Pharmacogn J. 2024; 16(6): 1373-1378
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Natural Compounds in Clot Waveform Analysis and D-Dimer Modulation: Implications for COVID-19 Diagnosis and Prognosis

Prafa Alif Rahmawan[1], Yetti Hernaningsih[2,3]*

ABSTRACT

Objectives: Patients diagnosed with coronavirus disease (COVID-19) may develop hypercoagulopathy. A thromboelastogram can detect hypercoagulopathy, but it is not commonly available in all healthcare facilities. Understanding the clot waveform analysis (CWA) parameters of the CS-2500 coagulation analyzer in patients diagnosed with COVID-19 may help determine whether it can serve as an alternative. **Methods:** This study measured the amounts of activated partial thromboplastin time (aPTT)-based CWA, aPTT, plasma prothrombin time (PPT), and D-dimer using the CS-2500 autoanalyzer in 177 patients confirmed with COVID-19 and 110 patients without COVID-19. Retrospective data collection was conducted using electronic medical records. COVID-19 and non-COVID-19 were distinguished by the SARS-COV-2 PCR results. **Results:** Substantial differences were observed in the aPTT-based CWA parameters, including maximum coagulation velocity (Vmax), maximum coagulation acceleration (Amax), and maximum coagulation deceleration (Dmax) ($p = 0.03$, $p = 0.03$, and $p = 0.02$), between the COVID-19 and non-COVID-19 groups but not between survivors and non-survivors. Additionally, a substantial difference was identified in the D-dimer between the two groups ($p = 0.002$ and $p < 0.001$). The difference in D-dimer between both groups could be explained by the fact that non-survivors have a more prominent hypercoagulable state. **Conclusions:** While the D-dimer may be a better indicator of mortality in COVID-19 patients, the aPTT-based CWA characteristics may be more helpful in differentiating between COVID-19 and non-COVID-19 patients. Further investigations on treatment interference and the specificity of this method to predict hypercoagulable states are warranted.

Keywords: COVID-19, D-dimer, Activated partial thromboplastin time, Clot waveform analysis.

Prafa Alif Rahmawan[1], Yetti Hernaningsih[2,3]*

[1]Student of Specialist, Clinical Pathology Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, INDONESIA.

[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, INDONESIA.

[3]Department of Clinical Pathology, Dr. Soetomo General Academic Hospital, Surabaya, INDONESIA.

Correspondence

Yetti Hernaningsih

Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga; Department of Clinical Pathology, Dr. Soetomo General Academic Hospital, Surabaya, INDONESIA.

E-mail: yetti-h@fk.unair.ac.id

History

- Submission Date: 01-10-2024;
- Review completed: 23-11-2024;
- Accepted Date: 29-11-2024.

DOI : 10.5530/pj.2024.16.221

Article Available online

http://www.phcogj.com/v16/i6

INTRODUCTION

Coronavirus disease (COVID-19) is a disease caused by the SARS-CoV-2 virus that was discovered in December 2019 in Wuhan, China.[1] This virus is categorized as a member of the coronavirus family but with a modest genetic variation.[1] In 2020, the World Health Organization confirmed 29,679,284 cases and 936,521 deaths. Cough, exhaustion, and dyspnea are the most frequent COVID-19 symptoms.[2] In addition, it can be manifested by muscle pain, sore throat, anorexia, nausea, vomiting, and diarrhea.[3] Sometimes, it manifests as anosmia (loss of smell).[4] Comorbidity is also essential for predicting the disease, prognosis, and severity.[3] Diabetes mellitus is one comorbidity that could exacerbate the patient's condition and necessitate an intensive care observation.[5] These symptoms may also manifest in certain conditions, such as hypertension and cardiovascular diseases.[6]

The risk and severity of COVID-19 can be predicted by a number of laboratory and auxiliary tests. The most common laboratory findings are a neutrophil/lymphocyte ratio greater than 3.13, lymphocytopenia, and thrombocytopenia, as well as elevated levels of D-dimer, ferritin, activated partial thromboplastin time (aPTT), C-reactive protein, lactate dehydrogenase, and others, which are used to assess the risk and prognosis of heart damage in individuals diagnosed with COVID-19.[7]

Examination of coagulation and markers of infection are the most exciting topics to discuss. Coagulation testing is essential because the hemostasis imbalance typically occurs in SARS-CoV-2 infection, and the tendency toward hypercoagulability exacerbates the condition of patients, particularly with comorbidity.[8] The protocol of coagulation markers for diagnosing COVID-19 includes aPTT, PPT, and D-dimer. The levels of D-dimer in individuals diagnosed with COVID-19 increase substantially and contribute to disease severity. The prognosis of individuals affected with COVID-19 is frequently predicted using this method.[8] In addition, aPTT levels tend to increase in patients with COVID-19.[9] Furthermore, a thromboelastogram (TEG) is used to thoroughly analyze the coagulation status in individuals affected with COVID-19.[10]

D-dimer and TEG examinations are available at referral health services, while aPTT and PPT examinations are more widely available. Due to the limited availability of D-dimer or TEG testing, alternative methods for assessing the coagulation status in patients with COVID-19 are required. Another alternative approach is to explore the clot waveform analysis (CWA) parameters available from coagulation instruments when tested for aPTT and PPT, which rely on optical detection, such as the scattered light detection method. This method measures variations in light transmission prior to clotting until clot formation.[11] This parameter is still hidden, unreported, and not widely explored when performing aPTT and PPT tests on coagulation studies with an optical-based method used to examine samples.

The application of CWA varies and can be employed in several clotting-based assays, such as the Clauss

Cite this article: Rahmawan PA, Hernaningsih Y. Natural Compounds in Clot Waveform Analysis and D-Dimer Modulation: Implications for COVID-19 Diagnosis and Prognosis. Pharmacogn J. 2024;16(6): 1373-1378.

fibrinogen assay [12] or aPTT.[11] CWA parameters are calculated based on clotting speed and derivate. CWA parameters can predict the deterioration of patients with severe bacterial or viral infections and signify the activation of altered coagulation processes and reduced fibrinolysis.[11] For this reason, this study aims to determine whether the CWA parameter can be utilized to investigate the prognosis and diagnosis of individuals affected by COVID-19. We also tried to correlate CWA with D-dimer, which has been established as a parameter in line with the disease severity of COVID-19.

MATERIAL AND METHODS

The design was an analytical, retrospective study by collecting, processing, and analyzing data from electronic medical records of all patients performing aPTT, PPT, and D-dimer assay in Dr. Soetomo General Academic Hospital Surabaya, Indonesia, from August to September 2020.

Data Collection

A total of 676 data sets comprised of aPTT and D-dimer were collected from Sysmex CS 2500i instruments (Sysmex Corporation, Kobe, Japan, and laboratory information systems). Three data sets were excluded because the results of CWA were invalid after being reviewed. Within 673 data sets, it could comprise serial tests of a patient. In that case, the last data was chosen. The data was chosen when aPTT, PPT, and D-dimer were tested simultaneously. Patients' data were separated into COVID-19 and non-COVID-19 groups using polymerase chain reaction (PCR) testing specifically applied to COVID-19 cases. The patients who had been positive for the PCR test were categorized as patients who confirmed COVID-19, and inversely. The final clinical outcome was determined based on whether the patient died during treatment as a non-survivor or was discharged from the hospital alive as a survivor. Patients were screened for COVID-19 in the ER and outpatient clinic during the data collection before being admitted to the ward/ICU or isolation ward/isolation ICU. CWA data was taken afterward.

Clotwaveform Analysis

The data collected was primarily for aPTT-based CWA tests. CWA is a different method of assessing hemostasis, which examines the kinetics of clot formation during routine clotting tests, such as PTT, PPT, or fibrinogen. The parameters of CWA comprised Vmax, Dmax, and Amax. Vmax is defined as the maximum coagulation velocity. Amax is maximum coagulation acceleration. Dmax is maximum coagulation deceleration. Vmax unit would be described as min1, the percentage of transmission changes in units %/s, which means the transmission velocity changes within a second. Amax unit is min2, the percentage of changes in units %/s2, which means the acceleration of transmission change within a second square, and Dmax unit is max2, the percentage of changes in units %/s2; which means the deceleration of transmission change within a second square.[13]

Statistical Analysis

The data were tested for normality using the Shapiro–Wilk and Kolmogorov–Smirnov tests. D-dimer levels in COVID-19 and non-COVID-19 groups were compared using the Mann–Whitney U test, while aPTT-based CWA parameter levels were compared using an independent Student's t-test. The data of D-dimer and aPTT-based CWA parameters in COVID-19 were correlated using Spearman's rho correlation test. The statistical analysis was done using SPSS 26.0 by IBM.

RESULTS

Two hundred eighty-seven data sets were obtained, comprising 177 Covid data sets and 110 non-Covid data sets (Table 1). These data were related to 177 COVID-19 and 110 non-COVID-19 patients. Those with COVID-19 were then categorized into 120 survivors and 57 non-survivors.

The COVID-19 and non-COVID-19 groups demonstrated a mean D-dimer level of 3,710 ± 6,800 ng/mL and 4,450 ± 5,450 ng/mL, respectively. Moreover, the mean levels of maximum coagulation velocity (Vmax) CWA, maximum coagulation acceleration (Amax) CWA, and maximum coagulation deceleration (Dmax) CWA in the group of COVID-19 were 6.54 ± 2,09 %/s; 1.03 ± 0.37 %/s^2; and 0.88 ± 0.33 %/s^2, respectively, while the values for the non-COVID-19 group were 5.99 ± 2.19 %/s; 0.94 ± 0.37 %/s^2; and 0.79 ± 0.33 %/s^2, respectively. Significant variations occurred in the levels of D-dimer or aPTT-based CWA parameters between the COVID-19 group and the non-COVID-19 group ($p < 0.05$) (Table 2 and Figure 1).

COVID-19, coronavirus disease; CWA, clot waveform analysis. Vmax, maximum coagulation velocity; Amax, maximum coagulation

Table 1. The characteristics of patients.

Characteristics	Number	
	Group of Covid-19 (n=177)	Group of non Covid-19 (n=110)
Age (years old), median (min-max)	51 (16-82)	51 (5-88)
Gender		
Male	94 (53.11%)	62 (56.36%)
Female	83 (46.89%)	48 (43.64%)
Diagnosis	Pneumonia COVID-19 (177; 100%)	Non COVID 19 Pneumoniae (58; 53%) Others (52; 47%) comprised diabetes mellitus, sepsis, anemia pro evaluation, neoplasm, and chronic kidney disease.
Comorbid	With comorbid= 158 (89.27%), the common diseases are hypertension, diabetes mellitus, obesity, and sepsis. Without comorbid= 19 (10.73%)	

Table 2. D-dimer and CWA parameter levels differ between patients with COVID-19 and non-COVID-19 patients.

	Group of COVID-19 (n = 177)	Group of non-COVID-19 (n = 110)	P-value
D-dimer level (ng/mL)	3,710 ± 6,800	4,450 ± 5,450	0.002*
Vmax CWA value (%/s)	6.54 ± 2.09	5.99 ± 2.19	0.032*
Amax CWA value (%/s^2)	1.03 ± 0.37	0.94 ± 0.37	0.032*
Dmax CWA value (%/s^2)	0.88 ± 0.33	0.79 ± 0.33	0.020*

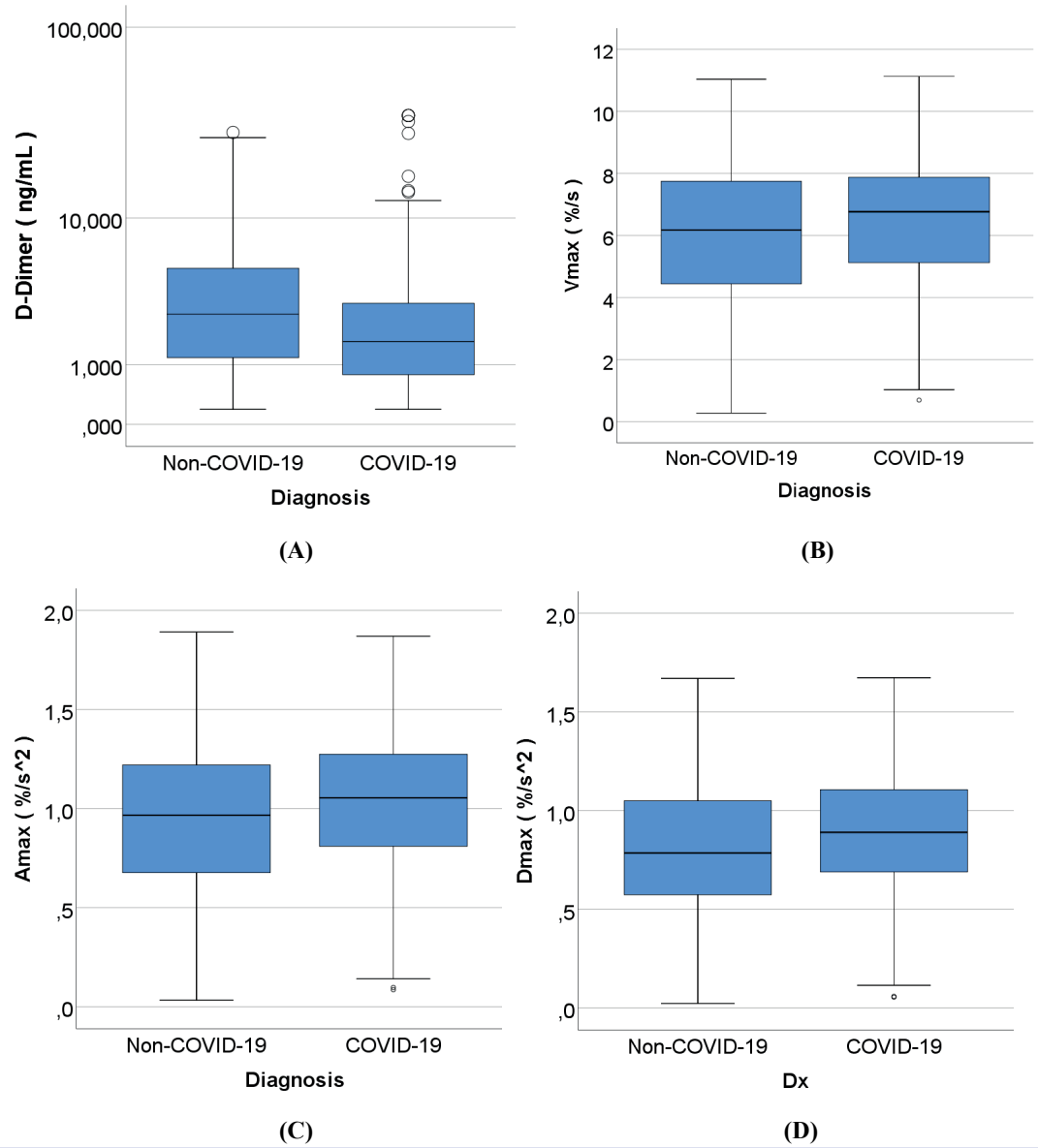

Figure 1. Boxplot values of **(A)** D-dimer, (B) Vmax CWA, **(C)** Amax CWA, and **(D)** Dmax CWA in COVID-19 and non-COVID-19 patients. The box shows the median and interquartile range values, while the upper and lower lines represent the minimum and maximum values.

acceleration; Dmax, maximum coagulation deceleration; s, second. *P-value<0.05.

Data from 177 patients with COVID-19 were grouped into 120 survivors and 57 non-survivors. The mean D-dimer level in survivors was 2,180 ± 3,880 ng/mL, while in non-survivors was 6,930 ± 9,880 ng/mL. Moreover, the mean levels of Vmax CWA, Amax CWA, and Dmax CWA in the group of survivors were 6.45 ± 1.88 %/s, 1.03 ± 0.32 %/s^2, and 0.89 ± 0.29 %/s^2, respectively, while they were 6.74 ± 2.49 %/s, 1.04 ± 0.44 %/s^2, 0.87 ± 0.39 %/s^2, respectively, in group of non-survivor. A remarkable difference in D-dimer levels ($p < 0.05$) was identified between the survivor and non-survivor groups, while no significant differences in aPTT-based CWA parameter levels ($p > 0.05$) were detected between these groups (Table 3 and Figure 2).

COVID-19, coronavirus disease; CWA, clot waveform analysis. Vmax, maximum coagulation velocity; Amax, maximum coagulation acceleration; Dmax, maximum coagulation deceleration; s, second. *P-value < 0.05.

Correlation analysis of D-dimer and Amax, Vmax, and Dmax of CWA revealed a negligible insignificant positive correlation with respective rho and p-value of 0.097;0.197 (Vmax), 0.055;0.465(Amax), and 0.036;0.638 (Dmax).

DISCUSSION

D-dimer is an end product of fibrinolysis, also known as fibrin degradation product, which occurs following normal or pathological coagulation.[14] In individuals infected with COVID-19, D-dimer production refers to a coagulopathy process focused primarily on peripheral alveoli, in contrast to disseminated intravascular coagulation, which occurs throughout the body.[15] Due to coagulopathy, those infected with COVID-19 have elevated D-dimer levels.[16]

This study revealed remarkable differences in D-Dimer levels between patients who tested positive for COVID-19 and those having other diseases (who tested negative for COVID-19). Non-COVID-19 diseases in this study included non-COVID-19 pneumonia, malignancy,

Table 3. The difference in D-dimer and CWA parameter levels between survivors and non-survivors.

	Group of survivors (n = 120)	Group of non-survivors (n = 57)	P-value
D-dimer level (ng/mL)	2,184 ± 3,881	6,928 ± 9,877	<0.0000*
Vmax CWA value (%/s)	6.45 ± 1.88	6.74 ± 2.49	0.439
Amax CWA value (%/s^2)	1.03 ± 0.32	1.04 ± 0.44	0.840
Dmax CWA value (%/s^2)	0.89 ± 0.29	0.87 ± 0.39	0.681

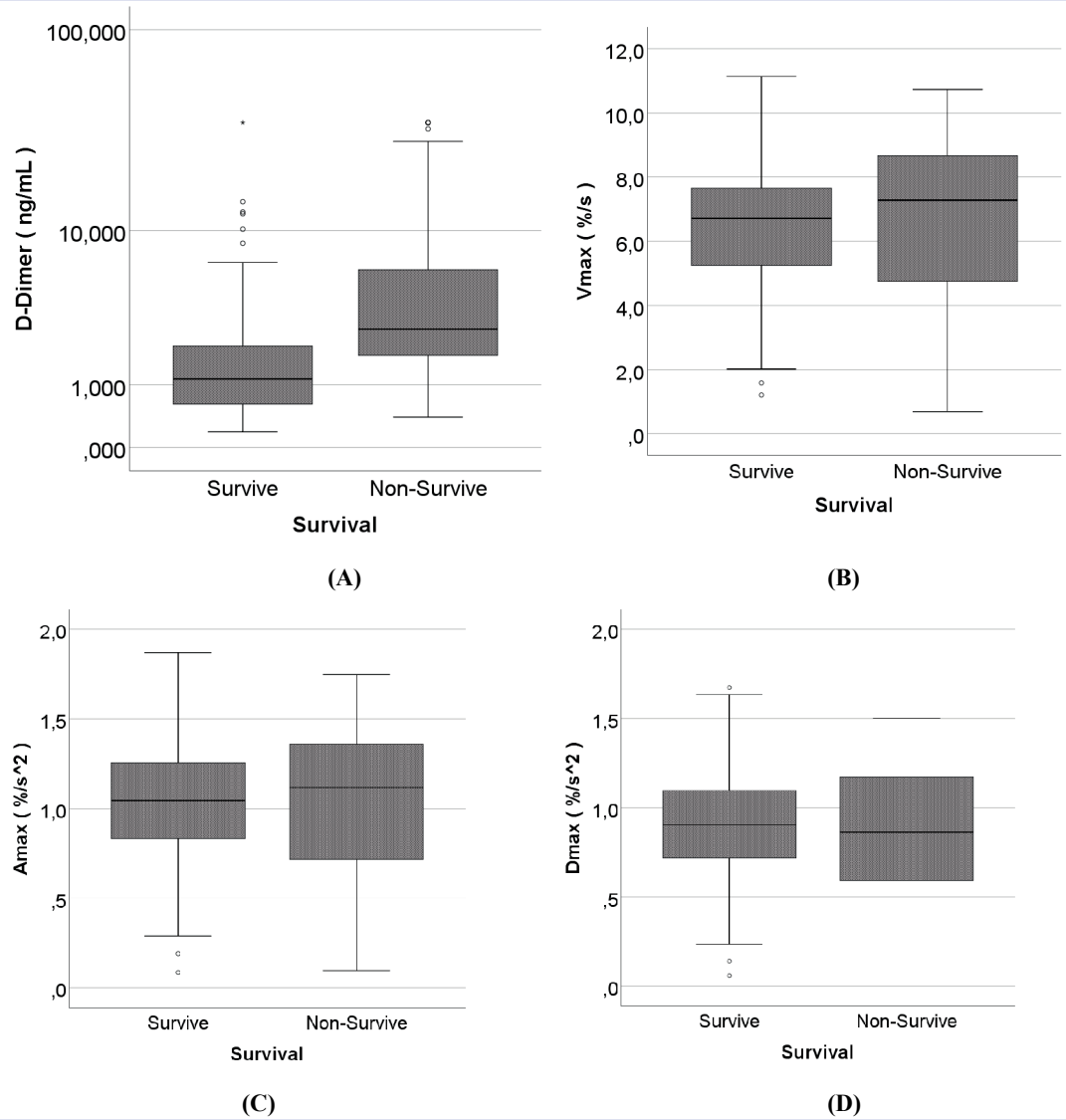

Figure 2. Boxplot values of **(A)** D-dimer, (B) Vmax CWA, (C) Amax CWA, and (D) Dmax CWA in the survivor and non-survivor groups. The box displays the interquartile range and median values, while the upper and lower lines represent the minimum and maximum values.

severe trauma, and other diseases. Other studies found that similar to COVID-19 pneumonia, the lung infection process associated with severe clinical pneumonia can also increase dimer levels.[17,18] Other inflammatory conditions, including other bacterial or viral infections,[19] inflammation or sepsis,[20] and malignancy,[21] increase fibrinogen production and induce vascular endothelial damage, promoting hypercoagulability and increasing D-dimer levels.[22] D-dimer of non-COVID-19 is higher than COVID-19, which might be due to the severity of the non-COVID-19 disease that we do not include in the research. Since we have not found any literature directly comparing COVID-19 with non-COVID, we found that some diseases can reach D-Dimer> 3,000 ng/mL.[23] The use of D-dimer to distinguish COVID-19 from non-COVID-19 disorders should consider additional parameters such as platelet, neutrophil, and lymphocyte ratios, among others.[9,24,25]

The study compared Vmax, Amax, and Dmax levels between patients who tested positive for COVID-19 and those who tested negative. Significant differences in CWA parameters are likely to occur due to differences in coagulation factor activities between patients who tested positive for COVID-19 and those who tested negative.[26] Research on CWA in patients with COVID-19 has revealed significant differences in comparison to healthy control subjects.[27,28] In non-COVID-19 research, CWA levels did not differ significantly between patients with viral infections and control subjects but significantly between those

with bacterial infections and control subjects.[13] No other studies have been conducted to compare aPTT-based CWA between patients with COVID-19 and non-COVID-19 patients (patients who tested negative in PCR but had flu-like symptoms and other illnesses, that is, were not healthy).

This study revealed that the COVID-19 survivor and non-survivor groups had remarkably different D-dimer levels, which were considerably higher in the non-survivor group (8,069 ± 10,301 ng/mL) than in the survivor group (3,996 ± 6,836 ng/mL). Also, these findings are consistent with several studies that conducted a comparison of the D-dimer levels between those who survived and those who did not, as well as between COVID-19 patients who were admitted to the intensive care unit (ICU) and those who did not.[24,29,30] Further investigations are warranted to determine D-dimer levels in mild clinical conditions and their association with mortality rates. In addition, Yao et al.[29] demonstrated that a high D-dimer level in patients with severe disease affects mortality rates.

The substantial disparity in D-dimer levels between survivors and non-survivors can be attributed to the pro-inflammatory response triggered by cytokine storms.[31,32] This pro-inflammatory effect can also be evidenced by the increased levels of inflammatory cytokines in non-survivors as opposed to survivors.[24] This response could also account for the prevalence of a hypercoagulable status in COVID-19 patients with elevated D-dimer levels.[10] A thromboelastogram in conjunction with a D-dimer assay can be used to detect hypercoagulability and determine the presence of fibrinolysis shutdown.[10,33] Within this research result, D-Dimer is still a strong predictor for patient prognosis but cannot differentiate between COVID-19 and non-COVID-19 patients.

APTT-based CWA parameters showed no substantial distinction between COVID-19 survivors and non-survivors, which may also be due to similar reasons for the results of COVID-19 and non-COVID-19, where CWA parameters only look at coagulation conditions and indirectly, the tool reaction principle of detecting conversion of fibrinogen to fibrin.[11] Any inflammatory condition in COVID-19 and non-COVID patients will increase fibrinogen levels.[28,34] Coagulation factors will affect these parameters, which fluctuate according to consumption, the patient's condition, and possible heparin administration.[16] This result shows that CWA could differentiate between COVID-19 and non-COVID-19, meaning that CWA will be higher in COVID-19 but not otherwise. CWA might not be able to be used to assess the prognosis and the outcome of the patient's survival.

The correlation between D-dimer and aPTT-based CWA was very weak and insignificant. This correlation was likely due to the varying retrieval times between survivors and non-survivors, as the study was not stratified according to the sampling time on the first day of entry. A study investigating the differences in conditions between admission and a few days later showed significant differences in fibrinogen and D-dimer levels.[16] This difference is conceivable because fibrinogen only reflects coagulation status, but D-dimer shows both coagulation and fibrinolysis status simultaneously.[14] Therefore, this disease could show no direct correlation between fibrinogens that affect CWA and D-dimer.

CONCLUSIONS

A difference in D-dimer and CWA parameter levels was observed between COVID-19 and non-COVID-19 patients. Although D-dimer levels differed between the survivor and non-survivor groups, CWA revealed no variation between these groups. The study's limitations arise from the retrospective nature of data collection. Therefore, prospective studies, more standardized sample selection, and more reasonable sampling times are recommended. Compared to D-dimer results, aPTT-based CWA parameters may not accurately predict mortality in COVID-19 patients, but they help distinguish between COVID-19 and non-COVID-19 diseases. Although COVID-19 showed a higher level of CWA parameters meaningfully different from the non-COVID-19 group, further research needs to be done to decide which CWA could differentiate between COVID-19 and non-COVID-19. Further investigations on treatment interference and the specificity of these methods to predict hypercoagulable states are warranted.

LIST OF ABBREVIATIONS

COVID-19	: coronavirus disease-19
CWA	: clot waveform analysis
aPTT	: activated partial thromboplastin time
PPT	: plasma prothrombin time
Vmax	: maximum coagulation velocity
Amax	: maximum coagulation acceleration
Dmax	: maximum coagulation deceleration
TEG	: thromboelastogram
PCR	: polymerase chain reaction

ACKNOWLEDGMENT

We are thankful to the laboratory technology analyst from Sysmex for extracting the data from the **CS-2500i.**

FUNDING

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE OF ANY CONFLICT OF INTEREST

This research did not have any conflict of interest.

REFERENCES

1. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*. 2020;395(10224):565-574. doi:10.1016/S0140-6736(20)30251-8
2. Hu Y, Sun J, Dai Z, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. *Journal of Clinical Virology*. 2020;127(March):104371. doi:10.1016/j.jcv.2020.104371
3. Siordia JA. Epidemiology and clinical features of COVID-19: A review of current literature. *Journal of Clinical Virology*. 2020;127(April):104357. doi:10.1016/j.jcv.2020.104357
4. Gane SB, Kelly C, Hopkins C. Isolated Sudden Onset Anosmia in COVID-19 Infection. A Novel Syndrome? *Rhinology journal*. 2020;58(3):299-301. doi:10.4193/Rhin20.114
5. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *Journal of Clinical Virology*. 2020;127(March):104354. doi:10.1016/j.jcv.2020.104354
6. Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *Journal of Clinical Virology*. 2020;127(March):104364. doi:10.1016/j.jcv.2020.104364
7. Goudouris ES. Laboratory diagnosis of COVID-19. *J Pediatr (Rio J)*. 2020;(xx):1-6. doi:10.1016/j.jped.2020.08.001
8. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *Journal of Clinical Virology*. 2020;127(March):104362. doi:10.1016/j.jcv.2020.104362

9. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. *Clinica Chimica Acta*. 2020;510(June):475-482. doi:10.1016/j.cca.2020.08.019

10. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *Journal of Thrombosis and Haemostasis*. 2020;18(7):1738-1742. doi:10.1111/jth.14850

11. Tan CW, Wong WH, Cheen MHH, et al. Assessment of aPTT-based clot waveform analysis for the detection of haemostatic changes in different types of infections. *Sci Rep*. 2020;10(1):1-7. doi:10.1038/s41598-020-71063-1

12. Suzuki A, Suzuki N, Kanematsu T, et al. Clot waveform analysis in Clauss fibrinogen assay contributes to classification of fibrinogen disorders. *Thromb Res*. 2019;174(November 2018):98-103. doi:10.1016/j.thromres.2018.12.018

13. Tan CW, Cheen MHH, Ng HJ, et al. Elevated activated partial thromboplastin time-based clot waveform analysis markers have strong positive association with acute venous thromboembolism. *Biochem Med (Zagreb)*. 2019;29(2):385-393. doi:10.11613/BM.2019.020710

14. Keohane EM, Otto CN, Walenga JM. *Rodak's Hematology*. 6th ed. Elsevier; 2020. doi:10.1016/C2013-0-19483-4

15. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol*. 2020;2(7):e437-e445. doi:10.1016/S2665-9913(20)30121-1

16. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *Journal of Thrombosis and Haemostasis*. 2020;18(7):1747-1751. doi:10.1111/jth.14854

17. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis*. April 2020:3-6. doi:10.1007/s11239-020-02105-8

18. di Mitri C, Arcoleo G, Mazzuca E, et al. COVID-19 and non–COVID-19 pneumonia: a comparison. *Ann Med*. 2021;53(1):2321-2331. doi:10.1080/07853890.2021.2010797

19. Schwameis M, Steiner MM, Schoergenhofer C, et al. D-dimer and histamine in early stage bacteremia: A prospective controlled cohort study. *Eur J Intern Med*. 2015;26(10):782-786. doi:10.1016/j.ejim.2015.10.024

20. Levi M, van der Poll T. Coagulation and sepsis. *Thromb Res*. 2017;149:38-44. doi:10.1016/j.thromres.2016.11.007

21. Dai H, Zhou H, Sun Y, et al. D-dimer as a potential clinical marker for predicting metastasis and progression in cancer. *Biomed Rep*. 2018;9(5):453-457. doi:10.3892/br.2018.1151

22. Linkins LA, Takach Lapner S. Review of D-dimer testing: Good, Bad, and Ugly. *Int J Lab Hematol*. 2017;39(January):98-103. doi:10.1111/ijlh.12665

23. Lippi G, Bonfanti L, Saccenti C, Cervellin G. Causes of elevated D-dimer in patients admitted to a large urban emergency department. *Eur J Intern Med*. 2014;25(1):45-48. doi:10.1016/j.ejim.2013.07.012

24. Wang F, Hou H, Wang T, et al. Establishing a model for predicting the outcome of COVID-19 based on combination of laboratory tests. *Travel Med Infect Dis*. 2020;36(May):101782. doi:10.1016/j.tmaid.2020.101782

25. Bastug A, Bodur H, Erdogan S, et al. Clinical and laboratory features of COVID-19: Predictors of severe prognosis. *Int Immunopharmacol*. 2020;88(July):106950. doi:10.1016/j.intimp.2020.106950

26. Shimura T, Kurano M, Kanno Y, et al. Clot waveform of APTT has abnormal patterns in subjects with COVID-19. *Sci Rep*. 2021;11(1):1-11. doi:10.1038/s41598-021-84776-8

27. Shimura T, Kurano M, Kanno Y, et al. Clot Waveform of APTT Has Abnormal Patterns in Subjects with COVID-19. *Res Sq*. 2020:1-18. doi:10.21203/rs.3.rs-43405/v1

28. Fan BE, Ng J, Chan SSW, et al. COVID-19 associated coagulopathy in critically ill patients: A hypercoagulable state demonstrated by parameters of haemostasis and clot waveform analysis. *J Thromb Thrombolysis*. October 2020. doi:10.1007/s11239-020-02318-x

29. Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *J Intensive Care*. 2020;8(1):49. doi:10.1186/s40560-020-00466-z

30. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*. 2020;18(4):844-847. doi:10.1111/jth.14768

31. Fung SY, Yuen KS, Ye ZW, Chan CP, Jin DY. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses. *Emerg Microbes Infect*. 2020;9(1):558-570. doi:10.1080/22221751.2020.1736644

32. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy*. 2020;75(7):1564-1581. doi:10.1111/all.14364

33. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. *Expert Rev Hematol*. 2020;0(0):1-11. doi:10.1080/17474086.2020.1831383

34. Zou Y, Guo H, Zhang Y, et al. Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China. *Biosci Trends*. 2020;14(4):285-289. doi:10.5582/bst.2020.03086

Cite this article: Rahmawan PA, Hernaningsih Y. Natural Compounds in Clot Waveform Analysis and D-Dimer Modulation: Implications for COVID-19 Diagnosis and Prognosis. Pharmacogn J. 2024;16(6): 1373-1378.