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Original Article

Urine microscopy and neutrophil–lymphocyte ratio are early predictors of acute kidney injury in patients with urinary tract infection

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KEYWORDS
Acute kidney injury; kidney injury molecule-1; Neutrophil–lymphocyte ratio; Quantitative urine microscopy score; Urinary tract infection

Abstract *Objective:* Urinary tract infection (UTI) is a common cause of morbidity and hospitalisation in the population worldwide. Upper UTI is indolent and causes subclinical acute kidney injury (AKI) resulting in preventable cause of scarring of renal parenchyma. We explored urinary and serum levels of kidney injury molecule-1 (KIM-1), haematological parameters and quantitative urine microscopy parameters to predict kidney injury.
Methods: Neutrophil–lymphocyte ratio (NLR) is obtained by dividing absolute neutrophil count with absolute lymphocyte count. Quantitative urine sediment microscopy was performed and correlated with clinical, biochemical and haematological findings to predict AKI in patients with UTI. Quantitative ELISA was performed for serum and urine levels of KIM-1. Seventy two adult patients with UTI were enrolled, 45 of whom had AKI while 27 were in the non-AKI group.
Results: NLR ($p=0.005$) and renal tubular epithelial cell-granular cast score in quantitative urine microscopy ($p=0.008$) are strong predictors of AKI in patients with UTI while rest of

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quantitative urine microscopy parameters and serum and urinary levels of KIM-1 molecule were not found to be useful in prediction of AKI.
Conclusion: NLR in haemogram is a novel and useful biomarker for predicting AKI in patients with UTI.

1. Introduction

Urinary tract infection (UTI) is the second most common infectious disease in the community. About 150 million people around the world are diagnosed with UTI per annum, among which 35% are hospital acquired infection [1,2]. The incidence of UTI in adult men up to the age of 65 years is extremely low. Women in this age group, however, more commonly experience UTI. Incidence of UTI in patients more than 65 years old increases dramatically for both genders, with a progressive decrease in female to male ratio [3]. Many microorganisms cause UTI, among which gram-negative bacilli are the most common. Gram-positive cocci play a lesser role in UTIs but Staphylococcus is an exception [4,5]. Bacteria gain access to the bladder through the urethra and the ascent of bacteria from the bladder is the most common cause for the acute kidney injury (AKI) in patients with UTI [4,5]. Patients with upper UTI have a higher risk of AKI than those with lower UTI [6].

AKI is a common disorder in hospitalized patients, and its incidence is increasing day by day [7] and has an important modifying effect on mortality, kidney recovery and health resource utilization [8]. AKI affects somewhere between 2% and 18% of all hospitalized patients and as many as 25%—30% of patients in the intensive care unit [9]. Kidney disease improving global outcomes (KDIGO), has defined AKI as a condition in which "increase in serum creatinine by 50% within 7 days, or increase in serum creatinine by 0.3 mg/dL within 2 days, or urine output $<$0.5 mL/kg/h for 6—12 h" [10]. KDIGO guideline for AKI using serum creatinine was used as our inclusion criteria.

Diagnostic approach of AKI has primarily revolved around serum creatinine over several decades. Innovative approaches for early prediction and stratification are essential to advance the identification of patients at the risk of AKI [11]. Hence early diagnosis of AKI could facilitate early initiation of supportive care and trials of novel therapeutic measures [12]. Various biomarkers are demonstrated for early diagnosis of AKI [13]. Urinary kidney injury molecule-1 (uKIM-1) is a marker of epithelial injury of renal tubules. Different uKIM-1 levels are associated with various degrees of renal injury.

Urine analysis is a simple and widely available tool for renal disease evaluation. The presence of renal epithelial cells, renal epithelial cell cast and granular cast are the conventional markers of acute tubular necrosis. In this study, utility of urine sediment examination is approached in a quantitative fashion for diagnosing the causes of AKI. The utility of urine sediment score derived from number of renal tubular epithelial casts (RTECs) and granular casts can differentiate pre-renal AKI from acute tubular necrosis (ATN) [14,15]. This study attempts to compare the relative utility of traditional urine analysis and the emerging biomarker uKIM-1 for early detection of AKI. Urine microscopy is one of the simplest investigations for evaluation in differential diagnosis of AKI. Its role in predicting renal outcomes has not been well described.

Neutrophil—lymphocyte ratio (NLR) has greater significance in predicting systemic infections. Since the NLR can be measured in almost all laboratories, it serves as a simple, economical, easy parameter in analysis of inflammation. NLR has a correlation in dimercaptosuccinic acid (DMSA) defect in paediatric patients with UTI [16]. NLR predicts AKI in paediatric patients with great sensitivity and specificity [17].

Hence we attempted to test our hypothesis that simple diagnostic tools like NLR, serum and urine KIM-1 levels as well as systematic urine sediment scoring system can predict AKI.

2. Patients and methods

2.1. Study design

The present study was a cross sectional study, conducted in the Department of Pathology, Jawaharlal Institute of Postgraduate Medical education and Research (JIPMER), Puducherry, for a period of 1 year from January 2017 to December 2017. Study was approved by Institute Ethics committee (JIP/IEC/2016/1027). Ethical clearance was obtained as the study involved collection of venous blood and urine samples as well as following up the patient with clinical and biochemical parameters. Informed written consents were obtained from all patients under "more than minimal risk category" as per Indian Council of Medical Research 2017 guidelines which follow the Declaration of Helsinki guidelines according to the latest version in October 2013 at Fortaleza, Brazil.

2.2. Setting and participants

Seventy two consecutive patients were enrolled for the study after obtaining the informed ethical consents, among which 45 participants had UTI fulfilling criteria for AKI as per KDIGO 2012 guidelines. Remaining 27 participants with UTI did not have AKI. Serum creatinine level alone was used to define and assess the severity of AKI as well as for statistical analysis. The values of serum creatinine and urine output correlated with the severity of AKI.

Adult patients with UTI and age more than 18 years old only were included in the study. Individuals with prior

kidney transplant, end stage kidney disease or chronic dialysis therapy, prior renal replacement therapy during index hospitalization, and catheter associated UTI were excluded from the study to avoid confounding factors for urine microscopy and urine KIM value assessment.

2.3. Study definitions

AKI was defined based on KDIGO 2012 guidelines [10] and UTI was defined by clinical features and presence of more than 5 pus cells in high power field of urine sediment microscopy [18].

2.4. Study protocol and data sources

Clinical data including patient demographics (age and sex), history of diabetes mellitus, hypertension, and base line laboratory findings such as serum creatinine were obtained from medical records and hospital information system. Blood and urine samples were collected from each patient at the time of enrolment.

2.5. Urine microscopy preparation

A fresh, midstream clean catch urine sample was collected in a sterile screw capped bottle. An aliquot of 15 mL urine was centrifuged at 2000 rpm for 5 min. Urine supernatant was removed but 0.5 mL of supernatant was retained in the tube and the pellet was resuspended with a pipette. Samples were processed immediately and analysed within 4 h of sample collection.

One drop (about 25 μL) of sediment was transferred on to a microscopic glass slide and a cover slip was placed over it. The slide was examined under a standard light microscope and a phase contrast microscope at 10×, 20× and 40×. RBCs, pus cells, renal tubular epithelial (RTE) cells, epithelial cells, RTE cell casts, red cell casts, white cell casts, hyaline casts, granular casts and microorganisms were identified based on standard definition and their numbers were recorded [14]. The urinary scoring system by Perazella et al. [14] (Table 1) was used for subsequent analysis. All the investigators who performed microscopy were blinded to the clinical history and outcome.

2.6. Serum and urine KIM-1

Two millilitres of blood was collected and transferred into a non-vacuum plastic tube without any anticoagulants for serum KIM-1. Blood was centrifuged after clot formation at 3000 rpm for 5 min and the serum and the urine supernatant for urine KIM-1 was stored at −80°C for batched analysis. ELISA was done with Human Kidney Injury Molecule-1 ELISA Kit (Bioassay Technology Laboratory, Shanghai, China).

Results were calculated from the standard curve constructed by plotting the average optical density for each standard on vertical Y axis against the concentration on the X axis. The curve was plotted and results were calculated by using Microsoft Excel software.

Table 1 RTE cell-granular cast scoring system[a].

Granular casts (per LPF)			
RTE cells (per HPF)	0 (0 point)	1—5 (1 point)	≥6 (2 points)
0 (0 point)	0	1	2
1—5 (1 point)	1	2	3
≥6 (2 points)	2	3	4

HPF, high power field; LPF, low power field; RTE, renal tubular epithelial.
[a] Adapted from Perazella et al. [14].

2.7. NLR

Complete haemogram was performed in Sysmex XT-2000i (Sysmex Corporation, Kobe, Japan) from ethylene diamine tetra acetic acid anticoagulated blood and NLR was obtained by dividing absolute neutrophil count with absolute lymphocyte count.

2.8. Statistical analysis

Continuous variables were summarized as mean (standard deviation [SD]) or median (inter-quartile range) based on normality. Categorical variables were summarized as frequency with proportions. Association of continuous variables that satisfied normality was compared between AKI and non-AKI group using independent *t*-test. Non-normally distributed data were compared using Mc-Nemar test. Association of various categorical variables between AKI and non-AKI groups were assessed using Chi-square test. A *p*-value <0.05 was considered as statistically significant. The agreement between techniques (light microscopy and phase contrast microscopy) was analyzed with kappa statistics. Similarly, agreement between methods for confirming AKI (serum creatinine and urine microscopy scoring system) was assessed with kappa statistics. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy, *etc*. were summarized as percentages with 95% confidence interval (CI). Association of clinical and laboratory markers with the binary presence/absence of AKI were assessed by stepwise multivariate logistic regression. Odds ratio and CI were calculated with 95% confidence. Variables having a *p*-value <0.05 in univariate analysis were considered for multivariate logistic regression. The sensitivity and specificity of NLR in predicting AKI in patients with UTI were obtained from receiver operating characteristic (ROC) curve. All the statistical analysis was performed by IBM SPSS Statistics Ver. 20.0 (IBM SPSS Inc., Chicago, IL, USA) and Open-Epi version 3.01 Software (Open source, MIT, Atlanta, GA, USA).

3. Results

3.1. Age and gender

Seventy two consecutive study participants were enrolled in the study. Among 72 study participants, 45 had UTI with AKI and their mean (SD) age was 53.4 (SD: 14.8) years. In this group, 58% were male and 42% were female. Mean (SD)

age of 27 UTI patients in the non-AKI group was 52.2 (SD: 12.4) years, with 41% male and 59% female patients. There was no statistical significance in the age ($p=0.71$) and gender ($p=0.16$) of patient in two groups (Table 2).

3.2. Serum creatinine

Patients were followed for 5 days of hospital admission and their serial rises in creatinine were noted and analyzed statistically by using independent *t*-test. In the study group with AKI, follow-up data of all 45 patients could not be collected as they had left the hospital against medical advice before complete recovery. Hence, the follow-up data on Days 3 and 5 were available only for 36 patients on Day 3 and 35 patients on Day 5 in the AKI group. Similarly in the non-AKI group, of the 27 patients Day 3 follow-up data were available for 21 patients and Day 5 data were available for 17 patients. As expected the *p*-value shows the higher significance ($p<0.001$) of rise in creatinine level during AKI (Table 3). No patient developed septicaemia and intensive care was not required.

Table 3 Significance of rise in creatinine in AKI.

Creatinine	Mean±SD		*p*-Value
	AKI ($n=45$)	No AKI ($n=27$)	
Day 1	3.8±3.1	1.14±0.5)	<0.001
Day 3[a]	3.22±2.4	1.10±0.04	<0.001
Day 5[b]	2.83±1.2	1.18±0.4	0.001

AKI, acute kidney injury; SD, standard deviation.
[a] AKI ($n=36$); no AKI ($n=21$).
[b] AKI ($n=35$); no AKI ($n=17$).

3.3. Urine microscopy score

RTE cell-granular cast score shows greater significance ($p = 0.008$) for predicting AKI in patients with UTI. A microscopy score greater than or equal to 2 (≥2) is suggestive of AKI (Table 4). Out of the 45 patients in group 1, AKI was identified in 31 (68.9%) by RTE-granular cast scoring system. Among the 27 (37.5%) patients in UTI group without AKI, the RTE-granular cast scoring system identified 26 (96.3%) as not having AKI. Kappa statistics across the binary variables in the test group was found to be 0.59, which indicates that there was a moderate agreement between RTE-granular cast scoring system and serum creatinine. RTE-granular cast scoring system has a sensitivity of 68.9% (95% CI: 54.3–80.5) and specificity of 96.3% (95% CI: 81.7–99.3). PPV and NPV were 96.9% (95% CI: 84.3–99.5) and 65% (95% CI: 49.5–77.9) respectively, for the prediction of AKI in patients with UTI. The score has a diagnostic accuracy of 79.2% (95% CI: 68.4–86.9). The likelihood ratio of positive test was 18.6 (95% CI: 2.5–135.9).

Table 4 RTE cell-granular cast score (Perazella scoring system).

RTE-granular cast score	*n* (%)	AKI, *n* (%)	No AKI, *n* (%)	*p*-Value
<2	54 (100)	29 (53.7)	25 (46.3)	0.008
≥2	18 (100)	16 (88.9)	2 (11.1)	

AKI, acute kidney injury; RTE, renal tubular epithelial.

3.4. Serum and urine KIM-1

Both serum and urine KIM-1 showed a normal distribution of data. However, both serum and urine levels of KIM-1 could not distinguish patients with and without AKI and results were not statistically significant (Table 5). The *p*-value for serum and urine KIM-1 were 0.85 and 0.75, respectively. ELISA could not be done in three serum samples due to visible lipemia after storage and thawing of the sample. Since lipemic, icteric and haemolysed samples affect the optical density and test values, these samples were not processed and considered for analysis.

3.5. NLR

NLR on first day of haemogram sample, predicted AKI in patients with UTI. NLR was expressed as median (inter-quartile range). Median (inter-quartile range) for NLR in AKI group was 7.2 (4.1–10.8) and in the non-AKI group, it was 3.2 (2.3–6.1). NLR was found to significantly predict AKI ($p = 0.005$). ROC curve was designed for NLR to identify sensitivity and specificity in prediction of AKI (Fig. 1). AUC to predict AKI using NLR was 0.704, with 95% confidence and CI of 0.574–0.835. The sensitivity and the specificity were 72.1% and 65.9% respectively using cut-off of 4.2 for NLR to predict AKI. If the NLR is considering as a screening tool, then 3.4 can be taken as the cut-off with a high sensitivity (Table 6). NLR with a cut-off with 4.2 is considered in this

Table 2 Basic demographic data of patients in study group.

Characteristics	AKI ($n=45$)	No AKI ($n=27$)	*p*-Value
Age, year, mean±SD	53.4±14.8	52.2±12.4	0.71
Male sex, *n* (%)	26 (58)	11 (41)	0.16
Female sex, *n* (%)	19 (42)	16 (59)	0.16
ANC, median (IQR for ANC)	8900 (7400–12 180)	7350 (5825–10 140)	0.14
ALC, median (IQR for ALC)	1400 (1100–2005)	1820 (1520–2430)	0.04
Diabetes, *n* (%)	22 (48.9)	14 (51.9)	0.81
Hypertension, *n* (%)	6 (13.3)	5 (18.5)	0.55

AKI, acute kidney injury; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; IQR, inter-quartile range; SD, standard deviation.

Table 5 Kidney injury molecule (KIM)-1 in patients with and without AKI.

KIM-1	AKI ($n=45$), mean±SD	No AKI ($n=27$), mean±SD	p-Value
Urine	3.22±1.4	3.33±1.3	0.75
Serum	2.91±1.5	2.98±1.2[a]	0.85

AKI, acute kidney injury; KIM-1, kidney injury molecule; SD, standard deviation.
[a] No AKI ($n=24$).

study for the prediction of AKI in patients with UTI. NLR shows statistically significant association with AKI ($p = 0.003$) with a relative risk of 1.77. A total of 45 (62.5%) UTI patients were diagnosed with AKI using serum creatinine levels as per KDIGO 2012 guidelines. Out of the 45 patients in group I, AKI was identified in 31 (68.9%) by NLR. Among the 27 (37.5%) patients in the non-AKI group, the NLR could independently identify 18 (66.6%) as not having AKI (Table 7).

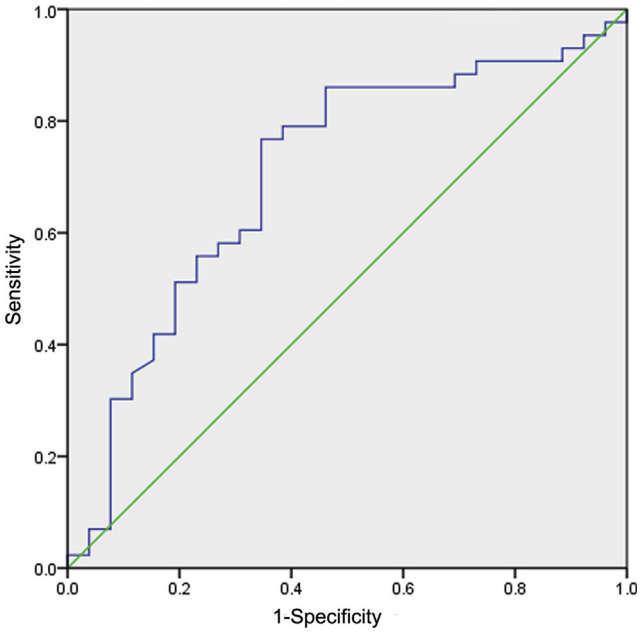

Figure 1 Receive operator characteristics curve of neutrophil—lymphocyte ratio to predict acute kidney injury.

4. Discussion

The prevalence of UTI in India is increasing due to higher incidence of co-existing morbidities such as diabetes mellitus, urolithiasis and iatrogenic causes such as catheterization [19,20]. Infection in the lower urinary tract ascends to the kidney parenchyma directly or through haematogenous route causing AKI. In some instances, AKI may be caused indirectly due to reflux of urine from lower urinary tract. AKI assessment is delayed due to high residual functional capacity of kidney and non-specific symptomatology thereby leading to delay in the diagnosis. This can result in permanent residual scarring of the kidney. Hence we attempted to identify simple diagnostic tools to predict AKI in the patients with UTI. Urine microscopy is a simple but often neglected tool which if performed sincerely can be useful in predicting renal dysfunction. In our study, we adopted the scoring system of Perazella et al. [14] who advocated the role of renal tubular epithelial cell-granular cast in prediction of AKI.

In our study, from urinalysis we found that RTE-granular cast score could predict AKI in patients with UTI. In univariate analysis, the p-values of RTE-granular casts score was 0.008. Subsequently these parameters were studied for agreement statistics using serum creatinine as the gold standard for predicting AKI. Renal tubular epithelial cell-granular cast (RTE-granular cast) scoring system showed moderate agreement with serum creatinine levels with a Kappa score of 0.59 to predict AKI in patients with UTI. In our study, the sensitivity and specificity of RTE-granular cast score in predicting AKI was 68.9% and 96.3%, respectively. Positive predictive value was 96.9% while the negative predictive value was 65% in the prediction of AKI in patients with UTI. The results were partially similar to that of Perazella et al. [14] who had a sensitivity of 73% and specificity of 75%. In our study, the specificity of RTE-granular cast score was much higher in predicting AKI in patients with UTI. Positive predictive value in our study was 96.9% in comparison with 100% in the study by Perazella et al. [14], while the negative predictive value in our study was much lesser, constituting 65% in comparison with 91% in the study by Perazella et al. [14]. The difference is most likely due to the variation in sample size. The utility of RTE-granular cast in predicting renal tubular injury and sepsis induced AKI is also described in other studies from Lakhmir Chawla et al. [21] and several other authors [8,14,15].

In our study, we did not find significant association with either urinary or serum levels of KIM-1 molecule with renal dysfunction. All the patients in our study group with AKI had significant recovery of serum creatinine and renal function within 5 days after diagnosis and administration of appropriate treatment. Thus our results are different from the studies from Vaidya et al. [12] and several other authors [22—26]. However, Petrovic et al. [27] have highlighted that urine and serum KIM-1 levels are not predictive of AKI. KIM-

Table 6 ROC values for neutrophil—lymphocyte ratio.

Cut-off threshold	Sensitivity (%)	Specificity (%)	AUC	p-Value
3.4	86.0	53.8	0.704 (95% CI: 0.574—0.835)	0.005
4.2	72.1	65.9		
6.9	51.2	80.8		

AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

Table 7 Association between serum creatinine and NLR.

Variables	Serum creatinine, *n* (%)		NLR total, *n* (%)	Relative risk	*p*-Value
	AKI	No AKI			
NLR				1.77	0.003
AKI present (≥4.2)	31 (77.5)	9 (22.5)	40 (100)		
AKI absent (<4.2)	14 (43.8)	18 (56.2)	32 (100)		
Serum creatinine total	45 (62.5)	27 (37.5)	72 (100)		

AKI, acute kidney injury; NLR, neutrophil—lymphocyte ratio.

1 levels in urine have been attributed as a prognostic parameter to predict poor outcome in patients with AKI. However, in our study, we could not validate the prognostic aspect due to lack of long-term follow-up. However, within the duration of the first 5 days of treatment and monitoring of our patients, we found that all of them had significant recovery of serum creatinine and renal function. Thus, it is possible that in our study, urine and serum KIM-1 levels did not have any prognostic significance as we did not have poor outcome patients, with the limitation of smaller sample size and lack of long-term follow-up.

In our study, NLR was a significant and an independent predictor of AKI. NLR had a cut-off value of 4.2 with an area under the curve of 0.704 (95% CI: 0.574—0.835) having the maximum sensitivity and specificity of 72.1 and 65.9 respectively to predict AKI in patients with UTI. Our results on the value of NLR were similar to the results of Yilmaz et al. [17]. However, we did not find any other reference on the value of absolute lymphocyte count having a predictive value on AKI. In Pearson correlation analysis, there was moderate correlation ($r=0.482$, $p=0.01$) between NLR and serum creatinine in non-AKI group, but there is a high correlation ($r=0.678$, $p<0.001$) between NLR and serum creatinine in AKI group.

Our study has validated the significance of a systematic scoring system for urine microscopy with the RTE-granular cast score developed by Perazella et al. [14], having independent diagnostic and predictive value in the detection of AKI in patients with UTI. Our study also highlights the significance of NLR with a cut-off value of 4.2, which is a novel tool in prediction of AKI.

The limitation of the study is the lack of long-term follow-up, which precludes us from assessing the prognostic value of serum and urine KIM-1 levels in our subset of patients. Another limitation is the relatively smaller sample size, but it is also due to rigid inclusion and exclusion criteria.

RTE-granular cast score with a cut-off of two and NLR are potentially useful and inexpensive tools in the diagnosis of AKI in patients with UTI. The findings in our study, if analyzed and validated in a larger cohort, shall probably be helpful in detection of AKI in remote and under-privileged settings and in developing countries where expensive resources may not be readily available.

Prediction of AKI is a critical requirement not only in the setting of UTI, but also in several patients with both neoplastic and non-neoplastic conditions. Acute tubular necrosis is an important and common cause of AKI. We have not studied the diagnostic role of urine microscopic scoring systems, serum and urine KIM-1 levels as well as NLR in a setting of acute tubular necrosis as renal biopsies were not assessed in our study. Another major potential application for prediction of AKI in immediate and long-term outcome will be in patients who undergo nephrectomy for malignancies [28]. Urine microscopy scoring systems, NLR as well as serum and urine KIM-1 levels may be extremely useful and it needs to be studied and validated in different clinical settings both in neoplastic and non-neoplastic conditions [29—31].

5. Conclusion

The study validates the RTE-granular cast score as an independent predictor and diagnostic tool in the detection of AKI in patients with UTI. Urine and serum KIM-1 did not have any role in the diagnosis or prediction of AKI in a setting of UTI. The prognostic value of the same could not be assessed in our study, due to the lack of long-term follow-up in our patients. NLR was found to be a novel and independent predictor of AKI in patients with UTI.

Author contributions

Study concept and design: Sreerag Kana, Rajesh Nachiappa Ganesh, Deepanjali Surendran, Rajendra G. Kulkarni, Ravi Kishore Bobbili, Jose Olickal Jeby.
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Conflicts of interest

The authors declare no conflict of interest.

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