The Relationship Between D-Dimer Levels and the Value of Prothrombin Time and Activated Partial Thromboplastin Time in Patients with COVID-19 At Rsup Dr. M. Djamil Padang

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ABSTRACT

Covid-19 spread widely resulting in a global pandemic that continues to this day. People who are confirmed to have severe COVID-19 will cause thrombosis which results in increased levels of D-dimer prolonging Prothrombin Time or Activated Partial Thromboplastin Time, increased fibrinogen, and thrombocytopenia. one of the parameters that determine the presence of coagulation can be seen from the levels of D-dimer, PT and APTT. The purpose of this study was to determine the relationship between D-dimer levels and the value of prothrombin time and activated partial thromboplastin time in Covid-19 patients. This research is analytic observational with a cross sectional study design. The sample in this study amounted to 30 respondents. The examination carried out was D-dimer levels using the ELFA (Enzyme Linked Fluorescent Assay) method using Vidas, Prothrombin Time and Activated Partial Thromboplastin Time using the Flouroscence Flowcytometry method using the Sysmex Cs 2500 tool. The data were analyzed using the Spearman's rho correlation test. The results of the study on Covid-19 average levels of D-dimer 1696.23 g/ml ±1567.448 SD, the value of Prothrombin Time 11.103±1.1898 seconds and Activated Partial Thromboplastin Time 32.643±17.3796 seconds. Conclusion There is a significant relationship between D-dimer levels with the Prothrombin Time P value of 0.003 and with Prothrombin Time and Activated Partial Tromboplastin Time P value of 0.031. There was no significant relationship between D-dimer levels and Activated Partial Tromboplastin Time P value 0.110. High D-dimer levels are accompanied by a prolonged prothrombin time.

Keywords: Covid-19, D-dimer levels, PT and APTT

INTRODUCTION

Covid-19 is a large family of viruses that cause disease in animals and humans. In humans, some Coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). Covid-19 is transmitted through droplets or splashes that come out when an infected person coughs, sneezes or talks (Aditia, 2021).

Based on the WHO report, as of August 30, 2020, there were 24,854,140 confirmed cases of Covid-19 worldwide with 838,924 deaths (CFR 3.4%). The Americas region has the most confirmed cases, with 13,138,912 cases. Covid-19 confirmed cases in Indonesia are still increasing. Based on the report of the Indonesian Ministry of Health, on August 30, 2020, there were 172,053 confirmed cases with 7343 deaths (CFR 4.3%). DKI Jakarta has the most cumulative confirmed cases, with 39,037 cases. The region with the fewest cumulative cases is East Nusa Tenggara with 177 cases (Fitriani, 2021).

Covid-19 significantly affects the hematopoiesis and hemostasis system. Lymphopenia is the most common

laboratory finding in clinical cases. An increase in neutrophil-lymphocyte ratio has prognostic value in Covid-19 cases. Inflammatory parameters such as C-reactive protein (CRP), lactate dehydrogenase (LDH), and IL-6 were found to be elevated in Covid-19. Other biomarkers such as ferritin and procalcitonin were also found to bind in Covid-19. Parameters of coagulation disorders that can be found in covid-19 include increased D-dimer concentration, prolongation of Prothrombin Time or Activated Partial Thromboplastin Time, increased fibrinogen, and thrombocytopenia (Willim, Hardigaloeh and Supit, 2020).

D-dimer examination is a laboratory examination aimed at helping diagnose diseases and conditions that cause hypercoagilability, with a picture of the presence or absence of clots in the blood (D. Rustandi.2018). Covid-19 patient data shows an increase in D-dimer and fibrinogen-degradation product (FDP) found to be higher in non-survivor patients compared to survivors (Adti, 2021). Elevated D-dimer is often found in severe Covid-19 patients and is a predictor of ARDS, the need for treatment in the intensive care unit, and death. Elevated D-dimer has been reported as one of the most common laboratory test results in Covid-19 patients who do not survive. D-dimer examination along with prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen, are hemostasic tests that are commonly used in daily practice (Syafri, Edi; Endrizal, 2013).

Prothrombin Time is the most commonly performed coagulation test. The reagents for PT are tissue thromboplastin and ionized calcium. Prothrombin time is used to test the speed of blood clotting through extrinsic and shared pathways involving clotting factors VII, X, V prothrombin and fibrinogen (Malik, Nasrul, and Asterina 2015). Activated Partial Thromboplastin Time is an examination to determine the mechanism of prothrombin activator formation through the intrinsic pathway of blood coagulation. Shortening of APTT is due to increased levels of various coagulation factors that play a role in the intrinsic pathway, including factor XI, factor VIII and factor IX (Malik, Nasrul and Asterina, 2015). Coagulation tests showed PT appeared to be mildly prolonged in severe Covid-19 patients. The APTT test has no significant correlation with the severity of Covid-19 cases.

According to Widarti Armah, Zulfian Herman Rahayu, Sri (2021) in their research proves that there is a relationship between D-dimer, PT and INR with the presence of comorbidities in COVID-19 patients and there is a relationship between APTT and gender characteristics (Widarti et al., 2021).

Based on the background of the problem, the researcher is interested in conducting research on "The relationship between D-dimer levels with Prothrombin Time and Activated Partial Thromboplastin Time values in patients with Covid-19 at Dr. M. DJamil Padang Hospital".

RESEARCH METHODS

The type of research used is Observational analytic with Cross sectional study design, which is a type of research to see the relationship that occurs between the variables studied. This research was conducted at DR. M. Djamil Padang Hospital from February to July 2022. The population used was 30 samples of patients with Covid-19 who received hospitalization at DR. M. Djamil Padang Hospital. Data analysis in this study is a correlation test chosen because it sees whether there is a relationship between D-dimer levels and the value of Pothrombin Time and Activated Partial Thromboplastin Time in patients with Covid-19. Data is normally distributed if the p value is obtained <0.05, but if it is not normal, the results are obtained (P> 0.05). Before the correlation test is carried out, first do a normality test.

The tools and materials used are venous blood samples, whole blood/serum, Reagent Strips and SPR Reagent examination, Sysmex Cs.2500 tool, Vidas, Centrifuge, yellow type, disposible syringe, test tube rack, beacker glass, micropipette, 70% alcohol cotton, plaster, tourniquet, sterile gauze, blue and yellow lid vacutainer tubes, plastic vacutainer, test strips, serum cup.

There are 2 working procedures for this study, namely the work procedure for checking PT and APTT using the sysmex cs 2500 tool: 1. Blood samples with blue caps containing 3.2% sodium citrate are centrifuged first at 3500 speed for 15 minutes. Stacked on the tool rack. 2. Place the centrifuge tube rack on top of the device. 3. The tool automatically performs the examination and then the results are output in the form of a printout.

Work procedure for checking D-dimer levels using the Vidas device:

1. The sample used is serum 2. Reagent strips and SPR reagents according to the examination are removed from the refrigerator and allowed to stand at room temperature. 3. Press order, then scan the patient's barcode. 4. Press the requested test button, select the crate menu and the newly checked test will appear in the column. 5. Insert the strip and SPR Reagent according to the test column. 6. Then pipette the serum according to the test into the reagent. 7. Press start. 8. The results come out online / in the form of a printout. 9. If the results obtained are too high, do a re-check with dilution.

RESEARCH RESULTS

Characteristics of Research Subjects Based on Age and Gender in Patients with Covid-19.

Karakteristik	Min	Mks	Mean ± SD	N (%)
Age	21	81	55,5±14,934	
Gender			1,53±0,507	14 (47)
-Male	-	-		16 (53)
-Female	-	-		
Total				**30(100)**

Based on the table, the characteristics of research subjects in patients confirmed with Covid-19 had an average age of 55.5 ± 14.934 years, the lowest age was 21 and the highest was 81 years. Judging from the gender of most women 53%.

Results of Examination of D-Dimer Levels, PT and APTT Values in Patients with Covid-19.

Parameter	Min	Maks	Mean ± (SD)
D-Dimer Level (µg/ml)	253	7022	1696,23±1567,448
PT (seconds)	9,7	14,6	11,103±1,1898
APTT (seconds)	19,8	115,7	32,643±17,3796

Based on the table that D-dimer levels in patients of 30 respondents with Covid-19 with the results of D-dimer levels averaged 1696.23 ± 1567.448 µg / ml, the lowest level was 253 µg / ml and the highest was 7022 µg / ml, the average PT value was 11.103 ± 1.1898 seconds, the lowest value was 9.7 and the highest was 14.6 seconds. and on average APTT was 32.643 ± 17.3796 seconds, the lowest value was 19.8 seconds and the highest was 115.7 seconds.

The Relationship of D-dimer Levels with Prothrombin Time and Activated Partial Thromboplastin Time Values in Patients with Covid-19.

Parameter	Mean±SD	P value	R
D-Dimer Level (µg/ml) PT (seconds)	1696,23±1567,44 11,103±1,1898	0,003	0,529
D-Dimer Level (µg/ml)	1696,23±1567,44 32,643±17,379	0,110	0,298

APTT (seconds)			
PT (sec)	11,103±1,1898		
APTT (sec)	32,643±17,379	0,031	0,395

Based on the table that the results of the examination between D-dimer levels with PT values There is a significant relationship with a P value of 0.003, D-dimer levels with APTT statistically There is no significant relationship with a P value of 0.110, and at PT and APTT values significantly There is a significant relationship with a P value of 0.031.

DISCUSSION

This study used an analytical observational method with a cross sectional study design where this study was to determine the relationship between D-dimer levels with Prothrombin Time and Activated Partial Thromboplastin Time values in Covid-19 patients. From the results of research that has been conducted at DR. M. Djamil Padang Hospital, namely in Covid-19 sufferers with a total sample of 30 respondents, most of them are female (53%). this is not in line with several previous studies, namely data (WHO) in 2020 that men suffer more Covid-19 and in Indonesia also said that men suffer more Covid-19. According to ((Widarti et al., 2021), most men suffer more from Covid-19 with data obtained from research conducted at Hasanuddin University Hospital, as many as 91 respondents who were treated in 2020-2021 male patients were 57.1% while women were 42.9%. This is because women have better immunity than men.

From the results of research that has been conducted at DR. M. Djamil Padang Hospital, namely in patients with Covid-19 with a total sample of 30 respondents based on an average age of 56 years, this is in line with several studies that have been conducted by researchers. According to (Adti, 2021) based on age at Mitra Medika Amplas General Hospital from a total of 111 samples, the age group ≤ 60 years was 58.8% (65 people), and in the age group > 60 years, 41.4% (46 people) were found. The age proportion of Covid-19 patients ≤ 60 years is 58.8%. This condition shows that Covid-19 patients are more aged not too old than old, namely above 60 years. According to Guan's research (2020) in China concluded that the average age of Covid-19 patients or over 40 years of age in comorbid, 48.8 years to be exact. In contrast to research by Escalera-Antezana et al. (2020) explains that the most dominant patient is age ≥65 years with an HR (hazard ratio) of 2.563, meaning that people or patients aged ≥65 years have a 2.563 times greater risk of developing Covid-19 than <65 years.

Of the 30 respondents with Covid-19, the average D-dimer level was 1696.23 ± 1567.44 µg / ml based on the normal value of <500 µg / ml that the results obtained in this study were above the normal threshold value. This is in line with research that has been done by several researchers. According to (Minuljo et al., 2020) which states that the average D-dimer level of Covid-19 confirmed patients at Dr. Kariadi Central General Hospital in 436 patients is 3937.4 µg/ml or equivalent to 3.9374 mg/L. According to Guan and colleagues (2020) analyzed 1,099 confirmed Covid-19 patients from more than 550 hospitals in China. The results of the analysis stated that patients who did not survive had significantly higher D-dimer levels (median, 2.12 µg/ml) than patients who survived (median, 0.61 µg/ml).

Of the 30 respondents with Covid-19, the average Prothrombin Time value was 11.103 ± 1.1898 seconds based on the normal value between 10-13 seconds that the results obtained in this study were normal. This is in line with research that has been conducted by several studies. that according to Zi et al (2021), the average PT value was 12.3 (11.2-13.1) seconds, in this study normal results were obtained because the patients were not at a high level of severity. According to (Wahdaniah and Tumpuk, 2017) The elongated clotting period in PT and APTT occurs because the factor deficiency will be corrected by the test. If correction is absent or incomplete with normal plasma, then coagulation inhibitors are suspected. Examination of bleeding time (BT) and clotting time (CT) has low sensitivity and specificity in predicting bleeding risk, while examination of activated partial thromboplastin time (APTT) is more sensitive and has better reproducibility than clotting time.

Of the 30 respondents with Covid-19, the average Activated Partial Thromboplastin Time in Covid-19 Patients was 32.643 ± 17.379 seconds based on the normal value between 23-25 seconds that the results obtained in this study were abnormal. This is in line with research that has been done by several studies. According to Zi et al (2021), the average Activator Partial Thromboplastin Time value was 28.3 (23-25) seconds. In this study, the results were slightly normal because this patient had just confirmed Covid-19. According to Lin et al (2020) shortened APTT has a significant relationship with patients with Covid-19. In Lin's study, APTT shortening had a significant relationship to severity because the study included other risk factors such as smoking, diabetes mellitus, hypertension, coronary heart disease, acute myocardial infarction and other ballast factors. Where factors such as those mentioned above can affect hypercoagulation resulting in dysregulation of intrinsic factors that cause APTT shortening.

Of the 30 respondents that the results of D-dimer levels with Prothrombin Time values showed a P value = 0.03 (<0.05) and an r value = 0.529. From these results, it shows that there is a significant relationship between D-dimer levels and Prothrombin Time in patients with Covid-19 with moderate strength. This can be seen from research according to (Willim, Hardigaloeh, and Supit 2020) on coagulation disorder parameters that can be found in Covid-19 including increased D-dimer concentrations, prolongation of prothrombin time (PT) or activated partial thromboplastin time (APTT), increased fibrinogen, and thrombocytopenia..

Of the 30 respondents that the results of the examination of D-dimer levels with the value of Activated Partial Thromboplastin Time showed a P value = 0.110 (>0.05) and an r value = 0.298. These results indicate that there is no significant relationship between D-dimer levels and the value of Activated Partial Thromboplastin Time in Covid-19 sufferers with weak strength. This can be seen from research According to (Syafri, Edi; Endrizal, 2013) D-dimer examination along with prothrombin time (PT), Activated partial thromboplastin time (APTT), and fibrinogen examination, are hemostasic tests that are usually used in daily practice. According to (Willim, Hardigaloeh and Supit, 2020) The APTT test has no significant correlation with the severity of Covid-19 cases and Covid-19 patients with an increase in D-dimer (3-4 times) need to be hospitalized even though there are no severe symptoms because this indicates that there is an increase in thrombin generation and is at risk of thrombosis.

Of the 30 respondents, the results of the examination of the Prothrombin Time and Activated Partial Thromboplastin Time values showed a P value = 0.031 (<0.05) and an r value = 0.395. These results indicate that there is a significant relationship between the value of Prothrombin Time and Activated Partial Thromboplastin Time in patients with Covid-19 with weak strength. This can be seen from research According to (Kahar and Salim, no date) Coagulation tests show PT appears to be mildly prolonged in severe Covid-19 patients. While the APTT test does not has a significant correlation with the severity of Covid-19 cases.

CONCLUSIONS

Based on the results of research that has been conducted on the Relationship between D-dimer Levels with Prothrombin Time and Activated Partial Thromboplastin Time Values in Patients with Covid-19 at DR. M. Djamil Padang Hospital, it can be concluded as follows:

1. The average D-dimer level in patients with Covid-19 suspects is 1696.23 µg / ml
2. The average value of Prothrombin Time in patients with Covid-19 suspects is 11.103 seconds
3. The average Activated Partial Thromboplastin Time value in Covid-19 suspected patients is 32.643 seconds
4. There is a significant relationship between D-dimer levels and Prothrombin Time values in Covid-19 patients, there is no significant relationship between D-dimer levels and Activated Partial Thromboplastin Time values in Covid-19 patients and there is a significant relationship between Prothrombin Time and Activated Partial Thromboplastin Time values at Dr. M. Djamil Padang Hospital.

Suggestion

From the research conducted, the authors suggest continuing research based on gender should use a larger sample because the case is more widespread throughout the world.

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