The roles of C-reactive protein-albumin ratio as a novel prognostic biomarker in heart failure patients: A systematic review

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ABSTRACT

C-Reactive Protein (CRP)-albumin ratio (CAR) is a novel prognostic biomarker that is predicted to be a more reliable indicator than CRP or albumin alone. Therefore, this systematic review aimed to evaluate the role of CAR in predicting poor outcomes of heart failure (HF) patients. We conducted a literature search across ProQuest, PubMed, ScienceDirect, Web of Science, and Scopus. All related studies assessing CAR and reporting mortality outcomes or other adverse outcomes were assessed. A total of five studies with a total of 1821 patients were included in this review. CAR is significantly associated with all-causes in-hospital mortality and out-hospital mortality in patients with acute and chronic heart failure. CAR is associated with higher hospitalization rates, the number of hospitalizations, severe New York Heart Association (NYHA) classification, and the...

Abbreviations: ACE, Angiotensin-Converting Enzyme; AHF, Acute Heart Failure; ARBs, Angiotensin Receptor Blockers; AUC, Area Under Curve; CAR, CRP-Albumin Ratio; CHF, Chronic Heart Failure; CRP, C-Reactive Protein; ESC, European Society of Cardiology; GDMT, Guideline-Directed Medical Therapy; HF, Heart Failure; HFmrEF, Heart Failure Mid-range Ejection Fraction; HFpEF, Heart Failure Preserved Ejection Fraction; HFrEF, Heart Failure Reduced Ejection Fraction; ICD, Implantable Cardiac Defibrillators; LoS, Length of Stay; LVEF, Left Ventricle Ejection Fraction; NOS, Newcastle-Ottawa Scale; NYHA, New York Heart Association; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; PROSPERO, the International Prospective Register of Systematic Reviews; ROC, Receiver Operating Characteristic.

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Introduction

Despite the developments of pharmacological and non-pharmacological treatment of heart failure (HF) patients which have increased the survival of the patients, the mortality rate remains high.\(^1\) The mortality rate for HF patients in 2004-2005 was still around 14\(\%\) specifically with acute heart failure (AHF) at 23.6\(\%\) and chronic heart failure (CHF) at 6.4\(\%\).\(^2\) The European Society of Cardiology (ESC) guideline also emphasizes that the problem of HF is not only from the cardiovascular aspect, but also nutrition, infection, and frailty that must be taken into account because it significantly increases patient morbidity and mortality.\(^3\)

C-reactive protein (CRP) is an acute-phase inflammatory protein, whose expression increases during inflammatory conditions.\(^4\) CRP could be used as a tool to monitor presence, severity, and prognostic of various infectious diseases such as COVID-19\(^5\) and malaria\(^6\) as well as non-infectious disorders such as advanced cancer\(^7\), HF\(^8\), and chronic obstructive pulmonary disease.\(^9\)

Another protein produced by the liver, albumin, is a broad marker for general health, nutritional status, and treatment response. Albumin could also be used as a prognostic marker for several diseases such as sepsis\(^10\), HF\(^11\), COVID-19\(^12\), and non-small cell lung cancer.\(^13\) Hence, the combination of these two markers, as the CRP to albumin ratio (CAR), is predicted to be a more reliable indicator than CRP or albumin alone.

However, the role of CAR as a prognostic biomarker for HF patients has not been widely discussed due to the lack of research. In fact, the CAR examination, which is routinely ordered, can provide more benefits in stratifying the prognosis of HF patients and evaluating frequent comorbidities such as inflammation, frailty, cachexia or nutritional problems. Therefore, this systematic review aimed to examine the role of CAR value in predicting poor outcomes in HF patients.

Material and methods

This review has been written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline\(^14\) (Table S1) and registered in the International Prospective Register of Systematic Reviews (PROSPERO), under the registration number CRD42024499776.

Eligibility criteria

This systematic review included cohort, cross-sectional, and case control studies. The inclusion criteria for this studies were as follows: (1) patients with a diagnosis of HF\(^3\), (2) Assessing CAR (or similar), (3) reporting mortality outcomes or other adverse outcomes, (4) and being written in English language. We excluded studies that did not conduct CAR analysis (either CRP only, Albumin only, or CRP and Albumin without ratio analysis). We also excluded studies that were only available in the abstract, case reports, reviews, meta-analyses, comments, editorials.

Data search strategy

An electronic search was conducted on December 1, 2023 through multiple databases, including ProQuest, PubMed, ScienceDirect, Web of Science, and Scopus. We also conduct manual searches in gray literature to ensure comprehensive coverage. Two reviewers independently screened search results, and any discrepancies were resolved through discussion with senior authors. The search terms used are (“C-Reactive protein to albumin ratio” OR “CRP to albumin ratio” OR “hs-CRP to albumin ratio” OR “CRP to prealbumin ratio” OR “CRP-Albumin ratio”) AND (“Heart Failure”) (Supplementary file, Table S2).

Data extraction and quality assessment

Relevant data from selected studies were extracted into a pre-design table consisting of author, publication year, study design, setting, sample size, age, place of CAR was conducted, CAR cut-off value, comorbidity, medication, and outcomes. The quality of included studies was examined using the Newcastle-Ottawa Scale (NOS) quality assessment tool.\(^15\) The NOS evaluates three quality parameters with possible total points are 4 points for selection, 2 points for comparability, and 3 points for outcomes. The quality of study is divided into 3 groups, specifically studies with ≥7 points were considered as “good”, 2 to 6 points were considered as “fair”, and ≤1 point were considered as “poor” quality.\(^15\) Bias assessment was carried out independently by two investigators, and consensus of any disagreement was discussed with senior author for solution (Supplementary file 1, Table S3).

Data analysis

Due to differences in population, setting of assessed CAR and various outcome measures in each study, we could not conduct a meta-analysis, but we narrated systematically included studies.
Results

Study selection and quality assessment

From the five databases, 239 titles and abstracts were obtained. A total of 31 titles and abstracts were removed due to duplication. Following the screening of 208 titles and abstracts, eleven studies were selected for full-text review. A total of four studies\textsuperscript{16-19} fulfilled predefined criteria and were included in this systematic review. Some articles were excluded because of inappropriate population\textsuperscript{20-22} and missing CAR group analysis.\textsuperscript{23} One additional study\textsuperscript{24} was also included from the references searching method while covering the grey literature. PRISMA flow diagram (Fig. 1) presented the selection process for included studies and the reasons for their exclusion. As a note (Table 1), all included studies in this systematic review were published in 2020-2023.

All included studies were retrospective cohorts except for one prospective cohort study conducted by Lima et al.\textsuperscript{18} The NOS quality assessment tool for cohort studies was used to evaluate the risk of bias in included studies.\textsuperscript{15} Risk of bias assessment showed four studies\textsuperscript{16,17,19,24} got 8/9 asterisks while Lima et al\textsuperscript{18} got 7/9 asterisks. All five studies were considered good quality of study (Supplementary file 1, Table S3).

Study characteristics

Collectively, 1821 participants were discussed in this systematic review. The average age ranged from 44-77 years old and was dominated by the male gender, accounting for 72 % of total participants. Three studies included patients with CHF\textsuperscript{16,18,24} and two studies included patients with AHF.\textsuperscript{17,19} It was only in the Cinier et al study\textsuperscript{16} in which the age of participants was older in the high compared to the low CAR group.

According to left ventricle ejection fraction (LVEF), Cinier et al\textsuperscript{16} and Yucel et al\textsuperscript{24} only included HF reduced ejection fraction (HFrEF) patients while Lima et al\textsuperscript{18} included patients with HF mid-range ejection fraction (HFmrEF). All the diagnosis of HF was defined according to the ESC Guideline for HF.\textsuperscript{3} In addition, all participants in the Cinier et al study\textsuperscript{16} were treated with implanted cardiac defibrillators (ICD) which reflect the severity of the disease.

CAR examination

All of the included studies had the primary aim of evaluating the roles of CAR in predicting poor outcomes among HF patients.\textsuperscript{16-19,24} In terms of laboratory examination, all included studies use the albumin test result as a component of CAR, except for Yamada et al which uses pre-albumin for CAR calculation.\textsuperscript{17} A different point of examination was observed between studies such as the emergency department,\textsuperscript{17,19} outpatient clinic,\textsuperscript{18,24} and in the morning following 12 hours of fasting before the ICD implantation.

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Fig. 1. PRISMA flowchart of study selection.
<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>Study Population</th>
<th>Age (Mean)</th>
<th>Male (%)</th>
<th>Setting of CAR value obtained</th>
<th>Comorbidity</th>
<th>Medication</th>
<th>Outcome</th>
<th>Adjusted OR/HR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cinier et al, 2021</td>
<td>Retrospective cohort study</td>
<td>Turkey</td>
<td>1011</td>
<td>CHF with EF &lt; 40 % and implanted ICD</td>
<td>63</td>
<td>813</td>
<td>Before device implantation</td>
<td>Hypertension, DM, chronic renal failure</td>
<td>Beta-blocker, ACE inhibitor/ARB, Aldosterone antagonists,</td>
<td>1-year all-cause mortality. Mean follow up duration 38 (17-77) months</td>
<td>5.69 (2.14 – 17.55)</td>
</tr>
<tr>
<td>2</td>
<td>Lima et al, 2022</td>
<td>Prospective cohort study</td>
<td>Brazil</td>
<td>77</td>
<td>CHF with EF &lt; 50 %</td>
<td>77</td>
<td>46</td>
<td>At the time of inclusion in the study</td>
<td>NA</td>
<td>Beta-blocker, ACE inhibitor/ARB, Aldosterone antagonists, sacubitril-valsartan</td>
<td>(Primary) 1 year-all-cause mortality (Secondary) Hospitalization for decompensated HF, number of days of hospital stay</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Sonsoz et al, 2023</td>
<td>Retrospective cohort study</td>
<td>Turkey</td>
<td>374</td>
<td>AHF</td>
<td>69</td>
<td>198</td>
<td>24 hours after admission</td>
<td>Hypertension, DM, CAD,CKD, CVD,</td>
<td>Anticoagulants, diuretic, ACE inhibitor/ARB, beta-blockers, aldosterone antagonist, ivabradine, digoxin, antiarrhythmics, inotropic agents, vasodilator,</td>
<td>(Primary) All-cause in-hospital mortality (Secondary) Acute kidney injury/worsening renal function, infection, acute ischemic hepatitis, coagulopathy, ventricular tachycardia, shock, length of stay</td>
<td>1.69 (1.02 -2.81)</td>
</tr>
<tr>
<td>4</td>
<td>Yamada et al, 2021</td>
<td>Retrospective cohort study</td>
<td>Japan</td>
<td>257</td>
<td>AHF</td>
<td>70.7</td>
<td>171</td>
<td>On admission</td>
<td>Hypertension, dyslipidemia, DM, smoking, AF</td>
<td>Loop diuretics, aldosterone antagonists, ACE inhibitors/ARB, Beta-blockers</td>
<td>(Primary) All-cause death including in-hospital and post-discharge, Median follow up 264 (71–460) days (Secondary) Cardiac and non-cardiac death</td>
<td>3.88 (1.91 -7.86)</td>
</tr>
<tr>
<td>5</td>
<td>Yucel et al, 2020</td>
<td>Retrospective cohort study</td>
<td>Turkey</td>
<td>102</td>
<td>CHF with EF &lt; 40 %</td>
<td>44</td>
<td>87</td>
<td>At the time of inclusion in the study</td>
<td>Hypertension, DM, CAD, AF</td>
<td>Antiplatelet, beta-blocker, ACE inhibitor/ARB, digoxine, diuretics, Aldosterone antagonist</td>
<td>Predicting poor NYHA functional capacity in chronic HF</td>
<td>3.08 (1.07– 3.85)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE (Angiotensin-converting Enzyme), AF (Atrial Fibrillation), AHF (Acute Heart Failure), ARB (Angiotensin Receptor Blocker), CAD (Coronary Artery Disease), CAR (C-Reactive Protein-Albumin Ratio), CHF (Chronic Heart Failure), CKD (Chronic Kidney Disease), CVD (Cerebrovascular Disease), DM (Diabetes Mellitus), EF (Ejection Fraction), HF (Heart Failure), ICD (Implantable Cardioverter-Defibrillator)
The included studies reported diverse cut-offs with different methods. Optimum CAR cut-off from receiver operating characteristics (ROC) analysis was reported by Yucel et al (1.5), Yamada et al (1.6), Sonzos et al (0.78), and Cinier et al (0.27). In addition, Cinier et al also classified patients according to CAR tertiles. Meanwhile, Lima et al obtained a cut-off (1.2) from a previous study conducted by Correa et al.

Medical history and previous heart failure treatment

These studies excluded diseases or conditions that affect CRP and albumin such as renal failure, liver disease, severe malnutrition, malignancy, infection or inflammation, glucocorticoid therapy, and recent surgery and trauma. The study with the most specific exclusion criteria was the study by Yucel et al.

Three consistent drugs recorded in studies (both AHF and CHF) are angiotensin-converting enzyme (ACE) inhibitors or Angiotensin receptor blockers (ARBs), aldosterone antagonists, and beta blockers. Several other heart medications consumed by patients include sacubitril-valsartan, antiplatelets, digoxin, and diuretics. In studies with AHF, patients were recorded as receiving intravenous diuretics, antiarrhythmics, inotropic agents, and intravenous vasodilator agents. The study by Lima et al showed the administration of guideline-directed medical therapy (GDMT) in 76.6% of CHF patients. However, the analysis of the all studies, none of these drugs were related to the CAR value, except that antiarrhythmics and inotropic agents were more frequently used in high CAR group in comparison to the low group. All included studies did not describe the medications that patients were taking other than cardiovascular drugs.

Primary outcomes: CAR in predicting mortality

All available evidence reported that high CAR was significantly associated with mortality in HF patients. There were different cut-offs and follow-ups of mortality outcomes among the included studies.

Cinier et al classified CAR groups according to their tertile value mentioned 0.2, 0.6, and 3.4 for T1, T2, and T3, respectively. The higher CAR groups appeared to have higher all-cause mortality (4.2% vs 11.0% vs 28.5%; p < 0.001) during 38 (17-77) months follow duration. It was observed that the mortality of the T3 group was significantly higher compared to other groups since the first month of follow-up. Multivariable analysis reveal that the T3 group was independently associated with higher long term all-cause mortality after being adjusted with other variables including age, gender, indication for the implantation, device types, and routine laboratory parameters (aHR 5.69; 95% CI, 2.14-17.55). The diagnostic performance of CAR to predict all-cause mortality was 70% sensitivity, 72% specificity, and 0.73 AUC. Its value was slightly higher compared to the AUC of each CRP and albumin when used separately.

Yamada et al reported that the number of patients who died in high and low CAR groups were 36% and 7.1%, respectively, during 264 (71-460) days of follow-up. As noted, half of the deaths in the Yamada et al study were due to cardiac causes. Multivariate analysis revealed that high CAR was independently associated with a higher all-cause mortality rate with adjusted HR 3.9 (95% CI, 1.91-7.86; p < 0.001). Separated analysis revealed that cardiac as well as non-cardiac causes significantly contributed to high CAR compared to low CAR groups. The diagnostic performance of CAR in predicting mortality was 67.5% sensitivity, 77.6% specificity, and 0.73 AUC. Its value was slightly higher compared to the AUC of each CRP and albumin when used separately.

In contrast, Lima et al showed that high CAR was not associated with higher all-cause mortality compared to high low CAR groups (7.1% vs 6.1%, respectively, p = 0.86) in 77 HF outpatients during 12-month follow-up.

In terms of in-hospital mortality, the Sonzos et al study showed that it was more prevalent in high compared to low CAR groups (36.7% vs 12%, p < 0.001). CAR could predict in-hospital mortality even after being adjusted with other variables including demographic characteristics, cardiac condition, and routine laboratory tests (adjusted aHR 1.69, 95% CI: 1.02-2.82; P = 0.042). The diagnostic performance of high CAR to predict in-hospital mortality was a 69% sensitivity, 66% specificity, and 0.78 AUC.

Secondary outcomes

Length of Stay (LoS) and rehospitalization

The study conducted by Sonzos et al showed that high CAR group had a slightly longer LoS compared to the low CAR group (11 vs 9 days, p = 0.042). In comparison, Lima et al reported there were no differences in LoS between high and low CAR groups (12.2 vs 14.2 days respectively, p = 0.36).

The study conducted by Lima et al showed that the hospitalization rate was higher in the high CAR compared to the low CAR group (35.7% vs 12.2%, p = 0.01). In addition, the number of recurrent hospitalizations in 12 months of follow-up was also higher in high compared to the low CAR group (14 vs 8, p < 0.001).

Cardiac symptoms and functions

Yucel et al reported that mean CAR was significantly higher in patients with New York Heart Association (NYHA) class III and IV compared to NYHA I and II (0.4 vs 0.12, p < 0.001). Sonzos et al and Cinier et al also showed that high CAR was associated with a higher NYHA class. The value of CAR also correlated with natriuretic peptide concentration in low-moderate strength among patients with stable HF.

The association between CAR value and LVEF varied between studies. Cinier et al study showed high CAR was associated with...
lower LVEF. On the contrary, Lima et al.\textsuperscript{18} Sonsoz et al.\textsuperscript{19} and Yamada et al.\textsuperscript{17} reported there were no differences in LVEF between high and low CAR groups. CAR was one of two variables that were significantly associated with the risk of advanced HF (OR 3.1, 95 %CI: 1.074–3.855, \textit{P} 0.036) after being adjusted with demographic characteristics, clinical conditions, routine laboratory tests, and HF medication.\textsuperscript{24}

**Complications and interventions**

In HF outpatient with ICD, appropriate shock was observed higher in the T3 CAR group compared to the T1 dan T2 CAR groups (38 \% vs 23.7 \% vs 19.3 \%, \textit{p} < 0.001). However, there was no differences in inappropriate shock among the three groups.\textsuperscript{16} Cinier et al.\textsuperscript{6} defined appropriate shock when the ICD delivered anti-tachycardia or shock therapy in response to ventricular fibrillation or ventricular tachycardia. While, the inappropriate shock was defined device therapy responded to sinus tachycardia, atrial fibrillation, and supraventricular tachycardia of device malfunction.\textsuperscript{19} In addition, Sonsoz et al.\textsuperscript{19} also showed a higher frequency of ventricular tachycardia in high CAR compared to low CAR groups (1.27 \% vs 5.6 \%, \textit{p} 0.015) during hospitalization of AHF.

From the included studies, Sonsoz et al.\textsuperscript{19} was the only study that comprehensively reported complications and interventions of AHF. CAR had a higher frequency of hemodialysis/ultrafiltration, infection, coagulopathy, acute ischemic hepatitis, invasive mechanical ventilation, non-invasive ventilation, and shock.\textsuperscript{19} However, there were no differences prevalence of acute kidney injury between both groups (74.4 \% vs 75.8 \%, \textit{p} 0.762).\textsuperscript{19}

**Discussion**

Heart failure (HF) is one of the most common clinical conditions associated with morbidity and mortality worldwide. HF requires holistic comprehensive management which is not just limited to the cardiovascular aspect. Prognostic biomarkers in HF patients are needed in risk stratification to provide the optimum management of HF patients.\textsuperscript{3}

This systematic review shows that CAR is independently associated with all-cause mortality of AHF and CHF patients. Increased mortality in high CAR group was contributed by the increase in cardiac death and non-cardiac death.\textsuperscript{17} Included studies show that CAR can predict long-term mortality that is observed since the early months of follow-up.\textsuperscript{16,17,19} Even CAR can also be used to predict in-hospital mortality of AHF patients.\textsuperscript{17,19}

This systematic review also comprehensively evaluates CAR to predict other outcomes. Included studies showed that CAR is not statistically associated with lower LVEF.\textsuperscript{17-19} However, high CAR is also associated with a more severe NYHA class.\textsuperscript{16,19,24} CAR is not only able to predict future mortality but also the risk of advanced HF with moderate diagnostic performance.\textsuperscript{22} HF is known to deteriorate multigorgan function which is observed to be higher in high compared to low CAR group.\textsuperscript{19} The need for defibrillator shock in ICD patients,\textsuperscript{16} invasive, and non-invasive ventilation were also higher in the high CAR group.\textsuperscript{19} The other complications such as malignant arrhythmia, coagulopathy, and shock are also more prominent in high CAR group.\textsuperscript{16,19} However, the results on LoS are conflicting between high and low CAR groups.\textsuperscript{16,19} This may be due to higher in-hospital mortality\textsuperscript{17,18} which is notably higher in high CAR compared to low CAR groups, thus, ‘falsifying’ shorter LoS in high CAR patients. In addition, hospitalization rates and the number of hospitalizations during 12 months of follow-up are significantly higher in high CAR compared to low CAR groups.\textsuperscript{18}

CRP is related to inflammatory conditions that may reflect the severity of HF or might be caused by various other factors. The intensity of inflammation is associated with increased mortality in HF patients.\textsuperscript{3} In addition, albumin concentration may reflect liver function\textsuperscript{26} and kidney function\textsuperscript{26} which are often impaired in HF patients.\textsuperscript{1} A study conducted by Yucel et al.\textsuperscript{27} showed that CAR is correlated with transaminase and creatinine levels among HF patients. In addition, almost half of HF patients suffer from frailty, a multidimensional condition independent of age that makes patients more vulnerable to various stressors.\textsuperscript{5} Hypoalbuminemia may reflect nutritional depletion in HF patients that commonly contribute to poorer outcomes\textsuperscript{28} thus, nutritional treatment as well as investigation into kidney and liver function is warranted. In this systematic review, CAR consistently had an AUC above 0.73 in predicting the mortality of HF patients. Compared to previous studies, AUC of CAR to predict mortality in HF is better than in severe sepsis/ sepsis shock patients (AUC 0.61)\textsuperscript{28}, critically ill patients (AUC 0.59)\textsuperscript{29}, and acute kidney injury (AUC 0.64).\textsuperscript{30} In comparison, CRP and albumin diagnostic performance was either, inferior or similar to CAR diagnostic performance in terms of AUC. Previous studies also showed that CAR diagnostic performance is non-inferior compared to CRP or albumin concentration when used separately.\textsuperscript{28-30}

This systematic review further had several strengths. The screening process was carried out by two independent reviewers carefully and the manuscript writing process closely follows PRISMA protocols. In addition, this is the first systematic review that provides a comprehensive evaluation of CAR roles in predicting poor outcomes in HF patients. On the other hand, we have some limitation. First, the reported cut-off is different among included studies for achieving optimum AUC. However, it is considered tolerable as it obtained from acceptable statistical methods. Second, the included studies exclusively included HFrEF and HFmrEF, thus, the generalizability of the findings for HF preserved EF (HFpEF) is questionable.

**Conclusion**

High CAR value is significantly associated with poor HF outcomes including all-cause mortality in patients with acute and chronic heart failure. CAR value is significantly higher in patients with higher NYHA class but it is not associated with LVEF value. High CAR is associated with higher complication, organ failure, and frequency of intervention. Nevertheless, to establish a more comprehensive understanding of the role of CAR value in predicting poor outcomes in HF patients, a further well-designed studies in different populations and ethnicity should be conducted.
Disclosure

The author(s) whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Availability of data and materials

All data are available in the manuscript and separated files as supplementary.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Roy Bagus Kurniawan: Conceptualization, Methodology, Formal analysis, Writing – original draft, Validation. Pratista Oktafia: Conceptualization, Methodology, Investigation, Writing – original draft, Resources. Pandit Bagus Tri Saputra: Conceptualization, Methodology, Writing – original draft, Project administration. Dinda Dwi Purwati: Conceptualization, Writing – original draft, Visualization. Mahendra Eko Saputra: Conceptualization, Writing – original draft, Visualization. Irma Maghfirah: Conceptualization, Writing – review & editing, Supervision. Novia Nurul Faizah: Conceptualization, Writing – review & editing, Supervision. Yudi Her Oktaviono: Conceptualization, Writing – review & editing, Supervision. Firas Farisi Alkaff: Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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