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Establishment and evaluation of a risk prediction model for venlafaxine plasma concentration exceeding alert levels

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ABSTRACT

Objective: To investigate the factors influencing venlafaxine blood concentration exceeding the alert threshold in patients with depression and to develop a risk prediction model for elevated venlafaxine concentrations, providing a reference for individualized VEN therapy.

Methods: A retrospective analysis was conducted on 590 hospitalized patients who received venlafaxine treatment and underwent TDM at the First Hospital of Hebei Medical University between January 2021 and August 2024. Patients were categorized into a target concentration group (100–400 ng/mL) and an above-alert group (> 800 ng/mL) based on their VEN plasma concentrations. Demographic and clinical variables, including sex, age, body mass index (BMI), average daily dose, plasma albumin level, concomitant medications, liver and kidney function, were collected and compared between groups. Logistic regression analysis was performed to identify independent risk factors associated with VEN concentrations exceeding the alert threshold. A nomogram prediction model was constructed based on the identified factors and was subsequently validated.

Results: Among the 590 patients, 516 were in the target concentration group and 74 were in the above-alert group. The proportion of females, patients with BMI < 24, average daily dose ≥ 225 mg, renal impairment, and concomitant use of CYP2D6 inhibitors was significantly higher in the above-alert group than in the target group ($P < 0.05$). Logistic regression analysis revealed that average daily dose ≥ 225 mg (OR = 26.628, 95 % CI: 12.912–54.916), renal impairment (OR = 2.429, 95 % CI: 1.215–4.854), and concomitant use of CYP2D6 inhibitors (OR = 5.232, 95 % CI: 2.781–9.844) were independent risk factors for VEN concentrations exceeding the alert threshold ($P < 0.05$). The nomogram model showed an AUC of 0.899 (95 % CI: 0.864–0.935), sensitivity of 48.65 %, specificity of 95.74 %, positive predictive value of 62.07 %, and negative predictive value of 92.86 %. Bootstrap validation demonstrated good consistency (Brier score = 0.072), and the Hosmer-Lemeshow test indicated good calibration ($\chi^2 = 3.16$, $P = 0.531$). Decision curve analysis demonstrated clinical utility for threshold probabilities of 0.05–0.80.

Conclusions: Average daily dose ≥ 225 mg, renal impairment, and concomitant use of CYP2D6 inhibitors are independent risk factors for VEN plasma concentrations exceeding the alert threshold. The constructed nomogram model effectively predicts the risk of venlafaxine concentration exceeding the alert range and has significant clinical application value.

Introduction

Venlafaxine (VEN) is an antidepressant that effectively inhibits the reuptake of serotonin (5-HT) and norepinephrine. Since its approval in 1995, VEN has been widely used in the treatment of major depressive disorder, generalized anxiety disorder, and panic disorder.[1] Its favorable safety and therapeutic efficacy have made it one of the most commonly prescribed antidepressants worldwide.[2] VEN is primarily metabolized by cytochrome P450 2D6 (CYP2D6) into its active metabolite, O-desmethylvenlafaxine (ODV). Under steady-state conditions, ODV plasma concentration is approximately two to three times higher than that of its parent compound. Dose adjustments are recommended

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in patients with hepatic or renal impairment, and factors such as sex and age may also influence VEN plasma concentrations at the same dosing regimen.[3] High interindividual variability results in significant differences in drug exposure among patients receiving the same dose, with excessive exposure potentially leading to adverse reactions or reduced therapeutic efficacy.[4] Therefore, The TDM guidelines recommend TDM for VEN-treated patients, with a grade II recommendation level.[5] Previous studies on factors influencing VEN plasma concentrations have reported inconsistent findings,[6,7] and limited evidence is available regarding factors associated with VEN concentrations exceeding the alert threshold. Nomograms, based on multivariate regression analysis, integrate multiple clinical indicators or biological attributes and present their predictive contribution to outcomes in an intuitive, scale-based graphical format. They have been widely applied in clinical risk prediction models.[8] This study aimed to identify independent risk factors associated with VEN concentrations exceeding the alert threshold using logistic regression analysis and to develop a nomogram prediction model. This model is intended to facilitate early identification of patients at risk for elevated venlafaxine plasma concentrations, thereby providing a scientific basis for the safe and individualized use of VEN in clinical practice.

Materials and methods

Study population

A total of 590 hospitalized patients diagnosed with depression, who received VEN treatment and underwent TDM at the First Hospital of Hebei Medical University between January 2021 and August 2024, were retrospectively included in this study. This study was approved by the Clinical Research Ethics Committee of the First Hospital of Hebei Medical University (No. 20220936). Inclusion criteria: (i) patients who met the diagnostic criteria for depression according to the International Classification of Diseases, 10th Revision (ICD-10); (ii) patients who received VEN treatment and underwent TDM with plasma concentration reaching a steady state. The steady-state plasma concentration of VEN was defined as blood samples collected 30 minutes prior to the next dose after at least three consecutive days of fixed-dose treatment; (iii) patients aged ≥ 18 years. Exclusion criteria: (i) patients with severe dysfunction of major organs such as the heart or lungs; (ii) patients undergoing hemodialysis; (iii) patients with plasma drug concentration of 400-800 ng/ml; (iv) patients with incomplete clinical data.

Data collection and analysis

All enrolled patients continuously received a fixed dose of VEN for at least three days. Once steady-state concentration was achieved, 3–5 mL of venous blood was collected prior to the next dose. The serum was separated by centrifugation and pretreated using a protein precipitation method. The steady-state trough concentrations of VEN were quantitatively determined using an ACQUITY-X ultra-performance liquid chromatography-tandem mass spectrometry system (Waters Corporation, USA). Clinical data, including sex, age, height, weight, BMI, plasma drug concentration results, plasma albumin levels, alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, serum creatinine, creatinine clearance rate, and concomitant use of CYP2D6 inhibitors, were collected. According to the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology (2017 Edition), the reference range for VEN therapeutic plasma concentration is 100–400 ng/mL, and concentrations exceeding 800 ng/mL are defined as above the alert threshold.[5] Patients were categorized into a target concentration group (100–400 ng/mL) and an above-alert group (> 800 ng/mL) based on their VEN plasma concentrations. The correlation between clinical factors and VEN concentrations exceeding 800 ng/mL was analyzed. Variables with clinical significance and statistical differences in univariate analysis were included in multivariate logistic regression analysis to identify independent risk factors, which were then used to construct a nomogram prediction model.

Statistical analysis

Statistical analyses were performed using SPSS (version 26.0). Categorical variables were expressed as percentages (%) and compared between groups using the chi-square test (χ^2 test). A P-value of < 0.05 was considered statistically significant. Binary logistic regression analysis was used to identify independent risk factors. The nomogram prediction model was developed using the RMS package in R software (version 3.6.1). Internal validation was performed using the bootstrap method. The predictive performance of the model was evaluated by receiver operating characteristic (ROC) curve analysis, calibration curve assessment, and decision curve analysis (DCA).

Results

Comparison of clinical characteristics between the target group and the above-alert group

A total of 590 patients were included in this study. Among them, 516 patients had VEN plasma concentrations within the recommended therapeutic range (100–400 ng/mL) and were assigned to the target group; 74 patients had concentrations exceeding 800 ng/mL and were assigned to the above-alert group. Univariate analysis showed statistically significant differences between the two groups in terms of sex, BMI, average daily dose, renal impairment status, and concomitant use of CYP2D6 inhibitors ($P < 0.05$, Table 1). There were no statistically significant differences in age, plasma albumin levels, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or serum creatinine levels between the two groups ($P > 0.05$, Table 1).

Logistic regression analysis of factors associated with VEN plasma concentration above the alert threshold

A binary logistic regression analysis was conducted with elevated VEN plasma concentration (above the alert threshold) as the dependent variable (No = 0, Yes = 1). Independent variables included factors with statistically significant differences from the univariate analysis: sex (male = 1, female = 0), BMI (< 24 = 0, ≥ 24 = 1), average daily dose (< 225 mg = 0, ≥ 225 mg = 1), renal impairment (No = 0, Yes = 1), and concomitant use of CYP2D6 inhibitors (No = 0, Yes = 1). The results revealed that average daily dose (OR = 0.038, 95 % CI: 0.018–0.077), presence of renal impairment (OR = 0.412, 95 % CI: 0.206–0.823), and concomitant use of CYP2D6 inhibitors (OR = 0.191, 95 % CI: 0.102–0.360) were independent risk factors for VEN plasma concentrations exceeding the alert threshold ($P < 0.05$, Table 2).

Development of a nomogram prediction model for above-alert VEN plasma concentration in patients with depression

Based on the results of the multivariate logistic regression analysis, a nomogram model was developed to predict the risk of VEN plasma concentration exceeding the alert threshold. The corresponding scores for the three independent risk factors (average daily dose, renal impairment, and concomitant use of CYP2D6 inhibitors) were 100, 30, and 51, respectively, with a total score of 181.The model demonstrated that as the individual scores corresponding to the three risk factors increased, the total score of the nomogram increased accordingly, indicating a higher predicted risk of venlafaxine plasma concentrations exceeding the alert threshold (Fig. 1).

Table 1
Comparison of clinical characteristics between the target group and the above-alert group of venlafaxine plasma concentration.

Characteristics	No. of cases (n = 590)	Target group (n (%))	Above-alert group (n (%))	χ^2(t) value	*P* value
Gender				**10.631**	**0.001**
Male	203	190 (36.8 %)	13 (17.6 %)		
Female	387	326 (63.2 %)	61 (82.4 %)		
Age (years)				2.061	0.097
> 60	211	179 (34.7 %)	32 (43.2 %)		
≤ 60	379	337 (65.3 %)	42 (56.8 %)		
BMI ($g{\cdot}m^{-2}$)				**4.869**	**0.018**
≥ 24	286	259 (50.2 %)	27 (36.5 %)		
< 24	304	257 (49.8 %)	47 (63.5 %)		
Average daily dose (mg)				**144.096**	**0.000**
< 225	430	419 (81.2 %)	11 (14.9 %)		
≥ 225	160	97 (18.8 %)	63 (85.1 %)		
VEN plasma concentration ($ng{\cdot}mL^{-1}$)	**345.8 + 293.5**	**250.4 + 87.3**	**1010.9 + 358.3**	**− 18.181**	**0.000**
Albumin ($g{\cdot}L^{-1}$)				0.519	0.294
> 35	532	467 (90.5 %)	65 (87.8 %)		
≤ 35	58	49 (9.5 %)	9 (12.2 %)		
ALT ($U{\cdot}L^{-1}$)				2.912	0.058
> 50	56	53 (10.3 %)	3 (4.1 %)		
≤ 50	534	463 (89.7 %)	71 (95.9 %)		
AST ($U{\cdot}L^{-1}$)				0.055	0.47
> 40	67	58 (11.2 %)	9 (12.2 %)		
≤ 40	523	458 (88.8 %)	65 (87.8 %)		
creatinine ($\mu mol{\cdot}L^{-1}$)				0.285	0.500
> 111	13	12 (2.3 %)	1 (1.4 %)		
≤ 111	577	504 (97.7 %)	73 (98.6 %)		
Renal impairment				**7.14**	**0.007**
No	448	401 (77.7 %)	47 (63.5 %)		
Yes	142	115 (22.3 %)	27 (36.5 %)		
Concomitant use of CYP2D6 inhibitors				**39.310**	**0.000**
Yes	169	125 (24.2 %)	44 (59.5 %)		
No	421	391 (75.8 %)	30 (40.5 %)		

Evaluation of the nomogram model for predicting VEN plasma concentration exceeding the alert threshold

The area under the receiver operating characteristic (ROC) curve (AUC) for the nomogram model predicting the risk of elevated VEN plasma concentration was 0.899 (95 % CI: 0.864–0.935), indicating strong discriminative ability. The model demonstrated a sensitivity of 48.65 %, specificity of 95.74 %, positive predictive value of 62.07 %, and negative predictive value of 92.86 % (Fig. 2).

Internal validation using the bootstrap method showed good agreement between the predicted and observed outcomes, with a Brier score of 0.072. The Hosmer-Lemeshow test indicated good calibration of the nomogram (χ^2 = 3.16, P = 0.531, Fig. 3).

Decision curve analysis (DCA) showed that when the threshold probability ranged from 0.05 to 0.80, using the nomogram to predict the risk of elevated VEN plasma concentration yielded a greater net clinical benefit compared to “treat-all” or “treat-none” strategies. This finding supports the favorable clinical utility of the nomogram model (Fig. 4).

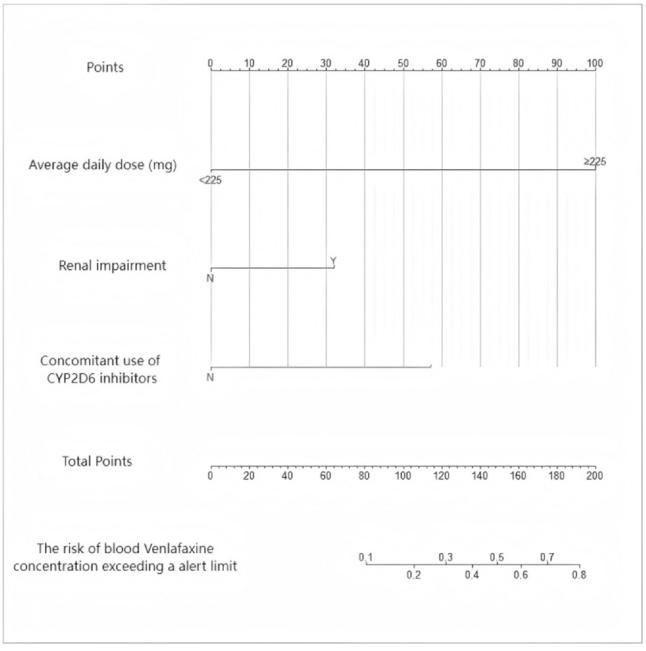

Fig. 1. Nomogram model for evaluating the risk of venlafaxine plasma concentration exceeding the alert threshold.

Discussion

The plasma concentration of VEN varies widely among individuals and is influenced by multiple factors, such as age, sex, pathophysiological

Table 2
Logistic regression analysis of factors associated with venlafaxine plasma concentration exceeding the alert threshold.

Variate	B	SE	Wald χ^2	P	OR (95 %CI)
Gender	− 0.707	0.378	3.51	0.061	0.493 (0.235, 1.033)
BMI ($g{\cdot}m^{-2}$)	− 0.487	0.326	2.227	0.136	0.614 (0.324, 1.165)
Average daily dose (mg)	**− 3.282**	**0.369**	**78.977**	**0.000**	26.638 (12.912, 54.916)
Renal impairment	**− 0.887**	**0.353**	**6.31**	**0.012**	2.429 (1.215, 4.854)
Concomitant use of CYP2D6 inhibitors	**− 1.655**	**0.322**	**26.337**	**0.000**	5.232 (2.781, 9.844)

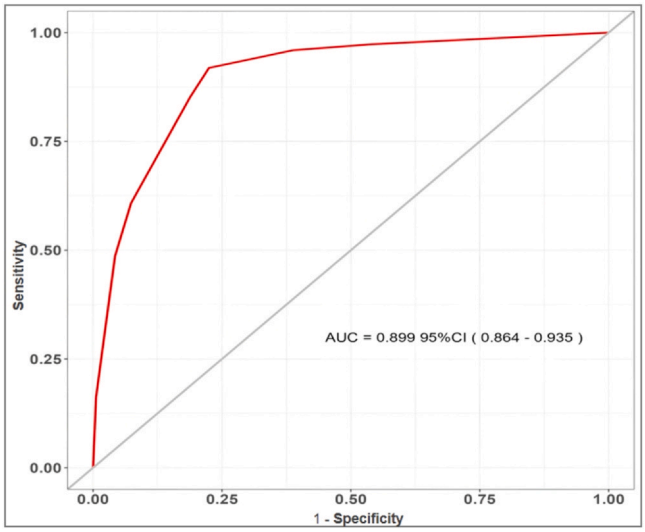

Fig. 2. ROC of the nomogram model predicting the risk of venlafaxine plasma concentration exceeding the alert threshold.

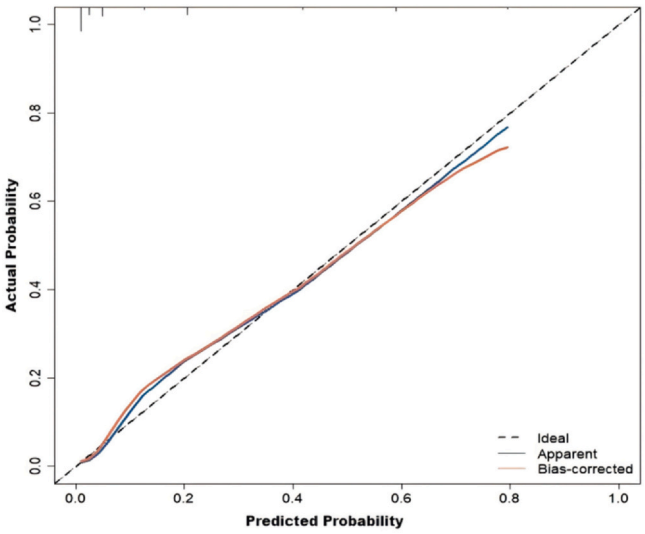

Fig. 3. Validation of the nomogram prediction model of venlafaxine plasma concentration exceeding the alert threshold.

status, dosing regimen, and drug-drug interactions, which may compromise therapeutic outcomes.[9,10] Early assessment of the risk of elevated VEN concentrations beyond the alert threshold is of great clinical significance. Previous studies have reported a strong correlation between plasma concentrations above the alert level and the occurrence of adverse reactions.[11] The nomogram model allows for intuitive visualization of the risk of VEN concentrations exceeding the alert threshold, enabling clinicians to more easily identify high-risk patients and to take preventive or corrective measures in advance, thereby improving prognosis and reducing the incidence of adverse events. The nomogram developed in this study demonstrated excellent predictive performance, with an AUC of 0.899, a sensitivity of 48.65 %, specificity of 95.74 %, positive predictive value of 62.07 %, and negative predictive value of 92.86 %. The calibration curve showed good agreement with the actual data (Brier score = 0.072), and the Hosmer-Lemeshow test confirmed good calibration (χ^2 = 3.16, P = 0.531). These findings are consistent with previously reported modeling methods used to predict drug concentration risks,[12,13] supporting the model's strong predictive value for identifying patients at risk of VEN plasma concentrations exceeding the alert threshold.

Logistic regression analysis identified three independent risk factors associated with elevated VEN plasma concentrations: average daily dose,

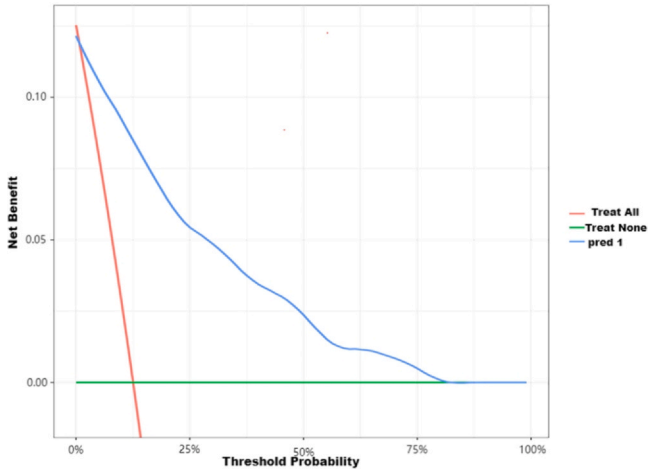

Fig. 4. Clinical decision curve for prediction model of venlafaxine plasma concentration exceeding the alert threshold.

renal impairment, and concomitant use of CYP2D6 inhibitors. To date, the dose-dependency and optimal target dose of VEN remain controversial. Clinical guidelines from different countries provide conflicting recommendations. For example, Swedish medical institutions do not support a clear dose-dependent effect within the therapeutic range, whereas the American Psychiatric Association recommends titration to the highest tolerable dose before reaching the therapeutic target concentration, suggesting a stepwise approach to increasing the dose depending on patient tolerance or side effect profile.[14,15] Furukawa et al.[16] conducted a comprehensive dose-response analysis of common antidepressants and found that the clinical efficacy of VEN significantly increases in the 75–150 mg/day range and continues to rise gradually with higher doses (151–375 mg/day). This is likely due to the norepinephrine reuptake inhibition becoming more pronounced only at higher doses, such as 225 mg/day or 375 mg/day. Another study[17] has reported a statistically significant linear relationship between daily VEN dose and the plasma concentrations of VEN, ODV, and their combined total. Patients receiving higher daily doses are more likely to exceed the alert threshold. In our study, 85.1 % of patients in the above-alert group had a daily dose of ≥ 225 mg, which is consistent with previous findings. This highlights the need for clinicians and clinical pharmacists to closely monitor patients receiving daily doses of 225 mg or more.

VEN and its metabolite ODV are predominantly excreted via the kidneys. In patients with chronic kidney disease (CKD), renal clearance of the drug may be reduced. Studies have shown that renal impairment may reduce the clearance of VEN and its metabolites by approximately 55 %, and significantly prolong their half-life. In patients with creatinine clearance (Ccr) < 30 mL/min, dose adjustments are necessary.[18] Xie et al.[19] reported that VEN plasma concentrations differ among patients with varying levels of creatinine clearance (< 80 mL/min, 80–120 mL/min, and > 120 mL/min), with plasma levels of both VEN and ODV decreasing as renal function improves. In our study, patients with impaired renal function (defined as abnormal creatinine clearance) were more prevalent in the above-alert group compared to the target group, and the difference was statistically significant (P < 0.05), indicating that renal function is an important factor influencing whether VEN plasma concentrations exceed the alert threshold.

The impact of drug-drug interactions on VEN concentrations remains controversial. VEN is metabolized primarily by hepatic enzymes, including CYP3A4, CYP2D6, and CYP2C19. Prior research[20] has shown significant differences in plasma VEN concentrations among different CYP2D6 metabolizer phenotypes. The *CYP2D6*10* allele significantly alters the pharmacokinetics of VEN and ODV in healthy Japanese and Korean individuals. However, some studies[21] did not find statistically significant differences in VEN concentrations among patients with different CYP2D6 genotypes. In our study, 59.5 % of patients in the above-alert group were concurrently using CYP2D6 inhibitors—a significantly higher proportion

than in the target group. The nomogram model showed that the predicted risk of exceeding the alert threshold increased in parallel with higher scores associated with CYP2D6 inhibitor co-administration.

This study has several limitations: (i) It was a single-center, retrospective study with a relatively limited sample size and population diversity, and lacked pharmacogenomic testing due to cost constraints. This may limit the generalizability of the findings, and future studies should involve larger, multicenter cohorts to validate the results. (ii) Control of unknown confounding variables was limited, which may have introduced bias into the analysis. (iii) The limited sample size may have reduced the statistical power, restricting extrapolation of the results. (iv) External validation was not performed using independent data; in future work, we plan to incorporate data from other institutions to improve the accuracy and generalizability of the model.

Conclusion

In summary, this study provides a comprehensive analysis of the risk factors associated with VEN plasma concentrations exceeding the alert threshold and establishes a novel nomogram-based prediction model. To our knowledge, similar models have not been reported in previous literature, underscoring the model's originality. Elevated VEN plasma concentrations in patients with depression were primarily associated with higher daily doses, impaired renal function, and concomitant use of CYP2D6 inhibitors. The developed nomogram demonstrated good predictive performance and clinical utility, offering a practical tool for quantitatively assessing the risk of excessive VEN exposure in individual patients. However, as the model was based on single-center data, further prospective, multicenter studies with larger populations are warranted to validate and refine its predictive power.

Declarations

Not applicable.

Authors' contributions

Y. Zhang: conception and design of the study, feasibility assessment, and drafting and revising the manuscript. J. Yu: quality control, critical revision, and overall supervision of the study. Y. Zhang, X. Li, Y. Liu, J. Wang: data collection, organization and analysis. Y. Zhang, C. Zhou, J. Yu: interpretation and analysis of the results.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of the First Hospital of Hebei Medical University (No. 20220936).

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Declarations of Competing interests

The authors declare that they have no competing interests.

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Authors' other information

Not applicable.

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