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A Clinical Nomogram for Predicting Substandard Serum Valproic Acid Concentrations in Chinese Patients With Epilepsy

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ABSTRACT

Background: It is well-known that substandard serum valproic acid (VPA) concentrations may lead to treatment failure of epilepsy. However, there is still a lack of a quick method to predict whether a patient's serum VPA concentration will reach the standard.

Objective: The aims of this study were to investigate the factors leading to substandard serum VPA concentrations in Chinese patients with epilepsy and develop a related nomogram for risk prediction.

Methods: From January 2019 to March 2022, a total of 1143 serum VPA concentrations were collected from 630 hospitalized Chinese patients with epilepsy who were monitored by the Department of Pharmacy of Lu'an People's Hospital, and complete clinical data were collected from the corresponding patients for retrospective analysis. All monitored serum VPA concentrations were further divided into a training cohort and a validation cohort. For the training cohort, serum VPA concentrations below 50 μg/mL and between 50 and 100 μg/mL were classified into the subtherapeutic group and therapeutic group, respectively. The variables were selected from the clinical data, and differences between the variables of the subtherapeutic and therapeutic groups were analyzed. The influencing factors leading to substandard serum VPA concentrations were screened via logistic regression analysis, and the screened influencing factors were used to establish the nomogram prediction model.

Results: Multivariate logistic regression analysis revealed that the daily dose per unit of body weight (mg/kg/d), route of administration, presence of hepatic lesions, hypoalbuminemia, and combination with carbapenems or barbiturates were independent factors influencing the occurrence of substandard serum VPA concentrations. On the basis of the results of the multivariate logistic regression analysis, a nomogram risk prediction model for substandard serum VPA concentration was established. The values of the C-index and internal verification results indicated that the nomogram model had good accuracy and discrimination. The decision curve revealed that the nomogram that predicted the risk of substandard serum VPA concentration had a greater net benefit value (ranging from 12% to 94%), indicating that the model had a wide prediction interval.

Conclusions: Our study established a nomogram risk prediction model for substandard serum VPA concentrations in Chinese patients with epilepsy, which can help doctors or patients control the serum VPA concentration within the target concentration range as soon as possible.

Introduction

Valproic acid (VPA) is widely used in various types of seizures, as well as in the prevention of migraine and in the treatment of bipolar disorder and other psychiatric or neurological diseases. The mechanisms underlying the effects of VPA are complex and may involve enhancement of the gamma-aminobutyric acid effect and attenuating the neuronal response to methyl-aspartate, which leads to the inhibition of neuronal excitation.[1] The oral form of VPA is rapidly and completely absorbed, with a bioavailability of approximately 90%, and after absorption into the blood, it mainly binds to albumin in plasma, with a protein binding rate of 90% to 95%.[2,3] In the human body, VPA is metabolized through glucuronidation and β oxidation, followed

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by ω and *CYP450* oxidation, and its metabolites are excreted in the urine through the kidney, with a half-life of 6 to 16 h.[4,5] Many studies have shown that VPA has nonlinear pharmacokinetic characteristics; that is, the dose of VPA has a poor correlation with its serum concentration.[6] However, studies have confirmed that the efficacy and adverse reactions of VPA are highly correlated with its serum concentration, and high serum concentrations are prone to cause toxic reactions; in contrast, low serum concentrations may lead to poor efficacy.[7] This result supports the necessity of regular monitoring of the serum concentration of VPA.

According to the guidelines published by Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (Association of Neuropsychopharmacology and Pharmacopsychiatry), the effective reference range of the serum VPA concentration is 50 to 100 μg/mL.[8] A substandard serum VPA concentration means that the steady-state serum VPA concentration is less than 50 μg/mL, which is common in clinical practice and can easily lead to treatment failure. Li et al.[9] reported that when the serum VPA concentration was within 50 to 100 μg/mL, the effective rate of treatment for patients with epilepsy reached 96.43%, whereas the effective rate decreased to only 46.43% when the serum VPA concentration was substandard. Various factors can significantly decrease the serum VPA concentration, such as inadequate dose, poor medication adherence, combination of hepatic enzyme inducers or carbapenems, hypoproteinemia, and uridine diphosphate glucuronyl transferase (UGT) gene mutations.[10–13] Multiple factors may exist in an individual at the same time, leading to challenges in maintaining standard serum VPA concentrations. Therefore, clinicians need an easy-to-use tool to quickly estimate whether a patient's serum VPA concentration will reach the standard and adjust the treatment regimen on the basis of its influencing factors.

For this reason, we used logistic regression analysis to screen the influencing factors that lead to substandard serum VPA concentrations in Chinese patients with epilepsy, and on the basis of these findings, a nomogram prediction model that can quickly determine whether the serum VPA concentration will reach the standard was constructed to provide an easy-to-use tool for individualized treatment with VPA.

Materials and Methods

Patient selection

In this study, data for 1143 serum VPA concentrations from 630 Chinese patients with epilepsy monitored by the Department of Pharmacy of Lu'an People's Hospital from January 2019 to March 2022 were collected, and complete clinical data of the corresponding patients were collected for retrospective analysis. The inclusion criteria were as follows: (1) the patient's age and sex were not limited; (2) the patient was Chinese; (3) the patient took valproate to prevent or treat epilepsy, and their serum VPA concentrations were monitored during clinical treatment; (4) the serum VPA concentration was ≤100 μg/mL; and (5) the relevant clinical data and information were complete. The exclusion criteria were as follows: (1) incomplete clinical medical records; (2) failing to follow the doctor's advice or failing to reach a steady-state serum concentration due to short medication time (0–5 d, excluding 5 d); (3) women who were pregnant or lactating; (4) acute hepatitis/chronic hepatitis or personal or family history of severe hepatopathy; (5) hepatic porphyria and clotting disorders; (6) history of urea cycle disorders; and (7) patients with uncorrected systemic primary carnitine deficiency (contraindications for taking VPA therapy). The selection process is illustrated in Figure 1.

Cohort definition and variable recoding

A total of 1143 serum VPA concentrations were collected and further divided at a ratio of 7:3 into a training cohort (799 samples) and a validation cohort (344 samples).

In the training cohort, 353 serum VPA concentrations below 50 μg/mL were classified into the subtherapeutic group, and 446 serum VPA concentrations in the effective concentration range of 50 to 100 μg/mL were classified into the therapeutic group. For the validation cohort, 344 samples were divided into a subtherapeutic group (152 samples) and a therapeutic group (192 samples) according to the serum VPA concentration.

Seventeen kinds of clinical data, including age, sex, daily dose per unit of body weight (mg/kg/d), route of administration, smoking status, alcohol consumption status, hypoalbuminemia status, hepatic lesion status, kidney damage status, and the use of other drugs, were collected and recorded to select variables for the nomogram. Differences between the variables of the subtherapeutic and therapeutic groups were compared. The factors influencing substandard serum VPA concentrations were screened via logistic regression analysis. The screened influencing factors were used to develop the nomogram prediction model, and the prediction efficiency of the model was verified.

The routes of administration included immediate-release formulation oral administration, sustained-release formulation oral administration, immediate release by gastric tube feeding, and immediate release by a micropump intravenous infusion. Sustained-release tablets of VPA can prolong the duration of drug action by controlling the release rate, which could reduce the number of medications and have better efficacy in controlling epilepsy. Patients with severe conditions are often in a coma and cannot take oral medication normally; thus, gastric tubes for enteral feeding and micropump intravenous infusion are often used.

(1) Immediate-release formulations included taking ordinary tablets or solutions of VPA (sodium salt) for more than 5 days, and the dose of VPA was adjusted according to the patient's weight and was taken orally twice a day or 3 times a day.
(2) For the sustained-release formulation, oral administration consisted of taking the sustained-release tablets of VPA (magnesium or sodium salt) for more than 5 days, and the dose of VPA was adjusted according to the patient's weight and taken orally once a day or twice a day.
(3) Gastric tube for enteral feeding: oral VPA (sodium salt) solution, or crushed immediate-release VPA tablets and dissolved in boiled drinking water cooled to 20 to 40°C for gastric tube feeding. Administration continued over 5 days, and the dose of VPA was adjusted for the patient weight 2 or 3 times a day.
(4) Micropump intravenous infusion: VPA (sodium salt) was injected via an IV drip using a microinjection pump at a uniform speed of 0.05 g/h.

Smoking and drinking status were assessed as follows[14]: smoking more than 10 cigarettes 1 day for more than 1 year until the day before admission; drinking more than 250 mL of alcohol each time and more than once a day for more than 1 year until the day before admission.

The reference definitions of hepatic lesion and kidney damage were as follows: Hepatic lesion[15]: ALT level 1.25 times the upper limit of normal value (50 IU/L) or total bilirubin 2.5 times the upper limit of normal (55.6 μmol/L). Kidney damage[16]: blood creatinine> 115 μmol/L and a glomerular filtration rate <90 mL/(min × 1.73 m^2).

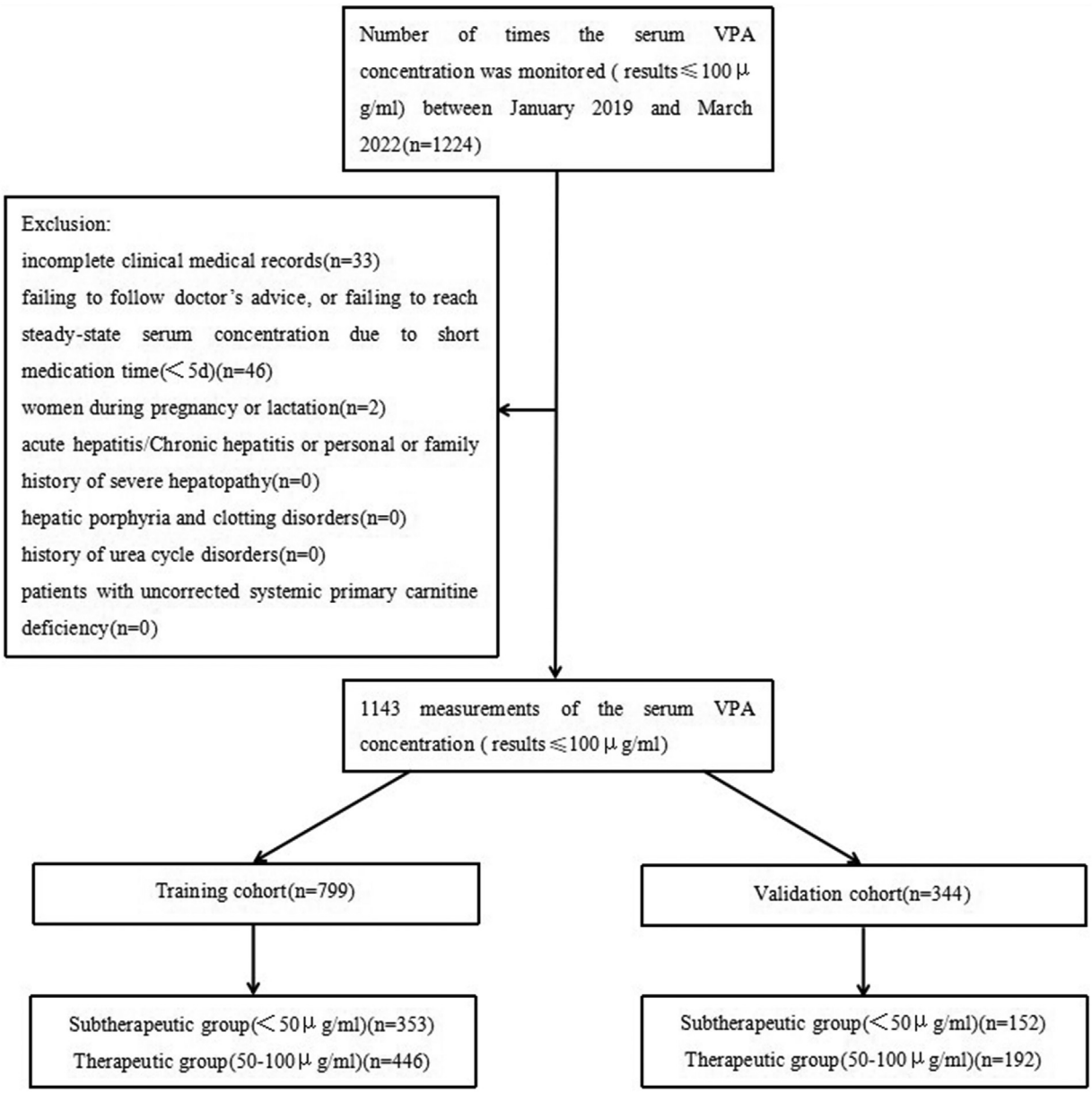

Figure 1. Flowchart displaying the number of included and excluded patients, as well as the definitions of the serum VPA concentration. VPA = valproic acid.

Reagents, instruments, and blood sample collection

Reagents and instruments: VPA test kit (Siemens, USA); Siemens Syva-E automatic biochemical analyzer. Blood sample collection: All patients' blood samples were collected via vacuum blood collection tubes without anticoagulant after at least 5 days of continuous administration (to reach the steady-state blood drug concentration) and before the next dose. After centrifugation at 3000 rpm, the serum was separated to monitor the trough concentrations of VPA.

Statistical analysis

Clinical data were analyzed via SPSS 20.0 statistical software (SPSS Inc. Chicago, IL, USA, 2011). Multicollinearity was assessed via the variance inflation factor (VIF). The measurement data are presented as the means ± standard deviations and were compared via *t* tests, and the enumeration data were compared between groups via the χ^2 test. $P < 0.05$ was considered to indicate statistically significant. The factors with $P < 0.05$ in the univariate analysis were included in the multivariate analysis, and the logistic regression equation was used to screen independent influencing factors. The R (R4.2.1) software package (AT&T Bell Laboratories, the University of Auckland, New Zealand, 2021) and the rms (regression modeling strategies) program package were used to establish the nomogram prediction model. Moreover, the Bootstrap package was applied for internal verification, and the consistency index was calculated via the rms package (C-index). The ROCR and rms programs were used to generate receiver operating characteristic curves.

Results

Univariate analysis was performed on the clinical data from the subtherapeutic and therapeutic groups. When the clinical data of the subtherapeutic and therapeutic groups were compared, there were no significant differences in sex; age; smoking

Table 1
Univariate analysis of the clinical data between the subtherapeutic and therapeutic groups.

Variable	Subtherapeutic group ($n = 353$)	Therapeutic group ($n = 446$)	Statistical value (t/χ^2)	P value
Sex				
Male	212	285	1.239	0.266
Female	141	161		
Age (y)				
≤6	48	64	1.057	0.788
>6–17 (including 17)	14	15		
>17–65 (including 65)	179	238		
>65	112	129		
Daily dose per unit of body weight (mg/kg/d)	13.63 ± 7.09	17.08 ± 7.09	6.831	<0.0001
Route of administration				
Immediate-release formulation oral	190	171	111.489	<0.0001
Sustained-release formulation oral	64	188		
Gastric tube feeding	76	18		
Micropump intravenous infusion	23	69		
Smoking status				
Yes	27	36	0.049	0.826
No	326	410		
Alcohol consumption status				
Yes	36	60	1.974	0.160
No	317	386		
Hepatic lesion				
Yes	60	12	49.188	<0.0001
No	293	434		
Kidney damage				
Yes	8	0	10.210	0.001
No	345	446		
Hypoalbuminemia (<38 g/L)				
Yes	78	26	46.051	<0.0001
No	275	420		
Combined with carbapenems				
Yes	58	6	60.855	<0.0001
No	295	440		
Combined with phenytoin sodium				
Yes	3	2	0.511	0.475
No	350	444		
Combined with carbamazepine				
Yes	9	12	0.015	0.902
No	344	434		
Combined with barbiturates				
Yes	77	53	14.261	<0.0001
No	276	393		
Combined with diazepam				
Yes	20	19	0.839	0.360
No	333	427		
Combined with lamotrigine				
Yes	6	15	2.131	0.144
No	347	431		
Combined with levetiracetam				
Yes	16	34	3.209	0.073
No	337	412		
Combined with oxcarbazepine				
Yes	14	20	0.130	0.719
No	339	426		
Combined with cholestyramine				
Yes	26	25	1.022	0.312
No	327	421		
Combined with nimodipine				
Yes	34	39	0.187	0.666
No	319	407		

status; alcohol consumption status; or combination with phenytoin sodium, carbamazepine, diazepam, lamotrigine, levetiracetam or oxcarbazepine, but the daily dose per unit of body weight (mg/kg/d), route of administration, hepatic lesion status, kidney damage status, hypoalbuminemia status, and combination with carbapenems or barbiturates were significantly different ($P < 0.01$), as shown in Table 1.

A multicollinearity analysis was first performed, with all VIF <2, which indicated that there was no multicollinearity problem among the independent variables. According to the results of univariate analysis of the clinical data between the subtherapeutic and therapeutic group, a logistic regression analysis was performed for daily dose per unit of body weight (mg/kg/d), route of administration, hepatic lesion, kidney damage, hypoalbuminemia, combined with carbapenems or barbiturates, and the results of the logistic regression analysis showed that: daily dose per unit of body weight (mg/kg/d) (OR = 0.902, 95% CI: 0.877–0.928), route of administration (OR = 0.353, 95% CI: 0.279–0.447), hepatic lesion (OR = 0.194, 95% CI: 0.077–0.490), hypoalbuminemia (OR = 0.342, 95% CI: 0.165–0.709), combination with carbapenems (OR = 0.056, 95% CI: 0.019–0.169), combination with barbiturates (OR = 0.471, 95% CI: 0.298–0.744)were independent influencing factors for substandard serum VPA concentration ($P < 0.05$)(details shown in Table 2).

Table 2
Multivariate logistic regression analysis of influencing factors between the subtherapeutic and therapeutic groups.

Risk factor	Regression coefficient	Standard error	Wald value	*P* value	Odds ratio	95.0% confidence interval	
						Lower limit	Upper limit
Daily dose per unit of body weight	−0.103	0.014	51.798	<0.0001	0.902	0.877	0.928
Route of administration	−1.041	0.120	74.722	<0.0001	0.353	0.279	0.447
Hepatic lesion	−1.639	0.473	12.025	0.001	0.194	0.077	0.490
Hypoalbuminemia	−1.073	0.372	8.319	0.004	0.342	0.165	0.709
Combined with carbapenems	−2.884	0.564	26.164	<0.0001	0.056	0.019	0.169
Combined with barbiturates	−0.754	0.233	10.432	0.001	0.471	0.298	0.744
Constant	8.641	0.830	108.432	<0.0001	5659.078		

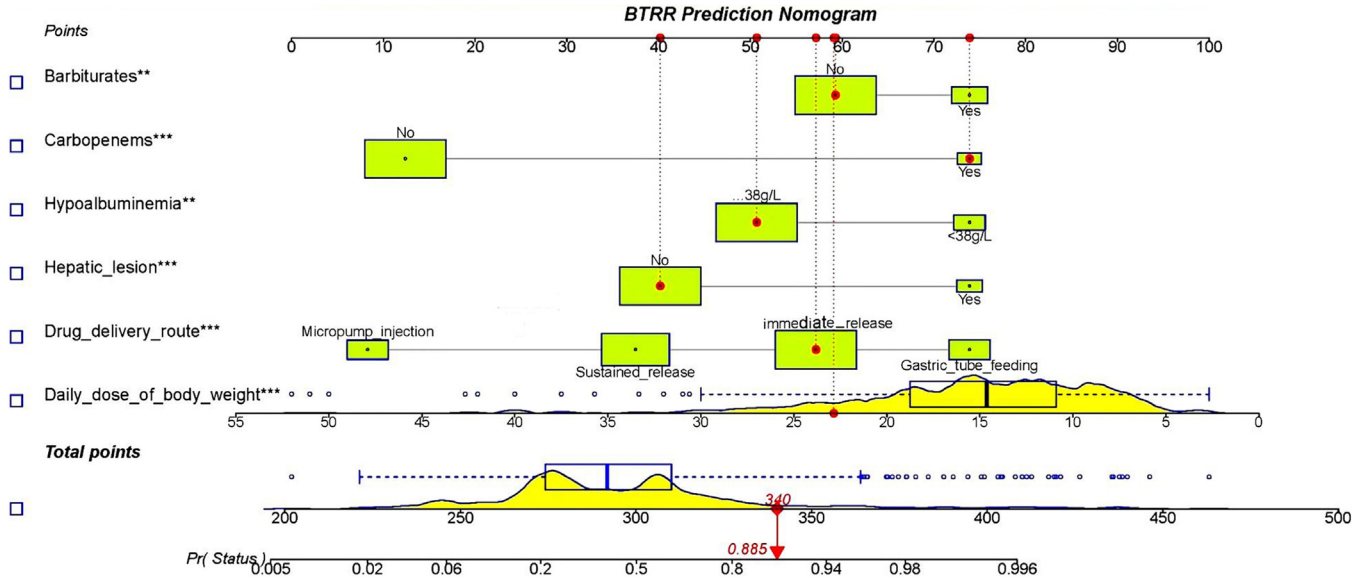

Figure 2. A constructed nomogram for predicting substandard serum VPA concentrations. In the nomogram, "Barbiturates," "Carbapenems," "Hypoalbuminemia," "Hepatic lesion," and "Drug delivery route" were categorical variables, and their distributions of samples were reflected by the size of the corresponding box. The "daily dose of body weight" was a continuous variable, and the distribution of the samples was reflected by the density plot of the total points. The clinical significance of each variable was reflected by the length of the axis that represented it. For example, in this patient, the score of each variable originated from the corresponding variable axis, and a red dotted line was drawn upward to the top-point axis to determine the score for each variable. The scores for the six variables were barbiturates (no, 60), carbapenems (yes, 74), hypoalbuminemia (no, 50), hepatic lesions (no, 40), the drug delivery route (immediate-release, 56), and the daily dose of body weight (23 mg/kg/d, 60). The sum scores of these variables (60 + 74 + 50 + 40 + 56 + 60 = 340) were located on the total points axis, and a vertical line was drawn downward to the Pr(status) axis to finally determine the probability of substandard serum VPA concentration (88.5%). VPA = valproic acid.

On the basis of 6 independent factors influencing the standard serum VPA concentration, which included the daily dose per unit of body weight (mg/kg/d), route of administration, hepatic lesions, and hypoalbuminemia combined with carbapenems combined with barbiturates, a related nomogram model for the prediction of substandard serum VPA concentration was established (as shown in Figure 2), and the model was also verified. The predicted value was essentially the same as the measured value, indicating that the nomogram prediction model of this study had good prediction ability (as shown in Figure 3). The C-index values reached 0.824 and 0.809 (as shown in Figure 4), indicating that the nomogram model of this study had good accuracy and discrimination. The decision curve revealed that the nomogram that predicted the risk of substandard serum VPA concentration had greater net benefit values from 12% to 94% (as shown in Figure 5), indicating that the model had a wide prediction interval.

Discussion

In the present study, we identified the influencing risk factors leading to substandard serum VPA concentrations in Chinese patients with epilepsy and constructed a relevant nomogram risk prediction model. Compared with the reported linear regression prediction model and population pharmacokinetic model, our nomogram model not only is easy to use but can also transform complex regression equations into concise figures, making the results of the prediction more visual and facilitating risk assessment for substandard serum VPA concentrations in patients with epilepsy.[17] Both external and internal validation revealed that the nomogram had good prediction efficiency and that the risk threshold range of the net clinical benefit was wide. In the nomogram, 6 predictors, that is, 6 independent influencing factors, are discussed in detail as follows.

Generally, the greater the dosage of a drug is, the greater its concentration in the body; this is true for the concentration of VPA. In the training cohort of this study, the dose of VPA taken by the patients ranged from 2.67 to 52 mg/kg/d, and the results of univariate analysis revealed that the mean daily doses per unit of body weight (mg/kg/d) were 17.08 ± 7.09 g and 13.63 ± 7.09 g for the therapeutic and subtherapeutic groups, respectively ($P < 0.01$), indicating that the trend of the serum VPA concentration increased with increasing daily dose per unit of body weight, which was also confirmed by multivariate logistic regression analysis. Therefore, the right dosage is very important for the serum concentration of VPA to reach the standard.

The formulations of VPA in our hospital included oral nonsustained-release formulations, oral sustained-release formulations, gastric tube feeding, and micropump intravenous infusions, and our study revealed that the probabilities of substandard serum VPA concentrations through these routes were 52.78%,

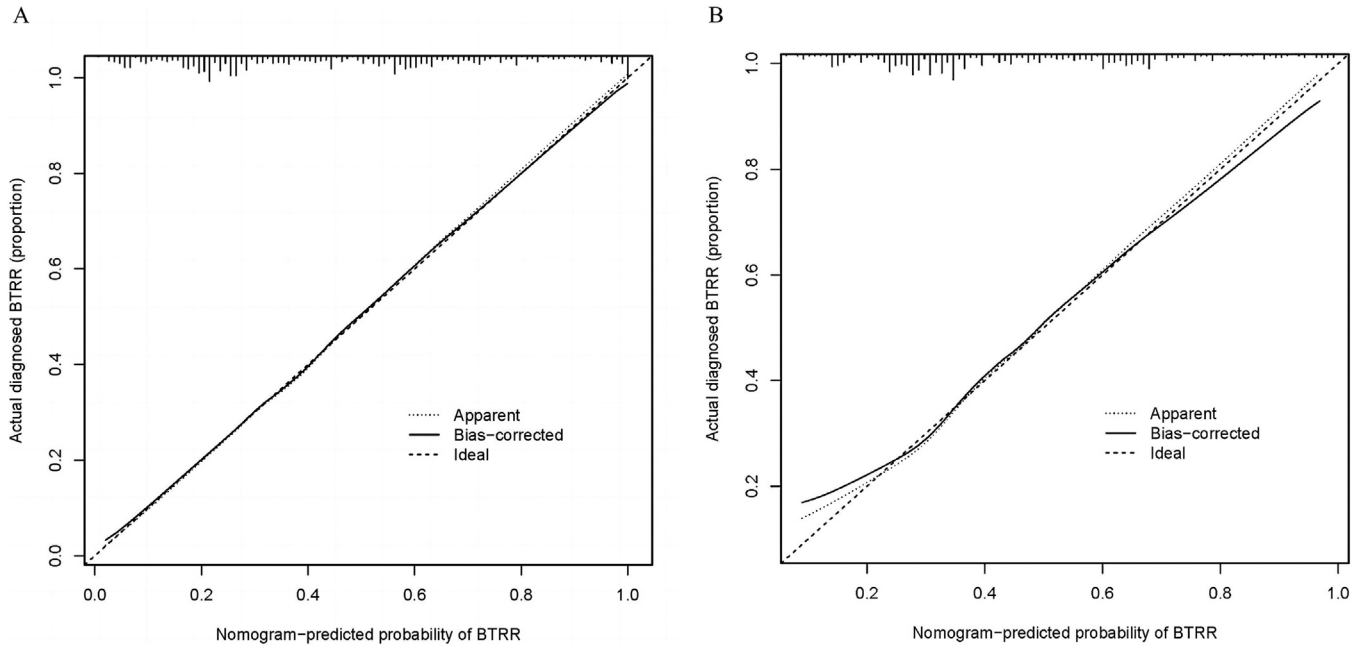

Figure 3. Calibration curve of the nomogram for predicting substandard serum VPA concentrations in the training cohort (A) and the validation cohort (B). The predicted probability of substandard serum VPA concentration is represented by the *x*-axis. The actual probability of substandard serum VPA concentration is represented by the *y*-axis. The diagonal dashed line represents a perfect prediction of an ideal model. The solid line indicates the performance of the nomogram, with values closer to the diagonal dashed line indicating better prediction. VPA = valproic acid.

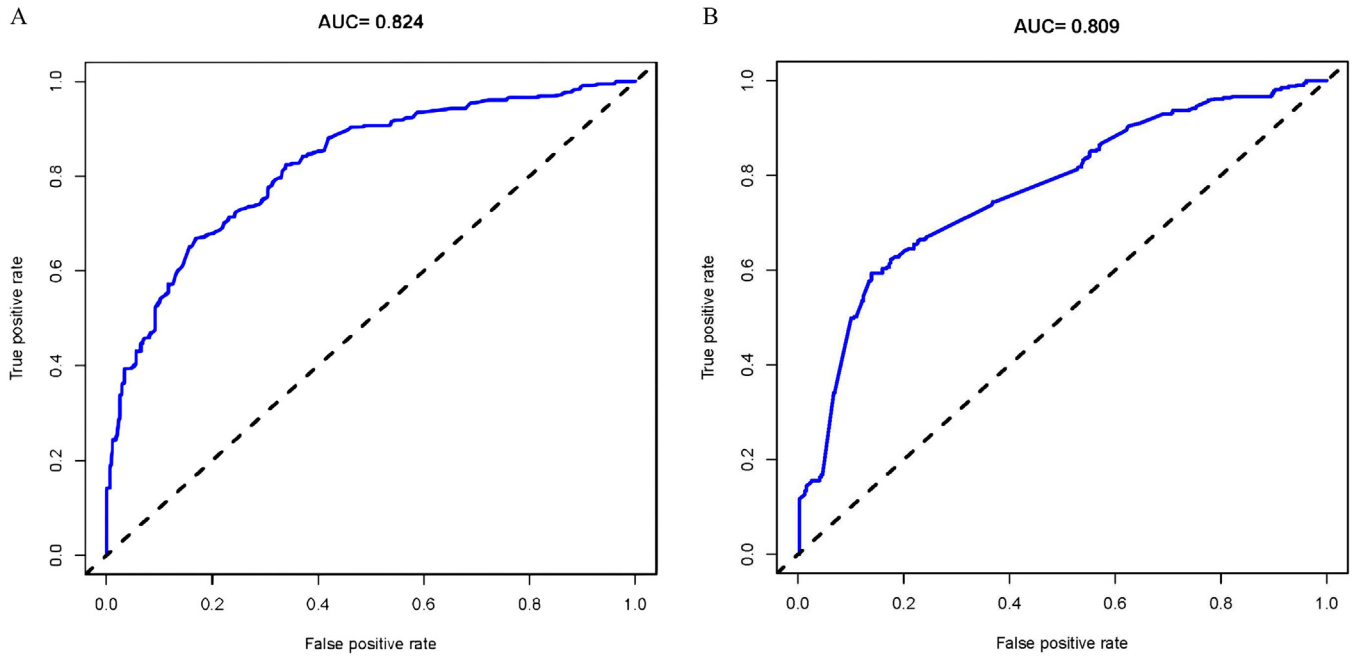

Figure 4. ROC curve of the nomogram model for predicting substandard serum VPA concentrations in the training cohort (A) and the validation cohort (B). AUC = area under the curve; ROC = receiver operating characteristic; VPA = valproic acid.

25.40%, 80.85%, and 25%, respectively. The probabilities of substandard serum VPA concentrations in patients receiving nonsustained-release formulations via oral administration and gastric tube feeding were significantly greater than those in patients receiving micropump intravenous infusion and sustained-release formulations via oral administration.

The serum VPA concentrations of nonsustained-release formulations, such as ordinary tablets or solutions of VPA (sodium salt), often fluctuate, resulting in low trough concentrations. For gastric tube feeding, the VPA tablets were ground and then dissolved. In this process, residual drug powder is ground in a mortar, and the dissolved drug solution adheres to the inner surface of a feeding tube made of polyvinyl chloride, which can cause the serum VPA concentration to be lower than the lower limit of the treatment window, thus affecting the effect of seizure control.[18] Therefore, improving the gastric tube-feeding process of VPA (sodium salt) tablets to reduce or prevent drug loss will help the serum concentration of VPA reach the standard.

Our results revealed that in the training cohort, the probabilities of substandard serum VPA concentrations in patients with hypoalbuminemia and patients without hypoalbuminemia were 75% and 39.57%, respectively, and patients with hypoalbumine-

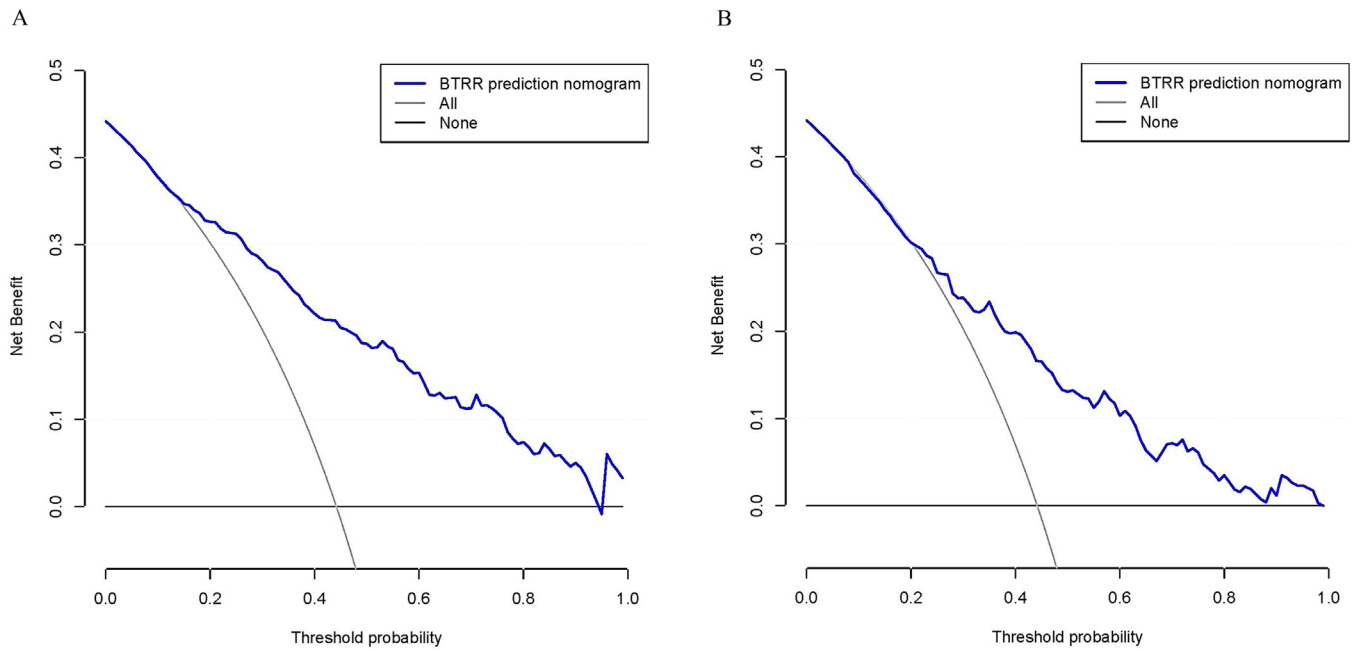

Figure 5. Decision curve of the nomogram model for predicting substandard serum VPA concentrations in the training cohort (A) and the validation cohort (B). The net benefit is represented by the *y*-axis. The solid blue line indicates the risk of substandard serum VPA concentrations predicted by the nomogram. The gray solid line represents the hypothesis that the serum VPA concentrations of all patients were substandard. The black solid line represents the hypothesis that no patients' serum VPA concentrations were substandard. The decision curve in the training cohort (A) showed that the use of this nomogram in the current study to predict substandard serum VPA concentration risk added more benefit than the intervention-all-patients scheme or the intervention-none scheme if the threshold probability was between 12% and 94%. VPA = valproic acid.

mia were significantly more likely to have substandard serum VPA concentrations ($P < 0.01$). Interestingly, contrary to what we expected, most of the patients with hepatic lesions had substandard serum VPA concentrations, and the probabilities of substandard serum VPA concentrations in patients with hepatic lesions and patients without hepatic lesions were 83.33% and 40.30%, respectively, which were significantly different ($P < 0.01$). Most drugs in plasma are bound to plasma proteins, but only unbound (free) drugs can diffuse from the vascular system to relevant receptor sites to play a pharmacological role.[19,20] VPA exerts its pharmacological effect by free VPA penetrating the blood–brain barrier to reach the cerebrospinal fluid and bind to related receptors.[21] The plasma protein binding rate of VPA is as high as 90% to 95%,[22] and hypoproteinemia results in low plasma protein levels in the human body; thus, the concentration of free VPA in patients with hypoalbuminemia increases significantly. Moreover, only free VPA, which is not combined with plasma proteins, can be metabolized by the liver. Therefore, the metabolic rate of VPA in the patients with hypoalbuminemia is greatly accelerated due to increased concentration of free VPA, which can ultimately lead to the substandard serum VPA concentration in these patients. In fact, in the present study, the majority of patients with hypoproteinemia who had samples with substandard serum VPA concentrations also presented with hepatic lesions, possibly because plasma proteins are synthesized in the liver, and hepatic lesions may hinder protein synthesis, leading to decreased plasma protein levels or even hypoproteinemia, which may eventually lead to substandard serum VPA concentrations. Kidney damage may cause protein loss, it may also lead to decreased plasma protein levels or even hypoproteinemia, so it was statistically significant in the univariate analysis of this study, but failed to retain in the multivariate analysis.[23] In addition, some diseases, such as repeated high fever, repeated infection, and malignant tumors, consume a large amount of albumin for a long time, resulting in hypoalbuminemia. There is some association between hypoalbuminemia status and the presence of hepatic lesions, but hepatic lesions are not the only cause of hypoalbuminemia. For patients with hypoalbuminemia or hepatic lesions, monitoring the serum-free VPA concentration is required for dose adjustment.[24]

The carbapenems used in our hospital include biapenem, meropenem, and imipenem/cilastatin. In this study, 64 patients in the training cohort used carbapenem. Among them, 58 patients had substandard serum VPA concentrations, and the probability of substandard serum VPA concentrations in patients who used carbapenems (90.63%) was far greater than that in patients without carbapenems (40.14%). We found that even if the infusion of carbapenems was stopped, it took some time for the serum VPA concentration to return to the initial level before the use of carbapenems.

Many scientific studies have reported that carbapenems can significantly reduce the serum VPA concentration. However, the mechanism of the interaction between carbapenems and VPA is still not clear.[25] It has been reported that carbapenems reduce the absorption of VPA on the basolateral membrane of intestinal epithelial cells by inhibiting membrane transporters in intestinal cells, which results in a reduction in the serum VPA concentration after oral administration of VPA (sodium salt).[26,27] VPA is metabolized mainly through the liver UGT into VPA-glucuronic acid (VPA-G), and some studies have reported that carbapenems may inhibit the activity of acetylphthalide hydrolase, thus inhibiting the depolymerization of VPA-G, leading to a reduction in the serum VPA concentration.[10,28–30] In addition, another study reported that carbapenems could inhibit the transporter protein associated with multidrug resistance (multidrug resistance protein 4) on the red blood cell (RBC) membrane, thus preventing the release of VPA from the RBC, leading to a decrease in the serum VPA concentration.[11,29,31]

Therefore, during routine clinical treatment, clinicians should avoid the combination of carbapenems and VPA. Carbapenems not only significantly reduce the serum VPA concentration, but may also exacerbate epilepsy.[32] But in the clinical treatment of epilepsy with severe infection, doctors firstly consider to control the infec-

tion to save the patients' lives, so there still exist combination of carbapenems and VPA in epilepsy with severe infection. However, in rare cases, this combination has been effective. For example, Khobrani et al.[33] reported a patient with excessive VPA (sodium salt) poisoning who was intentionally treated with meropenem under the guidance of a doctor, and the excessive-high serum VPA concentration successfully reduced.

Our results revealed that in the training cohort, compared with the probability of substandard serum VPA concentration being 41.26% (276/669) in patients without barbiturates, the probability was 59.23% (77/130) in patients who used barbiturates, with a significant difference ($P < 0.01$), indicating that the combined use of barbiturates may lead to a decreased serum VPA concentration.

Barbiturates are strong inducers of liver drug enzymes, which can increase the expression of cytochrome P450 (CYP450) and UGT-glucuronidation and increase hepatic blood flow to accelerate the metabolism of drugs.[34,35] VPA is extensively and complexly metabolized by the liver, and only a small amount is excreted from the urine in its original form. The metabolic enzymes of VPA mainly include UGT, CYP2C19 and CYP2C9. CYP2A6 and CYP2B6 are also involved in metabolism.[36] When phenobarbital is combined with VPA, the half-life of VPA is significantly reduced, and the metabolism of VPA is also accelerated, leading to a significant decrease in the serum VPA concentration,[37–39] which can be due to the induction of the expression of the metabolic enzymes UGT, CYP2C19 and CYP2C9 by phenobarbital. Therefore, when VPA is used in combination with barbiturates, dosage adjustment under the guidance of therapeutic drug monitoring is recommended.

Conclusion

In conclusion, through the collection and compilation of clinical data from Chinese patients with epilepsy monitored with serum VPA concentrations, a nomogram for predicting substandard serum VPA concentrations was established. This model not only can accurately predict the risk probability of substandard serum VPA concentrations in patients with epilepsy but is also convenient for allowing users to view the risk weights of the different influencing factors leading to substandard serum VPA concentrations visually. However, there may be some limitations in this study. First, this was a single-center study with a small sample size, and all the data were collected from Lu'an People's Hospital. Whether the findings can be extrapolated to other regions in China is unknown, and the conclusions still need to be verified in a multicenter study. Second, owing to conditional limitations, the role of gene polymorphisms in VPA metabolism was not explored in this study, and their effects on the serum VPA concentration in Chinese patients with epilepsy need to be further investigated.

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Ethics approval

The study was approved by the Ethics Committee of Lu'an People's Hospital (batch number: 2022LL005).

Informed consent

Written informed consent was obtained from all of the patients.

Availability of data and materials

All data for this study are presented in this paper.

Abbreviations

valproic acid (VPA); uridine diphosphate glucuronyl transferase (UGT); variance inflation factor (VIF); receiver operating characteristic (ROC); valproic acid-glucuronic acid (VPA-G); red blood cell (RBC); cytochrome P450 (CYP450); area under the curve (AUC)

Author contributions

Zi-Hao Duan and Jing Li designed the outline of the article, supervised it, wrote the manuscript, and responded to the reviewers' comments. Fa-Cai Wang and Zhi-Xiang Zhu revised the paper. Jing Li and Fa-Cai Wang edited the final manuscript. All relevant studies data were extracted by Jie-Chen and Jun-Jie Jiang, and Chun-Yuan He performed the data analyses. All authors read, reviewed, and approved the final manuscript.

Declaration of competing interest

We declare that we had no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service, and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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