

Clinical value of serum and urine endocan in children with hemolytic uremic syndrome

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ABSTRACT

Background. Endocan (endothelial cell-specific molecule-1) is a soluble dermatan sulfate proteoglycan of the extracellular matrix released into the circulation by vascular endothelial cells and involved in vascular processes in which endothelial cell activation occurs. In this study, we aimed to evaluate serum and urinary endocan levels in children with hemolytic uremic syndrome (HUS) during the acute disease and follow-up period, compared with controls, and to evaluate associated clinical and laboratory parameters.

Methods. Children were evaluated in three groups: HUS patients in the active stage (Group 1, HUS-active stage, n=15), HUS patients followed until the resolution of active disease (Group 2, HUS-follow-up, n=10) and healthy controls (Group 3, n=15). Clinical parameters and renal outcomes were compared between the groups based on serum and urinary endocan levels.

Results. The pairwise group comparisons of the urinary endocan levels (median; Q1-Q3) revealed statistically significant differences between Group 1 (2148; 1592-3068 ng/gCr) and Group 2 (1274; 733-1565 ng/gCr), and between Group 1 and Group 3 (954; 517-1966 ng/gCr) ($P<0.01$), but not between Group 2 and Group 3 ($P>0.05$). The serum endocan level showed no statistically significant difference between the groups ($p>0.05$). When all groups were evaluated together, urinary endocan level showed positive correlations with white blood cell counts ($r=0.63$, $P<0.001$), and with lactic dehydrogenase ($r=0.51$, $P<0.001$), blood urea nitrogen ($r=0.48$, $P<0.05$) and serum creatinine levels ($r=0.50$, $P<0.001$). However, urinary endocan levels showed negative correlations with hemoglobin ($r=-0.57$, $P<0.001$) and platelet levels ($r=-0.37$, $P<0.05$), and estimated glomerular filtration rate ($r=-0.45$, $P<0.001$). The urinary endocan levels of patients with HUS decreased significantly during follow-up ($P<0.05$).

Conclusions. Our findings suggested that urinary endocan levels were significantly elevated in HUS patients in the active stage. In addition, several important laboratory parameters in the HUS clinic were associated with urine endocan levels.

Key words: hemolytic uremic syndrome; endocan; endothelial damage; children.

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy, and it is characterized by hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI).^{1,2} It is more common in children under five years old, with an incidence of 5-6/100,000.

In HUS, microthrombi formed due to vascular damage, causes platelet aggregation and ultimately leads to thrombocytopenia. At the same time, hemolytic anemia occurs with damage to erythrocytes as they pass through thrombosed vessels. These events result in

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ischemic organ damage, especially in the kidneys. HUS presents with general disease symptoms, hematological findings, signs of AKI and extrarenal findings such as seizures, colitis, cholecystitis, pancreatitis, elevated liver enzymes, and myocardial dysfunction.² In 2016, the International Consensus proposed a new classification system for HUS.³

Endocan (endothelial cell-specific molecule-1) is a 50-kDa soluble proteoglycan consisting of dermatan sulfate and a mature polypeptide of 165 amino acids.^{4,5} It is expressed in vascular endothelial cells, pulmonary capillaries, kidneys (glomerular endothelial cells and tubular epithelial), cardiomyocytes, digestive system, liver, brain, thyroid gland, thymus, epididymis, skin, and lymph nodes.^{6,7} Endocan is involved in various vascular processes that regulate endothelial activation, endothelial permeability, and cellular adhesion and proliferation.⁸ Endocan may be an independent predictor or a new prognostic biomarker in immunoglobulin A (IgA) nephropathy⁷ cardiovascular events due to chronic kidney disease (CKD)⁹, chronic renal allograft injury¹⁰, coronary artery diseases¹¹, cancers¹² and diabetic nephropathy.¹³ Although endocan is present in extremely low concentrations in body fluids, it can be easily detected due to its stability in physiological conditions. Therefore, it can be a non-invasive diagnostic and prognostic marker in various systemic and renal diseases.⁴

Developing clinical prediction scores and rapid diagnostic tools is essential for early identification of patients with HUS and timely initiation of targeted therapies.² However, to date, no specific biomarker has been identified that can guide hospitalization decisions or reliably assess disease severity in children with HUS. Although endocan is associated with many diseases, no study has evaluated its relationship with HUS. Therefore, we aimed to evaluate serum and urinary endocan levels in children with HUS during the acute disease and follow-up period, compared to controls; and to evaluate associated clinical and laboratory parameters.

Material and Methods

Patients and study design

This study was prospectively conducted in the pediatric nephrology clinic of Atatürk University Faculty of Medicine in 2021 and 2022. Pediatric patients included in the study were evaluated in three groups: a) HUS patients in active stage (Group 1, HUS-active stage, n=15), b) HUS patients who could be followed until the resolution of active disease (Group 2, HUS-follow-up, n=10) and c) healthy controls (Group 3, n=15). The patients' age, sex, weight, and vital signs were recorded. Hematological and biochemical tests were performed. The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula.¹⁴ AKI was staged according to the KDIGO study.¹⁵ The diagnosis of HUS was based on the presence of the triad of renal dysfunction showing an elevated serum creatinine level for age and height, hemolytic anemia (hemoglobin <8 g/dL or hematocrit <30%), and thrombocytopenia (platelet count <150x10⁹/L).²

The clinical severity of HUS was evaluated on the following six items, with a score assigned to each item: 1) Prolonged anuria (longer than two weeks); 2) Kidney replacement therapy (KRT) requirement; 3) KRT lasting longer than four weeks; 4) Diagnosis of atypical HUS (aHUS), *Streptococcus pneumoniae*-associated hemolytic uremic syndrome (SP-HUS), cobalamin C-HUS, or atypical hemolytic uremic syndrome (aHUS) with diacylglycerol kinase epsilon (*DGKE*) gene variant; 5) Stage 3 AKI in the acute phase of the disease; and 6) Non-renal organ involvement (pancreatitis, elevated liver enzymes, colitis, cholecystitis, myocardial dysfunction, rhabdomyolysis, ulcerative-necrotic skin lesions, seizure, lethargy, and coma).^{1,2} Urinary blood and protein measurements were performed semi-quantitatively using the photometric method in a fully automated H-800 Dirui urine analyzer (DIRUI, H-800, China). The patients were treated following the most recent guidelines and discharged from the hospital upon clinical improvement.^{2,16,17}

Sample collection and storage

Blood and urine samples were collected from all patients: Group 1 within the first 48 hours of admission (mean: 2.0 ± 0.3 days), Group 2 during follow-up (mean: 2.2 ± 0.7 months after the first admission), and Group 3 during the whole study period. Blood samples (3.5 mL) were collected into biochemistry tubes, and urine samples (5 mL) were collected into sterile urine tubes. The blood samples were kept at room temperature for 20 minutes, and then centrifuged at 4,000 rpm for 15 minutes. Serum samples obtained after centrifugation were transferred to Eppendorf tubes and aliquoted. The urine samples were centrifuged at 2,000 rpm for 15 minutes, and then the supernatant was transferred to microcentrifuge tubes and aliquoted. The aliquoted serum and urine samples were stored in an ultra-low temperature freezer at -80°C until the study day.

Analyte assay techniques

For the measurement of serum and urine endocan levels, the BT LAB enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory, Cat. No. E3160Hu, lot no. 202205005, China) was used. The experimental steps in the kit insert were applied to the automatic ELISA reader device, and the samples were analyzed with the ELISA method using the automatic Dynex ELISA reader device (Dynex Technologies Headquarters, Chantilly, USA). The results were expressed as ng/L. The sensitivity of the ELISA kit was 2.56 ng/L, and its detection range was 5-2,000 ng/L. The intra-assay and inter-assay coefficients of variation were below 4% and 10%, respectively. Urine creatinine levels were determined through the kinetic colorimetric measurement using the Jaffe method on the Roche Cobas c702 device (Roche Diagnostics GmbH, Mannheim, Germany). Urine creatinine was measured in the same urine specimens. The urine endocan level was expressed relative to the creatinine concentration: endocan/creatinine (ng/gCr).

Statistical analysis

Data was analyzed using SPSS v. 25.0 for Windows software (IBM SPSS Inc., Chicago, IL, USA). The chi-square test was used to assess the sex distribution among the study groups. The Shapiro-Wilk test was used to determine the normality of the data. For nonparametric data, the Mann-Whitney U test was used to compare the means and medians of two groups. Analysis of variance (ANOVA) was used to compare group means. Pairwise comparisons were performed using the Duncan or Kruskal-Wallis tests (adjusted by the Bonferroni correction). The Spearman rho correlation test was applied to evaluate relationships among all continuous variables, both across the total sample and within groups. The results are shown as mean \pm standard deviation or median (Q1-Q3), depending on data distribution. An alpha significance level of $P < 0.05$ was considered statistically significant.

Ethics committee approval

This study was conducted after receiving ethical approval from the Clinical Research Ethics Committee of Atatürk University Faculty of Medicine (2021/06-55). Written consent was obtained from the parents of the patients/healthy controls.

Results

All Group 1 patients had clinical and laboratory findings consistent with HUS. Hemoglobin (Hb) and serum endocan levels were normally distributed ($P > 0.05$), whereas the other analyzed characteristics were not ($P < 0.01$). The demographic characteristics and the blood and urine results of the groups are given in Table I. The pairwise group comparisons of median urinary endocan levels revealed significant differences ($P < 0.01$) between Group 1 and Group 2, and between Group 1 and Group 3, but not between Group 2 and Group 3 ($P > 0.05$). Although the mean serum endocan

level was higher in Group 1, the difference between groups was not statistically significant. ($P>0.05$) (Table I, Fig. 1). There was also no significant correlation between the serum endocan levels and urinary endocan levels in all groups ($r=0.29$, $P>0.05$)

Most of the laboratory parameters in Group 1 differed significantly from those in the other groups (Table I). When all groups are evaluated together, the mean urinary endocan level positively correlated with most laboratory parameters (Table II). In Group 1, the serum

Table I. Demographic characteristics and laboratory findings of the study groups.

	Group 1 (n=15)	Group 2 (n=10)	Group 3 (n=15)	P value
Demographic characteristics				
Age (month)	40.0 (20.0-56.0)	37.5 (26.7-56.5)	47.0 (33.0-73.0)	0.576
Body weight (kg)	15.0 (10.0-21.0)	14.3 (10.3-20.1)	18.3 (14.0-24.0)	0.491
Female sex	7 (46.6%)	5 (50%)	8 (54.4%)	0.936
Laboratory findings				
eGFR (ml/min/1.73 m ²)	16.9 (13.3-26.0) ^b	133.5 (121.2-169.0) ^a	173.0 (153.0-244.0) ^{a*}	<0.001
WBC (N: 4.5–13.5 ×10 ³ /μL)	11.4 (9.8-20.3) ^a	9.05 (7.61-10.38) ^b	7.7 (6.7-9.6) ^b	0.001
Hemoglobin (N: 12–16 g/dL)	8.43±1.56 ^b	12.20±1.43 ^a	12.50±1.27 ^a	0.001
Platelet (N: 150–450 ×10 ³ /μL)	41 (28-51) ^a	301 (254-358) ^b	334 (302-461) ^b	<0.001
LDH (N: < 248 U/L)	2400 (2047-2834) ^a	289 (252-339) ^b	-	<0.001
BUN (N: 7-17 mg/dL)	64 (40-102) ^a	12.7 (10.8-15.8) ^b	-	<0.001
Cr (N: 0.4-1.2 mg/dL)	3.0 (2.4-5.9) ^a	0.39 (0.29-0.49) ^b	0.33 (0.22-0.40) ^b	<0.001
Serum endocan (ng/L)	496.42±104.02 ^a	488.1±93.59 ^a	424.9±139.8 ^a	0.212
Urinary endocan (ng/gCr)	2148 (1592-3068) ^a	1274 (733-1565) ^b	954 (517-1966) ^b	0.002

Data are presented as n (%), mean±SD or median (Q1-Q3).

^{a,b}The difference between means/medians with the same letter is not significant, but the difference between means/medians with different letters is significant.

BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile; WBC, white blood cell.

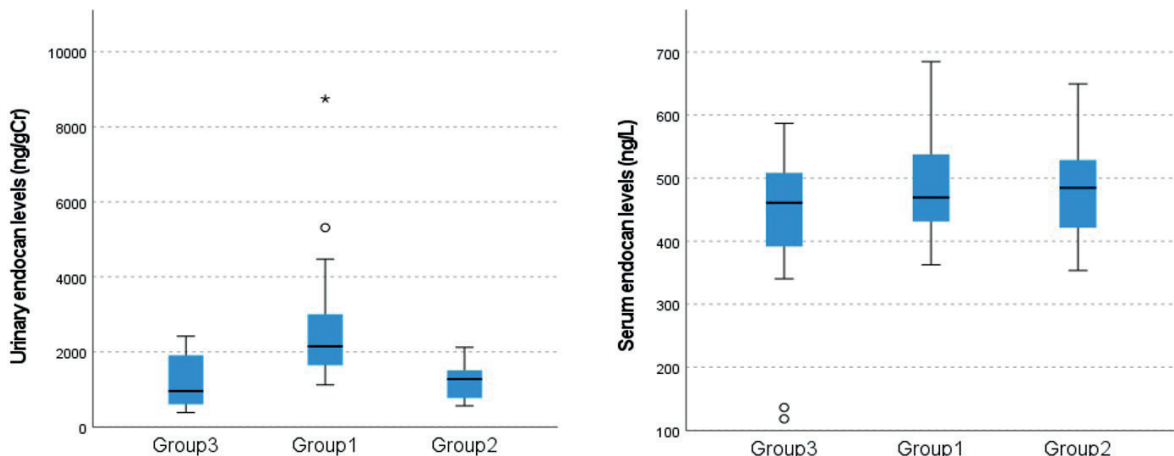


Fig. 1. Comparison of urinary and serum endocan levels of groups (Group 1: HUS-active stage, Group 2: HUS-follow-up and Group 3: healthy controls).

HUS, hemolytic uremic syndrome.

Table II. Correlation coefficients and significance levels in the parameters analyzed in the study groups.

	Correlation coefficient (r) with-	
	Serum endocan level	Urinary endocan level (normalized to Cr)
General		
White blood cell count	0.17	0.63**
Hemoglobin level	-0.21	-0.57**
Platelet count	0.07	-0.37*
Estimated glomerular filtration rate	-0.17	-0.45**
Serum creatinine level	0.16	0.50**
Blood urea nitrogen level	0.13	0.48*
Lactate dehydrogenase level	0.27	0.51**
Group 1		
Estimated glomerular filtration rate	-0.55*	-0.03
Stage of AKI in the acute phase of the disease	0.59*	0.09
Group 2		
The time taken until urine sample collection	-0.65*	-
Group 3		
White blood cell count	0.60*	0.60*
Serum endocan level	-	0.53*

*: P<0.05, **: P<0.01. AKI, acute kidney injury; Cr, creatinine.

and urinary endocan levels did not show a statistically significant correlation with the clinical severity score ($r=0.16$, $P=0.117$; and $r=0.05$, $P=0.863$), hypertension ($r=-0.03$, $P=0.908$; $r=0.36$, $P=0.187$), urine protein ($r=0.32$, $P=0.250$; and $r=-0.19$, $P=0.497$) and urine blood positivity ($r=0.40$, $P=0.143$; and $r=-0.23$, $P=0.408$), erythrocyte sedimentation rate ($r=0.31$, $P=0.417$; $r=0.05$, $P=0.898$), C-reactive protein (CRP, $r=-0.46$, $P=0.117$; $r=0.05$, $P=0.972$), respectively. Distribution of the clinical severity score and AKI stages of patients in Group 1 ($n=15$) is presented in Table III. In Group 1, patients with stage III AKI had a significantly higher mean serum endocan level (546.2 ± 89.32 ng/L), when compared to Group 1 patients with stage I (363.3 ± 1.20 ng/L) and stage II (419.3 ± 28.38 ng/L) AKI ($P<0.05$). No statistically significant difference was observed between urinary endocan levels according to AKI stages ($P>0.05$) (Table III). When Group 1 patients with ($n=5$) and without ($n=10$) hypertension were compared, there was no statistical difference

in terms of serum (means \pm SD: 496.2 ± 97.48 vs. 496.5 ± 112.28 ng/L, $P=0.953$) and urine (medians [Q1-Q3]: 2238.2 [2005.8-4891.9] vs. 1767.4 [1399.8-2965.9] ng/gCr; $P=0.206$) endocan levels. There was no significant difference in serum (means \pm SD: 506.0 ± 78.09 vs. 485.4 ± 133.67 ng/L; $P=0.463$) and urinary (medians [Q1-Q3]: 1644.7 [1307.2-2837.8] vs. 2274.4 [1863.6-4471.9] ng/gCr; $P=0.094$) endocan levels in patients who needed KRT compared to those who did not need KRT.

Discussion

HUS is a thrombotic microangiopathy characterized by thrombocytopenia, intravascular hemolysis and AKI.¹⁸ Although HUS has various etiological causes, including environmental triggers or genetic mutations, all forms of HUS present with endothelial damage, in which there are microvascular lesions characterized by the formation of fibrin and platelet-rich thrombi.² Non-invasive diagnosis

Table III. Distribution of Group 1 (n=15) patients in terms of clinical severity score and AKI stage.

		Serum endocan level (mean±SD)	Urine endocan level (mean±SD)	n	%
Acute kidney injury	Stage I	363.3±1.20 ^b	2384.8±773.8 ^a	2	13.3
	Stage II	419.3±28.38 ^b	2401.9±612.1 ^a	3	20.0
	Stage III	546.2±89.32 ^{a*}	3003.3±2460.8 ^a	10	66.7
Parameters of clinical severity [‡]	Stage III AKI in the acute phase of the disease			10	66.7
	KRT requirement			8	53.2
	Diagnosis of atypical HUS			2	13.3
	Anuria > 2 weeks			2	13.3
	Non-renal organ involvement			2	13.3
	KRT > 4 weeks			1	6.7
Clinical severity score	Score 0			3	20.0
	Score 1			1	6.6
	Score 2			5	33.3
	Score 3			4	26.7
	Score 4			0	0.0
	Score 5			2	13.3

^{a,b}While there is no significant difference between the means indicated with the same letter, there is a significant difference between the means indicated with different letters.

*P<0.05

[‡]Patients received 1 point for each present parameter, and the clinical severity score was determined by summing all scores. AKI, acute kidney injury; HUS, hemolytic uremic syndrome; KRT, kidney replacement therapy; SD, standard deviation.

of various kidney diseases remains a challenge in clinical practice. Blood urea nitrogen, serum creatinine levels and proteinuria are the commonly practiced diagnostic parameters to evaluate kidney pathologies; however, they are not specific.⁴ The diagnostic methods for AKI due to many causes, including HUS, are mainly based on serum creatinine measurement. However, the decreased sensitivity and specificity of this marker, which does not always reflect the extent of renal parenchymal destruction, has led to the evaluation of alternative markers associated with inflammation and endothelial dysfunction, such as endocan.¹⁹

In the current study, although the mean serum endocan level was higher in Group 1, mean serum endocan levels showed no statistically significant difference between the groups (P>0.05). However, the mean urinary endocan level in Group 1 patients was significantly higher than in the other groups (P<0.05). Our findings suggest that urinary endocan levels

may provide more valuable information than serum endocan levels in patients diagnosed with HUS. Also, higher urine endocan levels may indicate the active stage of the disease.

There is limited data on the metabolism and excretion of circulating endocan. Normally, endocan cannot pass through the negatively charged basement membrane in a healthy glomerulus, due to the presence of highly negatively charged dermatan sulfate, an essential component of endocan.⁷ It is unclear whether the increase in serum endocan levels in renal diseases is due to increased production or decreased renal clearance. In addition, it remains unclear whether the increase in urinary endocan levels results from the release of this molecule from damaged renal tubular cells or from its leakage from plasma due to an impaired glomerular basement membrane.^{4,9} In the literature, studies investigating serum endocan levels are more common than those investigating urinary endocan levels. In these

studies, serum endocan levels were found to be significantly higher in many diseases.^{7,9-11,13,19-24} In our study, urinary endocan levels were significantly higher in patients with HUS. This finding suggests that endocan release into the urine may differ from endocan release into the circulation due to impaired glomerular permeability caused by endothelial damage in HUS.

Lee et al.⁷ found that serum and urinary endocan levels were higher in adult patients with IGA nephropathy than in healthy controls. In the same study, plasma endocan levels did not differ significantly across CKD stages. However, patients with higher serum endocan levels had unfavorable renal outcomes. Urinary endocan levels were also higher in patients with poor renal function. In another study of adult patients, plasma endocan concentrations were significantly higher in CKD patients than in controls. They became progressively higher throughout the CKD stages. Plasma endocan concentrations were negatively correlated with eGFR and positively correlated with high-sensitivity CRP.⁹ As we did not have any patient with CKD as a result of HUS, we could not make an evaluation to determine the relation of endocan and the presence of CKD in children with HUS.

Since inflammation and endothelial dysfunction are involved in the pathogenesis of AKI, it has been assumed that elevated serum endocan levels may reflect renal dysfunction in this patient group.⁴ In our study, stage III AKI was detected in 10 of 15 patients in Group 1. The mean serum endocan level was significantly higher in 10 patients with AKI III than in the other five patients with AKI I and II ($P<0.05$). Furthermore, serum endocan levels were positively correlated with AKI stages ($r=0.59$, $P<0.05$). This finding suggests that serum endocan level may be used to determine patients with high AKI stage during the active stage of HUS.

Rahmania et al.²⁴ evaluated the predictive value of endocan in the requirement of KRT in a group

of intensive care patients with AKI. They found higher serum endocan and creatinine levels in those who required RRT. In our study, KRT was needed in 8 of 15 patients in the active disease group (Group 1). There was no significant difference in serum and urinary endocan levels between the patients who needed KRT and those who did not. This difference may result from the sample differences since our sample did not include KRT patients requiring intensive care.

In Group 1, the serum and urinary endocan levels did not show a statistically significant correlation with the clinical severity score ($P>0.05$). These findings may be explained by the small number of patients included in the study and the low mean clinical severity score (2.20 ± 1.56) in Group 1.

The clinical diagnosis of HUS is based on the triad of anemia (hemoglobin <8 g/dL), thrombocytopenia (platelets $<150 \times 10^9/L$), renal dysfunction, including hematuria, proteinuria, and an elevated serum Cr level.²⁵ Elevated white blood cell (WBC) count (greater than 20,000 per mm^3), and hematocrit (greater than 23%) are other risk factors for mortality and long-term complications from HUS.²⁶ In our study, when all groups were analyzed together, mean urinary endocan levels showed significant positive correlations with WBC count, and with lactate dehydrogenase, blood urea nitrogen, and creatinine levels, and significant negative correlations with hemoglobin level, platelet count, and eGFR. Taken together, these findings indicate that several key laboratory parameters relevant to the diagnosis and follow-up of HUS are closely associated with urinary endocan levels.

This study has certain limitations. One significant limitation is the small sample size, which was a result of the rarity of HUS cases. Therefore, larger-scale, multicenter clinical studies are needed to provide more meaningful insights into the applicability of endocan as a marker in the diagnosis, follow-up and prognosis of HUS patients.

In conclusion, urinary endocan levels were significantly higher in HUS patients in the active phase. The urinary endocan level may provide more valuable information than the serum endocan level in the clinical follow-up of patients with HUS. Also, serum endocan level may be used to evaluate AKI level during the active stage of HUS. We believe this study will guide future research investigating the long-term prognostic value of endocan in patients with HUS and exploring its potential as a target marker for the treatment and diagnosis of HUS.

Ethical approval

The study was approved by Clinical Research Ethics Committee of Atatürk University Faculty of Medicine (date: September 30, 2021, number: 2021/06-55). Written consent was obtained from the parents of the patients and healthy controls.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: MAG, MC; data collection: MAG; analysis and interpretation of results: MAG, MC; draft manuscript preparation: MAG, MC. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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