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High-leucine branched-chain amino acid supplementation improves C-reactive protein levels in critically ill patients: A randomised controlled trial

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ABSTRACT

Introduction: Higher C-reactive protein (CRP) levels in critically ill patients are associated with increased disease severity and mortality rates. While branched-chain amino acids (BCAAs) have been extensively studied for their potential to enhance immunity in various diseases, research on the relationship between BCAAs and CRP levels in critically ill patients is scarce. This study aimed to assess the effect of BCAA supplementation on CRP levels in critically ill adult patients. **Methods:** An experimental randomised controlled trial was performed on 40 critically ill adults between December 2023 and May 2024. All subjects were randomly assigned to BCAA supplementation and control, with a 1:1 comparison. Subjects in the BCAA group were given 40 grams/day of BCAA (19 g/day leucine) supplementation with a leucine:isoleucine:valine ratio of 2:1:1.2 for ten days. No supplementation was given to the control group. CRP was measured from blood serum pre- and post-intervention. **Results:** High CRP was found in all critically ill patients at baseline. Significantly lower CRP levels were found in the BCAA group compared to baseline (p=0.005) and control (p=0.001) post-intervention. **Conclusion:** High CRP was common in critically ill patients, and BCAA supplementation improved their CRP levels. This study implied that providing BCAAs for critically ill patients potentially improves their acute inflammation state.

Keywords: branched-chain amino acid, C-reactive protein, critical illness

INTRODUCTION

Critically ill patients experience severe inflammatory responses, with the occurrence of organ dysfunction and a high risk of death, if treatment is not provided (Kayambankadzanja *et al.*, 2022). Inflammatory responses involve the activity of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) (Yan *et al.*, 2021). Higher pro-inflammatory cytokine levels are correlated with worse clinical outcomes and higher mortality rates in patients in intensive care units (ICUs) (Koozi, Lengquist & Frigyesi, 2020). Further, CRP levels have been widely used as markers of inflammation

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and therapy responses in sepsis patients (Jiang *et al.*, 2023).

CRP is an acute-phase protein that is synthesised in the liver (Jiang *et al.*, 2023). During the acute phase of inflammation, CRP levels can increase by as much as 1,000-fold within 24 to 48 hours (Grondman *et al.*, 2020). Higher CRP levels can be observed in bacterial rather than viral infections during sepsis (Largman-Chalamish *et al.*, 2022; Fabio *et al.*, 2015). However, these elevated levels are not specific to infections. Factors other than infection that can cause an increase in CRP levels include surgery, hepatic failure, rheumatoid diseases, and heart failure (Jiang *et al.*, 2023; Banait *et al.*, 2022). This characteristic of CRP is important for assessing the inflammatory status of critically ill patients.

Numerous factors, including nutrition, influence inflammatory responses and immunity. One of the anti-inflammatory nutrients is branched-chain amino acids (BCAAs), which consist of leucine, isoleucine, and valine. Leucine, in particular, has been shown to improve the mammalian target of rapamycin (mTOR) (Kato *et al.*, 2016). The expression of mTOR suppresses IL-6 production, increases muscle synthesis and lymphocyte proliferation, and modulates other inflammatory responses (Ishihara *et al.*, 2014; An *et al.*, 2020; Kristian *et al.*, 2023). Further, a study observed the anti-inflammatory effect of BCAA supplementation, whereby it inhibited the activation of nuclear factor kappa B (NF-κB), consequently lowering the activation of pro-inflammatory cytokines (Li *et al.*, 2022).

Several human studies have shown that BCAA supplementation improves inflammatory responses. In older adults with sarcopenia, one study found that 6 g of leucine in combination with 800 IU of vitamin D for 13 weeks improved their pro-inflammatory cytokines (p=0.046) (Liberman *et al.*, 2019). Moreover, in specific diseases, such as hepatic cancers, BCAA supplementation and higher BCAA levels have been correlated with better albumin levels (Sideris *et al.*, 2023). Interestingly, the effect of BCAA on CRP levels was not only proven in diseased populations. A study showed that BCAA serum levels were also correlated with CRP levels in healthy women (r=0.24, p<0.001) (Hamaya *et al.*, 2021). Furthermore, another study found that high leucine BCAA supplementation of 12 g/day for five days and interval training in athletes significantly improved their IL-6 levels (p=0.028) (An *et al.*, 2020).

Although many studies have assessed the effect of BCAAs in different diseases and healthy populations, no studies have analysed the effect of BCAA supplementation on the CRP levels of ICU patients. This study assessed the effect of BCAA supplementation on CRP levels in critically ill adult patients. It was hypothesised that critically ill patients who received BCAA supplementation would show improved CRP levels.

METHODOLOGY

Ethic statements and study registration

Ethical clearance was obtained from Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia – Faculty of Medicine, Universitas Indonesia, with certificate number KET-1545/UN2.F1/ETIK/PPM.00.02/2023. All subjects' family members provided informed consent before participating in the study. This study was registered at ClinicalTrials.gov as NCT06167772.

Subjects

Sample size was determined by comparing two mean sample equations, with a significance level (α) of 0.05 and power (β) of 0.8. The mean difference

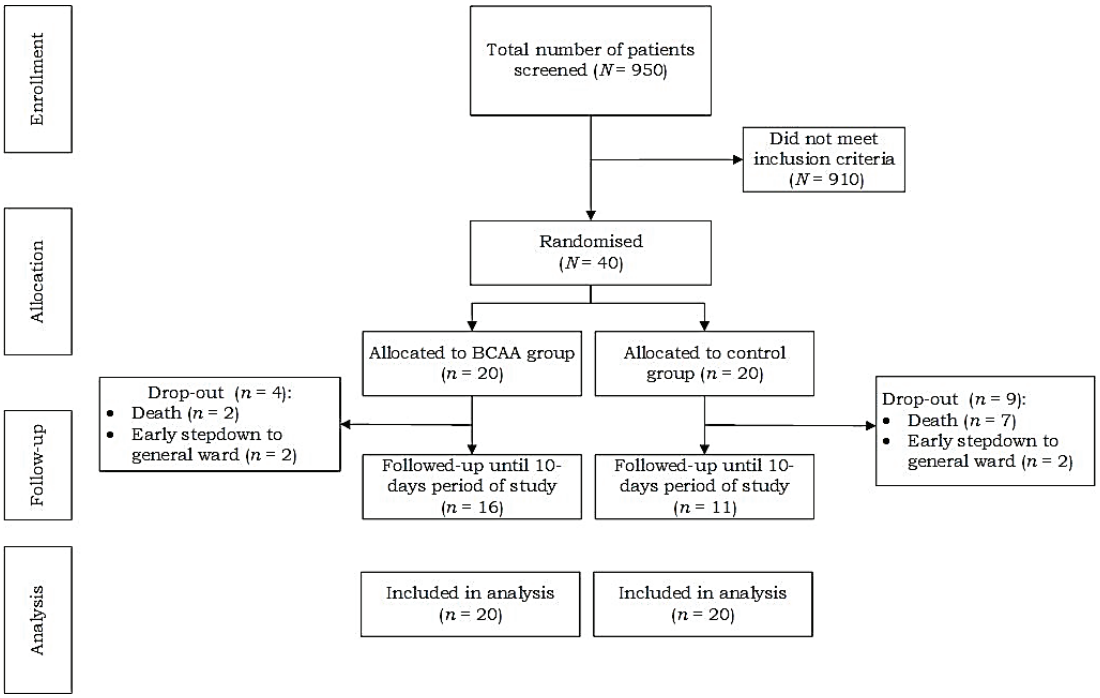

Figure 1. Subjects' sampling flow throughout the study

used was 2 (Ueyama *et al.*, 2020). The estimated drop-out rate was 15%, with a minimum of 34 subjects. A total of 40 critically ill adult patients participated in this study. The inclusion criteria were ICU patients aged 18-65 years with a sequential organ failure assessment (SOFA) score of ≥4, admitted under 24 hours. SOFA is a scoring system that assesses how well multiple organ systems are functioning in critically ill patients. It has a high sensitivity (90.1%) and specificity (96.6%) in the mortality rate of critically ill patients (Kumar *et al.*, 2020). Exclusion criteria were individuals with pregnancy, body mass index (BMI) <16 kg/m^2, non-dialysis chronic kidney disease, uncontrolled diabetes mellitus, neuromuscular and autoimmune diseases, and referral from other hospital ICUs. Drop-out criteria included refusal to continue participating, death, or self-discharge with less than ten days of treatment. There was a 33% drop-out rate at the end of the study due to death or early step-down to the general ward. The recruitment occurred at Dr. Cipto Mangunkusumo and Universitas Indonesia Hospital, Indonesia, from December 2023 to May 2024. Figure 1 shows the subjects' sampling flow throughout the study.

Study design

This study was a multi-centre, experimental, double-blinded, randomised controlled trial. Subjects were randomly assigned to either the intervention or control groups using block randomisation, maintaining a 1:1 ratio for comparison. The double-blinding process was conducted among the principal investigator, laboratory staff, and subjects (and family members/guardians). A third party, the Center for Clinical Epidemiology and Evidence-Based Medicine, Dr. Cipto Mangunkusumo Hospital, managed the

randomised allocation numbers using a computer-generated randomisation model and disclosed them after the data analysis was completed. Food delivery staff was responsible for delivering BCAAs to the intervention group. Both the principal investigator and laboratory staff were not informed about the subject allocation throughout the study.

Intervention

All subjects received enteral or partial parenteral nutrition according to the European Society for Clinical Nutrition and Metabolism (ESPEN) ICU guidelines, with an energy target of 20 kcal/kg/day (Singer *et al.*, 2023). The targeted energy was given since the first day of ICU admission. Standard enteral supplementation for both groups was given in the form of a commercial isocaloric enteral nutrition with a nutrient content of 22% protein, 11% fat, and 67% carbohydrate (Peptisol®, Kalbe Pharm). Subjects in the intervention group received 40 g/day of BCAA (including 19 g/day of leucine) supplementation with a leucine:isoleucine:valine ratio of 2:1:1.2, either enterally or partially parenterally, every day since ICU admission for ten days. Five sachets of high-leucine BCAA supplement were given daily, diluted into standard enteral nutrition. Each powdered sachet contained l-leucine of 3.808 mg, l-isoleucine of 1.904 mg, and l-valine of 2.288 mg. The powder was odourless and colourless. Further, similar containers were used for both groups. Thus, the supplement was not distinguishable. Partial parenteral supplementation was given to patients as indicated. Each 250 mL bag contained l-leucine of 2.575 mg, l-isoleucine of 1.275 mg, and l-valine of 1.550 mg (Nephrosteril®, Fresenius Kabi). The parenteral bags were covered during placement to ensure blinding from participants and investigators. There were no significant differences in BCAA serum levels for oral or parenteral supplementation (Lindgren *et al.*, 2015). No supplementation was given to the control group.

Outcome measurement

Subjects' baseline characteristics, such as age, sex, BMI, and diagnosis, were obtained. Subjects' diagnoses were categorised into medical or surgical. Further, BMI was categorised into underweight (16-18.5 kg/m^2), normal weight (18.5-22.9 kg/m^2), overweight (23-24.9 kg/m^2), obese I (25-29.9 kg/m^2), and obese II (≥30 kg/m^2) (WHO, 2000). Weight was measured with the Paramount A6 and Gamma bedscale series, while height was measured by their body length. 5-mL blood samples were obtained from the vein to analyse CRP levels on the first day of ICU admission and the 10th day of intervention. CRP levels were measured using immunoturbidimetry; delta CRP was determined from the differences between CRP level medians. Participants were monitored for gastrointestinal symptoms, such as diarrhoea, vomiting, abdominal distension, bleeding, and constipation. The subjects' compliance, gastric residual volume, and 24-hour nutritional intake were monitored with ICU medical records.

Statistical analysis

Intention-to-treat (ITT) analyses were conducted. The last observation carried forward (LOCF) approach was used to handle data of drop-out participants. A normality test was performed using Kolmogorov-Smirnov. Differences in CRP before and after intervention for each group were calculated using the Wilcoxon test. Differences between the intervention and control groups were calculated using an unpaired *t*-test for normal data and a Mann-Whitney

Table 1. Baseline demographic and clinical characteristics of subjects (*N*=40)

Variable	*BCAA group (n=20)*	*Control group (n=20)*	*p*	*95% CI*
Age (years)	48 (35; 58)	51 (41; 59)	0.570^{mw}	
Sex [*n* (%)]				
Male	15 (75)	16 (80)		
Female	5 (25)	4 (20)		
Body mass index, kg/m^2	24.6±4.7	23.5±4.2	0.397^{t}	(-1.50 to 3.69)
Obese [*n* (%)]	9 (45)	8 (40)		
Overweight [*n* (%)]	4 (20)	4 (20)		
Normal weight [*n* (%)]	6 (30)	5 (25)		
Underweight [*n* (%)]	1 (5)	3 (15)		
Diagnosis [*n* (%)]				
Surgical	10 (50)	12 (60)		
Medical	10 (50)	8 (40)		
SOFA score	7 (5;9)	9 (5;12)	0.376^{mw}	
Mean energy intake (kcal/day)	1142 (957; 1523)	1094 (936; 1342)	0.358^{mw}	
Mean energy intake (kcal/kg BW/day	20 (18; 24)	19 (15; 24)	0.330^{mw}	
Mean protein intake (g/kg BW/day)	1.0 (0.9; 1.3)	0.9 (0.7; 1.2)	0.096^{mw}	
Mean gastric residual volume (mL/day)	52 (11; 115)	72 (15; 234)	0.507^{mw}	
Gastrointestinal symptoms (*n*)	0 (0)	0 (0)		

BCAA: branched-chain amino acid; SOFA: sequential organ failure assessment; BW: body weight
Value in median (interquartile range) or mean±*SD*; *mw*: Mann-Whitney test; *t*: unpaired t-test

U test for non-normal data. Linear mixed model analysis was performed to analyse the effect of confounding variables. Statistical significance was determined at $p<0.05$. All analyses were performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp, Armonk, New York). The study utilised the Consolidated Standards of Reporting Trials (CONSORT) 2010 reporting guidelines (Schulz *et al.*, 2010).

RESULTS

The baseline characteristics of all subjects were equal between the two groups. Three obese II participants (15%) were found in the intervention group; none were found in the control group. There

Table 2. CRP levels of subjects at pre- and post-intervention (*N*=40)

Variable	*BCAA group (n=20)*	*Control group (n=20)*	*p*
CRP pre-intervention (mg/L)	98.6 (34.9; 233.0)	160.1 (53.8; 262.4)	0.194^{mw}
CRP post-intervention (mg/L)	57.6 (14.7; 78.7)	182.1 (68.6; 349.0)	0.001^{mw*}
	p=0.005^{W*}	p=0.455^{W}	
Delta CRP (mg/L)	-33.6 (-143.8; -7.9)	39.9 (-46.8; 124.9)	0.015^{mw*}

CRP: C-reactive protein; BCAA: branched-chain amino acid
Value in median (interquartile range); *mw*: Mann-Whitney test; W: Wilcoxon test
*$p<0.05$ significant

Table 3. Linear mixed model outcomes (*N*=40)

Variable	*CRP*		
	Coefficient B	*SE*	*P*
Effects of intervention and time on CRP			
Intervention (vs control) at baseline	40.91	34.81	0.173
Intervention * time	-101.55	43.20	0.024*
Time	28.28	30.55	0.360
Effect of subject's characteristics on CRP			
Age	0.75	1.45	0.607
Age × time	0.95	1.72	0.583
Female	-23.98	46.07	0.604
Female × time	-50.24	54.75	0.365
Medical	-14.15	38.95	0.717
Medical × time	63.62	45.30	0.168
BMI	-2.71	4.91	0.583
BMI × time	3.26	5.78	0.576
Obese II	-101.51	80.84	0.214
Obese I	13.83	50.00	0.783
Overweight	21.09	57.67	0.716
Mild malnutrition	26.22	95.41	0.784
Moderate malnutrition	3.67	95.41	0.969
Obese II × time	37.37	95.40	0.698
Obese I × time	-46.28	59.02	0.438
Overweight × time	40.63	68.06	0.554
Mild malnutrition × time	-144.86	112.59	0.207
Moderate malnutrition × time	-10.86	112.59	0.924
Effect of energy and protein intake on CRP			
Mean energy intake (kcal/day)	-0.04	0.06	0.500
Mean energy intake (kcal/day) × time	-0.12	0.07	0.088
Mean energy intake (kcal/kg BW/day)	-3.15	3.25	0.336
Mean energy intake (kcal/kg BW/day) × time	-8.98	3.93	0.028*
Mean protein intake (g/day)	-0.81	0.95	0.401
Mean protein intake (g/day) × time	-1.89	1.15	0.108
Mean protein intake (g/kg BW/day)	-55.95	54.59	0.309
Mean protein intake (g/kg BW/day) × time	-147.86	66.25	0.032*
Effect of gastric residual volume on CRP level			
Mean gastric residual volume (mL/day)	0.15	0.16	0.347
Mean gastric residual volume (mL/day) × time	0.15	0.20	0.434

CRP: C-reactive protein; SE: Standard error; BW: body weight
*p<0.05 significant

were no significant differences in mean energy and protein intakes between the intervention and control groups during the ten-day study period (Table 1). All participants who completed the study complied with supplementation for ten days. We observed no significant enteral or parenteral nutrition intolerances during the study period. Study participants reported no side effects.

All outcomes from 40 participants were analysed. Statistically, no differences

were found in CRP levels between groups pre-intervention. Post-intervention, the BCAA group had a significantly lower CRP level. Interestingly, higher CRP was found in the control group at post-intervention. Table 2 shows the CRP level differences between groups pre- and post-intervention.

The linear mixed model showed that BCAA improved CRP levels (*B*=-101.55, *SE*=43.20, *p*=0.02). Age, gender, disease, BMI, and gastric residual volume did not significantly influence the results. However, we found that protein and energy intakes might be potential confounders in this study. Table 3 shows the linear mixed model outcomes.

DISCUSSION

This study showed that high-leucine BCAA supplementation effectively enhances CRP levels in critically ill patients with medical or surgical diagnoses. Additionally, lower mean CRP levels were observed following ten days of 40 g/day BCAA supplementation. Further, insignificant higher gastric residual volumes (GRV) were observed in the control group in this study, which could be explained by higher SOFA scores observed in the control group. A study found that higher SOFA scores increased the odds ratio of higher GRV by 10.09 (1.01 to 99.97) (Faramarzi *et al.*, 2020).

High CRP levels were observed in all subjects at baseline. Additionally, higher CRP levels were found in the control group at the end of the study compared to baseline, with a median delta of 39.9 mg/L. On the contrary, in the intervention group, a median delta CRP level of -33.6 mg/L was observed, resulting in a median CRP level of 57.6 mg/L (*p*=0.005) at the end of the intervention. These significantly lower CRP levels showed potential CRP-suppressing effects of BCAAs in critically ill patients.

CRP reduction improves patients' outcomes. CRP level changes have been widely used to monitor the development of disease and therapy effectiveness (Yang *et al.*, 2016). Constantly high CRP levels after several days have shown a worse prognosis with a higher mortality rate in patients with sepsis. On the other hand, baseline CRP levels of around 110 mg/L, followed by lower CRP levels, showed the lowest 30-day in-hospital mortality rates (*p*<0.001) (Jiang *et al.*, 2023). We observed a 37% reduction in CRP levels from baseline. A study found that reducing CRP by 50% reduces the need for ventilation, inotropic support, and complications in patients with pneumonia (Chalmers, Singanayagam & Hill, 2008).

The effect of BCAAs on CRP levels found in this study was aligned with several other studies. One study assessed the effect of supplementing BCAAs at 12.5 g/day and found improved albumin and CRP levels in hepatic cancer patients. The participants also reported milder side effects from chemotherapy (Ishihara *et al.*, 2014). Another study supported these findings. Participants with cerebral palsy were given 192 mg/kg body weight (BW) leucine for ten weeks, resulting in significantly lower CRP at the end of the intervention (Cohen's d=-0.78, *p*=0.045) (Theis *et al.*, 2021). Although this study found a significant improvement in CRP levels, further studies are needed to explore the clinical significance of these findings.

The high-leucine BCAA group exhibited lower CRP levels, indicating the anti-inflammatory effects of BCAAs. The possible mechanism involves BCAA's effect on reducing pro-inflammatory cytokines and improving T-cell proliferation, enhancing the immune system response to infection (Kristian *et al.*, 2023; An *et al.*, 2020;

Liberman *et al.*, 2019). Notably, one of the pro-inflammatory cytokines, IL-6, is a key stimulus of liver CRP production. The effect of BCAAs in reducing IL-6 production and increasing the effectiveness of the immune system might lead to lower CRP levels (Naqash *et al.*, 2023).

Additionally, a correlation between BCAA levels, especially valine, and CRP levels (r=0.679, p=0.022) was observed, while other amino acids did not show an association with CRP levels (Kumar *et al.*, 2012). Conversely, higher BCAA levels were linked to heightened inflammatory responses, including CRP levels, fibrinogen, glycoprotein acetylation, and lipid profiles (Hamaya *et al.*, 2021). This suggests that derangement in BCAA metabolism may increase BCAA plasma availability and reduce BCAA's anti-inflammatory properties. For example, hydroxymethyl butyrate (HMB) is one of the leucine transamination metabolites that suppresses inflammation (Hsieh *et al.*, 2006), and transamination is lower in the middle-aged (Paolo, 2017). This may suggest that for middle-aged people, due to their metabolism differences, HMB might be superior to leucine. However, further studies are needed to confirm this.

In this study, we found that mean protein and energy intakes were confounding factors. We did not include BCAA supplementation in these intake analyses. Thus, the results reflected the actual intake of participants without intervention. This can be explained as BCAAs are a part of daily protein intake, and these results might be affected by the BCAA contents of the participants' intake.

This study has several strengths. Firstly, this is the first study exploring the effect of BCAAs on CRP levels in critically ill patients. Other studies have explored the effect of BCAAs on non-critically ill patients and measured different outcomes. Secondly, it upholds high research standards by conducting a multi-centre, experimental, double-blind, randomised controlled trial. Thirdly, it demonstrates the effectiveness of both enteral and parenteral BCAA supplementation, which could have broad applications for critically ill patients. Fourthly, the ITT analysis provided a more balanced interpretation and reflected actual practical findings in clinical settings. Lastly, the diverse range of illnesses represented by subjects in this study reflects the characteristics of typical ICU patients, in whom improvements in CRP levels were observed.

However, this study has some limitations. Firstly, the medication given was not considered as a confounding factor; several medications might have lowered CRP levels in subjects. Secondly, the short supplementation period in this study did not allow for exploring its long-term impacts on CRP levels, length of care, and mortality. Thirdly, the differences in enteral and parenteral routes of supplementation may influence the results. Patients in early ICU admission often show gastrointestinal dysfunction, such as gastric immobility and malabsorption, resulting in a higher prevalence of vomiting, diarrhoea, or high gastric residual volume. We did not report the absorption of BCAAs in this study, but a study showed relatively normal amino acid absorption in critically ill patients (Chapple *et al.*, 2022). However, there were no significant differences in gastric residual volume and gastrointestinal symptoms between each group. Fourthly, this study observed a high drop-out rate due to disease progression in the ICU. Lastly, we only measured the nutritional status pre-intervention. Post-intervention nutritional status might affect the results of this study as well, as CRP is correlated with malnutrition.

It is suggested that CRP >30 mg/L is a threshold for risk of malnutrition (Pourhassan *et al.*, 2021). However, our findings on both groups showed a post-intervention CRP higher than the suggested threshold, which suggests that all participants were still at risk of malnutrition despite their nutritional statuses.

Further studies are needed to analyse the effect of high-leucine BCAA supplementation on specific diseases in the ICU, including infections. Extended follow-up studies are required to investigate its effects on mortality and duration of hospital stay. Moreover, additional measures should be implemented to reduce the attrition rate of participants in future research.

CONCLUSION

Supplementing with high-leucine BCAA at 40 g/day (19 g/day of leucine) for ten days significantly improved CRP levels in critically ill patients. Further, lower mean CRP levels were observed in the BCAA supplementation group. The findings of this study suggest that providing BCAAs to critically ill patients could improve their acute inflammatory state.

Acknowledgement

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Authors' contributions

Wulandari Y, principal investigator, conceptualised and designed the study, led the data collection, analysis, and interpretation, and prepared the draft of the manuscript; Aditianingsih D, advised on the conceptualisation and study design, provided patients, and reviewed and edited the draft manuscript to its final form; Sunardi D, advised on conceptualisation and study design, and reviewed the manuscript.

Conflict of interest

The authors report no conflicts of interest in this work.

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