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ORIGINAL RESEARCH

Pulmonary Hypertension in Hemodialysis Patients and Its Determinants: A Hospital Based Cross-Sectional Study

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Purpose: Pulmonary hypertension (PH) is a serious complication in hemodialysis patients, which is associated with a significantly increased risk of morbidity and mortality. The present study aims to investigate PH frequency and associated factors in patients undergoing maintenance hemodialysis.

Patients and Methods: This cross-sectional study was conducted in the hemodialysis department of the Shandong Provincial Third Hospital, China, from January 2016 to December 2022. A total of 167 consecutive patients who underwent regular hemodialysis treatment for at least three months were included in the study. Patients with a systolic pulmonary artery pressure (sPAP) value >35 mmHg at rest were considered to have PH. The relationship between PH and various demographic, laboratory, and echocardiographic parameters was evaluated.

Results: A total of 93 patients (55.7%) were diagnosed with PH. Multivariate logistic regression analysis indicated that low serum levels of albumin (OR 0.89, 95% CI 0.82–0.98, p = 0.017), low serum levels of triglycerides (OR 0.32, 95% CI 0.15–0.69, p = 0.003), and high right atrial diameter (OR 1.19, 95% CI 1.04–1.37, p = 0.011) were significantly associated with an increased risk of PH.

Conclusion: PH is a common finding in hemodialysis patients and is independently associated with serum levels of albumin, serum levels of triglyceride, and right atrial diameter; this suggests that evaluating these non-invasive and relatively easily available parameters may be useful in identifying patients with a high risk of PH. However, further studies are required to confirm these findings.

Keywords: pulmonary hypertension, triglycerides, pulmonary artery, renal dialysis, echocardiography, albumins

Introduction

End-stage renal disease (ESRD) poses a significant public health challenge worldwide.[1] In high-prevalence regions, ESRD affects more than 150 individuals per million population. Hemodialysis represents the primary renal replacement therapy for approximately two-thirds of ESRD patients.[2] ESRD patients exhibit a heightened risk of various complications, including cardiovascular disease, mineral and bone disorders, and anemia,[3] as well as a substantial burden of psychiatric comorbidities,[4] which can significantly impact their overall health and treatment outcomes. Pulmonary hypertension (PH) is an important cardiovascular complication of ESRD, bringing a significant increase in mortality risk, especially with patients undergoing hemodialysis.[5] The prevalence of PH in patients with chronic kidney disease (CKD) is not precisely known, with the limited epidemiological studies available.[6] However, a systematic review and meta–analysis study reported a median prevalence of 38% (range 8–70%) for PH among patients undergoing any form of dialysis, with a rate of 19% (range 8–37%) in peritoneal dialysis and a significantly higher rate of 40% (range 16–70%) in hemodialysis patients.[1]

PH shows a strong association with morbidity and mortality in patients undergoing hemodialysis.[7] A meta-analysis including 7112 CKD and ESRD patients revealed that the presence of PH increases the risk of all-cause mortality by

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1.44-fold in CKD patients and by 2.32-fold in ESRD patients undergoing maintenance hemodialysis. The same study reported a 1.67-fold and 2.33-fold increase, respectively, in the risk of cardiovascular diseases in CKD and maintenance hemodialysis patients who developed PH.[8] Additionally, other studies have identified PH in chronic kidney disease patients receiving hemodialysis as an independent risk factor for all-cause death, cardiovascular events, and cardiovascular death.[9,10] A strong clinical suspicion is required for diagnosing PH, and early identification followed by appropriate management can slow the disease's progression over time.

Various mechanisms have been proposed to play a role in the development of PH in hemodialysis patients, including fluid overload, arterio-venous fistula-related increased pulmonary vascular flow, breathing-related sleep disorder, defective endothelium-dependent vasodilation, vascular calcification, anemia, thromboembolic disease, inflammation, left-sided cardiac dysfunction, bone mineral abnormalities, age, and duration of hemodialysis.[2,11] However, risk factors and causes vary across studies and are yet to be fully understood. Few studies have focused on the association of PH with echocardiographic parameters, and not all laboratory parameters have been investigated.

The present study aimed to investigate the frequency of PH in a population of maintenance hemodialysis patients and identify its associated laboratory and echocardiographic factors.

Material and Methods

This cross-sectional study was conducted in the hemodialysis department of the Shandong Provincial Third Hospital, China, from January 2016 to December 2022. A total of 167 consecutive patients aged 23–95 years who underwent regular hemodialysis treatment and showed stable clinical condition (no hospitalization, dry weight adjustment, or vascular access changes) were included in the study. All patients underwent hemodialysis for at least 3 months, with treatments occurring 3 times a week and lasting about 4 hours per session.

The exclusion criteria for patients included heart failure with reduced ejection fraction, moderate to severe mitral or aortic valve disease, left-to-right cardiac shunt, pulmonary embolism, obstructive sleep apnea syndrome, chronic obstructive pulmonary diseases, asthma, acute lung infection, liver failure, collagen vascular disease, connective tissue disease.

The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of Shandong Provincial Third Hospital, China. All study participants provided informed consent prior to inclusion.

Systolic pulmonary artery pressure (sPAP) was measured by a cardiologist using a standard echocardiography device within 24 hours after hemodialysis, when patients were at their optimal dry weight.

In each patient, a 2D color Doppler examination was performed with echocardiography, and the systolic velocity of the tricuspid regurgitation was measured via apical or parasternal views. Subsequently, the systolic pressure of the pulmonary artery was calculated based on the modified Bernoulli formula as follows: Bernoulli equation: sPAP = 4 × (tricuspid systolic jet) 2+10 mmHg (estimated right atrial pressure).

PH was defined as sPAP >35 mmHg. In previous studies, a Doppler-derived sPAP cut-off value of 35 mmHg has been one of the most commonly utilized thresholds for PH definition.[2–5,10,12]

In addition, the following data were collected for all patients: demographic parameters (age, gender, duration of hemodialysis); laboratory parameters (hemoglobin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, calcium, phosphorus, parathyroid hormone (PTH), triglyceride, total cholesterol, pro b-type natriuretic peptide (proBNP), high sensitivity troponin T (hs-TnT), c-reactive protein (CRP)); and echocardiographic parameters (left inner diameter (LID), right inner diameter (RID), ascending aortic diameter (AAD), main pulmonary artery diameter (MPAD), interventricular septum thickness (IST), anteroposterior diameter of left atrium (ADLA), right atrial diameter (RAD), right atrial transverse diameter (RATD), and left ventricular ejection fraction (LVEF)).

The statistical software was SPSS (Version 25.0). Quantitative variables were expressed as mean and standard deviation, while categorical variables were reported as frequency and frequency percentage. The independent *t*-test was used to compare continuous variables between the two groups, while the chi-square test was utilized to compare categorical variables. Multivariate regression models were used to evaluate the association of various parameters with the PH. Receiver operating characteristic (ROC) curve analysis was used to assess the cutoff value, sensitivity, and specificity of significant parameters for predicting PH. A p-value less than 0.05 was considered statistically significant.

Results

Out of 167 patients included in this study, 102 (61.1%) were male and 65 (38.9%) were female. The mean (± SD) age was 61.8 ± 13.9 years. A total of 93 (55.7%) patients were diagnosed with PH. Causes of kidney failure included diabetes mellitus (34.4% in the PH group and 28.4% in the non-PH group), hypertension (24.7% in the PH group and 29.7% in the non-PH group), chronic glomerulonephritis (19.4% in the PH group and 17.6% in the non-PH group), and other causes (21.5% in the PH group and 24.3% in the non-PH group). There was no significant difference in the distribution of these causes between the two groups. The two groups had significant differences in terms of age, phosphorus, triglyceride, total cholesterol, probnp, hs-TnT, LID, MPAD, ADLA, RAD, RATD, LVEF, and sPAP (all P<0.05, Table 1).

Univariate analysis showed that age, probnp, LID, MPAD, ADLA, RAD, and RATD were directly related to an increased risk of PH (OR>1, P<0.05, Table 2), while creatinine, phosphorus, triglyceride, total cholesterol, and LVEF were inversely related to an increased risk of PH (OR<1, P<0.05, Table 2). Multivariate logistic regression analysis indicated that low serum levels of albumin (OR 0.89, 95% CI 0.82–0.98, p = 0.017), low serum levels of triglycerides (OR 0.32, 95% CI 0.15–0.69, p = 0.003), and high right atrial diameter (OR 1.19, 95% CI 1.04–1.37, p = 0.011) were significantly associated with an increased risk of PH (Table 2).

Table 1 Differences of the Considered Parameters Between Patients with and without Pulmonary Hypertension

Variables	Non-PH (n=74)	PH (n=93)	All (n=167)	p-value
Gender, male	44(59.5%)	58(62.4%)	102(61.1%)	0.702
Age	58.7±14.8	64.2±12.8	61.8±13.9	0.030
Dialysis duration	40.9±27.6	39.9±28.8	40.3±28.2	0.653
Hemoglobin(g/L)	97.9±24.6	92.7±23.4	95.0±24.0	0.164
Albumin(g/L)	36.3±6.1	34.8±6.6	35.4±6.4	0.134
AST(U/L)	17.0±49.6	13.2±12.1	14.9±34.1	0.212
ALT(U/L)	16.6±21.8	16.7±14.9	16.7±18.2	0.534
BUN(mmol/L)	23.4±21.7	18.4±8.9	20.6±16.1	0.296
Creatinine(umol/L)	642.8±379.9	536.0±246.7	583.3±316.2	0.173
Calcium(mmol/L)	2.1±0.2	2.3±1.9	2.2±1.4	0.602
Phosphorus(mmol/L)	1.9±0.9	1.6±0.7	1.7±0.8	0.024
PTH(pg/mL)	335.1±290.7	309.3±283.9	320.8±286.3	0.252
Triglyceride(mmol/L)	1.7±1.1	1.1±0.5	1.4±0.9	<0.001
TC(mmol/L)	4.1±1.4	3.6±1.0	3.8±1.2	0.014
Probnp(ng/mL)	12.3±12.8	20.8±13.3	16.8±13.7	<0.001
hs-TnT(ng/L)	300.5±1150.0	280.7±1064.8	289.5±1100.0	0.037
CRP(mg/L)	33.8±49.7	30.8±41.9	32.1±45.4	0.383
LID(mm)	49.5±5.1	53.3±6.9	51.6±6.5	<0.001
RID(mm)	22.7±2.9	23.3±3.1	23.1±3.0	0.284
AAD(mm)	33.4±3.9	33.6±3.4	33.5±3.6	0.894
MPAD(mm)	22.3±2.2	25.7±20.7	24.2±15.5	0.003
IST(mm)	11.5±1.8	11.4±1.9	11.4±1.8	0.973
ADLA(mm)	38.6±6.4	42.8±5.6	40.9±6.3	<0.001
RAD(mm)	42.2±5.0	47.6±7.1	45.3±6.8	<0.001
RATD(mm)	36.5±5.5	41.4±6.7	39.3±6.6	<0.001
LVEF(%)	53.1±7.5	47.2±9.9	49.8±9.4	<0.001
sPAP(mmHg)	26.6±4.1	50.9±12.1	40.1±15.3	<0.001

Abbreviations: AAD, Ascending aortic diameter; ADLA, Anteroposterior diameter of left atrium; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BUN, blood urea nitrogen; CRP, c-reactive protein; hs-TnT, high sensitivity troponin T; IST, Interventricular septum thickness; LID, left inner diameter; LVEF, Left Ventricular Ejection Fraction; MPAD, Main pulmonary artery diameter; proBNP, pro b-type natriuretic peptide; PTH, parathyroid hormone; RAD, Right atrial diameter; RATD, Right atrial transverse diameter; RID, right inner diameter; sPAP, systolic pulmonary artery pressure; TC, Total cholesterol.

Table 2 Univariate and Multivariate Analysis of Predictors for Pulmonary Hypertension on Logistic Regression Analysis

Variables	OR	95% CI	P-value	OR	95% CI	P-value
Gender, male	1.130	0.604–2.112	0.702			
Age	1.030	1.006–1.054	0.013			
Dialysis duration	0.985	0.865–1.122	0.821			
Hemoglobin(g/L)	0.991	0.978–1.004	0.165			
Albumin(g/L)	0.963	0.917–1.012	0.135	0.895	0.817–0.981	0.017
AST(U/L)	0.997	0.986–1.007	0.505			
ALT(U/L)	1.000	0.983 −1.017	0.975			
BUN(mmol/L)	0.977	0.952–1.002	0.066			
Creatinine(umol/L)	0.895	0.808–0.992	0.034			
Calcium(mmol/L)	1.063	0.335–3.374	0.917			
Phosphorus(mmol/L)	0.551	0.363–0.836	0.005			
PTH(pg/mL)	1.000	0.999–1.001	0.563			
Triglyceride(mmol/L)	0.361	0.218–0.596	<0.001	0.320	0.149–0.686	0.003
TC(mmol/L)	0.721	0.552–0.943	0.017			
Probnp(ng/mL)	1.049	1.022–1.077	<0.001			
hs-TnT(ng/L)	1.000	0.997–1.003	0.908			
CRP(mg/L)	0.999	0.992–1.005	0.668			
LID(mm)	1.109	1.049–1.172	<0.001			
RID(mm)	1.071	0.960–1.195	0.221			
AAD(mm)	1.017	0.935–1.107	0.695			
MPAD(mm)	1.218	1.068–1.389	0.003			
IST(mm)	0.971	0.822–1.147	0.731			
ADLA(mm)	1.138	1.067–1.214	<0.001			
RAD(mm)	1.160	1.091–1.234	<0.001	1.192	1.041–1.366	0.011
RATD(mm)	1.144	1.077–1.214	<0.001			
LVEF(%)	0.926	1.891–0.963	<0.001			

Abbreviations: AAD, Ascending aortic diameter; ADLA, Anteroposterior diameter of left atrium; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BUN, blood urea nitrogen; CI, Confidence Interval; CRP, c-reactive protein; hs-TnT, high sensitivity troponin T; IST, Interventricular septum thickness; LID, left inner diameter; LVEF, Left Ventricular Ejection Fraction; MPAD, Main pulmonary artery diameter; OR, Odds Ratio; proBNP, pro b-type natriuretic peptide; PTH, parathyroid hormone; RAD, Right atrial diameter; RATD, Right atrial transverse diameter; RID, right inner diameter; sPAP, systolic pulmonary artery pressure; TC, Total cholesterol.

In the ROC analysis, the area under the curve (AUC) for albumin, triglyceride, and RAD were calculated as 0.575, 0.667, and 0.735, respectively (Table 3 and Figure 1). The cutoff value for albumin, triglyceride, and RAD were obtained as 34.55 g/L, 1.40 g/L, and 44.5 mm, respectively. Moreover, the results indicated that using a combination of these three parameters (albumin≤34.55 g/L, triglyceride≤1.40 mmol/L, and RAD≥44.5 mm) yields the highest sensitivity and specificity for PH prediction (sensitivity: 88.5%, Specificity: 83.3%, AUC: 0.800, 95% CI: 0.734–0.866, P<0.001).

Table 3 The Cutoff Value, Sensitivity, and Specificity of Albumin, Triglyceride, and Right Atrial Diameter for Detection of Pulmonary Hypertension

	Cutoff Value	Sensitivity	Specificity	AUC	P-value	95% CI
Albumin	34.55	52%	64%	0.575	0.096	0.488–0.663
Triglyceride	1.40	80%	54%	0.667	<0.001	0.582–0.752
Right atrial diameter	44.50	60%	77%	0.735	<0.001	0.660–0.810

Abbreviations: AUC, Area under the curve; CI, Confidence Interval.

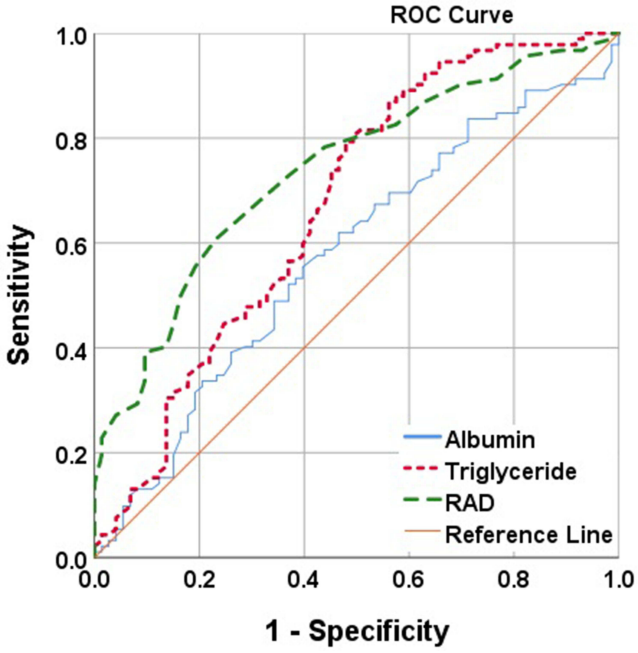

Figure 1 The receiver operating characteristic curve for albumin, triglyceride, and right atrial diameter (RAD) for detection of pulmonary hypertension.

Discussion

The results suggested a high prevalence of PH in patients with chronic kidney disease undergoing maintenance hemodialysis. Serum albumin and triglyceride levels and right atrial diameter (RAD) were independent determinants of PH.

The prevalence of PH in hemodialysis patients was 55.7% in this study. The reported prevalence for this condition markedly varies across the studies, ranging from much lower rates than our findings (eg 13.6%,[7] and 17%[12]) to nearly similar (eg 51%,[6] and 53.8%[11]), and even higher rates than ours (eg 62.3%,[13] and 66%[14]). The observed discrepancies among studies may partly stem from differences in the level of healthcare systems available to patients, early diagnosis, and treatment of this condition in certain regions. Additionally, variations in patient conditions (eg, duration and severity of disease), criteria used to define PH, and other methodological differences may all contribute to the discrepancies among studies.

Our findings indicated an inverse and independent association between serum albumin levels in hemodialysis patients and PH, with lower albumin levels significantly increasing the risk of PH (OR 0.895, 95% CI 0.817–0.981, P=0.017). There are reports regarding the association of albumin with mortality in hemodialysis patients.[15,16] Tang et al[15] measured serum albumin levels at the early phase of hemodialysis in 447 hemodialysis patients. The follow-up of these patients for a median duration of 6.5 years showed that early albumin level less than 34.2 g/L was an independent predictor of mortality in hemodialysis patients (HR 0.945, 95% CI 0.916–0.976). In our study, a cut-off point of 34.55 g/L was obtained for albumin, below which the patients showed a 1.78-fold increased risk of PH (OR 1.781, 95% CI 0.960–3.305). Similarly, the results of Yoo et al[16] revealed that low serum albumin level was an independent risk factor for all-cause mortality in hemodialysis patients (HR 0.117, 95% CI 0.019–0.714). In another study, Snipelisky et al[17] concluded that low serum albumin level (less than 33 g/L) was an independent predictor of mortality in patients with World Health Organization group I PH (HR 0.485, 95% CI: 0.284–0.829). In several other diseases, including congenital heart disease and chronic heart failure, low serum albumin levels have been associated with increased complexity and poorer prognosis as well.[18–20] The exact mechanism of hypoalbuminemia in patients with PH is unclear. However, serum albumin levels may decrease due to multiple factors, including malnutrition, systemic inflammation, and hepatic dysfunction.[17]

The study found that lower blood triglyceride levels independently associated with increased risk of PH in hemodialysis patients (OR 0.320, 95% CI 0.149–0.686, P=0.003). Hypertriglyceridemia is a typical finding in chronic renal failure and hemodialysis patients.[21] However, low triglycerides were found to be a risk factor for PH in the present study. In a study conducted on end-stage renal disease patients, triglyceride levels were significantly lower in patients with PH compared to

those without,[12] which is consistent with our findings. The exact mechanism of reduced triglyceride in hemodialysis patients with PH remains to be understood, but malnutrition and inflammation may be among the contributing factors.[22,23] In addition, some researchers hypothesize that TG levels are lower in PH patients, likely because liver function, crucial for TG synthesis, is often impaired first in those with right ventricular failure.[22,24] Fakhry et al[25] reported that lower triglyceride levels were associated with poor right ventricular performance in PH patients. Our findings suggest lower TG levels as a potential biomarker for PH in hemodialysis patients, but further research is necessary to confirm this.

Right atrial diameter (RAD) was established in the present study as another independent risk factor for PH. The association between PH and RAD was direct, meaning that higher RAD levels in hemodialysis patients were significantly associated with an increased risk of PH (OR 1.192, 95% CI 1.041–1.366). Consistent with our findings, Bozbas et al[12] found that the diameter of the right atrium in ESRD patients with PH were significantly larger than those in ESRD patients without PH. In another study on patients with atrial septal defect, Hartopo et al[26] showed that right atrial diameter had a significant and independent association with PH. Their findings corroborate ours despite differences in the studied population. The cut-off value of right atrial diameter for predicting PH was 46 mm in their study, with a sensitivity of 51% and specificity of 78%. Similarly, the cut-off value for RAD in the current study was 44.5 mm, with a sensitivity of 60% and specificity of 77%. Hartopo et al[26] stated that combining right atrial diameter with NT-proBNP (another independent predictor of PH in their study) improves the sensitivity and specificity of PH diagnosis. Similarly, the combined use of albumin, triglyceride, and right atrial diameter in our study demonstrated a sensitivity of 88.5% and specificity of 83.3% for predicting PH in hemodialysis patients, which was higher than each of these parameters alone.

The present study faces several limitations. A key limitation of this study is the relatively small sample size. This may have limited our statistical power to detect genuine associations between PH and certain demographic, laboratory, and echocardiographic parameters. Consequently, the observed relationships should be interpreted cautiously. Larger-scale studies are required to further explore and confirm the potential associations between these variables and PH. While right heart catheterization remains the gold standard for diagnosing PH, this study employed echocardiography. Echocardiography has limitations including operator dependence, indirect assessment of sPAP, potential for overdiagnosis in specific lung pathologies, and influence of certain altered hemodynamic conditions on its parameters.[27] Despite these shortcomings, echocardiography's non-invasiveness, cost-effectiveness, readily availability, convenience, and utility for serial assessments render it a valuable tool for PH screening and prognostication, justifying its widespread use in research.[2–5,10,12] Another limitation is that the exclusion of hemodialysis patients with pre-existing cardiac diseases restricts the generalizability of our findings to this specific subgroup of the hemodialysis population. Being a single-center and cross-sectional design are other limitations of the present study. Finally, potential confounding factors such as lifestyle, diet, comorbidities, and medication use may affect our findings.

Conclusion

Our findings suggest that PH is a common finding in maintenance hemodialysis patients and is independently associated with serum albumin levels, serum triglyceride levels, and right atrial diameter. Given the high prevalence of PH in hemodialysis patients, early screening and management are recommended to reduce adverse outcomes. In this regard, assessing serum levels of albumin and triglyceride, and right atrial diameter, which are easily measurable and non-invasive parameters, may help identify high-risk patients. However, further multi-center studies with larger sample sizes are necessary to confirm the findings of this study.

Abbreviations

AAD, ascending aortic diameter; ADLA, anteroposterior diameter of left atrium; BUN, blood urea nitrogen; CKD, chronic kidney disease; CRP, c-reactive protein; ESRD, end-stage renal disease; hs-TnT, high sensitivity troponin T; IST, interventricular septum thickness; LID, left inner diameter; LVEF, left ventricular ejection fraction; mmHg, millimetres of mercury; MPAD, main pulmonary artery diameter; PH, pulmonary hypertension; proBNP, pro b-type natriuretic peptide; PTH, parathyroid hormone; RAD, right atrial diameter; RATD, right atrial transverse diameter; RID, right inner diameter; ROC, receiver operating characteristic; sPAP, systolic pulmonary artery pressure; SPSS, statistical package for the social sciences.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of Shandong Provincial Third Hospital, China (KYLL-2024083). All study participants provided informed consent prior to inclusion.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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