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Original Article

# In-hospital Mortality Reduction among Heart Failure Patients Treated with Optimal Dose of Angiotensin-Converting Enzyme Inhibitors

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ABSTRACT

*Background* : Angiotensin-converting enzyme inhibitors (ACEI) should be titrated to the optimal dose for adequate inhibition of the Renin-Angiotensin-Aldosterone system (RAAS). The up-titration of ACEI to the optimal doses during in-hospital treatment is challenging.
*Objectives* : This study aimed to investigate whether the use of optimal dose of ACEI during in-hospital treatment could give more benefit to the outcome of heart failure (HF) patients.
*Methods* : We involved 171 HF patients in this prospective cohort study. 29 and 142 HF patients were treated with optimal dose and suboptimal dose of ACEI during in-hospital treatment, respectively. The primary endpoint was in-hospital and 30 days post-discharge mortality. The secondary endpoint was 30 days post-discharge rehospitalization due to worsening of HF.
*Results*: Only 17% of HF patients treated with optimal dose of ACEI during in-hospital treatment. In-hospital mortality in optimal dose of ACEI group was lower than in suboptimal dose of ACEI group (0% vs. 19.7%; p = 0.009). The 30 days post-discharge mortality (0% vs 2.7%; p = 0.375) and rehospitalization (6.9% vs 16.7%; p = 0.184) between both groups were not significantly different.
*Conclusion*: The use of optimal dose of ACEI during in-hospital treatment reduced in-hospital mortality in HF patients.

## 1. Introduction

HF patients suffered from decreased quality of life, intolerance to physical activity, frequent hospital admission, and increased mortality.[1,2] The latest data revealed that one-year all-cause mortality rates for ambulatory and hospitalized HF patients were 7% and 17%, respectively.[2] Rehospitalization rates of HF increased from 10-19% at two weeks to 50% at three months after hospital discharge.[3] High rehospitalization rate in HF patients was caused by inadequate therapeutic strategies, poor patient comprehension about their conditions, and also low compliance with the treatment regimens.[3–5]

The use of neurohormonal antagonists, such as ACEI, was the backbone of HF treatment strategies.[6] Chronic therapy with ACEI had been proven to effectively improve left ventricle (LV) function, improve exercise capacity, reduce hospitalization, and, most importantly, improve survival in HF patients.[7–9] ACEI should be titrated to the optimal dose to achieve adequate inhibition of the RAAS.[1,2] In daily clinical practice, the up-titration of ACEI to the optimal doses during in-hospital treatment is challenging because of its side effects or the presence of several comorbidities. Renal dysfunction was a major limitation of ACEI up-titration, in addition to hypotension, electrolyte disturbances, and low compliance levels.[10,11] However, few studies have compared optimal vs. suboptimal of ACEI on mortality and morbidity for HF patients.[10,12,13] This study aimed to investigate whether the use of optimal dose of ACEI during in-hospital treatment could give more benefit to the outcome of HF patients.

## 2. Methods

### 2.1. Study Design

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It was a prospective cohort study conducted at Saiful Anwar General Hospital Malang from October 1st, 2016, until August 31st, 2017. The investigation conformed with the principles outlined in the Declaration of Helsinki and was approved by the Ethical Committee of Saiful Anwar General Hospital.

*2.2. Study population*

All patients over 18 years admitted to Saiful Anwar General Hospital with an initial diagnosis of HF were screened. HF diagnosis was established by a cardiologist based on the presence of all of the following variables: signs and symptoms compatible with HF, cardiomegaly and/or pulmonary congestion assessed using chest X-ray, and also LV dysfunction assessed using echocardiography.[14] Informed consent was obtained from all HF patients who participated in this study. All patient's data such as demographic data, cardiovascular risk factors, medical history, symptoms, signs, laboratory examination, electrocardiography, chest X-ray, echocardiography, exercise stress test, Holter monitor, and also the treatment regimens were registered. Patients were not treated with or contraindicated to ACEI were excluded (See Figure 1).

*2.3. Study groups*

Patients were divided into two groups according to the treatment regimens during in-hospital treatment. Patients in optimal dose of ACEI group were treated with optimal dose of ACEI according to the 2016 European Society of Cardiology (ESC) guideline for HF (captopril 50 mg three times daily, ramipril 10 mg daily, or lisinopril 20 mg daily) during in-hospital treatment.[2] In suboptimal dose of ACEI group, patients were treated with suboptimal dose of ACEI during in-hospital treatment (See Figure 1).

*2.4. Follow up*

The follow-up period was 30 days following hospital discharge. At the end of the follow-up period, information regarding mortality, rehospitalization, symptoms of HF, New York Heart Association (NYHA) functional class, current treatment regimens, and compliance to the treatment regimens was obtained from patients or their family by phone call.

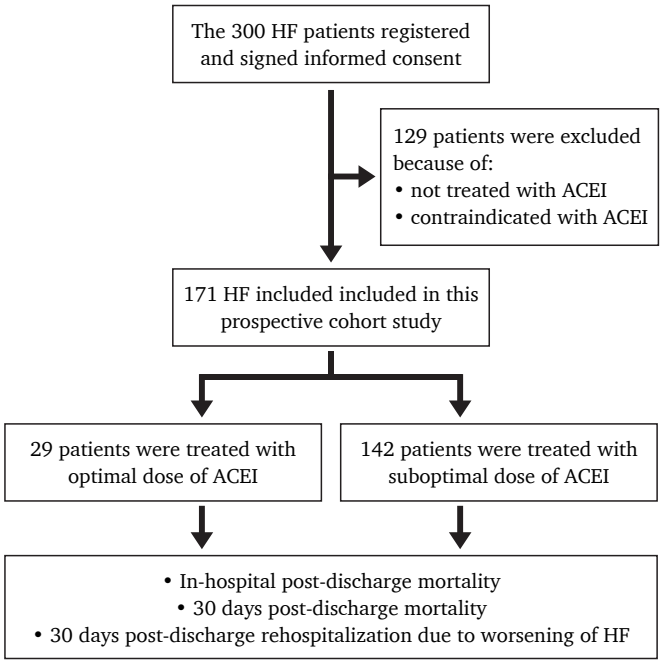


Figure 1. A flowchart of patients selection in this study

*2.5. Study endpoints*

The primary endpoint included in-hospital and 30 days post-discharge mortality. The secondary endpoint was 30 days post-discharge rehospitalization due to worsening of HF.

*2.6. Statistical analysis*

Categorical variables are presented as frequencies and percentages. The comparison between 2 categorical variables was tested using the Chi-square test or Fisher's test. The Spearman correlation test was used to assess the correlation between the two variables. P-value $\leq 0.05$ was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics 21.

## 3. Results

*3.1. Patients basic characteristics*

The patient's average age was 58 ± 12 years, and 61.4% of them were male. Among the 300 HF patients registered, 129 (43%) patients were excluded because they were not treated with ACEI or contraindicated with ACEI. Of 171 patients who involved in this study, 29 (17%) patients and 142 (83%) patients were treated with optimal doses and suboptimal dose of ACEI during in-hospital treatment, respectively (See Figure 1). There were no significant differences between both groups in age, gender, ethnic, level of education, occupation, marital status, history of HF, the main cause of HF, smoking status, atrial fibrillation, diabetes mellitus (DM), physical activity, history of myocardial infarction (MI) or angina, history of percutaneous coronary intervention (PCI), history of transient ischemic attack (TIA), history of chronic kidney disease (CKD), history of impaired liver function, history of HF hospitalization, history of chronic obstructive pulmonary disease (COPD), history of hypertension, NYHA functional class, history of medication (Angiotensin receptor blocker (ARB), beta-blockers, aldosterone antagonist, and diuretic). Both groups got similar concomitant treatments with beta-blockers, aldosterone antagonists, and diuretics (See Table 1). We also noted the reasons that optimal dose of ACEI could not be achieved during in-hospital treatment. It was because of shock or hypotension in 37 patients (26%), renal azotemia in 31 patients (22%), hyperkalemia in 4 patients (2.8%), and unclear reasons in 70 patients (49.2%).

*3.1. Clinical outcome*

In-hospital mortality

In optimal dose of ACEI group, no patient passed away during in-hospital treatment (0%), while in suboptimal dose of ACEI group, 28 patients passed away during in-hospital treatment (19.7%). The causes of death suboptimal dose of ACEI group were cardiogenic shock in 9 patients (32.1%), sudden cardiac death in 3 patients (10.7%), ventricular fibrillation in 3 patients (10.7%), and non-cardiac cause (respiratory failure, pneumonia, sepsis, and acute respiratory distress syndrome) 13 patients (46.5 %). The data analysis revealed that in-hospital mortality in optimal dose of ACEI group was lower than in suboptimal dose of ACEI group (0% vs. 19.7%; $p = 0.009$). It was also supported by the Spearman's correlation test (correlation coefficient value = -0.200; $p = 0.009$). It could be concluded that there was a significant correlation between optimal dose of ACEI and in-hospital mortality (See Table 2).

30 days post-discharge mortality

During the follow-up period of 30 days following hospital discharge, three patients in suboptimal dose of ACEI group were passed away. Two patients passed away because of cardiogenic shock, while one patient passed away because of sudden cardiac death. Data analysis

revealed no significant difference in 30 days post-discharge mortality between both groups (0% vs. 2.7%; p = 0.375) (See Table 3).

30 days post-discharge rehospitalization due to worsening of HF

In optimal doses of ACEI group, 30 days post-discharge rehospitalization due to worsening of HF occurred in 2 patients (6.9%). The precipitating factors of rehospitalization were poor compliance with the treatment regimen and infection. While in suboptimal doses of ACEI group, 30 days post-discharge rehospitalization due to worsening of HF occurred in 19 patients (16.7%). The precipitating factors of rehospitalization were inadequate treatment regimens in 16 patients (84%) and poor compliance with the treatment regimen in 3 patients (16%). Data analysis revealed no significant difference in 30 days post-discharge rehospitalization between both groups (6.9% vs. 16.7%; p = 0.184) (See Table 4).

Table 1. Patient's basic characteristic

| **Demographic characteristic** | **Category** | **Optimal dose of ACEI (n = 29)** | | **Suboptimal dose of ACEI (n = 142)** | | **p-value** |
|---|---|---|---|---|---|---|
| | | Frequency | % | Frequency | % | |
| Sex | Female | 9 | 13.6% | 57 | 86.4% | 0.359 |
| | Male | 20 | 19% | 85 | 81% | |
| Age (years) | <60 | 19 | 20.2% | 75 | 79.8% | 0.317 |
| | 60-69 | 8 | 16.7% | 40 | 83.3% | |
| | 70-79 | 1 | 4.2% | 23 | 95. 8% | |
| | >80 | 1 | 20% | 4 | 80% | |
| Ethnic | Java | 28 | 16.6% | 141 | 83.4% | 0.077 |
| | Chinese | 0 | 0% | 1 | 100% | |
| | Arabian | 1 | 100% | 0 | 0% | |
| Education | No school | 2 | 16.7% | 10 | 83.3% | 0.965 |
| | Not completed primary school | 1 | 25% | 3 | 75% | |
| | Completed primary school | 7 | 15.9% | 37 | 84.1% | |
| | Completed junior high school | 8 | 21.1% | 30 | 78.9% | |
| | Completed senior high school | 10 | 15.6% | 54 | 84.4% | |
| | Bachelor | 1 | 11.1% | 8 | 88.9% | |
| Occupation | Unemployed | 7 | 17.1% | 34 | 82.9% | 0.482 |
| | Student | 0 | 0% | 2 | 100% | |
| | Housewife | 6 | 28.6% | 15 | 71.4% | |
| | Government employees | 0 | 0% | 8 | 100% | |
| | Retired | 1 | 7.7% | 12 | 92.3% | |
| | Entrepreneur | 12 | 19% | 51 | 81% | |
| | Farmer | 3 | 18.8% | 13 | 81.2% | |
| | Labour | 0 | 0% | 7 | 100% | |
| Marital status | Single | 0 | 0% | 5 | 100% | 0.479 |
| | Married | 28 | 17.9% | 128 | 82.1% | |
| | Divorce/widow | 1 | 10% | 9 | 90% | |
| History of HF | No | 8 | 17.8% | 37 | 82.2% | 0.865 |
| | Yes | 21 | 16.7% | 105 | 83.3% | |
| Main cause | IHD documented by CAG | 5 | 23.8% | 16 | 76.2% | 0.312 |
| | IHD not documented by CAG | 15 | 16.1% | 78 | 83.9% | |
| | Dilated cardiomyopathy | 5 | 33.3% | 10 | 66.7% | |
| | Valve disease | 0 | 0% | 12 | 100% | |
| | Hypertension | 3 | 13% | 20 | 87% | |
| | Pulmonary hypertension | 1 | 25% | 3 | 75% | |
| | Others | 0 | 0% | 3 | 100% | |
| | Never | 14 | 16.5% | 71 | 83.5% | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Smoking status | Current | 4 | 13.3% | 26 | 86.7% | 0.748 |
| | Former | 11 | 19.6% | 45 | 80.4% | |
| Atrial fibrilation | Never | 26 | 18.4% | 115 | 81.6% | 0.463 |
| | Permanent | 2 | 14.3% | 12 | 85.7% | |
| | Persistent | 1 | 20% | 4 | 80% | |
| | Paroxysmal | 0 | 0% | 11 | 100% | |
| Di abetes melitus | Yes | 9 | 20% | 36 | 80% | 0.527 |
| | No | 20 | 15.9% | 106 | 84.1% | |
| Physical activity | Mild | 8 | 14.8% | 46 | 85.2% | 0.194 |
| | Moderate | 19 | 16.8% | 94 | 83.2% | |
| | Heavy | 2 | 50% | 2 | 50% | |
| History of MI /angina | No | 18 | 14.9% | 103 | 85.1% | 0.259 |
| | Yes | 11 | 22% | 39 | 78% | |
| History of PCI | No | 25 | 16 % | 131 | 84% | 0.294 |
| | Yes | 4 | 26.7% | 11 | 73.3% | |
| History of TIA /stroke | No | 29 | 18.4% | 132 | 81.6% | 0.141 |
| | Yes | 0 | 0% | 10 | 100% | |
| History of CKD | No | 29 | 17.4% | 138 | 82.6% | 0.360 |
| | Yes | 0 | 0% | 4 | 100% | |
| History of impaired liver function | No | 28 | 16.8% | 139 | 83.2% | 0.665 |
| | Yes | 1 | 25% | 3 | 75% | |
| History of HF hospitalization | No | 20 | 20.6% | 77 | 79.4% | 0.144 |
| | Yes | 9 | 12.2% | 65 | 87.8% | |
| History of COPD | No | 28 | 17% | 137 | 83% | 0.984 |
| | Yes | 1 | 16.7% | 5 | 83.3% | |
| History of hypertension | No | 19 | 17.8% | 88 | 82.2% | 0.719 |
| | Yes | 10 | 15.6% | 54 | 84.4% | |
| NYHA functional class | I | 1 | 50% | 1 | 50% | 0.397 |
| | II | 9 | 20% | 36 | 80% | |
| | III | 8 | 12.3% | 57 | 87.7% | |
| | IV | 11 | 18.6% | 48 | 81.4% | |
| Prior ARB | No | 28 | 17.9% | 128 | 82.1% | 0.266 |
| | Yes | 1 | 6.7% | 14 | 93.3% | |
| Prior blocker -bloker | No | 22 | 17.1% | 107 | 82.9% | 0.954 |
| | Yes | 7 | 16.7% | 35 | 83.3% | |
| Prior aldosterone antagonist | No | 25 | 17.4% | 119 | 82.6% | 0.746 |
| | Yes | 4 | 57.1% | 3 | 42.9% | |
| Prior diuretic | No | 23 | 18.3% | 103 | 81.7% | 0.450 |
| | Yes | 6 | 13.3% | 39 | 86.7% | |
| Current beta -bloker | No | 8 | 11.4% | 62 | 88.6% | 0.109 |
| | Yes | 21 | 20.8% | 80 | 79.2% | |
| Current aldosterone antagonist | No | 11 | 13.4% | 71 | 86.6% | 0.236 |
| | Yes | 18 | 20.2% | 71 | 79.8% | |
| Current diuretic | No | 13 | 13.7% | 82 | 86.3% | 0.202 |
| | Yes | 16 | 21.1% | 60 | 78.9% | |

Note; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAG = coronary angiogram; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; HF = heart failure; IHD = ischemic heart disease MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TIA = transient ischemic attack

Table 2. In-hospital mortality

| | Categories | Optimal dose of ACEI (n = 29) | | Suboptimal dose of ACEI (n = 142) | | Chi square | p-value | Spearman correlation | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | | Frequency | % | Frequency | % | | | | |
| In-hospital mortality | Yes | 0 | 0% | 28 | 19,7% | 6.838 | 0.009 | -0.200 | 0.009 |
| | No | 29 | 100% | 114 | 80.3% | | | | |

Note; ACEI = angiotensin-converting enzyme inhibitor; HF = heart failure

Table 3. 30 days post-discharge mortality

| | Categories | Optimal dose of ACEI (n = 29) | | Suboptimal dose of ACEI (n = 113) | | Chi square | p-value | Spearman correlation | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | | Frequency | % | Frequency | % | | | | |
| 30 days post-discharge mortality | Yes | 0 | 0% | 3 | 2.7% | 0.787 | 0.375 | -0.074 | 0.379 |
| | No | 29 | 100% | 110 | 97.3% | | | | |

Note; ACEI = angiotensin-converting enzyme inhibitor; HF = heart failure

Table 4. 30 days rehospitalization due to worsening of HF

| | Categories | Optimal dose of ACEI (n = 29) | | Suboptimal dose of ACEI (n = 114) | | Chi square | p-value | Spearman correlation | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | | Frequency | % | Frequency | % | | | | |
| 30 days post-discharge rehospitalization due to worsening of HF | Yes | 2 | 6.9% | 19 | 16.7% | 1.761 | 0.184 | -0.111 | 0.187 |
| | No | 27 | 93.1% | 95 | 83.3% | | | | |

Note; ACEI = angiotensin-converting enzyme inhibitor; HF = heart failure

## 4. Discussion

The benefit of optimal dose ACEI in HF patients is the reduction of mortality and rehospitalization. According to the current guideline for HF, the administration of ACEI gives more benefit for (1) all HF patients with left ventricular ejection fraction (LVEF) <40%; (2) HF patients with NYHA functional class II-IV; or (3) HF patients with asymptomatic LV dysfunction (NYHA functional class I).[2] The absolute contraindications of ACEI are (1) history of angioedema; (2) known bilateral renal artery stenosis; (3) pregnancy or risk of pregnancy; and (4) known allergic reaction or other adverse reaction.[2,15] Cautions for ACEI administration are (1) significant hyperkalemia (potassium level > 5 mmol/L); (2) significant renal dysfunction (creatinine level > 2.5 gr/dL or eGFR <30 mL/min/1.73 m2); and (3) symptomatic or severe asymptomatic hypotension (systolic blood pressure <90 mmHg).[2] Among 300 HF involved in this study, 171 (57%) patients were treated with ACEI. It was lower than the report from the previous real-world studies which revealed the use of ACEI for HF ranging from 70.1% to 81.6%.[16–18] The possible explanations of this result were: (1) the previous studies were conducted in the out-patient clinical setting; (2) most of the patient involved in the previous studies were in more stable clinical condition; and (3) our study was conducted in the in-hospital setting in which most of the patients involved in this study were on relative unstable clinical condition with several comorbidities. Nevertheless, our study provided data about the use of ACEI for HF during in-hospital treatment.

Among 171 patients treated with ACEI, only 29 patients (17%) received an optimal dose of ACEI during in-hospital treatment. It was lower than the report from the previous real-world studies which revealed the use of optimal dose of ACEI for HF ranging from 37.5% to 65%.[16–18] The possible explanations of this result were: (1) the previous studies were conducted in the out-patient clinical setting; (2) most of the patient involved in the previous studies were in more stable clinical condition; and (3) our study was conducted in the in-hospital setting in which most of the patients involved in this study were on relative unstable clinical condition with several comorbidities; (4) the up-titration of ACEI to the optimal dose could be conducted in the out-hospital setting; and (5) The guidelines did not give a specific recommendation to up-titrate ACEI to the optimal dose during in-hospital treatment.[2,19] In this study, the limitation of the up-titration of ACEI to the optimal dose during in-hospital treatment was caused by shock or hypotension in 37 patients (26%), renal azotemia in 31 patients (22%), hyperkalemia at four patients (2.8%), and unclear reasons in 70 patients (49.2%).

Our study revealed that the administration of optimal dose of ACEI during in-hospital treatment could reduce 19.7% of in-hospital mortality in HF patients. The higher mortality in suboptimal doses of ACEI group could be caused by suboptimal doses of ACEI itself or the presence of several comorbidities such as hypotension, hyperkalemia, or azotemia that prevent the administration of optimal dose of ACEI. According to the results of previous studies, hypotension (low systolic blood pressure and diastolic blood pressure), hyperkalemia, or azotemia increased mortality in HF patients independently.[17–20] According to our knowledge, there were no RCTs or prospective studies investigating the benefit of optimal dose of ACEI during in-hospital treatment for HF patients. Our study provided data about the benefit of optimal dose of ACEI for HF patients in reducing mortality during in-hospital treatment.

Our study also revealed no significant difference in 30 days post-discharge mortality and rehospitalization between HF patients who received optimal and suboptimal doses of ACEI. There are two RCTs compared low dose and high dose of ACEI for HF patients.[12,13] Study of Pacher et al. compared to low dose enalapril (5 mg twice daily) and high dose enalapril (20 mg twice daily). After 48 weeks of the follow-up period, the functional capacity assessed by NYHA functional

class improved more on the high dose group than on the low dose group (P=004). The benefit of survival was not different in both groups.[12] ATLAS study compared low dose lisinopril (2.5 to 5.0 mg daily) and high dose lisinopril (32.5 to 35 mg daily) on HF patients with NYHA functional class II to IV and an LVEF ≤30%. After minimum three years follow-up period, patients in the high-dose group revealed a nonsignificant 8% lower risk of mortality (p = 0.128) but a significant 12% lower risk of mortality or hospitalization for any cause (p = 0.002) and 24% lower risk hospitalizations for HF (p = 0.002) compared to the low-dose group.[13] The fundamental differences between our study and those RCTs were: (1) the administration of optimal dose of ACEI was conducted during in-hospital treatment; (2) the follow-up period in our study was shorter than in those RCTs; and (3) we used three kinds of ACEI (captopril, ramipril, and lisinopril).

Our study had several limitations. First, the small number of patients and a short follow-up period might cause biased study results. Second, this study was a single-center study that might also cause biased study results. Third, we included all HF patients regardless of the LVEF. According to the previous studies, the benefit of ACEI in reducing mortality and rehospitalization was proven only in heart failure with reduced ejection fraction (HFrEF).[13,24–26] Fourth, several factors are likely to be the confounders that might affect the study outcomes such as baseline hemodynamic profile, renal function, the presence of comorbidities, etiology of Hf, and also precipitating factors of HF. Multicenter research with (1) more specific and strict inclusion and exclusion criteria; (2) a large number of patients; and (3) longer follow-up duration is required.

## 5. Conclusion

Our studies data suggested that the proportion of HF patients treated with optimal dose of ACEI during in-hospital setting were still low. The use of optimal dose of ACEI during in-hospital treatment reduced in-hospital mortality in HF patients.

## 6. Declarations

*6.1. Ethics Approval and Consent to participate*
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

*6.2. Consent for publication*
Not applicable.

*6.3. Availability 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: YBU. Design: YBU. Control/supervision: MSR, YW. Data collection/processing: YBU. Extraction/Analysis/interpretation: YBU, MSR, YW. Literature review: MSR, YW. Writing the article: YBU. Critical review: MSR, YW, DS, SW, BS, SA. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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