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Original Article

Plasma interleukin 6 as an outcome predictor of traumatic brain injury patients

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Abstract

Traumatic brain injury is one of the leading causes of death and disability in young adults. Previous studies have suggested that neuroinflammatory process involves the overexpression of interleukin 6 (IL-6); however, data on the predictive ability of IL-6 is limited and conflicting in traumatic head injury patients. The aim of this study was to assess the ability of plasma IL-6 as a predictor of outcome in head injury patients. A cross-sectional study was conducted between June and December 2020 among traumatic head injury patients admitted to Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. Demographic, clinical data, and IL-6 level were collected and measured on admission. The outcome was assessed by the Glasgow outcome scale extended (GOSE) in the first- and third-month of post-injury. A total of 50 traumatic brain injury patients were recruited of which 54% were male, 64% had mild head injury, 82% had leukocytosis, and 60% had non-bleeding head CT scan. The mean of IL-6 level was 79.32 pg/mL while the GOSE scores ranged from 1 (death) to 8 (upper good recovery). Early IL-6 level (<24 hours post-injury) was significantly correlated with worse outcome in traumatic head injury, though the correlation strength was moderate (p<0.001; r=-0.42). As a predictor, IL-6 yielded the area under curve (AUC) value of 93.5% (p<0.001) and a cut-off point of 46.33 pg/mL. The sensitivity and specificity of this predictor were 87.5% and 95.24%, respectively. In conclusion, early IL-6 level can be used as a predictor for traumatic head injury. Nevertheless, further multi-center study with a bigger sample size is needed to confirm this finding.

Keywords: Head injury, interleukin 6, traumatic brain injury, Glasgow outcome scale extended, GOSE

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability in young adults [1]. According to the most recent reports from the Global Burden of Diseases Study, from 1990 to 2016, the age-standardized incidence and prevalence of TBI increased by 3.6% and 8.4%, respectively, and there were 27.08 million new cases of traumatic head injury in 2016 alone; making the injury more common than breast cancer, spinal cord injury, HIV/AIDS, and multiple sclerosis combined [2]. Head injury is a major cause of morbidity and mortality worldwide in individuals under 45 years old [3]. An epidemiological study estimated that 57 million people worldwide live with the neurological sequelae of head injury, of which 10 million require hospital-based care [2].

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The severity of a head injury depends on several factors, including the mechanism and location of the injury and force of the impact [4]. The impact of a head injury is not limited to the initial event. Injuries that occur are divided into primary and secondary injuries, including various cellular and molecular changes [5]. Within hours until the next day, secondary injury occurs in glial cells and neuronal dysfunction, metabolic changes, neuroinflammation, cerebral edema, and release of various inflammatory molecules derived from neurons, glial cells, and immune cells. This results in a wide range of physiological phenomena, including blood-brain barrier breakdown, hypoperfusion, mitochondrial dysfunction, and oxidative injury. Therefore, secondary injuries can be more damaging than primary injuries, making them crucial therapeutic targets [6].

Although inflammatory mediators are markers of immune activation, the extent to which cytokines can be determined as diagnostic factors in traumatic brain injury or as predictors of long-term outcomes still needs further investigation. The validity of cytokines as biomarkers has yet to be widely accepted [6]. Pro-inflammatory cytokines, such as interleukin 6 (IL-6), are biosynthesized more frequently during the inflammatory process. IL-6 is a cytokine that was first discovered as a B-cell differentiation factor approximately 30 years ago. It is involved in the maturation of B cells into antibodies-producing cells. Like many other cytokines, IL-6 has numerous essential functions in different physiological systems, including the neurological system and its role in the immune response. Recently, IL-6 has been suggested to play a role in neurogenesis (affecting both neurons and glial cells) and in the reaction of adult neurons and glial cells under normal circumstances and after various damage types. IL-6 belongs to neuropilin family owing to its behavior that is similar to neurotrophins. Moreover, IL-6 involvement in neuropathology has been extensively studied in animal models, where its expression is changed in several primary brain illnesses [7].

Data on the predictive ability of plasma IL-6 in head injury are limited and conflicting; in children, plasma IL-6 was reported to have no association with neurological outcome, while other studies have shown that high IL-6 is correlated with poor outcome [8,9]. Recently, measurement of plasma IL-6 within 17 hours after injury was shown to be able to identify patients at risk for increased intracranial pressure (ICP) [9]. However, the prognostic value of IL-6 decreases with increasing ICP if the patient also has extracranial injuries [8]. Indeed, the presence of multiple injuries is common in head injury patients and should be taken into consideration when searching for or with the aim of developing biomarkers. This is evidenced by an increase in serum concentrations of IL-6 after orthopedic injuries, burns, and sports accidents [9,10]. Therefore, this present study was performed to confirm the predictive ability of IL-6 on the outcome of traumatic head injury.

Methods

Study design and setting

This study is an observational analytic study using a prospective cohort approach, conducted at Dr. Zainoel Abidin Hospital Banda Aceh from June 2020 to December 2020. The aim of this study was to evaluate IL-6 level on admission as the predictor for head injury outcome. On admission, demographic data, clinical data, and image findings were collected. Blood sample on admission was also collected for laboratory analysis and serum IL-6 level measurement. The severity of head injury on admission was assessed with Glasgow Coma Scale (GCS). In the first- and third months following the admission, patients were assessed with the Glasgow outcome scale extended (GOSE). The assessment was carried out directly if the patient was still being hospitalized or via telephone if the patient had been discharged. This research was approved by the Clinical Research Ethics Committee of Dr. Zainoel Abidin Hospital Banda Aceh before conducting the study.

Participants

The research subjects (n=50) were traumatic brain injury patients hospitalized at Dr. Zainoel Abidin Hospital Banda Aceh from June 2020 to December 2020. The inclusion criteria included being aged ≥18 years and having head injury less than 24 hours. Patients were excluded if they

were having multiple traumas, a history of stroke, Parkinson's disease, brain tumor, and brain infection, and incomplete imaging data. Patients undergoing surgery were also excluded.

Data collection and endpoints

On admission, gender and age data were collected. GCS was assessed to determine the severity of head injury whether it was mild (13–15), moderate (9–12), or severe (3–8). Blood pressure, blood sugar level, leukocytes, and plasma sodium level were also collected on admission. Patients received computed tomography (CT) scan to observe the presence of bleeding lesions in the head. Intravenous bloods of the patients were analyzed for IL-6 levels using Quantikine D6050 Human IL-6 ELISA kit (Biotechne, Minneapolis, United States) with protocols following the guideline from the manufacturer. GOSE score was determined in the first and third months after the injury onset. The score of 1 was given for death, 2 – vegetative state, 3 – lower severe disability, 4 – upper severe disability, 5 – lower moderate disability, 6 – upper moderate disability, 7 – lower good recovery, and 8 – upper good recovery. Patients were then divided into unfavorable and favorable groups based on the GOSE score (1–4 and 5–8, respectively).

Statistical analysis

Continuous data were presented in mean ± standard deviation (SD), while the categorical data were presented as frequency (n) and percentage. Normality of the data distribution was evaluated based on Shapiro–Wilk test. Normally distributed data would be analyzed with Pearson correlation test, while data with abnormal distribution would be analyzed with Spearman correlation test. Receiver operating characteristic (ROC) curve was established to determine the area under the curve (AUC) and the cut-off point. Sensitivity, specificity, positive predictive value, and negative predictive value of IL-6 level in predicting the unfavorable and favorable outcomes were also determined. Statistical differences of IL-6 among patients with mild, moderate, and severe head injury were analyzed based on ANOVA test and Mann-Whitney post-hoc test at $p<0.05$. All statistical analyses were carried out on SPSS version 23.0 (IBMSPSS, New York, United States).

Results

Characteristics of patients

Characteristics of patients in this study are presented in **Table 1**. The data of this study showed the patient's gender, age, blood pressure, leukocytes, sodium, and head CT lesions. There was a higher number of men than women (54% versus 46%, respectively). Patients were mostly aged 18–25 years (n=16, 32%) or 26–45 years (n=16, 32%). The majority of the patients experienced mild head injury (n=32; 64%) with normal blood pressure (n=39; 78), blood sugar level (n=42; 84%), and sodium level (n=39; 78). Eighty-two percent of the total patients had leukocytes of more than 10,000/µL. Bleeding lesions were identified in 20 (40%) of the CT images.

Table 1. Basic characteristics of patients (n=50)

Characteristics	Frequency	Percentage
Gender		
Woman	23	46
Man	27	54
Age (years)		
18–25	16	32
26–45	16	32
46 – 55	8	16
>56	10	20
GCS		
Mild head injury (13–15)	32	64
Moderate head injury (9–12)	12	24
Severe head injury (3–8)	6	12
Blood pressure (mmHg)		
≤120/80	39	78
>120/80	11	22
Blood sugar level (mg/dL)		

Characteristics	Frequency	Percentage
< 60	3	6
60–200	42	84
>200	5	10
Leukocytes (/µL)		
4,500–10,000	9	18
> 10,000	41	82
Sodium (mmol/L)		
135–145	39	78
>145	11	22
Head CT		
Bleeding lesions	20	40
Non-bleeding lesions	30	60

Plasma IL-6 level and GOSE score

The distributions of GOSE scores in the first and third months are presented in **Table 2**. In the first month post-injury, most of the patients had 'upper good recovery' or the score of 8 (n=21, 42%). The number increased to 28 (56%) when observed in the third month. There were 7 patients (14%) who did not survive, where no further mortality was recorded in the third month. The average GOSE scores in the first and third months were 5.74±2.59 and 6.52 ±2.43, respectively (**Table 3**). As for the level of IL-6 on admission, the average value was 79.32±282.17 pg/mL (**Table 3**). The level of this cytokine was significantly correlated with GOSE scores observed in the first or third month (p<0.001 and p=0.003, respectively) (**Table 4**). The r values were -0.54 and -0.42 indicating the negative correlation with moderate strengths for both observations (**Table 4**).

Table 2. Distribution of GOSE score as observed in the first and third months of injury (n=50)

Observation	Description of GOSE score	Frequency	Percentage
First month	1 = Death	7	14
	2 = Vegetative state	0	0
	3 = Lower severe disability	4	8
	4 = Upper severe disability	7	14
	5 = Lower moderate disability	2	4
	6 = Upper moderate disability	1	2
	7 = Lower good recovery	8	16
	8 = Upper good recovery	21	42
Third month	1 = Death	7	14
	2 = Vegetative state	0	0
	3 = Lower severe disability	0	0
	4 = Upper severe disability	1	2
	5 = Lower moderate disability	3	6
	6 = Upper moderate disability	1	2
	7 = Lower good recovery	10	20
	8 = Upper good recovery	28	56

Table 3. Level of IL-6 and GOSE core in the first and third months of injury (n=50)

Variable	Minimum	Maximum	Average
IL-6 (pg/mL)	0.48	1517.55	79.32
1-month GOSE	1	8	5.74
3-month GOSE	1	8	6.52

Table 4. Correlation between the level of IL-6 and GOSE scores at first and third month of injury (n=50)

Observation	Variable	n	p	r
First month	IL-6 levels (pg/mL) GOSE score	50	<0.001	-0.54
Third month	IL-6 levels (pg/mL) GOSE score	50	0.003	-0.42

Predictor value of plasma IL-6 to determine the GOSE score

To determine the predictive ability of IL-6 against GOSE-based head injury outcome, an analysis was performed using the receiver operating characteristics (ROC) curve, where the curves are presented in **Figure 1**. It appears that IL-6 had good diagnostic values, in both first- and third-month observations, because the curve is far from the 50% line and close to 100% line. The area under the curve (AUC) for the first- and third-month observations were 78.3% (64.6%-92%, p=0.001) and 93.5% (86%-100%, p<0.001), respectively. Based on the optimum sensitivity and specificity in the ROC, the cut-off points of 16.52 pg/mL and 46.33 pg/mL were selected for the first- and third-month observations, respectively. The performance of IL-6 in predicting the head injury outcomes, as observed in the first and third months, is presented in **Table 5**. The sensitivity and specificity of the IL-6 in predicting first-month head injury outcomes were 77.8% and 75%, respectively, where the positive predictive value was 63.6% and the negative predictive value was 85.7%. As for the third-month outcomes, the biomarker had a sensitivity value of 87.5%, specificity of 95.24%, a positive predictive value of 77.78%, and a negative predictive value of 97.56%.

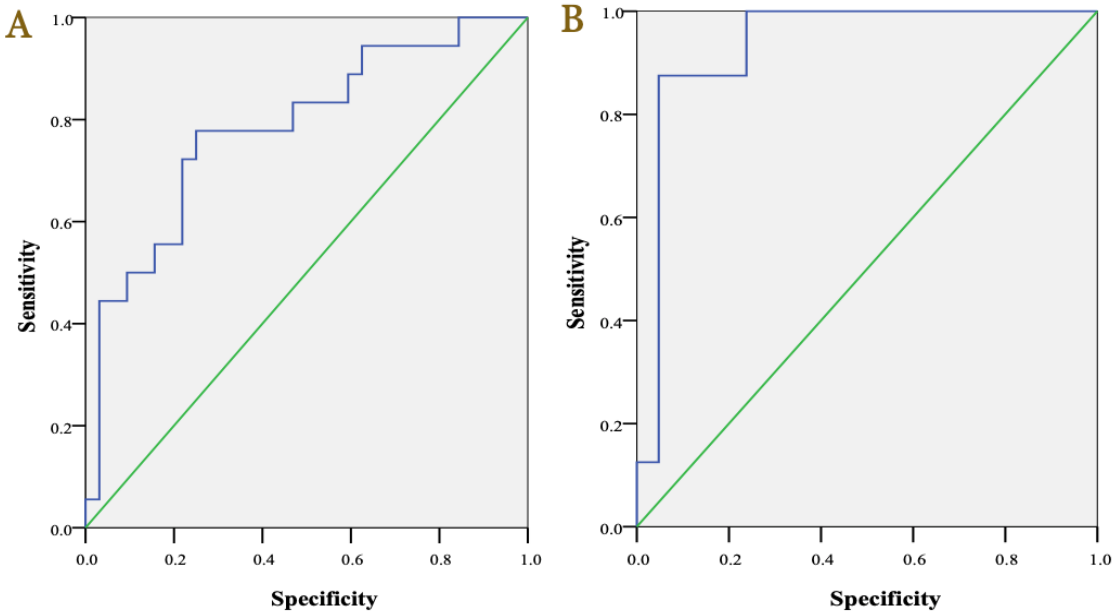

Figure 1. ROC curves for IL-6 as a predictor for head injury outcome observed in the first (a) and third month (b).

Table 5. Performance of IL-6 as the predictor of unfavorable and favorable outcomes in head injury

IL-6 (pg/mL)	GOSE score		Total
	Unfavorable outcome	Favorable outcome	
First month			
>16.52	14	8	22
<16.52	4	24	28
Third month			
>46.33	7	2	9
<46.33	1	40	41

Relationship between plasma IL-6 levels and head injury

Differences in IL-6 levels in groups of patients with mild, moderate, and severe head injuries were analyzed using the ANOVA test. In the normality test, IL-6 levels in mild and severe head injury groups were abnormal (p<0.05), hence further data were analyzed using the Kruskal-Wallis test and the results are presented in **Figure 2**. It was found that there was a significant difference of plasma IL-6 among patients with different severities of head injury (p=0.001). A post-hoc test was then carried out with the Mann-Whitney test to determine differences in IL-6 levels for each

head injury severity. Statistically significant differences were observed for mild versus severe (p<0.001) and moderate versus severe (p=0.003), but not for mild versus moderate (p=323).

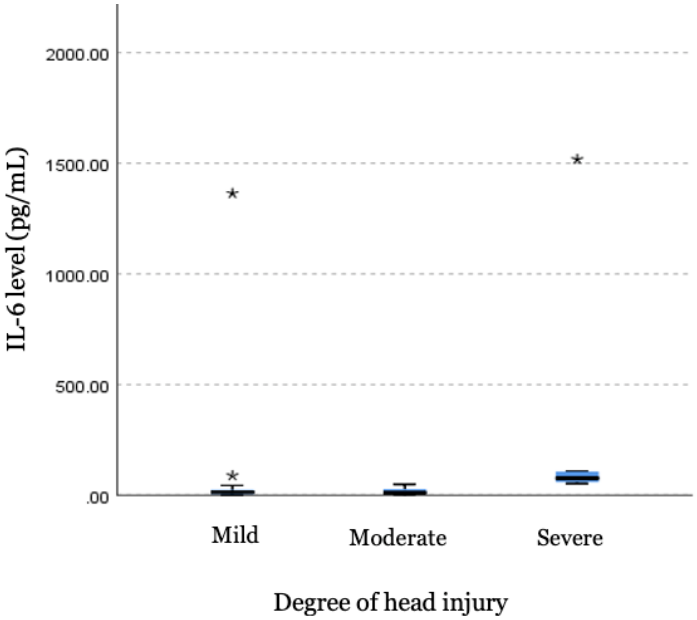

Figure 2. Level of plasma IL-6 in the patients with different severities of head injury.

Discussion

In this present study, 54% patients were men and 64% were 16-45 years old. Similarly, a previous study had 54.5% men and most of the overall patients aged 31.3±18.8 years [11]. Likewise, another study also reported higher proportion in men [9]. It was suggested that men were more likely involved in outdoor activities with high mobility, exposing this population to an increased risk of traffic or work-related accidents [9]. Previously, a higher incidence of head trauma has been reported in individuals aged under 45 years, which is also associated with intense outdoor activities and high mobility [11-13]. Additionally, the subjects in this present study exhibited characteristics similar to those in previous studies, where the majority of patients had mild head injuries [11-13], normoglycemia [15,16], and normal sodium level [17,18]. Furthermore, in this present study only 40% of the total patients had bleeding lesions such as subarachnoid hemorrhage, intracerebral hemorrhage, epidural hemorrhage, and subdural hemorrhage. Another 60% of the total patients had non-bleeding lesions (normal and cerebral edema). This is in line with a previous study where cerebral edema was the most common lesion [17]. It is worth noting that the presence of multiple bleeding lesions predicts poor outcomes in trauma patients. [18].

Herein, there were 39 patients (78%) with blood pressure of ≤120/80 mmHg and 11 patients (22%) with blood pressure of ≥120/80 mmHg. In patients with head injury, an increase in systemic blood pressure may occur due to the release of catecholamine, which is associated with regional damage involving insular and subcortical brain areas. Moreover, early brain damage frequently increases ICP due to localized mass effects and diffuse cerebral edema. This leads to complex neuroendocrine interactions by triggering the autonomic nervous system and releasing catecholamines. The systemic release of catecholamines increases arterial blood pressure [14].

In this present study, only 18% of the total patients had normal leukocytes, while the rest (82%) had leukocytosis. This finding is similar to previous studies, where leukocytosis was common in patients with head injury [14,17]. Head injury is a complex pathological process caused by focal or diffuse primary and secondary brain damage. Most head injuries result in distortion of axons, blood vessels, and brain cells due to kinetic forces acting on the brain tissue. A multilayer inflammatory response can be induced by releasing several inflammatory molecules and neurotransmitters via damaged neurons and glial cells. All primary damage-related

processes, such as altered blood flow (bleeding, ischemia), ongoing blood-brain barrier damage, cerebrospinal fluid dysregulation, altered metabolism of brain tissue (hypoxia or edema), neuroinflammation, and cell damage (excitotoxicity, oxidative stress, free radical production, apoptosis, or necrosis), are intimately linked to secondary damage. Leukocytosis is therefore frequently involved in head injuries [16].

IL-6 level and GOSE score

In this present study, the average plasma IL-6 level was 79.32 pg/mL, indicating that patients with acute head injuries had considerably high plasma IL-6. In comparison, previous studies found that the plasma IL-6 among patients with head injury could reach 22.00±4.66 pg/mL or 218.79 pg/mL, observed 24 hours post-injury [19,13]. In the brain, the cytokine is expressed by astrocytes, microglia, and neurons. IL-6 was suggested to play a role in inhibiting N-methyl-d-aspartate (NMDA)-mediated toxicity by promoting neuronal differentiation and survival [20]. In a healthy brain, IL-6 is frequently undetectable but is released in response to brain damage as suggested in an animal model study [20]. The levels of plasma IL-6 in this present study had a high SD (±282.17 pg/mL) which could be attributed to a variety in research subjects, including different severities of the head injury. Severe damage to the blood-brain barrier and inflammatory process affects the release of IL-6 by astrocytes, microglia, and neurons into peripheral blood circulation. In mild head injuries, damage to blood-brain barrier does not commonly occur which prevents the increased interleukins in peripheral circulation.

Herein, the average GOSE score assessed in the first and third months were 5.74 and 6.52, respectively. Higher GOSE score indicates better outcomes experienced by the patients after three months post-injury. This might be attributed to predominant proportions of patients with mild and moderate injuries. As suggested by a previous study, initial GCS along with other characteristics (such as age, race, educational level, mechanism of injury, duration of loss of consciousness, and blood pressure) could determine the GOSE score [21]. Therein, a significant improvement in GOSE score was also found following 1- and 3-month observations [21]. Another study revealed that GOSE improvements coincide with improvements in health systems and facilities (including fast patient transport and treatment, availability of CT scans, and good neurological and non-neurological monitoring) [22].

Herein, the Spearman test suggests that plasma IL-6 level was inversely correlated with GOSE scores. This is supported by the findings from a previous study, where the outcome of head injury could be predicted by plasma IL-6 within 24 hours post-injury [23]. According to a previous report, increased plasma IL-6 level on admission is associated with sepsis complications and multiple organ dysfunction [24]. Inflammatory mediators are overexpressed in injured or infected tissue, inducing immunological responses. Pro-inflammatory cytokines promote the expression of adhesion molecules, chemokines, immune cell migration into the parenchyma, and cellular activation. Several factors could stimulate the production of these cytokines. However, during trauma, hypoxia and the axoplasmic exudation that results from cellular necrosis act as the primary catalysts. Certain brain injury results in increased IL-6 levels [23]. The release of the cytokine IL-6 into the peripheral circulation following trauma appears to serve as an early indicator of the severity of the injury. The cytokine has both pro- and anti-inflammatory activities. It was discovered that IL-6's pro-inflammatory characteristics are more evident in the acute phase of the inflammatory response and contribute to its escalation. Previously, increased IL-6 levels were linked to bad outcomes among patients with head injuries [23].

In this present study, the AUC value for 1-month GOSE was 78.3% (95%CI: 64.6% - 92%; p=0.001). With a cut-off value of 16.52 pg/mL, the sensitivity, specificity, positive predictive value, and negative predictive value were 77.8%, 75%, 63.6%, and 85.7%, respectively. Meanwhile, in the ROC curve analysis for 3-month GOSE, better AUC value was obtained (93.5% [95%CI: 86% - 100%; p<0.001]). The recommended cut-off value was 46.33 pg/mL with a sensitivity value of 87.5% and a specificity of 95.24%, a positive predictive value of 77.78%, and a negative predictive value of 97.56%. Taken altogether, plasma IL-6 levels from samples collected <24 hours post-injury could predict the 3-month head injury outcomes. Our present study contradicts previous studies that suggested a higher cut-off value for predicting a poor prognosis and multi-organ failure syndrome [8,9].

Plasma IL-6 levels significantly differed among patients with varying severities of head injury according to the Kruskal-Wallis test (p<0.001). Post hoc analysis using the Mann-Whitney test revealed significant differences in IL-6 levels between the mild head injury and severe head injury groups, as well as the moderate head injury and severe head injury groups (p<0.001). These results are consistent with a previous study that found a significant relationship between plasma IL-6 levels at 6 hours post-injury and the severity of head injury as measured by the GCS [23]. It is worth noting that a high level of IL-6 in the first 24 hours also indicates high inflammation at the initial injury, characterized by more severe head injury.

Conclusion

Our data show a significant relationship between early plasma IL-6 levels (collected <24 hours post-injury) and outcome in patients with head-injury. The higher the plasma IL-6 level, the worse the outcome in head injury patients. Significant differences of IL-6 levels were observed in mild versus severe and moderate versus severe head injuries. We finally conclude that plasma IL-6 can be used as a predictor for head injury outcomes. Nonetheless, to confirm the findings in this present study, further research with a larger sample size and longer follow-up duration is required.

Ethics approval

This study was approved by the Health Research Ethics Committee of Dr. Zainoel Abidin Hospital Banda Aceh prior to conducting the study (No. 074/EA/FK-RSUDZA/2020).

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

Derived data supporting the findings of this study are available from the first author on request.

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