## Review Form 1.7

| | |
|---|---|
| Journal Name: | **Journal of Complementary and Alternative Medical Research** |
| Manuscript Number: | **Ms_JOCAMR_108945** |
| Title of the Manuscript: | **Profile of D-Dimer Levels in Patients Confirmed Positive for COVID-19 Aged 45 – 70 Years at UKI Hospital for the Period December 2020 – September 2021** |
| Type of the Article | **Record review** |

**PART 1: Review Comments**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
|---|---|---|
| **Compulsory** REVISION comments<br><br>**1. Is the manuscript important for scientific community?**<br>(Please write few sentences on this manuscript)<br><br>**2. Is the title of the article suitable?**<br>(If not please suggest an alternative title)<br><br>**3. Is the abstract of the article comprehensive?**<br><br>**4. Are subsections and structure of the manuscript appropriate?**<br><br>**5. Do you think the manuscript is scientifically correct?**<br><br>**6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form.**<br><br>**(Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)** | **Now. So many articles published by this time**<br><br>**Average**<br><br>**Objectives are missing**<br><br>**Ok. But, huge review of literature. This section can be included in introduction.**<br><br>**Need lot of revision.**<br><br>**Sufficient** | |
| **Minor** REVISION comments<br><br>**1. Is language/English quality of the article suitable for scholarly communications?** | OK. | |
| **Optional/General** comments | Spare some time and lot of revision is required in the methods section. This section needs to be increased and detailed description is required.<br>Discussion should be based on the objectives and important variables. | |

**PART 2:**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
|---|---|---|
| **Are there ethical issues in this manuscript?** | *(If yes, Kindly please write down the ethical issues here in details)* | |

## Review Form 1.7

**Reviewer Details:**

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|---|---|
| Name: | **K. Chandra Sekhar** |
| Department, University & Country | **Family Medicine Academy, Saudi Arabia** |

## Review Form 1.7

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**PART 1: Review Comments**

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| **Compulsory** REVISION comments<br><br>**1. Is the manuscript important for scientific community?**<br>(Please write few sentences on this manuscript)<br><br>**2. Is the title of the article suitable?**<br>(If not please suggest an alternative title)<br><br>**3. Is the abstract of the article comprehensive?**<br><br>**4. Are subsections and structure of the manuscript appropriate?**<br><br>**5. Do you think the manuscript is scientifically correct?**<br><br>**6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form.**<br><br>**(Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)** | **The paper examines the concentration of D-dimers levels in COVID-19 paptients. The results indicate a correlation between increased severe symptoms in older patients, with higher D-dimer formation. The paper is very crucial to global science and health.**<br><br>**Yes**<br><br>**Yes**<br><br>**Yes**<br><br>**Yes**<br><br>**Yes. Though further examination would have enhanced its quality.**<br><br>**Yes, I would suggest additional references.** | |
| **Minor** REVISION comments<br><br>**1. Is language/English quality of the article suitable for scholarly communications?** | Yes | |
| **Optional/General** comments | Additonal references<br><br>1. Nemec, H. M., Ferenczy, A., Christie, B. D., 3rd, Ashley, D. W., & Montgomery, A. (2022). Correlation of D-dimer and Outcomes in COVID-19 Patients. *The American surgeon*, *88*(9), 2115–2118. https://doi.org/10.1177/00031348221091940<br>2. Rostami, M., & Mansouritorghabeh, H. (2020). D-dimer level in COVID-19 infection: a systematic review. *Expert review of hematology*, *13*(11), 1265–1275. https://doi.org/10.1080/17474086.2020.1831383<br>3. Katsoularis I, Fonseca-Rodriguez O, Farrington P, et al. Risk of deep vein thrombosis, pulmonary embolism, and bleeding after COVID-19: nationwide self-controlled cases series and matched cohort study. BMJ 2022;377: e06959 | |

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| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
|---|---|---|
| **Are there ethical issues in this manuscript?** | *(If yes, Kindly please write down the ethical issues here in details)* | |

**Reviewer Details:**

| | |
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| Name: | **Daniel Nwibo** |
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## Review Form 1.7

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|---|---|
| Journal Name: | **Journal of Complementary and Alternative Medical Research** |
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| Type of the Article | |

**PART 1: Review Comments**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
|---|---|---|
| **Compulsory** REVISION comments<br><br>**1. Is the manuscript important for scientific community?**<br>(Please write few sentences on this manuscript)<br><br>**2. Is the title of the article suitable?**<br>(If not please suggest an alternative title)<br><br>**3. Is the abstract of the article comprehensive?**<br><br>**4. Are subsections and structure of the manuscript appropriate?**<br><br>**5. Do you think the manuscript is scientifically correct?**<br><br>**6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form.**<br><br>**(Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)** | **YES**<br><br>**YES**<br><br>**YES**<br><br>**YES**<br><br>**YES**<br><br>**YES** | |
| **Minor** REVISION comments<br><br>**1. Is language/English quality of the article suitable for scholarly communications?** | YES | |
| **Optional/General** comments | 1. Manuscript is well written<br>2. some suggestions are given in the manuscript and should be corrected<br>3. Some query has to be corrected<br>4. References should be as per the guidelines, as there is some missing of full citation in references | |

**PART 2:**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
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| **Are there ethical issues in this manuscript?** | *(If yes, Kindly please write down the ethical issues here in details)* | |

## Review Form 1.7

**Reviewer Details:**

| | |
|---|---|
| Name: | **Anil Kumar** |
| Department, University & Country | **Bihar Veterinary College, India** |

# Profile of D-Dimer Levels in Patients Confirmed Positive for COVID-19 Aged 45 – 70 Years at UKI Hospital for the Period December 2020 – September 2021


## Abstract

COVID-19 is a disease caused by the SARS-CoV-2 virus. COVID-19 is divided into several clinical symptoms based on a person's experiences. In severe clinical signs of COVID-19, D –Dimer will be significantly higher. This study aims to determine D-Dimer levels in COVID-19 patients aged 45 – 70 and uses a descriptive-analytic method with a retrospective cross-sectional design. The number of samples was 198 patients whose D-Dimer levels were checked and **among these**127 patients ~~who~~ received anticoagulant prophylaxis. The research samples were all medical records of patients suffering from COVID-19 aged 45 - 70 years and who had checked D-Dimer levels at RSU UKI from December 2020 to September 2021 found that 145 patients (73.2%) had normal D-Dimer levels,53 patients (26.8%) had increased D-Dimer levels. The distribution of womenwere 100 patients (50.5%), and men were 98 patients (49.5%), the highest range was aged 54 - 62 years with 74 patients (37.4%), clinical symptoms were being experienced by 122 patients (61.6%), and comorbid hypertension was the most common disease with 64 patients (32.3%). A significant relationship was found between D-Dimer levels and comorbidities (p=0.04). Anticoagulant prophylaxis was given to 127 patients, with mild symptoms experienced by five patients (3.6%), moderate symptoms experienced by 73 patients (57.5%), and severe symptoms experienced by 49 patients (38.6%). However, no significant relationship was found (p=0.66) between administering anticoagulant prophylaxis and D-Dimer levels in patients with mild, moderate, or severe symptoms.



**Keywords:** D-Dimer, Age, COVID-19, Anticoagulants



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## Introduction

Currently, people around the world are experiencing difficulties due to epidemics that arise and spread rapidly. This incident began at the end of 2019 when China reported a mysterious pneumonia infection to WHO [1] ~~W~~were 7,736 cases recorded in China on January 30, 2020, and they have spread worldwide [2]. The rapid development of the virus, called Coronavirus Disease 2019 (COVID-19) by WHO, is triggered by transmission from humans to other humans through droplets that come out when coughing or sneezing[3].

When someone is infected with COVID-19, that person will show symptoms of fever and at least signs of respiratory illness, such as coughing and shortness of breath, and require hospitalization. Diagnosis is made ~~base.d~~**based**on the results ~~In~~**in**NAAT, the recommended method is a Real-Time Reverse-Transcription Polymerase Chain Reaction [4]. In addition to NAAT, hematological examination is also essential for disease progression. In hematological analysis, the tests that can be carried out are Prothombin Time, Activated Partial Thromboplastin Time, and D-Dimer[5].

**Comment [H1]:** Write the full abbreviation

In patients with severe clinical symptoms, D-Dimer will be significantly higher. Increases in D-Dimer levels occur with age and during pregnancy. D-dimer levels themselves are related to the severity of the disease. Currently, D-dimer examination is

used as a prognostic biomarker in COVID-19 patients [6]. Diseases such as diabetes, cancer, and stroke, which are common in elderly patients, can also trigger D-Dimer levels in COVID-19 patients[7]. Several studies suggest that ~~C.OVID-19~~**COVID-19**makes patients more susceptible to arterial and venous thrombosis. Measuring D-dimer levels and coagulation parameters in the early stages of the disease can help control and manage COVID-19[8].

In COVID-19 patients with moderate, severe, and critical symptoms, administering anticoagulants is highly recommended as prophylaxis and treating macrothrombi [9]. Apart from that, anticoagulants can also be given to COVID-19 patients with mild symptoms after evaluating the patient's D-Dimer levels.

Based on this, researchers are interested in researching the profile of D-Dimer levels in patients confirmed positive for COVID-19 by RT-PCR examination at 45 - 70 years old at the Indonesian Christian University General Hospital. The problem in this research is: What is the profile of D-Dimer levels in patients confirmed positive for COVID-19 by RT-PCR examination aged 45 - 70 years at the UKI General Hospital from December 2020 - September 2021? The research aims to determine D-Dimer levels in patients confirmed positive for COVID-19.

Comment [DA2]: were

**Literature Review**

~~Coronavirus~~ Coronavirus is a single positive strand RNA virus encapsulated and not segmented[10]. Coronavirus has four main protein structures, namely, protein N (nucleocapsid), glycoprotein M (membrane), glycoprotein spike S (spike), and protein E (sheath)[11]. Coronaviruses belong to the order Nidovirales and the family Coronaviridae. There are four genera in the coronaviridae family, namely alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus[12].
Coronavirus has been around since the 1930s and is known to occur in animals. Extraordinary events occurred in 2002 and 2012, caused by betacoronavirus, namely SARS, which first appeared in China, and MERS, which first appeared in Saudi Arabia [13]. At the end of 2019, a new coronavirus was detected and classified by WHO as novel coronavirus 2019 (nCoV-2019), which CREVSG later changed to Severe Acute Respiratory Syndrome Coronavirus 2. SARS-CoV-2 belongs to the betacoronavirus genus and the disease it causes has been named COVID-19 by WHO [14].

Comment [H3]: Remove repeated words

Coronavirus Disease 2019 is caused by a new coronavirus first identified in Wuhan, China. COVID-19 was not initially identified as a coronavirus infection but rather a sudden occurrence of pneumonia of unknown cause. After carrying out a genome sequencing examination, it was found that the cause was SARS-CoV-2[13]. The first COVID-19 cluster is known to be associated with the Huanan Seafood Market in Wuhan, China. The SARS-CoV-2 virus is zoonotic, where the pathogen transfers from animals, in this case bats sold at the Huanan Seafood Market, to humans [15]. Like SARS and MERS, the symptoms that appear in COVID-19 patients are similar to pneumonia caused by viruses, namely fever, dry cough, difficulty breathing, and several additional symptoms such as headache, vomiting, weakness, and diarrhea[16]. COVID-19 has spread throughout the world and more than 219,000,000 people in the world ~~are~~**were**positive for COVID-19[13].

SARS-CoV-2 is a single-stranded RNA virus measuring 29.9 kb with an envelope containing a nucleocapsid. 10,12 Coronaviruses are divided into four major classifications, namely, α, β, γ, and δ. SARS-CoV, MERS-CoV, and SARS-CoV-2 are classified as betacoronaviruses, which can only infect mammals[17].Coronavirus has

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four primary proteins, namely, protein N (nucleocapsid), glycoprotein M (membrane), glycoprotein spike S (spike), and protein E (sheath), which have different functions[11]. The spike protein is a transmembrane trimetric glycoprotein that protrudes from the virus's surface. Two functional subunits form the spike; the S1 subunit is responsible for binding to host cell receptors, and the S2 subunit is responsible for binding to viruses and cell membranes. ACE2 in the lower respiratory tract has been identified as a functional receptor for the SARS-CoV and MERS-CoV spike glycoproteins. Structural and functional analysis revealed that the genetic sequence, almost the same as SARS-CoV, means that the SARS-CoV-2 spike protein can also bind to ACE2 to infect humans. The SARS-CoV-2 spike binds to the human ACE2 receptor with approximately ten to twenty times higher affinity than the SARS-CoV spike, allowing the virus to spread more easily from person to person. Once it enters the alveolar epithelium, SARS-CoV-2 replicates rapidly, eliciting a strong immune response and causing a cytokine storm and lung tissue damage. In addition, in COVID-19 patients, the total number of T cells, CD4+ T cells, and CD8+ T cells decreases and causes a decrease in immune function, which will worsen the patient's condition[13; 17].

The SARS-CoV-2 virus has a high level of pathogenicity and transmissibility. SARS-CoV-2 can be transmitted from humans to other humans through direct contact with sufferers, via droplets, and indirectly through objects or air contamination. [18] Droplets released by sufferers through coughing, sneezing, singing, or talking can be inhaled or stick to the mucous membranes of the eyes, nose, or mouth and cause a person to be infected with the SARS-CoV-2 virus [13; 18; 19]. Contamination of objects by droplets can also transmit COVID-19.

The incubation period for the SARS-CoV-2 virus is one to fourteen days. In general, COVID-19 is detected on the third to seventh day[20].According to Hidayani~~WR~~ (2020), there are several risk factors associated with COVID-19, including:

A person experiences symptoms when sick with COVID-19, ranging from asymptomatic or no signs, mild and moderate symptoms, to clinical conditions requiring mechanical ventilation and support in the ICU[21]. Mild symptoms are often defined as signs of acute upper respiratory tract infection without complications and may be accompanied by fever, fatigue, cough (with or without sputum), anorexia, malaise, sore throat, nasal congestion, or headache. COVID-19 patients with severe pneumonia are characterized by fever and one of the following symptoms: (1) respiratory rate of more than thirty breaths per minute, (2) severe shortness of breath, or (3) oxygen saturation of 93% without oxygen support[2].

Low lymphocyte counts and low monocyte, basophil, and eosinophil results are found in severe clinical cases. In addition, proinflammatory mediators (TNF-α, IL1, IL6, and IL 8) increased, but helper T cells, suppressor T cells, and regulatory T cells decreased [22]. X-rays of COVID-19 patients often show multiple ground glass shadows and infiltration shadows in both lungs. In severe cases, lung consolidation may occur. Apart from the respiratory organs, SARS-CoV-2 can cause disorders of the cardiovascular and gastrointestinal systems and acute kidney failure [18].

The normal mechanism carried out by the body in the process of stopping bleeding at the site of injury is called hemostasis[23]. The hemostasis stage or process can be divided into three main steps, namely (1) vascular vasoconstriction, (2) formation of platelet plugs (primary hemostasis), and (3) blood clotting (secondary

**Comment [H4]:** Already detailed on the top of literature

**Comment [DA5]:** Follow the journals guidelines

**Comment [H6]:** Complete the sentence

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hemostasis). The hemostasis process is balanced by blood clotting control mechanisms and the fibrinolysis process (tertiary hemostasis)[24].

In the blood coagulation (clotting) process, important substances can influence clotting, such as procoagulants, which function as substances that make clotting easier, and anticoagulants, which function as clotting inhibitors. When blood vessels are damaged, procoagulants are more active so that wounds can close [23]. The coagulation theory commonly used today, proposed by Mac Farlane, Davie, and Ratnoff, is a cascade or waterfall theory to describe the coagulation process [24].

The cascade theory explains that each coagulation factor is a proenzyme converted into an active enzyme, where some of these factors act as co-factors and some act as coagulant factors. The nomenclature of coagulation factors is a nomenclature that uses Roman numerals in the order in which they are found. For writing, fibrinogen (factor I), Prothrombin (factor II), tissue thromboplastin (factor III), Ca ions (factor IV), prekallikrein (PK), and HMWK are usually not written in Roman numerals[23; 24]. Factor V, Factor VII, HMWK, and thromboplastin are co-factors for other factors. Factor XII, Factor XI, Factor [24]. In the cascade theory, the blood clotting process is divided into two pathways: the intrinsic pathway, where all components are present in the blood, and the intrinsic pathway, which involves subendothelial membranes and tissue factors [24; 25].

**Comment [H7]:** ??

Contact factors (factors XII, Exposure to FXII (Hagemen Factor) on foreign surfaces converts XII to FXIIa. FXIIa converts prekallikrein to kallikrein, which in turn increases FXII activation. Simultaneously, kallikrein activates FVII to FVIIa in the extrinsic pathway, activates plasminogen to plasmin in the fibrinolytic system, and converts Kininogen to Kinin, which plays a role in the inflammatory response. FXIIa, with the help of the HMWK co-factor, divides FXI into FXIa, and then FIXa divides FIX into IXa. FIXa, FXa, and thrombin cleave FVIII to form FVIIIa. Finally, FIXa, FVIIIa, calcium ions, and negatively charged phospholipids form a three-molecule complex called tenase. Tenase then changes FX to FXa. FXa binds to the co-factor FVa to form a prothrombinase complex. This complex converts the proenzyme prothrombin into the enzyme thrombin. Thrombin converts fibrinogen into fibrin monomers, rapidly polymerizing to form fibrin clots [24; 25].

**Comment [DA8]:** Follow the journal guidelines It should be as [24, 25]

The injured vascular endothelium is the origin of the extrinsic pathway. FVII comes into contact with extravascular tissue factor and forms a tissue factor-FVIIa complex where FVII activation is carried out by tissue factor in a non-proteolytic manner. The binding between tissue factors FVIIa forms an enzyme complex that can convert FX to FXa. FXa formed in the extrinsic pathway functions almost the same as tenase in the intrinsic pathway, namely binding to the FV co-factor and ultimately converting fibrinogen into fibrin. The cascade will continue along a common pathway with FXa, formed from intrinsic and extrinsic pathways [25].

FX activation begins a common pathway through intrinsic, extrinsic, or both pathways. FXa is assisted by FV, calcium, and phospholipid ions to convert prothrombin into thrombin. The main function of thrombin is to catalyze the proteolysis of plasma-dissolved fibrinogen into soluble fibrin monomers. Monomeric fibrin then polymerizes into polymer fibrin, which will defend blood cells. In addition, thrombin can convert FXIII to FXIIIa and mediate cross-linking of fibrin polymers to form slightly soluble and stable fibrin. Thrombin can also catalyze the formation of co-factors FVa and FVIIIa, leading to increased coagulation [25]. The cascade coagulation theory is illustrated in Figure 1.

**Comment [DA9]:** In figure 1 there is BAR Diagram, correct it

UNDER PEER REVIEW

D-Dimer- The D-Dimer test determines whether there are blood clots in the body. The D-Dimer test is generally used as an additional test to rule out the diagnosis of DVT and pulmonary embolism and confirm the diagnosis of DIC. [26] D-Dimer itself is the final product of the fibrinolytic process in the form of fibrin degradation. [26] Fibrinolysis is a physiological mechanism that destroys fibrin deposits with a fibrinolytic system that continuously works through the coagulation system to ensure smooth blood flow to body tissues or peripheral organs [23; 24]. The fibrinolytic system is activated by the presence of a plasminogen activator, which breaks down plasminogen into plasmin. Active plasmin is divided into free plasmin, which is neutralized by antiplasmin, and fibrin-bound plasmin [24]. Fibrin-bound plasmin impairs fibrin formation by inducing FDP. Initially, an X piece will be formed. Piece X will be divided into pieces Y, D, and E[24; 27]. Two pieces of D and one piece of E will bond and form a D-Dimer [27; 28].

In testing D-Dimer concentration, the principle used is monoclonal antibodies. [26]There are several testing methods to check D-Dimer levels, namely ELISA, Latex Agglutination, Whole Blood Agglutination, immunoturbidimetry, and immunofiltration. The gold standard in D-Dimer testing is testing using the ELISA method [27].
Standardization of normal D-Dimer values does not exist to date. However, the D-Dimer levels commonly used range from 0 – 300 ng/mL. Increased D-dimer levels occur with age and during pregnancy [29]. In addition, increased D-Dimer levels also occur in CAP and COPD patients[29; 30]. The severity of the disease is related to D-Dimer levels; currently, D-Dimer examination is used as a prognostic biomarker in COVID-19 patients. [30] In the early stages of COVID-19 disease, D-Dimer and fibrinogen levels increase, which leads to a poor prognosis. D-Dimer greater than 1 µg/mL is a risk factor for death in COVID-19 patients[30].

Diseases such as diabetes, cancer, and stroke can also increase D-Dimer levels in COVID-19 patients. Several studies show that COVID-19 makes patients more susceptible to arterial and venous thrombosis. Measuring D-Dimer levels and coagulation parameters in the early stages of the disease can be useful in controlling and managing COVID-19[31].

Anticoagulants are substances used to prevent blood clotting by inhibiting certain blood clotting factors or inhibiting the formation of thrombin, which is needed to convert fibrinogen into fibrin[32]. In severe COVID-19 symptoms, a significant increase in D-Dimer levels was found, which could occur due to massive inflammation and impaired blood coagulation. Elevated D-Dimer levels can be a marker of thromboembolic events that occur in COVID-19 patients. Giving anticoagulants to COVID-19 patients can be a solution in preventing the formation of microvascular and macrovascular thrombi which can cause vital organ dysfunction. The International Society of Thrombosis and Haemostasis recommends administering prophylactic doses of LMWH to all COVID-19 patients, except those with contraindications and high bleeding activity. In moderate, severe, and critical COVID-19 patients, administering LMWH or UFH anticoagulants is highly recommended, both useful as prophylaxis and in treating macrothrombi[33]. Apart from that, anticoagulants can also be given to COVID-19 patients with mild symptoms after evaluating the patient's D-Dimer levels[54].

**Research Method**

**Comment [H10]:** Write the full abbreviation

**Comment [H11]:** Put full stop

**Comment [DA12]:** Follow the journal guidelines
It should be as [29, 30]

UNDER PEER REVIEW

This research type is analytical descriptive research with data collected retrospectively cross-sectionally from secondary data obtained from the Medical Records Archives Section of RSU UKI. The research was conducted in the medical records section of RSU UKI from December 2021 to January 2022. The population in this study were COVID-19 sufferers who were treated and had their D-Dimer levels checked. The research samples were COVID-19 patients who were treated and had their D-Dimer levels checked and recorded in the medical record at RSU UKI during the treatment period from December 2020 to September 2021. The sample size in the study was calculated using the Slovin formula: The sample size required in this research was 154 patients. This research used research instruments in the form of medical records obtained from the Medical Records Archives Section of RSU UKI from December 2020 to September 2021.

Comment [H13]: Sample size should 154 or 198?

The data from the data collection process ~~will be~~**were** displayed in descriptive tables and analyzed using the SPSS application with the Chi-Square correlation method or Fisher test on computer software. The data processing process by the SPSS program consists of several steps: a) Coding, to translate the data collected during the research into symbols suitable for analysis; b) Data entry, data entry into the computer; c) Verification, visually checking the data that has been entered into the computer; d) Computer output, prints the results of the analysis carried out by the computer in the previous step.

## Result and Discussion

In this study, data collection was carried out from December 18, 2021 to January 15, 2022. The data collected was secondary in the form of medical records of patients confirmed positive for COVID-19 who underwent inpatient treatment at RSU UKI from December 2020 to September 2021. Of 689 confirmed positive for COVID-19 patients, 198 research samples met the inclusion criteria. Of the 198 samples, 127 samples were given anticoagulant prophylaxis therapy. Data processing was carried out using the SPSS version 22 application. Research data is presented in the form of tables and diagrams. Of the 198 samples obtained in the study, there were 145 people (73.2%) with normal D-Dimer levels, namely <500 ng/dl, and 53 people (26.8%) with D-Dimer levels >500 ng/dl (increase)**(Figure 1).**

Comment [DA14]: Add it

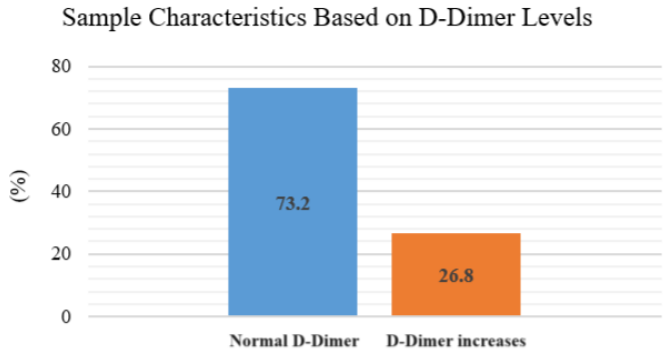


**Figure 1.** Sample Characteristics Based on D-Dimer Levels

### Sample Characteristics Based on Age

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The age group most exposed to COVID-19 at RSU UKI from December 2020 to September 2021 was 54 - 62, namely 74 people (37.4%), followed by 63 - 70 years old, 66 people (32.3%). ), and aged 45 – 53 years, as many as 60 people (30.3%)**(Figure 2).**

Comment [DA15]: Add it

Comment [DA16]:


**Figure 2.** Sample Characteristics Based on Age

**Sample Characteristics Based on Gender**

The research results on patients confirmed positive for COVID-19 aged 45 - 70 years found that 100 patients were female (50.5%) and 98 were male (49.5%)**(Figure 3).**

Comment [DA17]: Add it

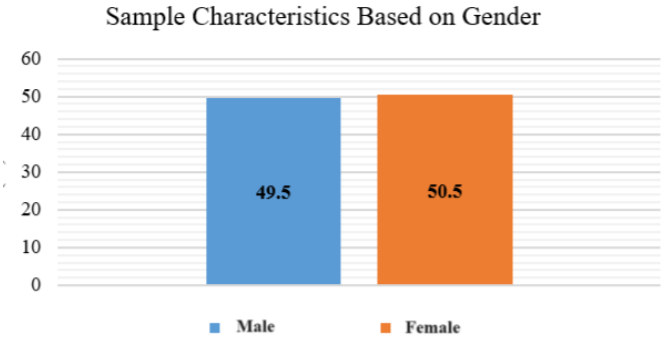


**Figure 3.** Sample Characteristics Based on Gender

**Sample Characteristics Based on Clinical Symptoms**

The most clinical symptoms experienced by COVID-19 patients at RSU UKI were moderate clinical symptoms in as many as 122 people (61.6%), followed by severe clinical symptoms in as many as 60 people (30.3%) and mild clinical symptoms in as many as 16 people (8 .1%).

Comment [DA18]: Write Table 1

**Table 1.** Sample Characteristics Based on Clinical Symptoms

| Clinical Symptoms | Total(n) | Percentage(%) |
|---|---|---|
| COVID-19 Mild Symptoms | 16 | 8,1 |
| COVID-19 Moderate Symptoms | 122 | 61,6 |
| COVID-19 Severe Symptoms | 60 | 30,3 |
| Total | 198 | 100 |

Comment [DA19]: Should be 8.10

Comment [DA20]: Should be 61.60

Comment [DA21]: Should be 30.30

**Characteristics of Clinical Symptoms Based on D-Dimer Levels**

Of the 122 people (61.6%) who experienced moderate symptoms of COVID-19, 96 people (48.5%) had normal D-Dimer levels, and 26 people (13.1%) had increased D-Dimer levels. Furthermore, of the 60 people (30.3%) who experienced severe symptoms of COVID-19, 37 people (18.7%) had normal D-Dimer levels, and increased D-Dimer levels were experienced by 23 people (11.6%). Next, of the 16 people (8.1%) who experienced mild symptoms of COVID-19, 12 people (6.1%) had normal D-Dimer levels, and four people (2%) had increased D-Dimer levels.

**Table 2.** Characteristics of Clinical Symptoms Based on D-Dimer Levels

| | | | D-Dimer results (ng/dl) | | |
|---|---|---|---|---|---|
| | | | D-Dimer Normal | D-Dimer Increases | Total |
| Degree of COVID-19 | COVID-19 Mild Symptoms | Total | 12 | 4 | 16 |
| | | Percentage | 6,1% | 2% | 8,1% |
| | Covid-19 Moderate Symptoms | Total | 96 | 26 | 122 |
| | | Percentage | 48,5% | 13,1% | 61,6% |
| | Covid-19 Severe Symptoms | Total | 37 | 23 | 60 |
| | | Percentage | 18,7% | 11,6% | 30,3% |
| Total | | Total | 145 | 53 | 198 |
| | | Percentage | 73,2% | 26,8% | 100% |

**Sample Characteristics Based on Concomitant Diseases**

The most common comorbidity experienced by patients at RSU UKI was hypertension, 64 people (32.3%).

**Table 3.** Sample Characteristics Based on Concomitant Diseases

| Concomitant Diseases | Total (n) | Percentage(%) |
|---|---|---|
| Hypertension | 64 | 32,3 |
| DM Type 2 | 20 | 10,1 |
| Hypertension and Type 2 DM | 20 | 10,1 |
| Hypertension and heart problems | 9 | 4,5 |
| Hypertension and CKD | 5 | 2,5 |
| Type 2 DM and heart problems | 3 | 1,5 |
| Hypertension, Type 2 DM, and ACKD | 3 | 1,5 |
| Heart problems | 3 | 1,5 |
| DM Type 2 and ACKD | 2 | 1 |
| Hypertension, Type 2 DM, ACKD, and heart problems | 2 | 1 |
| Hypertension, Type 2 DM, and CKD | 2 | 1 |
| Hypertension, Type 2 DM, and heart problems | 2 | 1 |

**Comment [DA22]:** Write Table 2

**Comment [DA23]:** 6.1

**Comment [DA24]:** 8.1

**Comment [DA25]:** 48.50

**Comment [DA26]:** Correct in percent column

**Comment [DA27]:** Write Table 3

UNDER PEER REVIEW

| | | |
|---|---|---|
| COPD | 2 | 1 |
| CA Nasopharynx | 1 | 0,5 |
| CKD | 1 | 0,5 |
| Type 2 DM, ACKD, and heart problems | 1 | 0,5 |
| Type 2 DM and COPD | 1 | 0,5 |
| Drug eruption | 1 | 0,5 |
| Hypertension and ACKD | 1 | 0,5 |
| Hypertension and mammary CA | 1 | 0,5 |
| Hypertension and Dementia | 1 | 0,5 |
| Hypertension, Type 2 DM and Bronchial Asthma | 1 | 0,5 |
| Hypertension, Type 2 DM and CA colon | 1 | 0,5 |
| Hypertension, Type 2 DM, CKD, and heart problems | 1 | 0,5 |
| Hypertension, Type 2 DM, CKD, and Stroke | 1 | 0,5 |
| Hypertension and Parkinson's | 1 | 0,5 |
| Hypertension and COPD | 1 | 0,5 |
| Hypertension and stroke | 1 | 0,5 |
| Hypertension and transaminitis | 1 | 0,5 |
| Schizophrenia | 1 | 0,5 |
| Pulmonary TB | 1 | 0,5 |
| Transaminitis | 1 | 0,5 |
| No disease | 42 | 21,2 |
| Total | 198 | 100 |

Comment [DA28]:

**Relationship Between Concomitant Diseases and D-Dimer Levels in COVID-19 Patients**

Of the 156 people (78.8%) who had comorbidities, 47 people (23.7%) had increased D-Dimer levels, and 109 people (55.1%) had normal D-Dimer levels. Furthermore, of the 42 people (21.2%) who did not have comorbidities, six people (3%) had increased D-Dimer, and 36 people (18.2%) had normal D-Dimer levels.

Comment [DA29]: Write Table 4

**Table 4.** Relationship between Concomitant Diseases and D-Dimer Levels in COVID-19 Patients

| | D-Dimer Results (ng/dl) | | | |
|---|---|---|---|---|
| | D-Dimer Normal | D-Dimer Increases | Total | p-value |

UNDER PEER REVIEW

| | | | | | | |
|---|---|---|---|---|---|---|
| Concomitant Diseases | Yes | Total | 109 | 47 | 156 | 0. |
| | | Percentage | 55,1% | 23,7% | 78,8% | 0 |
| | None | Total | 36 | 6 | 42 | 4 |
| | | Percentage | 18,2% | 3% | 21,2% | 0 |
| Total | | Total | 145 | 53 | 198 | |
| | | Percentage | 73,2% | 26,8% | 100% | |

From statistical analysis, p = 0.04 was obtained, which means a relationship exists between comorbidities and D-Dimer levels in COVID-19 patients.

**Comment [DA30]:** Correct it as there should be dot in place of comma

**Sample Characteristics Based on Administration of Anticoagulant Prophylaxis**

In this study, it was found that prophylactic anticoagulant therapy was given to 127 COVID-19 patients, and when an evaluation was carried out by checking D-Dimer levels, it was found that 81 people (64%) had normal D-Dimer levels, and 46 people (36%) had D-Dimer levels. -Dimer increases.

**Comment [DA31]:** Write Table 5

**Table 5.** Sample Characteristics Based on Anticoagulant Prophylaxis

| D-Dimer Results(ng/dl) | n | % |
|---|---|---|
| D-Dimer Normal | 81 | 64 |
| D-Dimer Increases | 46 | 36 |
| Total | 127 | 100 |

**Correlation between Anticoagulant Prophylaxis and D-Dimer Levels in Patients with Mild, Moderate, and Severe Clinical Symptoms**

From the data collected, five people (3.6%) had mild clinical symptoms and were given anticoagulant prophylaxis, of which three people (2.3%) had normal D-Dimer levels, and two people (1.6%) had D-Dimer levels. -Dimer increases. Followed by 73 people (57.5%) with moderate clinical symptoms and given anticoagulant prophylaxis, of which 49 people (38.6%) had normal D-Dimer levels, and 24 people (18.9%) had increased D-Dimer levels. Then, there were 49 people (38.6%) with severe clinical symptoms and were given anticoagulant prophylaxis, of which 29 people (22.9%) had normal D-Dimer levels, and 20 people (15.7%) had increased D-Dimer levels.

**Comment [DA32]:** Write Table 6

**Table 6.** Relationship between anticoagulant prophylaxis and D-dimer levels in patients with mild, moderate, and severe clinical symptoms

**Comment [DA33]:** Correct in percent column as there should be dot in place of comma

| | | D-Dimer Results(ng/dl | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | D-Dimer Normal | | D-Dimer Increases | | Total | | p-value |
| | | (n) | (%) | (n) | (%) | (n) | (%) | |
| Giving Anticoagulant Prophylaxis to Patients With Clinical Symptom | Mild | 3 | 2,3 | 2 | 1,6 | 5 | 3,9 | 0.660 |
| | Moderate | 49 | 38,6 | 24 | 18,9 | 73 | 57,5 | |
| | Severe | 29 | 22,9 | 20 | 15,7 | 49 | 38,6 | |
| Total | | 81 | 63,8 | 46 | 36,2 | 127 | 100 | |

From statistical analysis, p = 0.66 was obtained, meaning no relationship exists between administering anticoagulant prophylaxis and D-Dimer levels in COVID-19 patients with mild, moderate, and severe symptoms.

**Characteristics of D-Dimer Levels in Patients Who Have Concomitant Diseases and Are Receiving Anticoagulant Prophylaxis**

UNDER PEER REVIEW

The data showed that 107 patients had comorbidities and were given anticoagulant prophylaxis. It was found that 66 patients (62%) had normal D-Dimer levels, and 41 patients (38%) had increased D-Dimer levels.

**Table 7.** Characteristics of D-Dimer Levels in Patients Who Have Concomitant Diseases and Are Receiving Anticoagulant Prophylaxis

| D-Dimer Results(ng/dl) | n | % |
|---|---|---|
| D-Dimer Normal | 66 | 62 |
| D-Dimer Increases | 41 | 38 |
| Total | 107 | 100 |

**Discussion**

Coronavirus Disease 2019 is caused by the SARS-CoV-2 virus, first identified in Wuhan, China. When the SARS-CoV-2 virus enters the human body, the virus will bind to the ACE2 receptor, causing a cytokine storm and damage to lung tissue [13]. In patients with severe clinical symptoms, D-Dimer will be significantly higher. D-dimer levels themselves are related to the severity of the disease, and currently, D-dimer examination is used as a prognostic biomarker in COVID-19 patients [30].

The UKI RSU Laboratory determines the normal level of D-Dimer at <500 ng/dL. Of the 198 samples obtained in the study, 145 COVID-19 patients (73.2%) did not experience increased D-Dimer levels. Meanwhile, 53 patients (26.8%) experienced increased D-Dimer levels of >500 ng/dL. It is in line with research conducted by Djajalaksana et al[34]. in Malang, which stated that there was an increase in D-Dimer levels above normal limits in patients confirmed positive for COVID-19. D-Dimer is found if there is fibrin degradation and is a specific indicator for fibrinolysis, where increasing D-Dimer levels can be related to the severity of the disease[34]. Elevated D-Dimer is also the most characteristic finding in patients with COVID-19 and coagulopathy.

**Comment [DA34]:** Correct it, as there should be as Listyoko et al

The age group with the most positive cases of COVID-19 was in the 54 – 62 year age range, totaling 74 people (37.4%). It aligns with research conducted by Khaerunisa et al. in Bekasi, where the age most exposed to COVID-19 was 46 – 59[35]Apart from that, in research conducted by Elviani et al. [36] in Palembang, it was found that the age range of 56 - 69 years was the second highest. People of all ages can be infected with COVID-19. However, an elderly person has many risk factors for being infected with the disease. One of the risks experienced is the deterioration of body cells, which triggers a decrease in the function of the body's tissues and organs, making it easier for disease to enter due to a decrease in immunity.

**Comment [DA35]:** Give full stop here

Based on gender, most COVID-19 sufferers at RSU UKI from December 2020 to September 2021 were women, namely 100 people (50.5%) and 98 people (49.5%) were men. It is in line with research conducted by Widjaja et al[37].In Bandung, where the results obtained were that women were more exposed to COVID-19 than men. However, based on the literature, men are more susceptible to being infected with COVID-19. It is because men are more often outside the home due to work factors and are thought to be more active smokers than women. Smoking can increase the risk of exposure to COVID-19 because there is an increase in ACE2 receptors, making it easier for the SARS-CoV-2 virus to enter the body. The lower incidence of COVID-19 cases in women can be attributed to protection from sex hormones, progesterone, and the X chromosome, which provide innate and adaptive immunity.

UNDER PEER REVIEW

In this study, the degree of clinical symptoms of COVID-19 that most patients experienced was moderate clinical symptoms with 122 people (61.6%), of which 96 people (48.5%) had normal D-Dimer levels, and 26 people (13 .1%) had increased D-Dimer levels. Of the 26 people with elevated D-Dimer levels, 22 were given anticoagulant prophylaxis and comorbidities, and two were given anticoagulant prophylaxis and did not have comorbidities. Followed by severe clinical symptoms in 60 people (30.3%), of which 37 people (18.7%) had normal D-Dimer levels, and 23 people (11.6%) had increased D-Dimer levels. Of the 23 people with elevated D-Dimer levels, 20 were given anticoagulant prophylaxis and had comorbidities. Then, the clinical symptoms were mild in 16 people (8.1%), of which 12 people (6.1%) had normal D-Dimer levels, and four people (2%) had increased D-Dimer levels. Two of the four people who experienced increased D-Dimer levels were given anticoagulant prophylaxis and had comorbidities. Statistical analysis of the relationship between administration of anticoagulant prophylaxis and D-Dimer levels in mild, moderate, and severe levels of clinical symptoms showed $p = 0.66$, which means there is no relationship between administration of anticoagulant prophylaxis and D-Dimer levels in mild and moderate clinical symptoms, and heavy.

This research shows that the most common comorbidity experienced by patients is hypertension, with a total of 64 people (32.3%). This study's results align with research by Berger et al. [38] in New York; hypertension is the most common comorbidity experienced by COVID-19 patients. The incidence of hypertension and COVID-19 is related to endothelial dysfunction and RAAS dysregulation. The Renin-Angiotensin-Aldosterone System itself is a system that controls blood pressure through aldosterone, angiotensin II, and angiotensin 1-7 with the help of the enzymes ACE1 and ACE2. When the SARS-CoV-2 virus enters the human body, the virus will bind to the ACE2 receptor, causing a decrease in the ACE2 enzyme in the RAAS and ultimately causing endothelial dysfunction, disruption of blood pressure regulation processes, and cytokine storms.

**Comment [DA36]:** In there is addition of dot after et al, but in some place only et al , follow the guide lines

Based on the relationship between comorbidities and D-Dimer levels, of the 156 people (78.8%) who had comorbidities, 47 people (23.7%) had increased D-Dimer levels, and 109 people (55.1%) had normal D-Dimer levels. Elevated D-Dimer levels continued to occur in 42 people with comorbidities despite being given prophylactic anticoagulant therapy. Furthermore, of the 42 people (21.2%) who did not have comorbidities, six people (3%) had increased D-Dimer, and 36 people (18.2%) had normal D-Dimer levels. The statistical analysis showed that $p = 0.04$, which means a relationship exists between comorbidities and D-Dimer levels in COVID-19 patients.

In 107 patients who had comorbidities and were given anticoagulant prophylaxis, 66 people (42.3%) had normal D-Dimer levels, and 41 people (26.3%) had increased D-Dimer levels. In the study, it was found that as many as 127 people were given anticoagulant prophylaxis. It aligns with research by Pratiwi and Adhityasmara [39] in Semarang, which stated that anticoagulant therapy is recommended in treating COVID-19 patients because it can reduce the risk of death. Research conducted by Nugroho et al [40]. in Semarang also found that after giving anticoagulant therapy to COVID-19 patients for several days, there was a significant reduction in D-Dimer levels. The latest management guidelines recommend administering anticoagulant therapy to all patients who have or have not been proven to have thrombosis[39]. It can prevent the risk of thromboembolism in patients and the risk of death [40].

UNDER PEER REVIEW

## Conclusion

Based on the results of research conducted at the Medical Records of the Indonesian Christian University General Hospital, the following conclusions were obtained: a) 145 people (73.2%) had normal D-Dimer levels for the period December 2020 – September 2021 D-Dimer increased by 53 people (26.8%); b) The highest proportion of COVID-19 patients based on age were patients aged 54 – 62 years, 74 people (37.4%) and the lowest proportion were patients aged 45 – 53 years, 60 people (30.3%); c) There were 100 female COVID-19 patients (50.5%) and 98 male (49.5%) and d) Based on clinical symptoms, there were 122 COVID-19 patients with moderate clinical symptoms ( 61.6%), with severe clinical symptoms as many as 60 people (30.3%) and mild clinical symptoms as many as 16 people (8.1%). a) The most common comorbidity experienced by COVID-19 patients from RSU UKI is hypertension with 64 people (32.3%); b) Of the 156 people (78.8%) who had comorbidities, 47 people (23.7%) had increased D-Dimer levels, and 109 people (55.1%) had normal D-Dimer levels. Furthermore, of the 42 people (21.2%) who did not have comorbidities, six people (3%) had increased D-Dimer, and 36 people (18.2%) had normal D-Dimer levels; c) Prophylactic anticoagulant therapy was given to 127 COVID-19 patients, and when an evaluation was carried out by checking D-Dimer levels it was found that 81 people (64%) had normal D-Dimer levels, and 46 people (36%) had increased D-Dimer levels; d) This research shows that there is no relationship between the administration of anticoagulant prophylaxis and D-Dimer levels in COVID-19 sufferers with mild, moderate and severe clinical symptoms (p=0.66); and e) Of the 107 patients who had comorbidities and were given anticoagulant prophylaxis. It was found that 66 patients (62%) had normal D-Dimer levels, and 41 patients (38%) had increased D-Dimer levels.

Based on the conclusions outlined, suggestions that can be taken into consideration and included are as follows: a) Hospitals are advised to continue paying attention to counseling/education to the public regarding preventing the spread of COVID-19; b) Hospital staff are advised to check D-Dimer levels on the first day the patient is treated after the patient is declared positive for COVID-19 via RT – PCR examination, and provide anticoagulants for prophylaxis or therapy; c) For further research, it is highly hoped that the filling in of medical records will be carried out more completely, such as always including the results of laboratory examination of D-Dimer levels so that further research can obtain complete information; and d) It is hoped that future researchers can expand this research to a higher and more specific level of evidence, as well as analyze factors that can prevent an increase in D-Dimer levels.

UNDER PEER REVIEW

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**Comment [H37]:** Provide Journal name, volume, year of publication

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**Comment [DA38]:** Write full deatils

**Comment [DA39]:** Remove it

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[39] Pratiwi AD, Adhityasmara D. Description of the use of anticoagulants in COVID-19 patients at one of the COVID-19 referral hospitals in the city of Semarang. Sebatik. 2021 Dec 1; 25(2):442-8.
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**Comment [DA40]:** What is this/cite properly

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## Review Form 1.7

| | |
|---|---|
| Journal Name: | **Journal of Complementary and Alternative Medical Research** |
| Manuscript Number: | **Ms_JOCAMR_108945** |
| Title of the Manuscript: | **Profile of D-Dimer Levels in Patients Confirmed Positive for COVID-19 Aged 45 – 70 Years at UKI Hospital for the Period December 2020 – September 2021** |
| Type of the Article | |

**PART 1: Review Comments**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
|---|---|---|
| **Compulsory** REVISION comments<br><br>**1. Is the manuscript important for scientific community?**<br>(Please write few sentences on this manuscript)<br><br>**2. Is the title of the article suitable?**<br>(If not please suggest an alternative title)<br><br>**3. Is the abstract of the article comprehensive?**<br><br>**4. Are subsections and structure of the manuscript appropriate?**<br><br>**5. Do you think the manuscript is scientifically correct?**<br><br>**6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form.**<br><br>**(Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)** | **I think there has been a lot of research on Covid and it has been around for quite a long time, but it still provides an interesting data**<br><br>**Maybe the author could change profile to characteristic**<br><br>**Yes**<br><br>**I don't know, because there is a subsection about literature review. I think it is not important in research study. Could be simpler in introduction or discussion**<br><br>**I think so**<br><br>**yes** | |
| **Minor** REVISION comments<br><br>**1. Is language/English quality of the article suitable for scholarly communications?** | yes | |
| **Optional/General** comments | | |

**PART 2:**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
|---|---|---|
| **Are there ethical issues in this manuscript?** | *(If yes, Kindly please write down the ethical issues here in details)* | |

## Review Form 1.7

**Reviewer Details:**

| | |
|---|---|
| Name: | **Eric Hartono Tedyanto** |
| Department, University & Country | **Udayana University, Indonesia** |

**Editor's Comment:**

Manuscript can be accepted for the publication.

**Editor's Details:**

Dr. Suma B V
Assistant Professor, M.S amaiah University of Applied Sciences, India.

**Editor's Comment:**

The MS is now acceptable.

**Editor's Details:**

Prof. Nawal Kishore Dubey
Centre for Advanced Studies in Botany, Applied Microbiology, Banaras Hindu University, India.