation disorders. The coagulation parameters used by COVID-19 patients include PT, aPTT, INR, d-dimer and platelet count examinations.

Based on table 1 demographic characteristics of respondents according to data obtained from research results at Bitung City Health Service from July to October 2021, 59.1% of the patients were male and 40.9% female.[10] According to data from research by Ajay Pradhan et al, male patients in several countries such as Peru, Italy, Spain, England, the United States, Mexico and Sweden are more likely to be infected COVID-19 at an older age. Gender differences in the increased risk of COVID-19 infection are often caused by differences in the immune system. Women produce more type 1 interferon (IFN) and antiviral cytokines such as receptor 7 than men, which play an important role in the early response to the virus. Increased IFN is associated with sex hormone levels and the number of X chromosomes. Men have one X chromosome, while women have two copies of the X chromosome. [11]

Gender differences will also influence ACE-2 and TMPRSS2 as regulations for viruses to infect the body. Circulating levels of ACE-2 are higher in men, besides that TMPRSS-2 is predominantly expressed in the prostate epithelium of men with its involvement in priming the viral S protein so that Sars-CoV-2 can infect the body.[12]

Referring to table `1 demographic characteristics in the comorbid category are linked to table 2. frequency distribution based on comorbidities in line to research in Kuwait by Alshurkry et al it is found that there are 14.7% of patients with hypertension without diabetes and 83% of hypertension with diabetes which is in line with this research.[13]Another research by Widjaja.T et al in Bandung found 61.3% of patients with hypertension, followed by 19.4% of diabetes patients.[14]

Hypertension is one of the comorbidities that increase the risk of death in COVID-19 patients. This is because the RAAS (Renin Angiotensin Aldosterone System) is a cellular receptor for SARS-CoV-2 infection. Patients with hypertension use ACE-2 as the main regulator of the vasoconstrictive and proliferative effects caused by angiotensin II. In theory, ACE converts angiotensin I into

angiotensin II, which stimulates the release of aldosterone, resulting in increased blood pressure. ACE-2, on the other hand, metabolizes angiotensin I and angiotensin II, then binds and activates angiotensin II, resulting in vasodilation and a decrease in blood pressure. As a result, patients with hypertension are more likely to be exposed to COVID-19 due to the use of antihypertensive medications.[15]

Diabetes mellitus type II has a higher vulnerability to COVID-19 exposure. The fundamental mechanism of this occurs due to a decrease in innate immunity in a person to fight SARS-CoV-2. In a literature study conducted by Pain A. Panua et al that diabetes mellitus can significantly contribute to the occurrence of COVID-19. Patients with diabetes will be much more prone to experiencing inflammatory storms that lead to more severe damage due to COVID-19. The fatal damage in question is the release of enzymes related to tissue injury, an uncontrolled inflammatory response that leads to a state of hypercoagulation related to dysregulation of glucose metabolism.[16]

Patients with COVID-19 diabetes mellitus will have a more severe inflammatory response and lung infiltration due to higher levels of neutrophils, total bilirubin, blood urea nitrogen, cardiac troponin I, c-reactive protein, procalcitonin, and d-dimer. In addition, there are lower levels of lymphocytes and albumin. The increase in CRP, fibrinogen, and d-Dimer in patients with diabetes mellitus will also lead to a state of hypercoagulation.[16]

The comorbidities of COVID-19 patients in this study were mostly hypertension and diabetes mellitus which could affect the results of coagulation tests in COVID-19 patients. In accordance with table 5 regarding coagulation examination, this is in line with research by Christine Tan et al., which states that patients with hypertension can develop due to endothelial damage, increased FVIII/VWF and increased tissue factor. Endothelial damage and increased FVIII and VWF can increase tissue factor exposure to the point of placing the patient in a hypercoagulable state.[17]

The occurrence of hypercoagulability in patients with diabetes mellitus and COVID-19 can also occur due to an imbalance between the surface of blood vessels and blood coagulation factors. Increased antihemophilic FVIII is often associated with patients with diabetes mellitus. In addition, hyperglycemic conditions contribute to endothelial dysfunction and vascular damage.[18] Until now, there have been no studies specifically examining the relationship between hypertension and diabetes mellitus in COVID-19 patients with hemostasis disorders, so they cannot provide data on the comparison of coagulation disorders through blood test results, given that this disease is still a relatively new disease.

Based on table 3 regarding the distribution of the main clinical symptoms of COVID-19 patients in accordance with research by Hildan Hadian et al which found that shortness of breath is the main complaint or symptom that dominates, namely 91 out of 100 people (91%) followed by coughing for 91 out of 100 people (91%) and fever as many as 87 out of 100 people (87%).[19] Apart from that, this research also in line with research by Tian et al which states that there are three main clinical symptoms that dominate, namely fever, cough, and shortness of breath in severe COVID-19 patients. In the study, it states that 37 patients (80.4%) had fever and 25 patients (54.3%) had cough.[20]

Shortness of breath is caused by a decrease in ACE-2 regulation, which leads to excessive production of angiotensin II by the associated ACE enzyme. Stimulation of the angiotensin II type 1a receptor AGTR1A increases the permeability of the pulmonary blood vessels, potentially increasing the pathological state of the lungs when ACE-2 expression decreases. SARS-CoV-2 infects the cells that line the nose, then the virus replicates, which results in the migration of infection to the pulmonary tract and alveoli, including type II alveolar cells that are rich in angiotensin receptors that produce surfactant. The virus will cause cytoplasmic effects and cilia damage, causing cell death. COVID-19 will increase pro-inflammatory cytokines in the serum as a defense of the body, namely IL1B, IL6, IL12, IFNγ, IP10, and MCP1, which are associated with lung inflammation.[21]

Fever has been proven to be a common symptom experienced by COVID-19 patients. This occurs as a systemic reaction with an increase in body temperature to fight infection. This increase in body temperature acts as a body's warning system to activate the immune system, including dendritic cells, macrophages, T and B lymphocytes, neutrophils, and vascular endothelial cells. In its pathophysiology, fever is mediated by the pyrogenic activity of prostaglandins, especially PGE-2. PGE-2 activity begins when there are exogenous pyrogens, such as bacteria or viruses like SARS-CoV-2, to stimulate endogenous pyrogens such as interferon (IFN), which plays an important role in the early response to Sars-CoV-2. This can change the hypothalamus through the organum vasculosum of the lamina terminalis and increase the core body temperature.[22]

COVID-19 symptoms can be distinguished by severity. One of the symptoms of severe COVID-19 described in this study is impaired hemostasis, which is a coagulation disorder. Referring to table 4 on the distribution of coagulation parameter test results, namely PT, aPTT, INR, d-dimer and platelet count. These results are in line with the study by Hui Long et al which states that patients with critical cases found aPTT with a range of values <21 seconds as many as 1 person (0.8%), 21-37 seconds as many as 13 patients (11.3%) and > 37 as many as 14 patients (12.2%).[23] In a study by id et al., it was found that aPTT values were elevated more than normal. The study found that 196 patients had prolonged aPTT values, while 193 patients had normal values. This increase occurred in 41 patients (21%) of 90 patients (100%). With this finding, the increase in aPTT in patients with severe COVID-19 is consistent with the theory of coagulation disorders in the ICU (Intensive Care Unit).[24]

Based on the PT values, this study is consistent with the study by Faiq Azzaki, which found that PT was normal in 151 people (85.8%).[25] Similarly, the study by id et al., found that PT was normal in 220 people with a total of 455 patients. Other coagulation tests are also determined based on the INR value.[24] This is consistent with the study by Yanhong Zhang et al which states that the normal value for patients with mild COVID-19 is 1.02 (0.96-1.05) and for patients with severe COVID-19 is 1.07 (0.70-1.30). There is an increase in the INR value for severe COVID-19, but it is not significant and remains within the normal range.[26]

Coagulation parameter abnormalities such as aPTT, PT, and INR are associated with SARS-CoV-2 infection, which directly enters endothelial cells through the ACE-2 receptor that plays an important role in platelet aggregation. Endothelial damage caused by the virus increases the exposure of endothelial tissue factor. The expression of tissue factor (TF)/FVIIa in monocytes becomes active and increases, which will activate the extrinsic coagulation pathway and the intrinsic coagulation pathway.[27]

Patients aPTT values showed more prolongation compared to PT, this is in accordance with study by Ortega-Paz et al which stated that in the group of patients who survived, the PT was found to prolong more than in the group who were in critical condition. Meanwhile, the prolongation of the aPTT value is more often experienced by patients in critical condition and even death.[28]

Coagulation disorders in COVID-19 can also be significantly seen through d-dimer testing. This is in line with research by Yanhong Zhang et al which states that 15 people (88.2%) with severe COVID-19 had elevated d-dimer levels, out of a total of 17 people (100%).[26] The coagulopathy status of COVID-19 patients can be assessed from the patient's platelet count. This is in line with research by Hakan Keski et al which states that 254 patients (84.1%) had normal platelet counts, 43 patients (14.2%) had thrombocytopenia, and 5 patients (1.7%) had platelet counts above the normal range.[29] The results of the research found that 21 patients with severe to fatal COVID-19 had normal platelet counts and only 5 people had a decrease in platelet counts.

Other research conducted by Richard Christian et al found that the number of platelets in non-critical patients was higher than in critical patients. This can occur because each person's body has different resistance and the maturity level of platelets is significantly correlated with the severity of the disease.[30] Thrombocytopenia is caused by a number of factors, including cytokine storm, lung injury caused by platelet activation, disruption of megakaryocyte fragmentation in the lungs, and decreased platelet production.[31] The presence of a cytokine storm can trigger the destruction of bone marrow progenitor cells, which can lead to platelet destruction. Lung injury can also cause platelet aggregation and excessive platelet consumption, which can lead to a decrease in platelet levels in the bloodstream.[32]

CONCLUSIONS AND SUGGESTIONS

Coagulation tests such as aPTT, PT, INR, d-dimer and platelet count were important in the examination and determination of the prognosis in patients with COVID-19. The study found that the frequency of increased aPTT and d-dimer occurred in most patients, while the values of PT, INR, and platelet count were still within the normal range. In addition, based on the cross-tabulation between specific comorbidities, namely hypertension and type II diabetes mellitus, the most common experienced were increased aPTT and d-dimer, with values of PT, INR, and platelet count still within the normal range in most patients.

This study suggests that coagulation parameter tests should have been carried out on all COVID-19 patients to prevent severity, complications, and even death in patients by providing therapy that is appropriate with the results of coagulation parameter tests. As for the next study that was planned to be conducted, it was hoped that it would figure out the relationship between coagulation parameter variables with the prognosis of COVID-19 by adding some more varied variables.

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