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Kardiyojenik Şok ile Komplike Olmuş ST Yükselmeli Miyokard Enfarktüslü Hastalarda C-reaktif Proteinin Albümin Oranına Prognostik Etkinliği

Prognostic Efficacy of C-reactive Protein to Albumin Ratio in Patients with ST Elevation Myocardial Infarction Complicated by Cardiogenic Shock

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ÖZ

GİRİŞ ve AMAÇ: *Bu çalışmada, yakın zamanda geliştirilen enflamasyon dayalı risk indeksi olan C-reaktif proteinin (CRP) /Albümin oranının (CAR), pompa yetersizliğine bağlı kardiyojenik şok ile komplike olmuş ST yükselmeli miyokard enfarktüs hastalarında (STYME) prognostik bir değere sahip olup olmadığını araştırmayı amaçladık.*

YÖNTEM ve GEREÇLER: *Primer perkutan koroner girişim uygulanmış ve kardiyojenik şok ile komplike olmuş 79 ardışık STYME hastası geriye dönük olarak çalışmaya alındı.*

BULGULAR: *Hastane içi takip sırasında 79 hastanın 40'ı (% 50,6) öldü. Ortalama CAR değeri sağ kalımı olmayanlarda sağ kalanlarına göre anlamlı derecede yüksekti (8.58 [4.68–12.25] vs. 4.67 [4.21–6.03]; p <0.001). Çok değişkenli regresyon analizi, CAR'ın hastane içi mortalitenin bağımsız bir belirleyicisi olduğunu ortaya koydu (HR: 1.053, % 95 CI: 1.006-1.101; p = 0.027). Kaplan-Meier analizi, CAR ≥8.4 olan hastaların ölüm sıklığı CAR <8.4 olanlara göre anlamlı derecede yüksek olduğunu gösterdi (p <0.001).*

TARTIŞMA ve SONUÇ: *Bu çalışma, kardiyojenik şok ile komplike olmuş STYME hastalarında CAR'ın hastane içi mortalite için prognostik bir değere sahip olduğunu gösteren ilk çalışmadır.*

Anahtar Kelimeler: *C-reaktif protein / albümin oranı, ST yükselmeli miyokard enfarktüsü, kardiyojenik şok.*

ABSTRACT

INTRODUCTION: *In this study, we aimed to investigate whether C-reactive protein (CRP) to albumin ratio (CAR), recently developed inflammation based risk index, has a prognostic value in patients with ST elevation myocardial infarction (STEMI) complicated by cardiogenic shock due to a pump failure.*

METHODS: *We retrospectively enrolled 79 consecutive STEMI patients who underwent a primary percutaneous coronary intervention and complicated by cardiogenic shock.*

RESULTS: *During the in-hospital course, 40 of the 79 patients (50.6%) died. The mean value of CAR was significantly higher in patients with non-survivors than those who survived (8.58 [4.68–12.25] vs. 4.67 [4.21–6.03]; p<0.001). A Cox multivariate regression analyses revealed that the CAR was an independent predictor of the in-hospital mortality (HR: 1.053, 95%CI: 1.006-1.101; p=0.027). Kaplan-Meier analysis showed that the patients with CAR≥8.4 had a significantly higher the incidence of death compared to those with CAR<8.4 (p<0.001).*

DISCUSSION and CONCLUSION: *The present study is the first to demonstrate that the CAR may have a prognostic value for the in-hospital mortality in patients with STEMI complicated by cardiogenic shock.*

Keywords: *C-reactive protein to albumin ratio, ST elevation myocardial infarction, cardiogenic shock.*

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INTRODUCTION

The effect of inflammation on the development of complications in cardiovascular diseases has been more clearly understood in recent years; hence, the inflammatory biomarkers are now increasingly being used not only for screening but also for prognosis in patients with coronary artery disease (CAD) [1]. C-reactive protein (CRP), one of the most commonly used biomarker for this purpose, has been associated with short- and long-term poor prognosis in ST elevation myocardial infarction (STEMI) patients [2–4]. On the other hand, the inflammation may also cause reduction in serum albumin level owing to the reduced synthesis and increased catabolism of it. Previous studies reported that hypoalbuminemia has been associated with the occurrence of myocardial infarction [5] and increased mortality among these patients [6]. Newly introduced inflammation based risk index, CRP/Albumin ratio (CAR), has been demonstrated to better reflect the inflammatory status and prognosis in patients with acute critical conditions and malignancy [7–9]. However, to the best of our knowledge, no previous study has investigated the association between the CAR and STEMI complicated by cardiogenic shock. Therefore, in the present study, we aimed to investigate whether CAR, calculated from the admission blood sample, has a prognostic value in STEMI patients suffered from cardiogenic shock on admission or during the in-hospital course.

MATERIALS AND METHODS

1. Study population

Between January 2012 and January 2018, a total of 102 STEMI patients complicated with cardiogenic shock on admission or occurred during in-hospital course were retrospectively screened. The patients with previous history of coronary artery disease (n: 14), known heart failure (n: 2), referred to emergency coronary aorta by-pass grafting (n: 2), and with mechanical complications (n: 5) were excluded from the study (Fig. 1). The remaining 79 patients constituted the study population. The demographic as well as echocardiographic, angiographic, and laboratory data of all patients were obtained from the hospital's electronic database. STEMI was defined based on the following criteria; ongoing ischemic symptoms (within 12 hours), typical rise or fall in the cardiac biomarkers, and a new ST elevation in ≥ 2 contiguous leads with leads V1, V2, and V3 measuring ≥ 0.2 mV or ≥ 0.1 mV in the remaining leads or new developed left bundle-branch block pattern [10]. Cardiogenic shock is defined as the presence of signs of hypoperfusion with persistent hypotension (systolic blood pressure <90mm/Hg) despite adequate filling status or needing inotropes and/or mechanical support to maintain systolic blood pressure >90 mm/Hg. All patients were treated with the standard therapy in accordance with the current guidelines during hospital stay. The study protocol was approved by the Ethics and Research Committee of our hospital, and it was performed according to the Principles of the Declaration of Helsinki. The need for written informed consent was waived due to the retrospective study design.

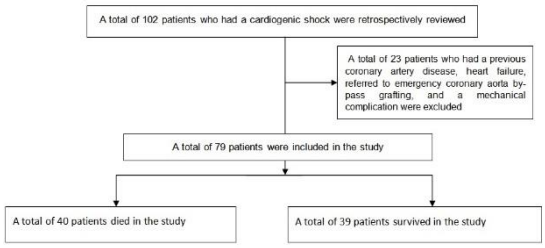


Figure 1 Flow chart of the study participants

2. Coronary angiography and percutaneous coronary intervention

Coronary angiography was performed within 90 minutes via femoral artery in all patients. All patients received an anticoagulation therapy with unfractionated heparin (70-100 units (U)/kg, maximal dose 10.000/U) and dual-antiplatelet therapy with aspirin (300 mg) and a loading dose of clopidogrel (600 mg) before the procedure. The culprit lesion was treated with balloon angioplasty and/or stent implantation. The no-reflow was defined as post-procedural thrombolysis in myocardial infarction (TIMI) flow <3 or TIMI flow of 3 with myocardial blush grading <2. The thrombus burden was assessed according to the TIMI thrombus grading scale that ranged from grade 0 (no thrombus) to grade 5 (very large thrombus causing a vessel occlusion). The patients with grade 5 thrombus were re-classified into grade 0, 1, 2, 3, or 4 after recanalization with a guide-wire or a small balloon [11].

3. Laboratory analysis and echocardiographic examination

All blood samples were obtained on admission before the coronary angiography. Troponin I and creatinine kinase-myocardial band (CK-MB) measurements were repeated at six hours' interval until their peak values were achieved. Serum albumin and CRP levels were measured using an automatic biochemical analyzer (Roche Diagonistics Cobas 8000 c502). The CAR was calculated a s the ratio of CRP to albumin level and the neutrophil to lymphocyte ratio (NLR) was calculated as the ratio of the number of neutrophil to lymphocytes, both of which obtained from blood sample upon admission prior to primary percutaneous coronary intervention (pPCI). A nephelometry method was used to measure CRP. In this study, serum albumin level was determined using bromocresolgreen method. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Transthoracic echocardiography was performed in all patients within 24 hours by using the GE Vivid 5 and 7 system echocardiography machines (GE Vivid 5 and 7; GE Healthcare, Piscataway, New Jersey). Left ventricular ejection fraction (LVEF) of each patient was calculated using biplane the Simpson's method.

4. Statistical analyses

Medicalc trial version 16.8.4 (Medicalc Software Bvba, Ostend, Belgium) and SPSS version 22.0 (IBM, Chicago, Illinois) were used to perform statistical analysis. Normality of the data was analyzed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution are expressed as mean (± standard deviation) values and were compared using the Student-t test. Continuous variables without normal distribution are expressed as median (0.25–0.75 percentiles) values and compared using the Mann-Whitney U test. The categorical variables are expressed as numbers (percentages) and were compared using Fisher's exact test or $\chi 2$-test. Event-free survival curves of the CAR tertiles were demonstrated using Kaplan-Meier survival curve analysis and compared using the log-rank test. The risk factors for in hospital mortality were analyzed using multivariate Cox proportional hazard analyses with variables that showed statistically significant associations with mortality in the univariate analyses. The receiver operating characteristic (ROC) curve was utilized to derive the best cut-off value of the CAR for predicting all-cause mortality. A p value < 0.05 was considered statistically significant.

RESULTS

The present study retrospectively included 79 STEMI patients in whom presented with cardiogenic shock on admission or occurred during hospital stay. The mean age of study population was 63±13 years, 27 patients (34.2%) were women. During in-hospital course, 40 patients (50.6%) died in the cohort. The baseline demographics, clinical, laboratory, and angiographic characteristics of patients died during in-hospital course (n: 40) compared with those survived (n: 39), and it is summarized in Table 1. The results of comparison demonstrated that patients died during in-hospital course had a higher frequency of diabetes mellitus, and the lower rate of smoking than those survived. There were no statistically significant differences in terms of systolic or diastolic blood pressure, heart rate, Killip class >1 on admission between the groups. The usage of intra-aortic balloon pump and mechanical ventilation were more common in patients died than those survived. Even though the infarct-related artery, total ischemic time, left main coronary artery disease, and no-reflow were not different between the groups ($p>0.05$ for each), patients died during in-hospital course had a longer door to balloon time, lower LVEF, more frequent multi-vessel (≥2 vessel) disease, and proximal or ostial culprit lesion than those survived. In terms of laboratory findings, patients died during in-hospital course had an increased white blood cell count, blood glucose, peak CK-MB and CRP levels, decreased eGFR and serum albumin levels compared to those survived. The median value of CAR was significantly higher in patients with non survivors than those survived (8.58 [4.68-12.25] vs. 4.67 [3.21-6.03]; $p<0.001$).

Table 1. Demographic, clinical, laboratory and angiographic characteristics of all patients, patients with and without survival, with P value

	Patients with cardiogenic shock						
	All patients (n=79)		No Death (n=39)		Death (n=40)		P value
Age, year	63.0	±13.0	62.0	±13.0	65.0	±14.0	0.259
Female gender, n (%)	27.0	(34.2)	12.0	(30.8)	15.0	(37.5)	0.531
Diabetes, n (%)	39.0	(49.4)	12.0	(30.8)	27.0	(67.5)	0.001
Hypertension, n (%)	36.0	(45.6)	15.0	(38.5)	21.0	(52.5)	0.213
Chronic obstructive lung disease, n (%)	4.0	(5.1)	1.0	(2.6)	3.0	(7.5)	0.320
Peripheral artery disease, n (%)	29.0	(36.7)	12.0	(30.8)	17.0	(42.5)	0.283
Dyslipidemia, n (%)	23.0	(29.1)	11.0	(28.2)	12.0	(30.0)	0.862
Family history of CAD, n (%)	6.0	(7.6)	4.0	(10.3)	2.0	(5.0)	0.381
Smoking, n (%)	26.0	(32.9)	19.0	(48.7)	7.0	(17.5)	0.003
Acetylsalicylic acid, n (%)	1.0	(1.3)	0.0	(0.0)	1.0	(2.5)	0.323
***B*-Blocker, n (%)**	2.0	(2.5)	2.0	(5.1)	0.0	(0.0)	0.149
ACEI/ARB, n (%)	12.0	(15.2)	7.0	(17.9)	5.0	(12.5)	0.503
Statin, n (%)	11.0	(13.9)	6.0	(15.4)	5.0	(12.5)	0.713
Systolic blood pressure, mmHg	72	±14	73	±15	71	±13	0.715
Diastolic blood pressure, mmHg	39	±10	40	±10	38	±9	0.683
Heart rate, bpm	88	±33	90	±28	86	±37	0.918
Killip class > 1 on admission, n (%)	71.0	(89.9)	36.0	(92.3)	35.0	(87.5)	0.482
IABP use, n (%)	58.0	(73.4)	25.0	(64.1)	33.0	(82.5)	0.066
Mechanical ventilation, n (%)	45.0	(57.0)	8.0	(20.5)	37.0	(92.5)	<0.001
White blood cell count, x10^3/mm^3	17.65	±5.42	15.74	±3.96	19.50	±6.03	0.002
Hemoglobin, g/dL	13.1	±2.1	13.1	±2.2	13.0	±2.1	0.757
Blood sugar on admission, mg/dL	189.0	136.0-291.0	157.0	109.0-232.0	236.0	162.5-346.5	0.003
C-Reactive protein, mg/dL	21.75	12.40-36.7	18.70	11.20-27.30	32.10	17.60-43.60	0.016
Serum albumin, g/dL	3.39	±0.72	3.59	±0.8	3.19	±0.58	0.019
C-Reactive protein/Albumin ratio	5.38	4.03-9.50	4.67	3.21-6.03	8.58	4.68-12.25	<0.001
eGFR, mL/min/1.73m^2	65.15	±31.61	75.90	±31.69	54.68	±28.15	0.001
Peak CK-MB, ng/mL	429.0	297.0-636.0	354.0	267.0-499.0	465.5	329.5-729.0	0.010
Peak troponin I, ng/mL	265.0	156.0-365.0	212.0	130.0-314.6	343.5	201.4-393.0	0.001
Left ventricular ejection fraction, (%)	36.9	±8.0	40.5	±7.4	33.4	±6.9	<0.001
Door to balloon time, min	37	±9	34	±6	41	±9	<0.001
Total ischemia time, min	240.0	140.0-350.0	252.0	140.0-390.0	227.50	144.5-339.0	0.695
IRA LAD	45.0	(57.0)	24.0	(61.5)	21.0	(52.5)	0.371
Cx	11.0	(13.9)	5.0	(12.8)	6.0	(15.0)	
RCA	19.0	(24.1)	9.0	(23.1)	10.0	(25.0)	
Other coronaries (Diagonal etc.)	4.0	(5.1)	1.0	(2.6)	3.0	(7.5)	
Proximal/ostial lesion for IRA, n (%)	70.0	(88.6)	31.0	(79.5)	39.0	(97.5)	0.012
High-grade thrombus burden, n (%)	66.0	(83.5)	30.0	(76.9)	36.0	(90.0)	0.119
Stent length, mm	23.38	±8.82	22.53	±6.90	24.18	±10.36	0.609
Stent diameter, mm	3.08	±0.37	3.03	±0.34	3.14	±0.39	0.321
Corrected TIMI frame count	28	23-35	26	19-44	28	24-35	0.412
No-reflow, n (%)	20.0	(25.3)	12.0	(30.8)	8.0	(20.0)	0.274
LMCA, n (%)	4.0	(5.1)	1.0	(2.6)	3.0	(7.5)	0.320
No. of diseased vessels, n (%) 1	29.0	(36.7)	20.0	(51.3)	9.0	(22.5)	0.006
2	33.0	(41.8)	14.0	(35.9)	19.0	(47.5)	
3	17.0	(21.5)	5.0	(12.8)	12.0	(30.0)	
TIMI risk score	8	±3	7	±2	9	±2	<0.001

CAD: Coronary artery disease; Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; IABP: Intra-aortic balloon pump; eGFR: Estimated glomerular filtration rate; CK-MB: Creatine Kinase-Myocardial band isoform; IRA: Infarct-related artery; LMCA: Left main coronary artery; TIMI: Thrombolysis in Myocardial Infarction.

To identify independent predictors of in-hospital mortality, a multivariate Cox regression analyses with a stepwise backward model were performed using the variables that showed marginal association with all-cause mortality in a univariate analysis. These variables were diabetes mel litus, smoking, blood glucose, CAR, eGFR, peak CK-MB, LVEF, and door to balloon time (Table 2). The CAR (hazard ratio [HR]:1.053, 95% confidence interval [CI]: 1.006-1.101; p=0.027), eGFR (HR: 0.989, 95% CI: 0.979-0.999; p=0.049), and door to balloon time (HR: 1.055, 95% CI: 1.021-1.089; p=0.001) were found to be independent predictors of in-hospital mortality.

Table 2 Univariate and multivariate logistic regression analysis for prediction of mortality

	Univariate analysis of mortality					
	Odds ratio	95% C.I.	P value	Odds ratio	95% C.I.	P value
C-Reactive protein/Albumin ratio	1.073	1.029-1.120	0.001	1.053	1.006-1.101	0.027
eGFR	0.989	0.978-0.999	0.045	0.989	0.977-0.999	0.049
Door to balloon time	1.060	1.028-1.092	<0.001	1.055	1.021-1.089	0.001

eGFR: Estimated glomerular filtration rate.

The ROC analysis was used to show the optimal cut-off value of the CAR for predicting in-hospital mortality. The optimal cut-off value of CAR was ≥8.4 with a sensitivity of 47.6% and a specificity of 91.9% (area under the curve [AUC]: 0.742; 95% CI: 0.635-0.849) (Fig. 2). Kaplan-Meier analysis was drawn and showed that patients with CAR <8.4 (n: 56) had a significantly lower incidence of death compared to those with CAR ≥8.4 (n: 23) (35.7%, n: 20 vs. 87%, n: 20; p<0.001) (Fig. 3).

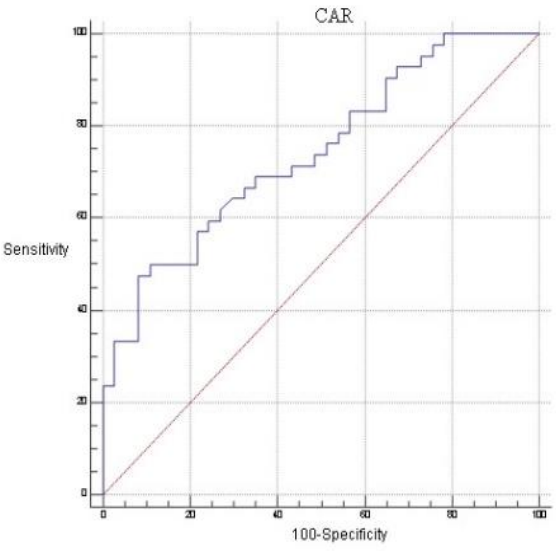


Figure 2. *In receiver operating characteristic (ROC) analysis, the optimal cut-off value of the CAR for predicting in-hospital mortality was≥8.4 with a sensitivity of 47.6% and a specificity of 91.9% (area under the curve [AUC]: 0.742; 95% CI: 0.635-0.849).*

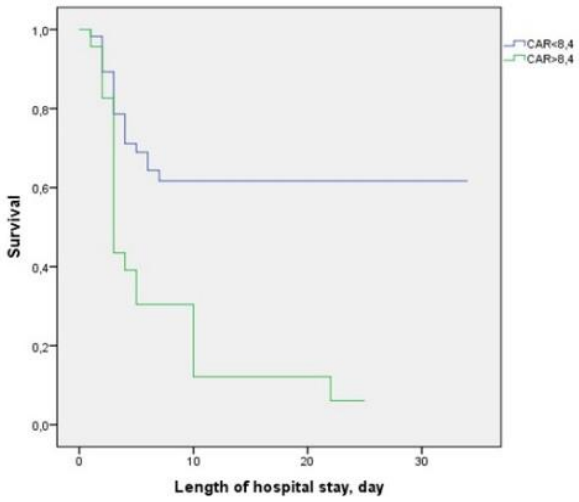


Figure 3. *Kaplan-Meier analysis showed that patients with CAR<8.4 had a significantly lower incidence of death compared to those with CAR ≥8.4.*

DISCUSSION

The present study demonstrated that the elevated CAR value was associated with in-hospital mortality among STEMI patients who suffered from cardiogenic shock due to the pump failure. The CAR independent predictor of in-hospital mortality.

Cardiogenic shock is a clinical condition of inadequate tissue (end-organ) perfusion due to the inability of the heart to pump an adequate amount of blood. The reduction in tissue perfusion results in decreased oxygen and nutrient delivery to the tissues and, if prolonged, potentially end-organ damage and

multi-system failure. Cardiogenic shock is the leading cause of death in patients with acute myocardial infarction, and the hospital mortality rates may approach 50% [12]. In accordance with current knowledge, the mortality rate of our cohort was 50.6%. Al though post-myocardial infarction mechanical complications are important cause of cardiogenic shock, it mainly arises from the pump failure due to severe left ventricular dysfunction. Autopsy studies in patients dying with cardiogenic shock due to acute myocardial infarction have revealed that 40% or more percent of the LV myocardium had been infarcted (old or new) [13]. In our study, the infarct size was not quantitatively measured, but patients who died had increased door to balloon time, more frequent proximal or ostial lesions as the infarct-related artery, lower LVEF, and higher peak CK-MB values compared to survived patients.

Diabetes mellitus has been known as a major risk factor for coronary artery disease. It has also been established that diabetes mellitus is associated with increased in-hospital mortality in STEMI patients complicated by cardiogenic shock as shown in our study [14]. Chronic kidney disease has been increasingly recognized as an independent risk factor for the development of coronary heart disease. Furthermore, eGFR below 60 ml/min upon admission is associated with poor short-term prognosis in patients with cardiogenic shock treated with veno-arterial extracorporeal membrane oxygenation [15]. A consisting finding was found as reduced eGFR level was an independent predictor of in-hospital mortality in our cohort.

Besides that being a strong risk factor for development of new cardiovascular events [16, 17]; elevated CRP has been shown to be associated with poor short- and long-term prognosis in STEMI patients [18]. Moreover, it has been established that STEMI patients with cardiogenic shock had a higher CRP levels than those without on admission [2], and elevated levels of CRP has been associated with in-hospital and one year mortality among STEMI patients complicated by cardiogenic shock [19]. On the other hand, in contrast to elevation of CRP levels, the inflammatory response of the body might cause hypoalbuminemia via decreasing its synthesis and increasing its degradation. Hypoalbuminemia is found to be related with increased mortality in patients with acute coronary syndrome [20,21]. Furthermore, Oduncu et al. demonstrated that decreased serum albumin level is a strong independent predictor of long-term mortality and development of advanced heart failure in patients with STEMI [6]. In accordance with above-mentioned studies, we observed that patients died during in-hospital course had significantly higher CRP and lower serum albumin level than those survived. The inverse relationship between CRP and serum albumin level in response to inflammation has emerged CRP to albumin ratio (CAR). The CAR has been previously studied in patients with acute medical conditions [7, 8] and malignancy [9]; it was observed that an elevated CAR was closely related with poor prognosis. In accordance with these previous findings, we observed that elevated admission CAR values was associated with higher in-hospital mortality in STEMI patients complicated by cardiogenic shock. Serum albumin and CRP levels are not only innocent indices of the inflammation; but also they are active participant in the progression of inflammatory condition. Both serum albumin and CRP levels are associated with endothelial dysfunction and pro-thrombotic state which have a great effect on the progression of cardiogenic shock (22,23).

Limitations of the study

The certain limitations of the present study need to be acknowledged while interpreting the results of this study. The present study had a retrospective design; therefore, the results might be biased. Second, patients with a previous history of coronary artery disease, with mechanical complication, and referred to emergency CABG were excluded; thus, these results cannot be generalized to all STEMI patients. Finally, the prognostic value of CAR needs to be validated in further prospective studies.

Conclusion

To the best of our knowledge, the present study is the first study to demonstrate the prognostic value of CAR in STEMI patients complicated by cardiogenic shock. The elevated CAR on admission was found to be an independent predictor of the in-hospital

mortality in patients with STEMI complicated by cardiogenic shock.

Declaration of Conflicting Interests:

All authors declare that they do not have conflicts of interests.

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