



ORIGINAL ARTICLE

Correlation between Coagulation Tests Parameter with Padua Prediction Score in Covid-19 Patients at General Hospital of Prof. Dr. R. D. Kandou Manado

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) was associated with hypercoagulability state, some changes in parameter of coagulation tests, and also cause venous thromboembolism (VTE), which can be predicted with Padua Prediction Score (PPS). In this study, we are going to seek correlation of PPS and some parameter of coagulation tests between mild and moderate - severe COVID-19 patients in isolation room for COVID-19 patients at General Hospital of Prof. dr. R. D. Kandou Manado.

Methods: Our cross-sectional study was conducted in August - October 2020 in COVID-19 isolation room of RSUP Prof. dr. R. D. Kandou Manado. Coagulation tests parameter in this research was prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), platelets and D-dimer, as for risk screening of VTE, we used PPS. Then Mann-Whitney test was conducted to see mean difference of PPS and other coagulation test parameters between mild and moderate-severe symptoms of COVID-19 patients. We then use Spearman test to see correlation between PPS and the coagulation tests.

Results: From 42 sample, there were 25 patients with mild symptoms, and 17 with moderate - severe symptoms, and from Mann - Whitney test there was a significant difference of PPS, D-dimer and PT between mild and moderate-severe COVID-19 patients. From Spearman correlation of PPS and parameters of coagulation tests, we found that there was a moderate and significant correlation with D-dimer ($r = 0.432$, $p = 0.004$), strong and significant correlation with PT ($r = 0.586$, $p = 0.00$), very weak and not significant correlation with a PTT ($r = 0.073$, $p = 0.64$), and moderate yet significant correlation with INR ($r = 0.345$, $p = 0.02$).

Conclusions: There was a significant difference between PPS, D-dimer and PT from mild symptoms with moderate - severe symptoms of COVID-19 patients, and there was a strong and significant correlation of PT with PPS, medium and significant correlation of D-dimer and INR with PPS and a very weak and not significant correlation of a PTT with PPS.

Keywords

Padua prediction score, D-dimer, PT, aPTT, INR, COVID-19

Background

It is estimated that there were 63.360.234 confirmed cases of coronavirus 2019 disease (COVID-19) (as per December 2020) caused by the novel coronavirus (SARS-COV-2), including 1,475,825 deaths in around 220 countries [1].

Recently, it is known that the COVID-19 is related to hypercoagulability state [2]. Other clinical features found in COVID-19 patients were coagulopathy, in the form of mild thrombocytopenia, increased D-dimer and fibrin(-ogen) degradation products (FDP), prolonged prothrombin time (PT), and increased levels of fibrinogen and factor VIII [3-5]. In studies by Zhang, et al. from 140 COVID-19 patients, there was a significant increase of D-dimer value (2 times) in patients with a severe disease compared to lighter degree [6].

Coagulopathy can cause venous thromboembolism



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Table 1: Padua prediction score.

Active cancer (local or distant metastases; chemotherapy and/or radiotherapy in the last 6 months)	3
Previous VTE (with exclusion of superficial vein thrombosis)	3
Reduced mobility (bedrest with bathroom privileges for at least 3 days)	3
Already known thrombophilia	3
Recent trauma and/or surgery in the last month	2
Age ≥ 70	1
Heart and/or Respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or Rheumatologic disorder	1
Obesity (BMI ≥ 30)	1
Ongoing hormonal treatment	1

Table 2: Demographic characteristics.

	Categories	n (%)
Severity	Mild	25 (59%)
	Moderate - severe	17 (41%)
Sex	Male	24 (57%)
	Female	18 (43%)
Age	< 65 years	28 (66%)
	≥ 65 years	14 (34%)

(VTE), and this can be predicted with several scores, such as Padua Prediction Score (PPS). High PPS levels are also associated with poor prognosis in COVID-19 patients who require hospitalization [7].

In this study, we will see the correlation between several coagulation parameters with PPS in patients with mild with moderate-severe COVID-19 patients treated in the isolation room of COVID-19 patients at General Hospital of Prof. dr. R. D. Kandou Manado.

Methods

This cross sectional study was conducted during August - October 2020 in COVID-19 isolation room at General Hospital of Prof. dr. R. D. Kandou Manado. The inclusion criteria of sample population taken with consecutive random sampling were patients aged ≥ 18 years suffering from COVID-19 and was willing to participate in the research, and exclusion criteria was having any kind of hematological or oncological malignancy, had Acquired Immune Deficiency Syndrome (AIDS), autoimmune diseases, were using corticosteroid and anticoagulants, and are undergoing hemodialysis.

Coagulation parameters included in this study include PT, activated partial thromboplastin time (APTT), international normalized ratio (INR), platelets, D-dimer and fibrinogen. Padua Prediction Scores (Table 1) have components such as active cancer, previous VTE history, reduced mobility, previously known thrombophilic conditions, each of which has a score of +3, history of trauma and/or surgery less than equal to 1 month ago with a score of +2, and age more than 70 years, heart failure and/or respiratory failure, acute

myocardial infarction and/or ischemic stroke, acute infections and/or rheumatology disorder, obesity, and ongoing hormonal therapy with a score of +1 each. PPS more than/equal to 4, have a high risk of VTE, and less than 4 was considered low VTE risks [8].

Classification of severity symptoms of COVID-19 Patients Based on the criteria of the Coronavirus Disease Prevention and Control (CDC) Guidelines released by the Ministry of Health in July 2020, as follows: considered as mild symptoms if patients has a non-specific symptoms such as fever, coughing, pain throat, nasal congestion, malaise, headache, muscle aches, without criteria that meet the symptoms of medium symptoms such as shortness of breath and clinical signs of pneumonia (fever, coughing, shortness of breath and rapid breath), or severe symptoms such as breathing frequency $> 30x/minute$, SPO₂ $< 90\%$ in room air or worse [9]. In this study we classified into two category: mild and moderate-severe symptoms.

The statistical test was carried out with a computer statistical program with a descriptive statistical analysis of the univariate method to see the amount and mean value of the research variable, then a non-parametric Mann-Whitney test was carried out to see the difference of the average PPS and the coagulation test between light with moderate-severe symptoms of COVID-19 patients. Bivariate analysis is carried out to determine the relationship between coagulation tests and PPS using simple regression analysis with Pearson correlation test when the distribution of data is normal, and Spearman correlation test if the data distribution isn't normal. The test results were said to be significant if the value of $p < 0.05$.

Results

From 42 samples that we took, there were 25 patients of COVID-19 with a mild symptom and 17 with moderate-severe symptoms (Table 2); 24 of them were male and 18 were female; 28 people were less than 65 years old, and there were 14 people were ≥ 65 years old. While for the risk of VTE from PPS, there were 33 patients had low risk (score < 4), and 9 people were high risk (score ≥ 4).

The sample was then conducted with a univariate descriptive analysis test from each coagulation test parameter was carried out to obtain an average value of platelets, fibrinogens, D-Dimer, PT, APTT, and INR in patients with mild symptoms respectively, 292,520/ μ L, 479.36 mg/dl, 1.77 μ g/ml, 13.9", 35.7" and 1.11", while for PPS there are an average of 0.56. For the mean value of platelets, fibrinogen, D-dimer, PT, APTT, and INR in patients with moderate-severe symptoms, different results are obtained compared to mild symptoms respectively, 187,876/ μ L, 456.76 mg/dl, 9.06 μ g/ml, 15.2", 36.3" and 1.21", where the average for PPS was 2.82 (Table 3).

Then we did normality test with the Saphiro Wilk test, and we found that the data was not distributed normally, then the Mann-Whitney test was carried out from PPS and each coagulation, and we found that there was a significant difference from the PPS value ($p = 0.000$), platelets ($p = 0.011$), D-dimer ($p = 0.003$) and PT ($p = 0.036$) of COVID-19 patients with mild symptoms with moderate-severe symptoms, while there is no significant difference in fibrinogen ($p = 0.808$), aPTT ($p = 0.663$) and INR ($p = 0.071$) between the two groups in this study (Table 4).

The correlation test between PPS and each coagulation test was carried out with Spearman correlation test (Table 5). Spearman correlation test results between PPS and platelets showed that there were moderate but insignificant correlation

(correlation coefficient (r) = -0.27, $p = 0.08$), whereas a moderate and significant correlation was found between PPS with D-dimer ($r = 0.432$, $p = 0.004$), very weak and insignificant correlation ($r = 0.08$, $p = 0.95$) with fibrinogen. For the correlation test between PPS and coagulation test, there was a strong and significant correlation with PT ($r = 0.586$, $p = 0.00$), very weak and insignificant correlation with aPTT ($r = 0.073$, $P = 0.64$), and moderate and significant correlation with INR ($r = 0.345$, $p = 0.02$).

Discussion

From the study that we conducted for 2 months, there were 42 samples, from which 24 patients were male (57%) and 17 were female (43%). Zhang, et al. also conducted research with similar samples, of which 49% were female [6] and around 60% of cases were dominated by men in Guan, et al. [10]. There were 28 patients (66%) aged < 65 years old and 14 people (34%) were ≥ 65 years old, similar to reports from CDC in early 2020 where 31% were ≥ 65 years old and around 69% were < 65 years old [11].

After the calculation of PPS from all samples, mean PPS analysis was carried out from mild and moderate-severe symptoms, with results of 0.56 points for patients with mild symptoms, and 2.82 points with moderate-severe symptoms. When compared between patients with mild and moderate - severe symptoms, there was a significant difference in value ($p = 0.00$). Xeng, et al. also reported that patients with severe symptoms had

Table 3: Mean of PPS and coagulation tests parameter of COVID-19 patients.

	Mild COVID-19 (n = 25)	Moderate-Severe COVID-19 (n = 17)
Padua prediction score	0.56	2.82
Platelete (μ L)	292.520	197.876
Fibrinogen (mg/dL)	479.36	456.76
D-dimer (μ g/mL)	1.77	9.06
PT (")	13.9	15.2
aPTT (")	35.7	36.3
INR (")	1.11	1.21

Table 4: Mann Whitney tests for coagulation tests between mild and moderate-severe COVID-19 patients.

	Padua Prediction Score	Platelet	Fibrinogen	D-dimer	PT	aPTT	INR
Mann whitney	0.000	0.011	0.808	0.003	0.036	0.663	0.071

Table 5: Correlation test between PPS and coagulation test in COVID-19 patients.

	Padua prediction score	
	Correlation coefficient (r)	Sig. (2-Tailed) (p)
Plateletes	-0.271	0.083
Fibrinogen	0.008	0.959
D-dimer	0.432	0.004
PT	0.586	0.000
INR	0.345	0.025
aPTT	0.073	0.648

higher PPS than moderate symptoms (4 vs. 1, $p < 0.001$) [12].

The mean value of platelets in this study were 292,520/ μL for mild symptoms and 197,876/ μL for moderate-severe symptoms, while D-dimer was 1.77/ μL for mild symptoms, and 9.06/ μL for moderate-severe symptoms. There are differences in mean platelet ($p = 0.011$) and D-dimer ($p = 0.003$) values between mild and moderate-severe symptoms, and there is a moderate but insignificant correlation between PPS and platelets ($r = -0.27$, $p = 0.08$), while correlation between PPS and D-dimer, there is a moderate and significant correlation ($r = 0.432$, $p = 0.004$). A meta-analysis study carried out by Lippi, et al., there's a significantly lower platelet calculations in patients with severe diseases (average differences -31,000/ μL , 95% CI: -35,000/ μL to -29,000/ μL) [13], while other studies found that the higher PPS, the platelet value tends to be lower [11]. Tang, et al. reported that an increase in D-Dimer is related to poor prognosis in patients affected by the Coronavirus novel [14]. D-dimer is also reported to had a different levels in patients who require ICU (about 2.5 times normal) [15] and those who do not require ICU (twice normal value) [16]. In research conducted by Xeng, et al., reported that the higher PPS, the higher is the D-Dimer [12].

Increased fibrinogen was associated with poor prognosis in other study [14], but in our study we did not find any differences in fibrinogen between mild and moderate-severe symptoms ($p = 0.808$), and a very weak yet not significant correlation between PPS and fibrinogen ($r = 0.008$, $p = 0.959$). Unlike study from Xeng, et al., [12] we found a tendency for fibrinogen to be higher in severe symptoms compared to moderate symptoms (4.01 vs. 3.27, $p = 0.031$), and the higher the PPS value, the higher the fibrinogen level.

Thrombocytopenia and an increase in D-dimer can be explained by the excessive activation of coagulation and platelets. Viral infection triggers systemic inflammatory responses and causes imbalance between procoagulant and anticoagulant homeostatic mechanisms [17]. Various mechanisms were related in it, including endothelial dysfunctions, increased von Willebrand factors, Toll-like receptor activation, and activation of the tissue-factor pathway [17-19]. Platelets, when recognizing the presence of antigens, become active and interact with leukocytes to facilitate pathogenic clearance through leukocyte activation and clot formation [20]. Platelets are an inflammatory and sensor mediators from infectious agents through the interaction of cell surface receptors with pathogens (pathogen pattern recognition receptors) or from the immune system derivative (immunoglobulin Fc and complement receptors). Activation of macrophages, monocytes, endothelial cells, platelets and lymphocytes plays important part on the procoagulant effect of viral infections [18,21].

Prothrombin Time (PT) represents the universal coagulation test needed in the DIC and VTE therapy [22]. Prolonged of PT was related with poor prognosis [14]. In our study, the average PT was 13.9 "for mild symptoms and 15.2" for moderate-severe symptoms and there is a differences in PT value between mild and moderate-severe symptoms ($p = 0.036$), and there is a strong correlation between PPS and PT ($r = 0.586$, $p = 0.00$). Similar to what was reported by Xeng, et al., the higher the PPS value, the longer the PT, and the value of PT in critically ill patients were longer than severely ill ones (15.35 vs. 13.3", $p < 0.001$) [12].

PT results were corrected mathematically into INR by raising the PT-ratio to a power equal to the international sensitivity index (ISI) [22]. In our study, we have an INR average of 1.11" in patients with mild symptoms and 1.21" ($p = 0.071$), and had moderate yet significant correlation with PPS ($r = 0.345$, $p = 0.02$). In contrast to what was reported by Xeng, et al., [12] they did not found a differences between INR in severe symptoms and critical patients, possibly because they compare severely ill and critically ill patients, while we compare mild with moderate - severe symptoms.

The significance of the PT difference was based on the admission status to the Intensive Care Unit (ICU) in two different studies, [15,16] while other studies shows that the prolonged PT at the admission and follow-up was a predictor for severity and mortality of the disease [23-26]. The standardized INR value was also reported to be related to the severity of the disease [27,28].

Measurement of APTT in our study found that it had a very weak and not significant correlation with PPS ($r = 0.073$, $p = 0.64$), and the same thing was also reported by Xeng, et al., saying that there were no differences in APTT between their study groups ($p = 0.663$) [12].

Limitations

There are several limitations in this study. First, this study is a retrospective study and limited to one location. More sample size was needed to confirm the results and to eliminate bias. Second, the number of sample between low and high risk of VTE group was very different, and we use the number of PPS scores and not classified between high and low risk for VTE.

Conclusion

From 42 samples of COVID-19 patients, which consists of 25 mild symptoms and 17 moderate-severe symptoms, there was a significant difference from the values of PPS, platelets, D-Dimer and PT between mild and moderate-severe symptoms group, whereas for correlation with PPS there is a correlation strong and significant correlation with PT, and a moderate and significant correlation with D-dimer and INR. As for with platelets, there was a moderate yet insignificant correlation with PPS, and a very weak and insignificant correlation between PPS with aPTT and fibrinogen.

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