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NEPHROLOGY - ORIGINAL PAPER

Low prognostic nutritional index associated with cardiovascular disease mortality in incident peritoneal dialysis patients

Fenfen Peng[1] · Wenjing Chen[1] · Weidong Zhou[1] · Peilin Li[1] · Hongxin Niu[1] · Yihua Chen[1] · Yan Zhu[1] · Haibo Long[1]

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Abstract
Purpose The prognostic nutritional index (PNI), a variable based on serum albumin concentration and total lymphocyte count in peripheral blood, is reported as a predictor of mortality in a variety of malignant tumor population. This study is aimed to evaluate whether PNI has prognostic value in patients on peritoneal dialysis (PD).
Methods This was a single-center, retrospective observational cohort study conducted in incident PD patients from January 1, 2006 to June 30, 2014, and followed until June 30, 2015. The associations of PNI levels with mortality were evaluated by Kaplan–Meier method and Cox proportional hazards models.
Results A total of 345 patients were included in this study. Median PNI level at baseline was 40.7 (range: 18.8–75.5) for all patients. During follow-up, 59 (17.1%) died during follow-up, among which 31 (52.5%) were due to cardiovascular diseases (CVD). In crude analysis, the patients with low PNI had a significant increase risk of CVD and all-cause mortality [hazard ratio (HR) 3.07, 95% confidence interval (CI) 1.51–6.25 and HR 2.18, 95% CI 1.28–3.72, respectively)]. After adjusting age, Davies comorbidity score, hemoglobin and leukocytes, the patients with low PNI still had a significant increased risk of CVD mortality (HR 2.37, 95% CI 1.10–5.12). However, there was no significant difference in risk of all-cause mortality (HR 1.72, 95% CI 0.97–3.06).
Conclusions Low PNI at initiation of PD was independently associated with an increased CVD mortality.

Keywords Cardiovascular disease · Prognostic nutritional index · Peritoneal dialysis · Mortality

Introduction

Peritoneal dialysis(PD) has been a well-accepted dialysis modality in patients with end-stage renal disease in the past decades [1]. According to various national and regional studies, the prevalence of the cardiovascular mortality remains high in patients on dialysis due to various risk factors [2, 3]. Protein-energy wasting (PEW), characterized by markedly decreased serum albumin levels, the presence of inflammation and oxidative stress and greater levels of protein breakdown than synthesis, is highly prevalent in PD patients [4]. Accumulating evidence indicates that PEW is an important predictor of mortality in these PD patients [5, 6]. Recently, International Society for Peritoneal Dialysis (ISPD) cardiovascular and metabolic guidelines in adult PD patients suggest nutritional status should be assessed within 6–8 weeks after commencement of PD for reducing the risk of cardiovascular disease (CVD) mortality [7]. Therefore, prevention and treatment of PEW form a crucial part in the management of PD patients. However, no single method is precisely indicative of PEW [8]. It was be cautiously and complicated evaluated by data combined from several parameters, including questionnaire, weight loss, body mass index and serum albumin. Therefore, identification of an accurate and simple prognostic indicator is warranted to supplement and recognize PD patients at high risk of mortality.

The prognostic nutritional index (PNI), a variable based on serum albumin concentration and total lymphocyte

Fenfen Peng, Wenjing Chen and Weidong Zhou have contributed equally to this study.

✉ Haibo Long
Longhb1966@163.com

[1] Department of Nephrology, Zhujiang Hospital of Southern Medical University, Guangzhou 510280, China

count in peripheral blood, was originally designed to assess perioperative immunonutritional and surgical risk in patients undergoing gastrointestinal surgery [9]. Recently, the prognostic value of the PNI has been validated in a variety of malignant tumor [10–14]. However, few studies have investigated the prognostic role of PNI in patients on PD. We hypothesized that immunonutritional status assessed by PNI is associated with poor survival in patients on PD. Therefore, the aim of this cohort study was to evaluate whether PNI has prognostic value in patients on PD patients after adjusting for potential confounding factors.

Methods

Participants

Patients were recruited from the PD center at Zhujiang Hospital of Southern Medical University from January 1, 2006 to June 30, 2014. The inclusion criteria for this study were all incident patients in our center and completed PD therapy for more than 3 months. Patients who aged <18 years old, referred from other PD centers, transferred from permanent hemodialysis, failed renal transplantation or refused to response were excluded from this study. The study was conducted in compliance with the ethical principles of the Helsinki Declaration and approved by the Human Ethics Committees of Southern Medical University.

Study protocol

This was a retrospective observational cohort study. Baseline demographic data included age, gender, blood pressure, primary cause of ESRD, a history of diabetes, hypertension, CVD and biochemical parameters data included leukocyte, lymphocyte, hemoglobin, serum albumin, serum creatinine, total cholesterol, triglycerides, corrected serum calcium, phosphorus and serum uric acid were collected during the first 1–3 months of PD. All parameters were measured in the center laboratory of our hospital. The PNI was calculated as 10 × serum albumin value (g/dl) + 0.005 × peripheral lymphocyte count (per mm3) [9]. Diagnosis of diabetes at the initiation of PD was based on diagnostic criteria from the American Diabetes Association [15]. Hypertension was recorded if the patient was taking antihypertensive drugs or had 2 separate blood pressure measurements ≥140/90 mmHg. Total Kt/V were calculated using PD Adequest software 2.0 (Baxter Healthcare Ltd). The Davies score assigns 1 point for each of the following conditions: ischemic heart disease (defined as prior myocardial infarction, angina, or ischemic changes on electrocardiogram), left ventricular dysfunction (defined as clinical evidence of pulmonary edema not due to errors in fluid balance, or history of congestive heart failure), peripheral vascular disease (includes distal aortic, lower extremity and cerebrovascular disease), malignancy, diabetes, collagen vascular disease and other significant pathology(e.g., chronic obstructive pulmonary disease) [16].

The primary outcome of this study was CVD mortality. The second outcome was all-cause mortality. CVD mortality was defined as death due to acute myocardial infarction, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, congestive heart failure, cardiac arrest, intracranial hemorrhage, cerebral infarction and peripheral vascular disease [17]. All of the patients were followed until cessation of PD, death or June 30, 2015.

Statistical analysis

The patients were stratified into two groups by PNI quartiles. The patients with first quartile PNI were defined as patients with low PNI (PNI ≤ 36.6), while patients with another three quartiles PNI level were defined as patients with high PNI (PNI > 36.6). Data were presented as mean ± standard deviations or median (inter-quartile range) for continuous variables and number (percentages) for categorical variables. The characteristic differences between two groups were tested by using the Student's *t* test, the nonparametric Mann–Whitney test, or the Chi-square test as where as appropriate. The correlations between PNI group with nutrition and inflammation parameters were assessed by Spearman rank correlation analysis. Kaplan–Meier method was used to calculate survival curves. Gray test was used to calculate survival, taking into account the competitive risks of drop out due to other causes than death. Cox proportional hazards regression was used to evaluate the association of PNI groups with CVD and all-cause mortality. Cox model assumptions were checked using Schoenfeld residuals. Statistical analyses were performed using SPSS, version 17.0 for Windows (SPSS Inc) and R. *P* values < 0.05 were considered statistically significant.

Results

Characteristics of patients

A total of 345 eligible incident PD patients were recruited in this study (Fig. 1), among which 5 patients were on automated PD. Conventional PD solutions (Dianeal 1.5, 2.5 or 4.25% dextrose, Baxter Healthcare, Guangzhou, China), Y-sets and twin-bag systems were utilized in continuous ambulatory PD patients. Baseline demographic and clinical characteristics of the cohort study categorized according to PNI value are given in Table 1. The primary cause of ESRD

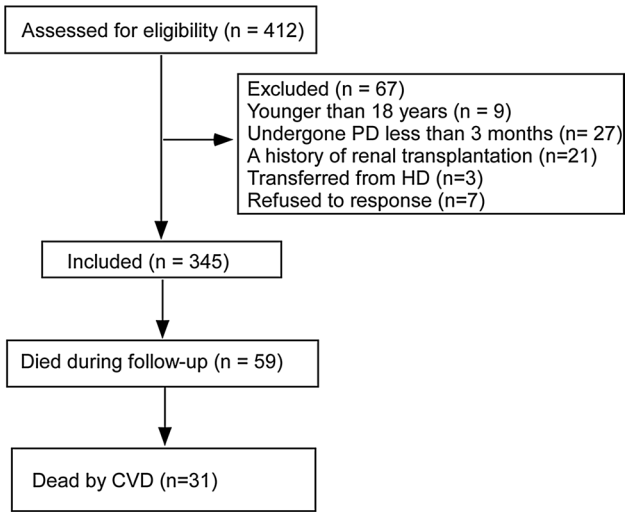

Fig. 1 Study flow, including patient enrollment and outcomes. Abbreviation *CVD* cardiovascular disease; *PD* peritoneal dialysis; *HD* hemodialysis

was glomerular disease (175, 50.7%), followed by hypertension (50, 14.5%) and diabetic nephropathy (17, 13.6%). Median PNI level at baseline was 40.7 (range: 18.8–75.5) for all patients. The patients with low PNI had a higher rate of cardiovascular disease, and hypertension, but a lower leukocyte, lymphocyte, albumin, hemoglobin and serum uric acid. Spearman rank correlation analyses indicated that PNI levels positively correlated with leukocyte, hemoglobin and serum uric acid (Table 2).

PNI and mortality

During median of 25.2 months (range: 3.1–108.8) follow-up period, 42 (12.2%) patients were transferred to hemodialysis, 19 (5.5%) patients received kidney transplantation, 32 (9.3%) patients were lost to follow-up, and the rest 193 (55.9%) patients were still followed-up at our PD center. A total of 59 deaths (17.1%) were recorded, among which 31 (52.5%) were caused by cardiovascular disease. Kaplan–Meier estimates of

Table 1 Patient baseline characteristics grouped by prognostic nutritional index

	Low PNI group $n = 86$	High PNI group $n = 259$	P value
Prognostic nutritional index	32.96 ± 3.44	43.78 ± 5.72	NA
No. of men/women	48/38	156/103	0.470
Age (years)	56.87 ± 13.45	48.81 ± 14.87	<0.001
Body mass index (kg/m^2)	23.36 ± 3.10	23.49 ± 3.52	0.822
Cardiovascular disease	24 (28.6%)	45 (16.6%)	0.015
Diabetes mellitus	25 (29.8%)	56 (20.7%)	0.083
Hypertension	44 (52.4%)	105 (38.7%)	0.027
Systolic BP (mmHg)	135.98 ± 15.23	136.42 ± 17.17	0.864
Diastolic BP (mm Hg)	77.36 ± 9.91	78.55 ± 10.35	0.855
Davies score			0.015
0	24 (30.4%)	133 (50%)	
1	27 (34.2%)	75 (28.2%)	
2	22 (27.8%)	45 (16.9%)	
>2	6 (7.6%)	13 (4.9%)	
Leukocytes (*10^9/L)	6.18 ± 2.03	7.06 ± 2.28	0.002
Lymphocyte (*10^9/L)	1.24 ± 0.46	1.86 ± 1.04	<0.001
Hemoglobin (g/L)	94.24 ± 17.53	104.13 ± 19.50	<0.001
Serum albumin (g/L)	26.77 ± 3.54	34.49 ± 4.18	< 0.001
Albumin-corrected calcium (mmol/L)	2.42 ± 0.22	2.38 ± 0.23	0.132
Serum phosphorus (mmol/L)	1.56 ± 0.64	1.76 ± 0.71	0.062
Total cholesterol (mmol/L)	4.74 ± 1.31	4.71 ± 1.15	0.885
Total triglycerides (mmol/L)	1.34 ± 0.81	1.53 ± 0.91	0.218
Total Kt/V	1.98 ± 0.71	2.11 ± 0.64	0.289
Serum uric acid (μmol/L)	402.12 ± 115.40	443.99 ± 114.12	0.013
Serum creatinine (μmol/L)	744.23 ± 320.16	801.57 ± 270.97	0.106

Abbreviations *BP* blood pressure; *PNI* prognostic nutritional index

Table 2 Correlation between prognostic nutritional index group and parameters of anemia, nutrition and inflammation

	PNI group	Leukocytes	Hemoglobin	Phosphorus	Uric acid	Creatinine	Total cholesterol	Triglycerides
Leukocytes	0.17**	1	0.07	0.02	0.11	−0.05	−0.01	0.17*
Hemoglobin	0.22**	0.07	1	−0.05	−0.01	−0.15**	0.14*	−0.02
Phosphorus	0.11	0.02	−0.05	1	0.30**	0.42**	0.01	0.04
Uric acid	0.15*	0.11	−0.04	0.30**	1	0.36**	−0.14	0.04
Creatinine	0.09	−0.05	−0.15**	0.45**	0.36**	1	−0.07	−0.18**
Total cholesterol	−0.01	−0.01	0.16*	0.01	−0.14	−0.07	1	0.24**
Triglycerides	0.08	0.17*	−0.02	0.04	0.04	−0.18**	0.24**	1

** Correlation is significant at 0.01 level (two-tailed), * Correlation is significant at 0.05 level (two-tailed)

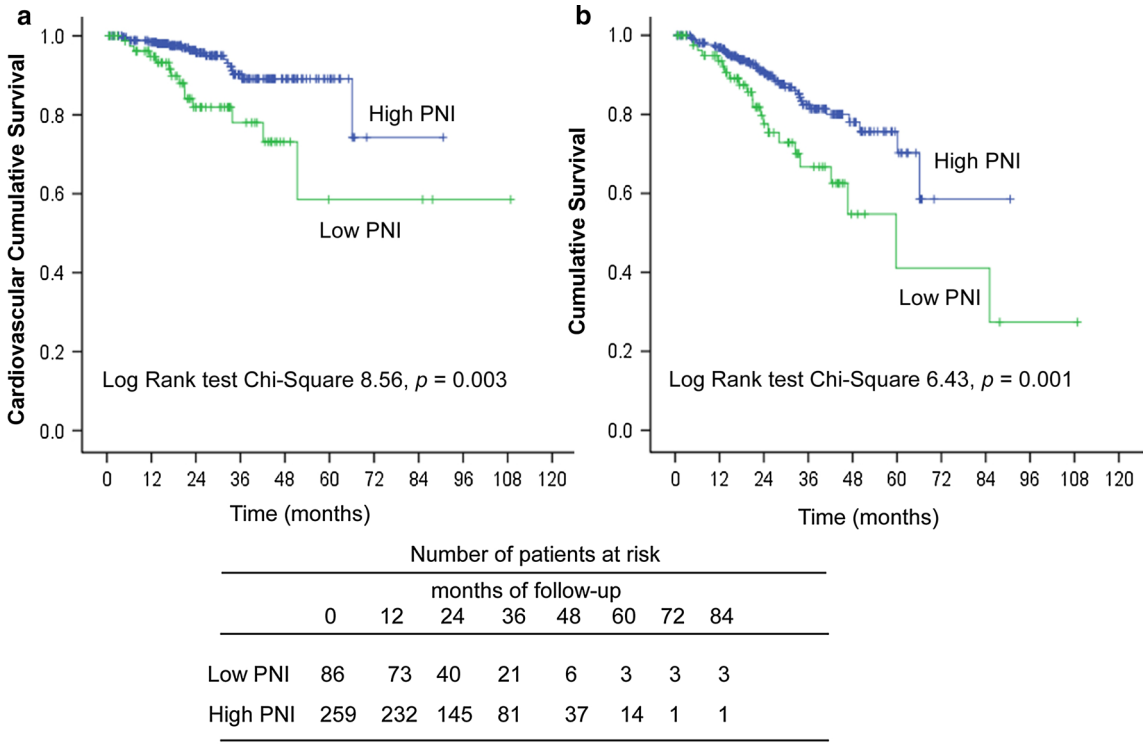

Fig. 2 Crude analyses of cardiovascular disease and all-cause mortality between PNI groups. Kaplan–Meier estimates of **a** cardiovascular and all-cause **b** mortality

CVD and all-cause mortality for patients in two PNI groups are shown in Fig. 2. At the end of 1, 3 and 5 years, cardiovascular cumulative survival rate was 84, 75, 60% in patients with low PNI, 96, 89, 78% in patients with high PNI, respectively (log-rank = 8.56, $P = 0.003$); cumulative survival rate was 80, 61, 48% in patients with low PNI, and 91, 78, 58%, in the patients with high PNI, respectively (log-rank = 6.43 $P = 0.011$); compared to the patients in high PNI, the all-cause and CVD mortality was significantly higher in the patients with low PNI. Furthermore, when accounting for drop out due to other causes as competing risks, the risk of mortality was significantly increased in the patients with low PNI level (Gray test 5.78, $P = 0.016$) (Fig. 3).

The associations of PNI level with CVD and all-cause mortality are listed in Table 3. In crude analysis, the patients with low PNI had a significant increase risk of CVD and all-cause mortality [hazard ratio (HR) 3.07, 95% confidence interval (CI) 1.51–6.25, $P = 0.002$ and HR 2.18, 95% CI 1.28–3.72, $P = 0.004$, respectively)]. After adjusting age, Davies comorbidity score, hemoglobin and leukocytes, the patients with low PNI still had a significant increased risk of CVD mortality (HR 2.37, 95% CI 1.10–5.12, $P = 0.029$).

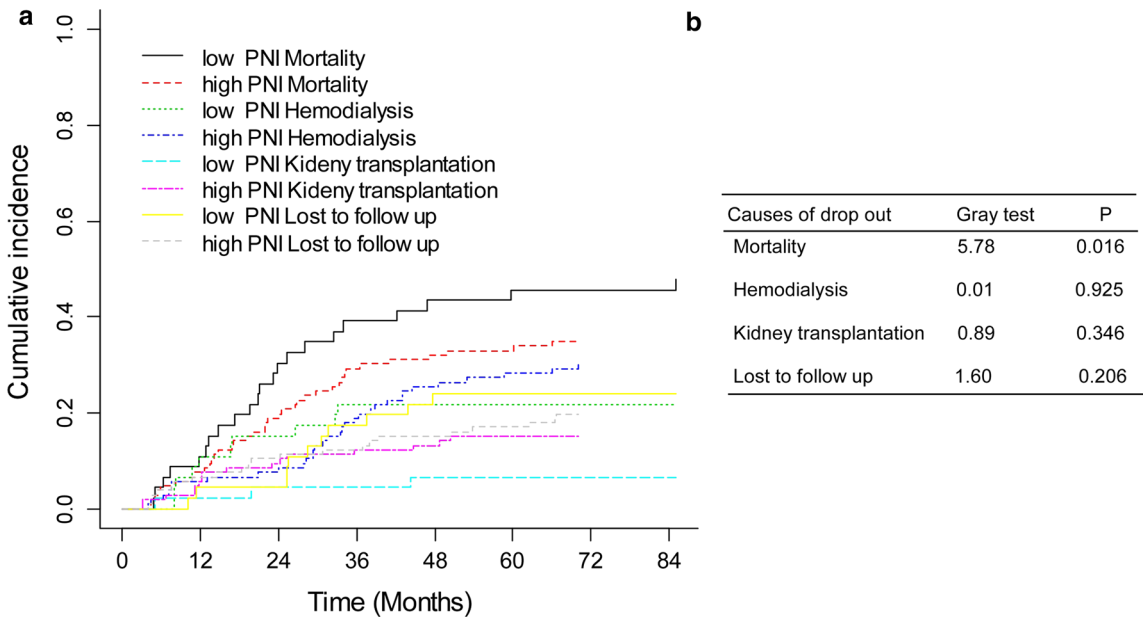

Fig. 3 All the cumulative incidence of drop out causes between PNI groups

Table 3 Relationship between prognostic nutritional index and CVD and all-cause mortality

	CVD mortality HR (95% CI), *P*	All-cause mortality HR (95% CI), *P*
Univariate		
Low PNI (vs) high PNI	3.07 (1.51, 6.25), 0.002	2.18 (1.28, 3.72), 0.004
Age	1.05 (1.03, 1.08), <0.001	1.05 (1.03, 1.07), <0.001
Sex	0.70 (0.34, 1.42), 0.321	1.07 (0.63, 1.80), 0.813
Davies	2.42 (1.71, 3.42), <0.001	2.05 (1.06, 2.63), <0.001
Leukocytes	1.18 (1.04, 1.35), 0.012	1.14 (1.03, 1.25), 0.010
Hemoglobin	0.99 (0.97,1.004), 0.135	0.99 (0.98, 1.004), 0.168
Uric acid	1.00 (0.99, 1.001), 0.668	1.00 (0.99, 1.001), 0.384
Multivariate		
Low PNI (vs) high PNI	2.37 (1.10, 5.12), 0.029	1.72 (0.97, 3.06), 0.063
Age	1.03 (1.01, 1.07), 0.036	1.03 (1.01, 1.05), 0.010
Sex	–	–
Davies	1.94 (1.29, 2.90), 0.001	1.67 (1.25, 2.22), <0.001
Leukocytes	1.18 (1.03, 1.35), 0.019	1.12 (1.01, 1.24), 0.025
Hemoglobin	0.99 (0.96, 1.01), 0.288	0.99 (0.97, 1.01), 0.238
Uric acid	–	–

Abbreviations *CVD* cardiovascular disease; *PNI* prognostic nutritional index; *HR* hazard ratio

However, there was no significant difference in risk of all-cause mortality (HR 1.72, 95% CI 0.97–3.06, $P = 0.063$).

Discussion

In this contemporary cohort of 345 adult incident PD patients, we found that lower PNI levels were associated with comorbidities and impaired immunonutritional status, including lower serum albumin, lower hemoglobin, lower leukocytes, lower lymphocytes and lower serum uric acid. Compared with patients with a PNI > 36.6 as the reference, the CVD and all-cause mortality risk were increased. The CVD mortality risk of a lower PNI persisted after adjustment for potential confounders, while the all-cause mortality risk of a low PNI nullified. Therefore, PNI may represent a novel biomarker for PEW and predicting CVD mortality in PD patients.

There are various indicators that reveal nutrition status but lacking an ideal standard and simple marker. The PNI,

which bases on serum albumin and lymphocyte count, has been demonstrated as a prognostic factor in various malignant tumors [12]. A low PNI level means a decrease in albumin and or lymphocytes. Serum albumin is an important marker of the nutritional status and inflammation or hydration status and has been documented to be related to the survival in PD patients [18]. Hypoalbuminemia is caused by malnutrition combined with inflammation or hydration status usually in dialysis patients and associated with a reduced quality of life [19]. The result from Canada-USA Peritoneal Dialysis Study Group showed that 1 g/L increase in serum albumin is associated with 6% decrease in mortality [5]. Meanwhile, higher serum albumin can stabilize the circulating levels of inflammatory cytokines and oxidative stress markers [20]. Therefore, lower albumin may suggest impaired immunonutritional status.

The other aspect of PNI, the absolute lymphocyte count, a malnutrition marker, initiates cytotoxic immune response. Lower percentage of lymphocytes is also reported to be associated with all-cause mortality in non-dialysis-dependent choric kidney patients [21]. Our study showed that PNI was positively correlated with some interrelated prognostic factors for inflammation, including leukocyte and hemoglobin, suggesting that the PNI may integrate and represent the prognostic value of all of these factors. Taken together, the existing evidence indicates that PNI may serve as a ideal indicator of immunonutritional in PD patients.

According to numerous studies, CVD is the leading cause of death in PD patients due to various risk factors [2, 3]. Of risk factors, PEW is an important predictor of mortality in these patients, which the findings reported herein were consistent with. In our study, compared to patients with high PNI, the CVD and all-cause mortality risk with low PNI were increased in unadjusted model. The CVD mortality risk of a low PNI persisted after adjustment for potential confounders, while the all-cause mortality risk of a low PNI nullified. To our knowledge, only 1 study reported the relationship between PNI and mortality in PD patients. The study reported low PNI was associated with increased risk of all-cause mortality in 522 PD patients, which is conflicting with our result [22]. However, the study was limited to Korea subjects and did not explore the relationship between PNI and CVD mortality, the leading cause of death. Conflicting results may be due to differences in race of study population, definition of PNI thresholds and adjustment for confounders. Widely validation of the PNI in different population is necessary in future.

There are some limitations need to be noted in this study. Firstly, this was a single-center retrospective observational study and may have some potential bias. Second, we did not adjust all factors associated with mortality due to the restriction of sample size. So some confounding factors may not be fully ruled out. More studies with multi-center prospective study and more patients are required to validate this result.

In summary, this study suggests that PNI may help to stratify PD patients CVD outcomes. Measurement of the PNI during routine assessments may help to improve survival outcomes in patients on PD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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