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Original Article

Benefits of Low Dosage of Colchicine Administration on Decreasing Rehospitalization and Mortality within 30 Days in Post-Acute Coronary Syndrome Patients with ST-Segment Elevation Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Background: The role of inflammation in myocardial infarction and post-infarction MI remodeling has become a concern for the development of treatment in the last decade. Colchicine can prevent increased inflammation during acute injury.
Objective: This study focused on the role of colchicine as an on-top medical treatment, hoping it can reduce mortality and short-term rehospitalization in patients with STEMI.
Methods: 347 AMI patients (18-80 year old adults) who visited RSUD dr. Saiful Anwar Malang, between February 2022 and January 2023, participated in this prospective, randomized, double-blinded, placebo-controlled experiment. Patients were split into two groups and given either a placebo or colchicine 0.5 mg daily for a month. Standard medical therapy was administered concurrently to both groups as an approachable guideline. The study endpoints were mortality and rehospitalization rates.
Results: After one month of follow-up, there was a reduction in rehospitalization due to cardiovascular causes (2 [1.3%] vs. 4 [2.7%], HR 3.42 [1.36-8.56], p<0.05), which was significant in the treatment group compared to the control group. Also, there was a reduction in all-cause mortality, but not statistically significant (2 [1,3% v 3 [2,0%], HR 3,38 [0,53-7,48], p>0,05). In the treated group, there was also a lower non-cardiovascular rehospitalization rate compared to placebo, but not significant (4 [2.6%] vs. 7 [4.7], HR 0.42 [0.15-1.02], p<0.05)
Conclusion: The administration of low-dose colchicine for one month has shown benefits in reducing rehospitalization in patients with STEMI who receive PCI therapy.

1. Introduction

Treatment of Acute Myocardial Infarct (AMI) depends on the speed of diagnosis and treatment. In ST-Segment Elevation Myocardial Infarct (STEMI), reperfusion measures can be performed by administering fibrinolytic or Primary Percutaneous Coronary Intervention (PCI). Restoration of infarct-related artery (IRA) blood flow within the first 12 hours of symptom onset through an early invasive strategy is currently considered the best approach to treating STEMI. Reducing the delayed treatment time for myocardial infarction is a primary concern of reperfusion therapy STEMI.[1,2] A study of 12,675 STEMI patients in the FITT-IMA-EST (KMP) study showed a strong correlation between delayed revascularization time and death rate, Particularly in STEMI patients who have experienced cardiogenic shock or outside-of-hospital cardiac arrest. Every 10 minutes of treatment delay between 60 and 180 minutes from the initial medical contact will result in an extra 3.3 fatalities per 100 patients treated with PCI in STEMI with shock but without out-of-hospital cardiac arrest. In fact, in developing countries, including Indonesia, STEMI patients generally arrive late (more than 12 hours after the initial onset of chest pain symptoms) at health facilities. Hence, the incidence and death rates are higher when compared to developed countries. One-third of STEMI patients in Indonesia do not receive timely reperfusion therapy. Data from RSUD dr. Saiful Anwar Malang (2019) shows that out of 427 cases, 33% of IMA-EST cases came to the hospital with an onset of more than 12 hours.[1,3]

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In addition to revascularization interventions with PCI, inflammation's role in myocardial infarction and post-infarction MI remodeling has become a concern for the development of treatment in the last decade.[4] Several studies of inflammation in coronary heart disease found a correlation between anti-inflammatory drugs in suppressing inflammasome activation and the resulting pro-inflammatory cytokines, such as canakinumab, darapladib, lasmapimod, inclacumab, and what is currently being widely discussed is colchicine.[5,6] Colchicine has been shown to reduce infarct size as indicated by decreased muscle-brain creatinine kinase (CK-MB) and infarct size from cardiac MRI patients with myocardial infarction.[7,8] Several preliminary studies regarding the administration of colchicine on the levels of pro-caspase-1 mRNA, serum caspase-1, IL-1β, IL-6, IL-18, and hs-CRP in AMI patients undergoing PCI compared to controls showed a significant decrease.[4] Colchicine reduced 24-hour inflammation in AMI (preventing increased inflammation during acute injury). Still, it did not reduce the risk of PCI-related myocardial injury or recurrent cardiovascular events in 30-day follow-up compared with placebo.[8,9]

Based on the consideration of the success of previous studies, researchers were interested in knowing the benefits of giving colchicine to reduce rehospitalization and mortality in the STEMI patient population who received revascularization. Until now, studies of the benefits of colchicine in revascularization settings with early and delayed PCI have never been carried out. This study focused on the role of colchicine, as an on-top medical treatment, with the hope that it can reduce mortality and short-term rehospitalization in patients with STEMI who receive delayed revascularization.

2. Material and Methods

This study was a prospective, randomized, double-blinded, placebo-controlled trial that included 347 AMI patients (18-80 years old adults) who visited RSUD dr. Saiful Anwar Malang from February 2022 until January 2023. All patient has clinical symptoms and investigations leading to a diagnosis of STEMI within the last seven days. All patients undergoing PCI and medical therapy based on guidelines therapy. STEMI patients were included in two groups with either the onset of myocardial infarction under 12 hours or above 12 hours. The main exclusion criteria were the presence of co-morbidities, cardiogenic shock, severe renal failure (eGFR <30 mL/kg/min), hypersensitivity to colchicine, and having contraindications to colchicine.

Colchicine (1 mg loading dose, 0.5 mg per day until 30 days) plus standard medical treatment or standard medical treatment plus a placebo (2 capsules first, continued with one tablet a day until 30 days) was given to patients randomly. An independent packaging team not involved in the rest of the trial was responsible for creating the containers of the study drugs. To design a non-biased controlled trial, the investigators, patients, and follow-up team members were all completely ignorant.

2.1 Trial Procedure

The patient was given informed consent after fulfilling the inclusion and exclusion criteria. The patient will then receive treatment according to the guidelines. Patients were given therapy according to the randomization results: 1 mg colchicine loading followed by 0.5 mg per day for up to 30 days in the colchicine group, and two capsules placebo loading continued one capsule per day for up to 30 days in the placebo group. On admission, Echocardiography was performed within 24 hours of the PCI. Patients were evaluated at one monthly follow-up, both face to face and by phone, regarding death and rehospitalization within 30 days and evaluation of drug adherence.

2.2 Trial Outcome

The primary efficacy end point's components constituted the outcomes: rehospitalization for a cardiac reason, rehospitalization without cardiac cause, and overall mortality in assessments of times to events.

2.3 Statistical analysis

The gathered information was entered into SPSS Inc.'s statistical package for social sciences, version 23. The data were described using descriptive statistics, such as mean (standard deviation) for quantitative variables and number (%) for qualitative factors. The independent sample T-test and Chi-square test were used for data analysis. The mean of the parameters in the two groups was compared using the t-test. The Chi-square test was also used to compare the qualitative traits and characteristics between the two groups. The frequency histograms and Shapiro-Wilkes test were used to assess the normality of the distributions. The sensitivity study used a Cox regression with group assignment as the independent variable, clustering over individuals and providing robust standard errors to account for many correlated events occurring within an individual. The study's findings are hazard ratios (HR) and their respective 95% confidence intervals (95%CI). Statistically significant was defined as a P-value of 0.05 or below (two-tailed).

2.4 Sample size

The sampling technique in this study used randomized sampling in all patients with a diagnosis of IMA-EST at Dr. Saiful Anwar Malang. Based on the purpose and type of research, based on previous studies, assuming an error of 5%, power of 80%, and an effect size of around 40% or a risk ratio of about 3% in both groups and a ratio of 1:1 in both groups are all measured with formula10:

$$n = \frac{2\bar{p}(1-\bar{p})(z_{1\_}\alpha_{/2} + z_{1-\beta})^2}{(\partial)^2}$$

It is estimated that there are 5% drop out from the number of samples counted, so a minimum of 150 pieces in every group, a total of 300 samples minimum.

3, Result

The research was conducted from February 2022 to January 2023 at Dr. Saiful Anwar Malang. This study involved 347 patients diagnosed with IMA-EST who underwent PCI. After matching the inclusion and exclusion criteria, the patients were randomized into two treatment groups. The first group was the treatment group with a loading dose of 1 mg of colchicine followed by 1x0.5 mg per day for one month, and the second group was the control group with placebo given for one month. A total of 311 patients met the inclusion and exclusion criteria. 158 patients entered the treatment group, and 153 patients who joined the control group. Of the 311 patients, 13 patients dropped out. Five of the 12 patients who dropped out experienced gastrointestinal side effects (diarrhea) and refused to continue the study. Five patients died, and three patients because they could not be contacted. (Figure 1).

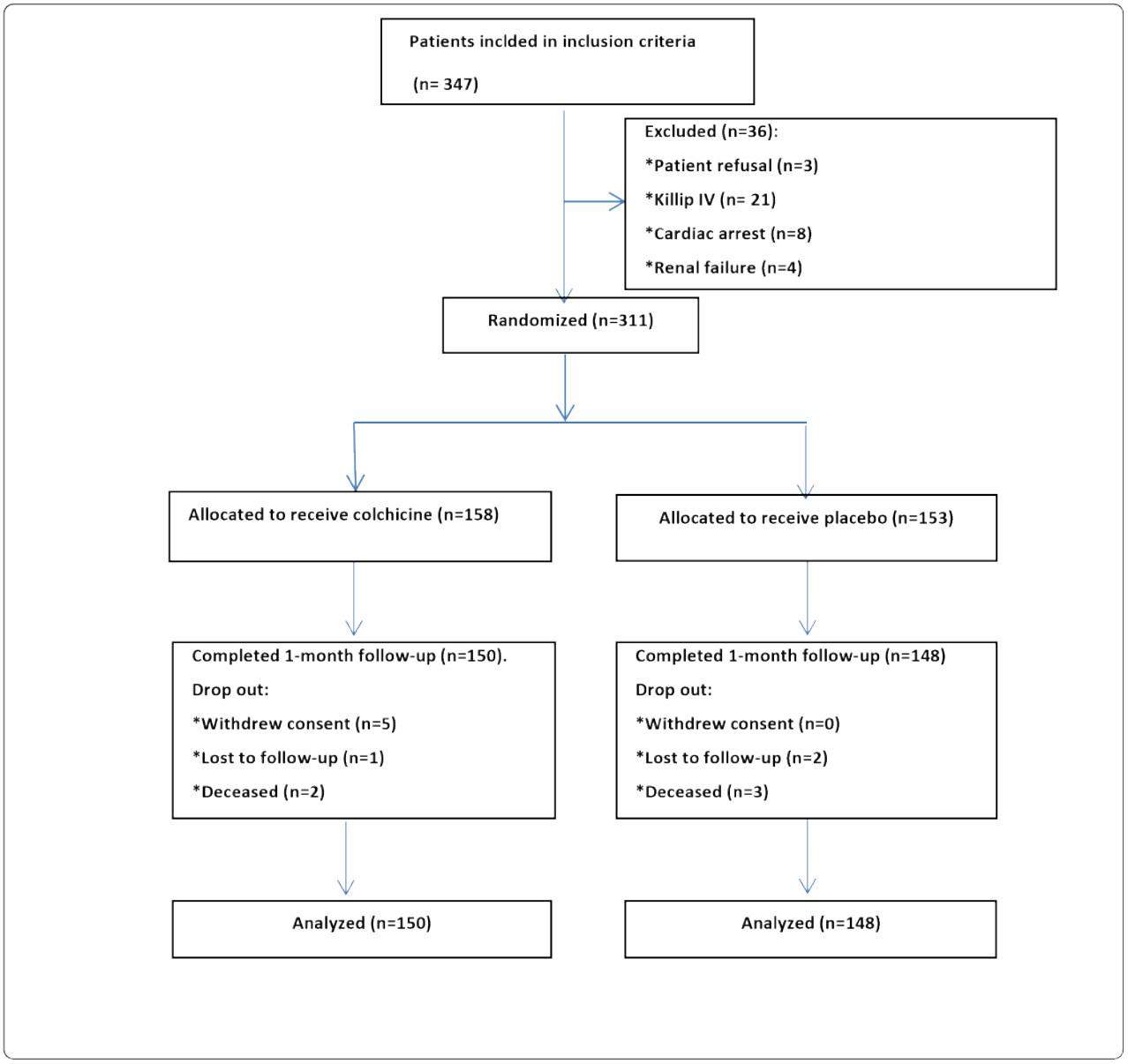

Figure 1. Research Flowchart. 347 patients were enrolled in this study. After matching with exclusion criteria, 311 patients were randomized, of which 158 were assigned to the colchicine group, and 153 were assigned to the placebo group. At 1 month follow-up, there were 8 drop-out patients in the colchicine group and 5 in the placebo group.

In the treatment group, there was a male dominance of 78.4% with an average age of 58.72+10.66. In the control group, there was also a male dominance of 79.2% with an average age of 57.69+11.2; no significant difference was found for these two groups ($p>0.05$). However, there were more diabetes mellitus risk factors in the control group (54% with $P<0.05$) (Table 1). In the treatment group, there were side effects from giving colchicine, namely gastrointestinal complaints (diarrhea) in many patients, which were 5 (3.3%). They decided not to continue this study, where no side effects were found in the control group. At the end of the study, it was also found that two patients died in the treatment group, and three patients died in the control group, where the deaths were due to heart problems. Based on guidelines, all patients received OMT (DAPT, statins, ACE-I, and β-blockers) as standard ACS therapy. Adherence was measured using the memory call method, which was considered adherent if the patient consumed more than 80% of the drug given. We also compared baseline laboratory values and ejection fraction (EF) in the two groups (Table 2).

3.1 Follow Up Results after 1 Month

At the study's completion, after one month of follow-up, there was a reduction in rehospitalization due to cardiovascular causes (2 [1.3%] vs. 4 [2.7%], HR 3.42 [1.36-8.56], $p<0.05$) which was significant in the treatment group compared to the control group. Also, there was a reduction in all-cause mortality, but not statistically significant (2 [1,3% v 3 [2,0%], HR 3,38 [0,53-7,48], $p>0,05$). In the treated group, there was also a lower non-cardiovascular rehospitalization rate compared to placebo, but not significant (4 [2.6%] vs. 7 [4.7], HR 0.42 [0.15-1.02], $p<0.05$) (Table 3).

Table 1. Baseline characteristics of the patients.

Characteristic	Colchicine (n=150)	Placebo (n=148)	p-value
Age, year (+SD)	58.72+10.66	57.69+11.2	0.292
Male, (%)	117 (78.4)	117 (79.2)	0.827
Hypertension (%)	94 (63.2)	97 (65.6)	0.575
Diabetes (%)	74 (49.0)	79 (54.0)	0.562
Active smoker (%)	99 (66.0)	97 (66.0)	1.000
Hyperlipidemia (%)	135 (90.0)	126 (85.2)	0.103
Medication			0.122
ACE-I/ARB	83 (55.6)	89 (60.1)	
β-Blocker	83 (55.6)	89 (60.1)	
High-intensity statin	150 (100)	148 (100)	
DAPT	150 (100)	148 (100)	
Adherence	150 (100)	148 (100)	0.148
STEMI Onset			0.580
<12 Hour	30 (19.6)	32 (21.6)	
>12 Hour	120 (80.4)	116 (78.4)	
Infarct Related Artery (IRA)			0.094
LAD	83 (55,6)	89 (60,1)	
Non-LAD	67 (44,4)	59 (39,8)	

*note: ACE-I: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; DAPT: Dual Anti Platelet Therapy; STEMI: ST Elevation Myocardial Infarct; LAD: Left Anterior Descending Artery

Table 2. Biomarkers of both groups and their correlation with cardiac rehospitalization

Biomarker	Colchicine		Placebo	
	Mean + SD	p-value	Mean + SD	p-value
WBC	10.04 +13.84	0.792	12.57 + 4.71	0.525
Troponin	9.16 + 16.70	0.216	8.05 + 14.80	0.205
TG	125.75 + 89.25	0.101	126.03 + 84.63	0.890
Cholesterol	177.71 + 49.26	0.557	174.59 + 44.08	0.394
LDL	116.44 + 43.21	0.816	97.74 + 27.60	0.029
HDL	39.98 + 15.60	0.162	37.93 + 6.86	0.888
BUN	33.98 + 13.81	0.154	30.26 + 16.24	0.003
Cr	0.96 + 0.31	0.653	0.97 + 0.58	0.992
SGOT	75.78 + 98.61	0.840	129.63 + 147.91	0.966
SGPT	40.42 + 43.41	0.532	47.37 + 37.25	0.361
EF	56.55 + 12.24	0.451	56.90 + 10.31	0.288

*note: WBC: White Blood Cell; TG: Triglyceride; LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, Cr: Creatinin, EF: Ejection Fraction

Table 3. Clinical outcomes (colchicine and placebo groups)

Primary Endpoint	Colchicine (n=133)	Placebo (n=128)	Hazard ratio (95%CI)	p-value
Rehospitalization				
Non-cardiovascular	4 (2.6)	5 (3.3)	0.42 (0.15 - 1.02)	0.057
Cardiovascular	6 (4.0)	11 (7.4)	3.42 (1.36 – 8.56)	0.009
All-cause mortality	2 (1.3)	3 (2.0)	3.38 (0.53 - 7.48)	0.364

Table 4. Rehospitalization and mortality by Onset

Secondary Endpoint	Onset < 12 hours		Hazard ratio (95%CI)	P-value
	Colchicine (n=120)	Placebo (n=116)		
Rehospitalization				
Non-Cardiovascular	3 (2,5)	4 (3,4)	0,99 (0,20 – 4,93)	0,996
Cardiovascular	5 (4,1)	9 (7,7)	1,81 (0,60 – 5,40)	0,287
All-cause mortality	2 (1,6)	2 (1,6)	1,06 (0,15 – 7,57)	0,949
Secondary Endpoint	Onset < 12 hours		Hazard ratio (95%CI)	P-value
	Colchicine (n=30)	Placebo (n=32)		
Rehospitalization				
Non-Cardiovascular	1 (3,3)	1 (3,1)	4,24 (0,47 – 37,99)	0,196
Cardiovascular	1 (3,3)	2 (6,6)	9,64 (0,82 – 76,10)	0,332
All-cause mortality	0 (0)	1 (3,1)	7,22 (0,01 – 64,10)	0,461

After analyzing the primary endpoint, we continue the analysis to prove the secondary endpoint. We wanted to see whether the benefits of colchicine in reducing rehospitalization and mortality are based on the onset of IMA-EST. From this analysis, at the onset of <12 hours, the results of rehospitalization and mortality rates were lower in the colchicine group compared to the placebo group but not statistically significant. The same results were found in both groups with onset >12 hours but were also not statistically significant.

4. Discussion

This study has shown that adding low-dose colchicine in post-PCI STEMI patients with optimal medical treatment can reduce rehospitalization due to cardiovascular disease at 1-month follow-up. This aligns with several previous studies that adding low-dose colchicine in patients with ACS reduces rehospitalization due to heart failure and recurrent ACS and increases survival rates at 6-month follow-up.10 Despite standard therapy based on guidelines, patients generally have a high risk of developing cardiovascular disease afterward due to ongoing inflammatory pathways. Walls of diseased blood vessels undergoing an atherosclerotic process are susceptible to injury and instability from plaques. Based on the CANTOS study shows that canakinumab can inhibit inflammatory pathways and shows benefits as an anti-inflammatory to reduce cardiovascular events. Still, this drug is not widely available due to its price, lack of beneficial effects, and increased severe infections during this study.[11,12] Therefore, colchicine has several advantages, namely widely available, affordable price, and with the results of this study, it can be considered to be added to standard therapy from STEMI. Additionally, colchicine genetically functions as a cytoskeletal micro-tubules-disassembling agent. It prevents co-localization with NLRP3 and has broad anti-inflammatory properties, thereby preventing the inflammasome complex from forming and activating. Colchicine also inhibits microtubules with its mitotic effect and suppresses the upregulation of IL-1β and IL-6, which is its anti-inflammatory role.10 Although colchicine at a dose of 1 mg/day could not reduce inflammation and hs-CRP in patients with ACS or acute ischemic stroke in the study by Raju et al.[13-15] In the study by Martinez et al., it was demonstrated that patients with ACS who received short-term colchicine treatment experienced a decrease in inflammatory cytokines such IL-1, IL-18, and IL-6.[16,17]

This study could not be proven regarding the benefits of colchicine in reducing mortality. In this study, there was a lower mortality rate in the colchicine group compared to the placebo group, but it was not statistically significant. We strengthen this condition through clinical analysis of patients who died. In Table 6, we summarize the clinical information of patients who died. In the colchicine group, two patients died after returning from KRS. In the first patient, the patient had a respiratory infection. The patient then stopped the drugs given before it got worse and died. The second patient was found dead the following day by the family. In the placebo group, a third patient had symptoms of AMI before dying. The fourth patient experienced severe headaches accompanied by decreased consciousness, which was suspected of a bleeding stroke event. And in the fifth patient, it was suspected that he had worsened symptoms of heart failure before the patient was declared dead. From these data, we cannot conclude whether the reduction in mortality in the colchicine group was due to the use of colchicine.

We also conduct further analysis to prove the secondary objectives of this study. We wanted to know the benefit at the onset of which colchicine was given. From the analysis results, we found lower rehospitalization and mortality rates in the colchicine group with <12 hours of onset in the group compared to the placebo group with <12 hours of onset. The reason that might explain this finding is that at <12 hours of onset, the acute inflammatory response occurs earlier, so earlier administration of colchicine can prevent the development of inflammation that occurs during IMA-EST. In the colchicine group with an onset of >12 hours, there was also a reduction in rehospitalization and mortality rates when compared to the placebo group with an onset of >12 hours.[18] Nonetheless, this finding was not significant in our statistical analysis.

Regarding the safety of using colchicine, this study found five patients who experienced gastrointestinal side effects (diarrhea), which made all patients stop their colchicine. According to some literature, the highest side effect that can occur due to the use of colchicine is gastrointestinal disorders.[19] This study did not have a clinical interaction between colchicine and the other drugs. From the 1-month follow-up, we did not get any clinical signs of rhabdomyolysis or bleeding. From some literature, colchicine interacts with the statin group, in which statins are the main therapy of IMA-EST. This shows the safety of using colchicine in STEMI, although a laboratory evaluation is needed to discover more about these two drugs' interactions.

Our study has several limitations that should be noted. First, the number of patients involved is insufficient to represent the benefits of low-dose colchicine administration. Second, this study evaluates short-term benefits but cannot look at long-term benefits. Third, this study cannot see time-to-time intervention, so we cannot conclude the most appropriate time for administering colchicine to IMA-EST patients to provide maximum benefit. Fourth, we cannot conclude whether the cause of death was due to a cardiovascular or non-cardiovascular event due to a lack of data. Fifth, in this study, patient compliance was evaluated using the memory call method, which has a memory bias. Other methods, such as the Morisky Medication Adherence Scale (MMAS), are more tested, but we did not use them in this study.

5. Conclusion

In conclusion, administering low-dose colchicine for one month has shown benefits in reducing rehospitalization in patients with STEMI who receive PCI therapy. Adding colchicine as adjuvant therapy in STEMI patients who receive PCI and optimal medical treatment according to guidelines can potentially improve quality of life, through-intervention from the inflammasome pathway.

6. Declarations

6.1 Ethics Approval and Consent to participate

The subjects in this study are humans, so ethical rules must be followed. This research has passed the ethical due diligence, approved based on the Certificate of Ethical Eligibility No. 400/235/K.3/302/2020 issued by the Health Research Ethics Committee at Dr. Saiful Anwar Malang.

6.2. Consent for publication

Not applicable.

6.3 Availibility of data and materials

Data used in our study were presented in the main text.

6.4 Competing interests

Not applicable.

6.5 Funding Source

Not applicable.

6.6 Authors contributions

Idea/concept: BS, YWA. Design: BS,YWA. Control/supervision: MSR, CTT, SA. Data collection/processing: BS, YWA. Analysis/interpretation: BS, YWA, CTT. Literature review: YWA, BS. Writing the article: BS, YWA. Critical review: MSR, SA, CTT. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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