

# Comparative study of SOFA, WSESSSS, and CPIRO scoring systems as mortality predictors in a patient with complicated intra-abdominal infection



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## ABSTRACT

**Background:** A widespread intra-abdominal organ infection or complicated intra-abdominal infection (cIAI) causes localized peritonitis, intra-abdominal abscess, and diffuse peritonitis. Patients suffer from morbidity and mortality as a result of this condition. Sepsis indicators such as SOFA, WSESSSS, and CPIRO scores were predictors of mortality in cIAI patients. We aimed to examine the performance of WSESSSS, CPIRO, and SOFA scoring systems to predict mortality in patients with cIAI.

**Methods:** A retrospective cohort, analytic observational study was conducted to assess differences in SOFA, WSESSSS, and CPIRO scoring systems' sensitivity, specificity, and accuracy as predictors of death during treatment in cIAI patients in Dr. Soetomo General Hospital, Surabaya.

**Results:** A total of 265 patients were evaluated. The optimal cutoff for SOFA was score 5 with sensitivity, specificity, PPV, NPV, and accuracy of 77.2%, 87.9%, 77.2%, 87.9%, and 84.2%, respectively. The optimal cutoff for WSESSSS was score 8 with sensitivity, specificity, PPV, NPV, and accuracy of 83.7%, 82.7%, 72.0%, 90.5%, and 83.0%, respectively. The optimal cutoff for CPIRO was 4 with sensitivity, specificity, PPV, NPV, and accuracy values of 62.0%, 90.2%, 77.0%, 81.7%, and 80.4%, respectively. Patients with high scores had a higher percentage of being hospitalized longer and cost higher than patients with a low score.

**Conclusion:** The SOFA, WSESSSS, and CPIRO scoring systems had comparable performance in predicting mortality in patients with cIAI. Considering the performance of WSESSSS, the use of WSESSSS alone may be sufficient enough to predict the outcome of patients with cIAI in Indonesia.

**Keywords:** cIAI, CPIRO score, predictors of mortality, SOFA score, WSESSSS score.

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## INTRODUCTION

Complicated intra-abdominal infection (cIAI) is a condition with a wide spectrum, including localized peritonitis, intra-abdominal abscess, and diffuse peritonitis. This condition is a medical emergency situation with potentially high morbidity and mortality rates. According to the global AbSes study from 2019, the mortality rate from cIAI was 29.1% worldwide, and this number would rise to 40.3-54.9% if the patient had septic shock.<sup>1</sup> During the 2015-2016 period, 608 instances of cIAI were reported in Indonesia by six tertiary medical institutes, with a prevalence of 10% and a fatality rate of 16.6%. A previous study reported that 1.2% of cIAI patients died without evidence of sepsis, 4.4% died without severe sepsis, 27.8% died from

severe sepsis, and 67.8% died if the patient went into septic shock.<sup>2</sup>

The mortality rate for intra-abdominal sepsis is higher in a developing country than in a developed country. According to epidemiological data in Indonesia, there were 193 cases of cIAI during 2020-2021, with perforated appendicitis accounting for the majority of etiologies (32.64%), followed by gastroduodenal perforation (24.87%) and intestinal perforation (25.91%). Another rare cause of generalized peritonitis is gallbladder perforation.<sup>3</sup> In addition, almost half of the cIAI cases at Dr. Soetomo Hospital Surabaya had developed sepsis. A previous study in Indonesia also reported that gastric perforation might lead to sepsis or severe sepsis.<sup>4</sup> Sepsis is an important predictor of mortality in cIAI patients.

By early sepsis identification, therapy can proceed more quickly, and the death rate can be decreased.<sup>5-9</sup> Early systemic infection and systemic inflammation could be identified by various laboratory parameters, such as leucocyte, lactate level, and C-reactive protein.<sup>10,11</sup>

Currently, there are various sepsis severity score systems available, and they are useful for predicting mortality in cIAI patients. The SOFA (Sequential Organ Failure Assessment) score could be used generally in cases of sepsis, while the CPIRO (Calgary Predisposition Infection Response and Organ Dysfunction) scores and the WSESSSS (World Society of Emergency Surgery Sepsis Severity Score) were thought to be accurate in a large population with cIAI. The mortality rate of cIAI patients was increased with

greater SOFA, WSESSSS, and CPIRO scores.<sup>12-14</sup> The findings of the analysis of multiple sepsis severity score systems in the Tolonen *et al.* study concluded that the three scoring systems were adequate for predicting the mortality of cIAI patients.<sup>15</sup>

WSESSSS, CPIRO, and SOFA scoring systems may be useful for clinicians in daily practice. However, currently, there is no valid study of WSESSSS, CPIRO, and SOFA scoring systems in Indonesia despite the fact that there have been several studies on the validity studies of these three scoring systems worldwide. In this study, we aimed to examine the performance of WSESSSS, CPIRO, and SOFA scoring systems to predict mortality in patients with cIAI.

## METHODS

### Study design and participants

This is a retrospective cohort study conducted at Dr. Soetomo General Hospital (Surabaya, Indonesia). We examined a total of 265 patients' medical records with cIAI between 2020 and 2021. Based on inclusion and exclusion criteria, samples were drawn using randomized purposive sampling. The inclusion criteria were adults aged more than 18 years old, Indonesian citizens, and having been diagnosed with cIAI or secondary/tertiary peritonitis. The exclusion criteria were an incomplete medical record.

### Scoring systems assessment

In this study, we assessed the degree of sepsis using the SOFA score as previously described.<sup>16</sup> The score component is determined by evaluating the cardiovascular, central nervous, respiratory system, liver function, coagulation, and renal function.

The measurement of the WSESSSS (World Society of Emergency Surgery Sepsis Severity Score) uses a scoring system that is calculated based on a prospective global-scale WSESSSS observational study in cIAI patients. We measure the WSESSSS score as previously described.<sup>17</sup> The variables evaluated in WSESSSS are patient's age, immune status, setting of sepsis acquisition, primary cIAI disease, and delay in source control of more than 24 hours are the components to measure total WSESSSS score.<sup>2,12</sup>

Measurement of the CPIRO score system in this study (Calgary Predisposition, Infection Response and Organ Dysfunction) using a scoring system that is calculated based on disease predisposition, source of infection, response and organ dysfunction that occurs in patients due to cIAI.<sup>14</sup> Components were measured based on indicators of age and comorbid predisposing factors, the body's response to sepsis in the form of leukopenia and hypothermia, and the presence of organ dysfunction in the form of cardiovascular, respiratory, renal, and central nervous system dysfunction.<sup>14</sup>

In this study, the SOFA, WSESSSS, and CPIRO scores measurement data were taken from the patient's medical record before undergoing source control measures.

### Data collection

For cIAI patients who had source control surgery and therapy at Dr. Soetomo Hospital Surabaya between 2020 and 2021, medical record data will be gathered by researchers. Sample data will be chosen in accordance with the study's inclusion-exclusion criteria. The patient's pre-operative parameters will be used to calculate the SOFA, WSESSSS, and CPIRO scores. During patient care, information on dependent and confounding variables will be collected and documented for further analysis.

The patient data will be classified as a high or low sepsis severity score group based on the cutoff value of previous studies.<sup>15-17</sup> Each group of scores will be analyzed for the incidence of mortality during treatment in a cohort.

### Statistical analysis

The research data were analyzed using SPSS version 23.0 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The chi-square test was used to analyze the variables for statistical comparison. A P value of less than 0.05 was considered statistically significant. In this study, we compared the performance of the three scoring systems. The scoring system performance was evaluated by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

## RESULTS

### Patient demographic data

In this study, we collected a total of 265 subjects, consisting of 173 males (173/265; 65.3%) and 92 females (92/265; 34.7%). The mean age of the research subjects was  $42.6 \pm 17.5$  years. Based on age group, most patients were in the age group under 30 years (74/265; 27.9%), followed by the age group of more than 60 years (55/265; 20.8%), the age group 30-33 years (52/265; 19.6%), age group 50-59 years (47/265; 17.7%), and age group 30-39 (37/265; 14.0%). The demographic data of the research subjects are presented in [Table 1](#).

### Patient characteristics

Researchers analyzed patient characteristics based on the body mass index parameters, comorbidities, septic shock, immune conditions, and the causes of peritonitis ([Table 2](#)). We found that the majority of research subjects had a normal body mass index (194/265; 73.2%). There were 42 patients with above-normal BMI (42/265; 15.8%) and 29 underweight subjects (29/265; 10.9%). Meanwhile, based on the comorbidity aspect, there were 196 patients who had at least 1 comorbid disease (196/265; 74.0%).

Our data revealed that there were patients that arrived at the hospital in septic shock condition (54/265; 20.4%). Regardless of the source of the immunological problem, 21 patients (21/265; 7.9%) exhibited reduced immune function. We discovered that appendicitis was the most frequent cause of peritonitis (94/265; 35.5%), followed by gastroduodenal perforation (57/265; 21.5%). Nearly equal numbers of patients developed peritonitis as a result of jejunioileal and colonic perforations (35 subjects and 38 subjects, respectively). The splenic abscess was the least frequent cause of peritonitis, occurring in only 2 subjects (2/265; 0.8%).

### The performance of the scoring systems to predict outcomes

In order to predict patient outcomes, in this case, patients who died, we examined the performance of three distinct scoring systems from three different guidelines ([Table 3](#)). The sensitivity, specificity, PPV, NPV, and accuracy values were

**Table 1. Demographic data of patients in this study.**

Demographic variable	n	Percentage (%)
<b>Sex</b>		
Male	173	65.3
Female	92	34.7
<b>Age</b>		
<30	74	27.9
30-39	52	19.6
40-49	37	14.0
50-59	47	17.7
≥60	55	20.8
<b>Total</b>	265	100

**Table 2. Characteristics of research subjects in this study.**

Characteristic	n	Percentage (%)
<b>Body mass index</b>		
Underweight	29	10.9
Normal	194	73.2
Above normal BMI*	42	15.8
<b>Comorbidity</b>		
No	69	26.0
Yes	196	74.0
<b>Shock septic</b>		
No	211	79.6
Yes	54	20.4
<b>Immunity</b>		
Normal	244	92.1
Abnormal	21	7.9
<b>Cause</b>		
Appendicitis	94	35.5
Gastroduodenal perforation	57	21.5
Jejunioileal perforation	35	13.2
Colonic perforation	38	14.3
Liver abscess	11	4.2
Splenic abscess	2	0.8
Intra-abdominal abscess	8	3.0
Leakage anastomosis	8	3.0
Others	12	4.5

\*BMI group was determined using the WHO classification for weight status. Above normal BMI comprised overweight and obese patients

85.9%, 77.5%, 66.9%, 91.2%, and 80.4%, respectively, when utilizing the cutoff value of 4 for the SOFA score according to the prior. With regard to the sample used in this study, we analyzed the new cutoff. We discovered that the SOFA score 5 was the best cutoff to achieve the maximum accuracy value, with sensitivity,

specificity, PPV, NPV, and accuracy values of 77.2%, 87.9%, 77.2%, 87.9%, and 84.2%, respectively.

Our research demonstrates that the optimal WSESSSS cutoff analyzed in our study was similar to the cutoff value used in previous studies. The WSESSSS score of 8 was shown to be the most optimal cutoff

to obtain the highest accuracy value. Its sensitivity, specificity, PPV, NPV, and accuracy values were 83.7%, 82.7%, 72.0%, 90.5%, and 83.0%, respectively.

By using the cutoff value of the CPIRO score of 3 from the previous study, we revealed that the sensitivity, specificity, PPV, NPV, and accuracy values were 91.3%, 71.7%, 63.2%, 93.9%, and 78.5. %, respectively. However, it was found that the most optimal cutoff for CPIRO to get the highest accuracy value was score 4, which showed sensitivity, specificity, PPV, NPV, and accuracy values of 62.0%, 90.2%, 77.0 %, 81.7%, and 80.4%, respectively.

### Performance of the scoring system combination to predict outcomes

In this study, we also analyze the performance of the combination of two or three types of scoring systems simultaneously (Table 4). The combined results of SOFA and WSESSSS scores showed similar accuracy as the combined results of SOFA and CPIRO (accuracy = 83.4% for both). The combination of SOFA and WSESSSS had better sensitivity values than the combination of SOFA and CPIRO (93.5% vs. 83.7%, respectively) but had a lower specificity (78.0% vs. 83.2%, respectively). The combination of WSESSSS and CPIRO has sensitivity, specificity, PPV, NPV, and accuracy values of 88.0%, 78.0%, 68.1%, 92.5%, and 81.5%, respectively. The combination of the three scoring systems showed sensitivity, specificity, PPV, NPV, and accuracy values of 94.6%, 74.6%, 66.4%, 96.3%, and 81.5%, respectively.

### The association between the scoring system and the length of stay

We analyzed the relationship between the scoring system and the length of stay of patients in the hospital (Table 5). In this analysis, we excluded patients who died during treatment in the hospital. Based on the results of the analysis of the SOFA scoring system, we found that the majority of patients with high SOFA scores required more than 11 days of treatment (16/21; 76.2%). Meanwhile, there were no patients requiring treatment for less than 6 days (0/21; 0.0%), and only 3 patients were treated between 6 – 8 days (3/21; 14.3%). In contrast, patients with low SOFA scores

**Table 3.** Performance of each scoring system to predict the outcome.

Guideline cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
<b>SOFA</b>					
2	97.8	43.4	47.9	97.4	62.3
3	92.4	64.2	57.8	94.1	74.0
4	85.9	77.5	66.9	91.2	80.4
5	77.2	87.9	77.2	87.9	84.2
6	59.8	93.1	82.1	81.3	81.5
<b>WSESSSS</b>					
7	82.6	80.3	69.1	89.7	81.1
8	83.7	82.7	72.0	90.5	83.0
9	42.4	89.0	<b>B</b>	74.4	72.8
10	35.9	95.9	80.5	73.7	74.7
<b>CPIRO</b>					
2	100	38.2	46.2	100	59.6
3	91.3	71.7	63.2	93.9	78.5
4	62.0	90.2	77.0	81.7	80.4
5	43.5	98.9	93.0	76.6	79.2
6	13.0	100	100	68.4	69.8

**Table 4.** Performance of score system combination to predict the outcome.

Guideline combination	Sensitivity	Specificity	PPV	NPV	Accuracy
<b>2 guidelines</b>					
SOFA + WSESSSS	93.5	78.0	69.4	95.7	83.4
SOFA + CPIRO	83.7	83.2	72.6	90.6	83.4
WSESSSS + CPIRO	88.0	78.0	68.1	92.5	81.5
<b>3 guidelines</b>					
SOFA + WSESSSS + CPIRO	94.6	74.6	66.4	96.3	81.5

**Table 5.** Relationship between score system and length of stay in hospital.

Scoring*	n	Length of stay			
		<6 days	6-8 days	9-11 days	>11 days
<b>SOFA</b>					
High	21	0 (0.0)	3 (14.3)	2 (9.5)	16 (76.2)
Low	152	52 (34.2)	55 (36.2)	22 (14.5)	23 (15.1)
<b>WSES</b>					
High	30	2 (6.7)	5 (16.7)	6 (20.0)	17 (56.7)
Low	143	50 (35.0)	53 (37.1)	18 (12.6)	22 (15.4)
<b>CPIRO</b>					
High	17	0 (0.0)	4 (23.5)	3 (17.6)	10 (58.8)
Low	156	52 (33.3)	54 (34.6)	21 (13.5)	29 (18.6)

\*The high and low scores were determined using the optimal cutoff analyzed in this study

mostly only needed 6 – 8 days of treatment (55/152; 36.2%), followed by the length of treatment for less than 6 days (52/152; 34.2%). There were only 23 patients (23/152; 15.1%) who required treatment

for more than 11 days.

Based on the WSESSSS scoring system, it was found that patients with high WSESSSS scores mostly required treatment time of more than 11 days

(17/30; 56.7%). Meanwhile, there were only 2 patients who were treated for less than 6 days (2/30; 6.7%). In contrast, the majority of patients with low WSESSSS only required treatment for 6 – 8 days (53/143; 37.1%), followed by the length of treatment for less than 6 days (50/143; 35.0%). There were only 22 patients (22/143; 15.4%) who required treatment for more than 11 days.

Finally, based on the CPIRO scoring system, it was found that patients with high CPIRO scores mostly required more than 11 days of treatment (10/17; 58.8%). We found that none of the patients with high CPIRO scores were admitted for less than 6 days (0/17; 0.0%). In contrast, the majority of patients with low CPIRO required treatment for 6 – 8 days (54/156; 34.6%) and followed by a length of stay for less than 6 days (52/156; 33.3%). There

**Table 6.** Relationship between scoring system and maintenance costs.

Scoring*	n	Cost					
		<\$1,500	\$1,500-\$2,499	\$2,500-\$3,499	\$3,500-\$4,499	\$4,500-\$5,499	>\$5,500
<b>SOFA</b>							
High	21	0 (0.0)	5 (23.8)	2 (9.5)	4 (19.0)	4 (19.0)	6 (28.6)
Low	152	53 (34.9)	49 (32.2)	26 (17.1)	10 (6.6)	5 (3.3)	9 (5.9)
<b>WSES</b>							
High	30	1 (3.3)	6 (11.1)	8 (26.7)	4 (13.3)	3 (10.0)	8 (26.7)
Low	143	52 (36.4)	48 (33.6)	20 (14.0)	10 (7.0)	6 (4.2)	7 (4.9)
<b>CPIRO</b>							
High	17	0 (0.0)	3 (17.6)	5 (29.4)	5 (29.4)	2 (11.8)	2 (11.8)
Low	156	53 (34.0)	51 (32.7)	23 (14.7)	9 (5.8)	7 (4.5)	13 (8.3)

\*1 USD equals 14,740 IDR

\*The high and low scores were determined using the optimal cutoff analyzed in this study

were 29 patients (29/156; 18.6%) who required hospitalization for more than 11 days.

### The association between the scoring system and the cost of treatment

We also analyzed the relationship between the scoring system and the cost of hospitalization (Table 6). In this analysis, we excluded patients who died and included only patients who lived to the completion of hospitalization. We analyzed the cost and converted it into USD (1 USD equals 14,740 IDR). The results of the analysis showed that the majority of patients with high SOFA, WSESSSS, and CPIRO scores required treatment costs of more than 5,500 USD (6/21; 28.6%, 8/30; 26.7%, and 6/21; 28.6%, respectively). In patients with low SOFA, WSESSSS, and CPIRO scores, the majority required treatment costs under 1500 USD (53/152; 34.9%, 52/143; 36.4%, and 53/156; 34.0%, respectively).

## DISCUSSION

In order to predict the prognosis of patients with widespread peritonitis, three scoring methods from three different guidelines are being compared in this study. In this study, SOFA, WSESSSS, and CPIRO scores are the three grading systems that we compared. We employed two different kinds of cutoff values: the cutoff value suggested by earlier validation studies and the best cutoff value determined using the data from this study. In general, we found that the performance of the three

scoring systems was comparable, showed by the accuracy of each scoring system. We discovered that a score of 5 was the ideal cutoff value in the SOFA score analysis, which is higher than the SOFA score of 4 reported in other research, and this cutoff had a slightly higher accuracy. The ideal cutoff value for the WSESSSS scoring system in this study is consistent with the cutoff value from the prior study. Meanwhile, the cutoff value in the CPIRO scoring system was higher than the cutoff displayed in the prior study (cutoff 4 vs. cutoff 3, respectively). The performance displayed was essentially comparable, despite the somewhat differing cutoff values. It is likely that the difference in population characteristics accounted for the difference in performance.<sup>15</sup> Our study demonstrated that these three scores could be used to predict mortality accurately in patients with cIAI. The clinicians should consider what scoring system would be used. In our health center, we noticed that WSESSSS is relatively easier and faster to perform, even in the emergency department. Therefore, considering the performance of WSESSSS shown in this study, the use of WSESSSS alone may be sufficient enough to predict the outcome of patients with cIAI.

Based on demographic data, we found that the majority of patients were male, and most were in the younger age group of fewer than 30 years. This data description is in accordance with our data which shows that the most common cause of generalized peritonitis in this study is appendicitis, where patients

with appendicitis are generally male and younger than 30 years old. In a study conducted by Kidwai and Sharma, the incidence of perforated appendicitis was 23.67% of a total of 96 patients and was dominated by male patients aged 21-40 years.<sup>18</sup> Another common cause is gastroduodenal perforation and colonic perforation.<sup>19,20</sup> Gastroduodenal perforation is mainly caused by peptic ulcer perforation.<sup>19</sup> A study reported that gastric ulcers, especially giant ulcers, are the main cause of gastric leakage. Risk factors that increase the likelihood of peptic ulcers include the consumption of non-steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* infection.<sup>21-23</sup>

Our data also showed that almost all patients with generalized peritonitis came to the healthcare facility in septic shock condition. This indicates that there may be a delay in seeking immediate medical attention or being taken to a hospital. Thus, many patients who came to the hospital have already fallen into a systemic infection condition. Delayed treatment in cases of peritonitis was a predictor of a worse patient's condition.<sup>24-25</sup> This condition will affect patient care. In patients with diverticulitis, Coccolini *et al.* found an increase in mortality if initial treatment was delayed by more than 24 hours.<sup>17</sup> In patients with perforated peptic ulcer, every hour of delay between hospital admission and surgery was associated with a 2.4% increase in mortality. In a Japanese study of patients with septic shock due to gastrointestinal perforation, the hourly delay was associated with a high increase

in mortality.<sup>25</sup> In a large multi-center study by Bloos *et al.* reported that the mortality increased by 1% within every hour of delay in source control of infection.<sup>26</sup>

In this study, we also analyzed the performance of the scoring system, which had been combined together to predict the patient's outcome. We found that the combination of two or more can increase the accuracy value for predicting prognosis. This result was in accordance with the research conducted by Tolonen *et al.*, which showed that the combination of SOFA scores with WSESSES had a slightly higher detection rate.<sup>15</sup> However, the increase was found to be insignificant compared to the use of one type of scoring system. However, although it can improve the performance of the ability to predict outcomes, the application of a combined score system should be carefully considered in healthcare centers. Importantly, to use a combination scoring system, we need to get more data included in each scoring system. This requires longer time, higher cost, and effort to perform. Moreover, with an insignificant increase in performance, the use of one type of scoring system can be a simple option that is easier, practical, inexpensive, and effective in making decisions.<sup>27</sup>

In this study, we also analyzed the relationship between the scoring system and the length of hospital stay. We found that patients with high SOFA scores had a higher percentage of patients being hospitalized for more than 11 days. In contrast, the majority of patients with low SOFA scores required less than 8 days of treatment. Similar to our result, previous studies also showed that patients in the high SOFA score group (SOFA score >5) had a significantly higher risk of death and length of stay than patients in the low SOFA score group (SOFA score <5).<sup>28,29</sup> The same pattern was also found when we analyzed the WSESSES and CPIRO scoring systems, where patients with high scores tended to require longer treatment than patients with low scores.<sup>15</sup> The three scoring systems are commonly used to calculate the severity of an emergency or sepsis in patients. Higher values indicate greater severity and a greater likelihood of sepsis. Subsequently, this will have an impact on the length of treatment in the

hospital. A study also showed that higher cumulative scores across various scoring systems could indicate an increased risk of mortality in patients.<sup>15</sup> Our data show that all three scoring systems can consistently predict the length of hospital stay.

The length of patient care in the hospital also has a direct impact on the cost of treatment.<sup>30,31</sup> Patients with high SOFA, WSESSES, and CPIRO scores tend to be hospitalized longer, which in turn results in higher treatment costs compared to patients with low SOFA, WSESSES, and CPIRO scores. This shows that the three scores can be used as a parameter to predict hospital care costs.

There are limitations to this study. First, this study was conducted in one hospital. Therefore, this study could not represent the Indonesian population in general. Second, the number of subjects in this study is relatively low. Second, there were various causes for cIAI in this study. Therefore, the management may vary depending on each patient's diagnosis and condition.

## CONCLUSION

The SOFA, WSESSES, and CPIRO scoring systems had comparable performance in predicting mortality in patients with cIAI. Considering the performance of WSESSES, the use of WSESSES alone may be sufficient enough to predict the outcome of patients with cIAI in Indonesia.

## CONFLICTS OF INTEREST

No competing interests were declared.

## ETHICAL CLEARANCE

This study was reviewed and approved by the Medical Ethical Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (Ref. No: 0956/LOE/301.4.2/XII/2022) following the guidelines of the Declaration of Helsinki.

## AUTHOR CONTRIBUTION

Conceived the study: GLN. Designed the study: GLN, DS, and TL. Analyzed the data: GLN, DS, and TL. Wrote the manuscript: GLN and DS. Review the manuscript: DS and TL.

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