Nomograms based on clinical factors to predict abnormal metabolism of psychotropic drugs

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Abstract. Interindividual variability in drug metabolism serves a critical role in the occurrence of adverse drug reactions. Factors such as age, sex, body mass index (BMI) and liver and renal function can influence the metabolism of antipsychotic medications. To the best of our knowledge, however, clinical prediction models based on these factors for estimating drug-metabolizing capacity have not yet been developed. Between January 2022 and September 2023, 185 adult patients (aged ≥18 years) who did not have cancer and were not critically ill, with or without comorbidities such diabetes, hypertension and liver and kidney diseases, who underwent pharmacogenetic testing at The First Hospital of Jilin University (Changchun, China) were enrolled. Clinical data were collected, and the participants were divided into training and validation cohorts. Logistic regression was performed to identify significant risk factors, which were incorporated into multivariable models to construct nomograms predicting psychotropic drug metabolism. A total of eight clinical indicators (BMI, hypertension, alkaline phosphatase, aspartate aminotransferase, cholinesterase, albumin to globulin ratio, urea, and uric acid) were significantly associated with psychotropic drug metabolism (all $P<0.05$). Based on these indicators, along with age and sex, prediction models for psychotropic drug metabolism were developed. The areas under the receiver operating characteristic curves for haloperidol, olanzapine, paroxetine, mirtazapine/venlafaxine and oxazepam/lorazepam in the validation dataset were 0.767, 0.767, 0.705, 0.740 and 0.789, respectively, indicating the models had moderate diagnostic efficiency. Nomograms were constructed to demonstrate the contribution of each indicator to drug metabolism capacity. To the best of our knowledge, the present study is the first to develop predictive models for psychotropic drug metabolism. These models offer clinicians practical tools to identify patients with impaired drug-metabolizing capacity, thereby enabling more precise and personalized medication management.

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Introduction

Psychotropic drugs are widely regarded as the cornerstone of mental illness treatment (1,2). Antidepressant therapy can typically occur for 2-3 years, whereas maintenance therapy with antipsychotics may occur for up to 5 years; in certain cases, maintenance therapy may require lifelong administration (3). However, variations in pharmacokinetics and pharmacodynamics between patients may lead to suboptimal responses or increased susceptibility to adverse effects, even when standard therapeutic doses are used (4,5). Phillips *et al* (6) reported that interindividual differences in drug metabolism may contribute to nearly half of all adverse drug reactions (7). Although pharmacogenetic testing has demonstrated its potential for increasing the efficacy and safety of psychotropic drugs by identifying genetic polymorphisms linked to drug metabolism (8-10), its widespread application in mental health care is limited by high costs. Therefore, there is need to develop affordable and effective tools for evaluating metabolic capacities for antipsychotic medications to guide clinical decision-making.

In addition to genetic factors, non-genetic factors such as age, sex, weight, smoking status, comorbid disease and liver and renal function have been shown to influence the metabolism of antipsychotic drugs (11-14). To the best of our knowledge, however, there are currently no clinical prediction models based on these factors. Therefore, the present study systematically collected patient data on demographics, lifestyle habits, past medical history and serological indicators to construct accurate clinical prediction models for assessing metabolic capacities for psychotropic drugs. Such models provide robust, evidence-based guidance for personalized medication management. Multivariable logistic regression analysis was initially performed on the total dataset to identify potential risk factors associated with the metabolic capacity for antipsychotics, antidepressants and anxiolytics. Based on these significant factors, prediction models and nomograms were developed for various psychotropic drugs. As a graphical predictive tool, the nomogram provides a visual and intuitive approach to forecast outcomes by integrating multiple influencing factors (15). By transforming these factors into intuitive

predictive components, the nomogram generates a total score that corresponds to the probability of a specific outcome (16). This personalized, user-friendly method provides an accessible way to predict outcomes, enabling an intuitive prediction of ability to metabolize psychotropic drugs. Additionally, the quality of the prediction models was evaluated using multiple validation methods to ensure their reliability and applicability in clinical practice.

Materials and methods

Clinical specimens and study design. Using the sample size formula for case-control study design in PASS version 21.0.3 software (NCSS, LLC), a total sample size of 112 participants (confidence level=0.95, power=0.8, assumed odds ratio=4.0) was required to ensure the accuracy, reliability and statistical power of the study results. As diabetes, hypertension and liver and kidney function are associated with drug metabolism, and these factors are important to consider when building a model to predict drug metabolism, a broad range of patients was included. Therefore, a total of 185 adult patients (age, ≥18 years), who did not have cancer and were not critically ill, with or without comorbidities such diabetes, hypertension and liver and kidney diseases, and underwent pharmacogenomic testing at The First Affiliated Hospital of Jilin University (Changchun, China) between January 2022 and September 2023 were initially. However, due to excessive missing clinical data, 31 patients were excluded, resulting in 154 patients being available for analysis. The dataset was initially used to screen potential risk factors and was subsequently split into a training dataset and a validation dataset at a 6:4 ratio. Variables that were identified as being significant following multivariable adjustments were incorporated into the final predictive models.

Clinical information, including pharmacogenetic testing results for psychotropic drugs (four antipsychotics, ten antidepressants and two anxiolytics), demographic information [age, sex and body mass index (BMI)], lifestyle habits (smoking and alcohol consumption status), past medical history (hypertension and diabetes) and serological indicators [liver and renal function, fasting blood glucose (FBG), blood lipids and hypersensitive C-reactive protein (hs-CRP)], was collected from the hospital records of all patients. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Jilin University (approval no. AF-IRB-032-06), and due to its retrospective nature, the requirement for informed consent was waived. Psychotropic drugs associated with serious adverse reactions, as well as those that are not commonly used in clinical practice, including one antipsychotic (clozapine) and three antidepressants (amitriptyline, doxepin and desipramine), were excluded from the study. Furthermore, serological indicators that are infrequently measured by clinical laboratories, including the glomerular filtration rate, α-L-fucosidase, collagen type IV, glycocholic acid, adenosine deaminase, monoamine oxidase, 5'-nucleotidase and cystatin C, were excluded. Missing values in the remaining dataset were addressed via multiple imputation; mean values obtained following five rounds of imputation were used for analysis. There were 125 male and 29 female participants, with a median age of 61 years (range, 20-91 years). After rigorous screening (excluding patients with excessive missing clinical information, drugs with uncommon use or severe adverse reactions, as well as serological indicators that are infrequently measured) and processing (imputing missing values), the dataset contained 154 patients and 31 clinical indicators [age, sex, BMI, smoking and alcohol consumption status, hypertension, diabetes, hs-CRP, homocysteine, FBG, triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol, aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), cholinesterase (CHE), prealbumin, total protein, albumin, globulin (GLOB), albumin to GLOB ratio (AGR), total (TBIL), conjugated and unconjugated bilirubin, total bile acid (TBA), urea, uric acid (UA) and creatinine]. These indicators were analysed for potential associations with the metabolic capacity of 12 psychotropic drugs (three antipsychotics: Haloperidol, olanzapine and risperidone; seven antidepressants: Citalopram, escitalopram, sertraline, bupropion, paroxetine, mirtazapine and venlafaxine and two anxiolytics: Oxazepam and lorazepam).

To enhance clinical applicability, continuous variables (age, BMI and serological indicators) were converted into categorical variables based on established criteria for statistical analysis (17-21). As age follows a normal distribution, the mean age (60.57) was used as the cut-off point to divide the patients into younger (age ≤60 years) and older (age >60 years) groups. BMI categories were classified according to Working Group on Obesity in China criteria as follows: Underweight (BMI <18.5), normal weight (BMI ≥18.5 and <25), overweight (BMI ≥25) and obese (BMI ≥28 kg/m^2) groups (17). Similarly, serological indicators were categorized as normal, decreased or elevated based on the standardized clinical ranges reported by First Hospital of Jilin University (18-21).

Screening potential indicators related to the abnormal metabolism of psychotropic drugs. A case-control analysis study design was utilized to individually analyse psychotropic drugs. For each analysis, individuals with normal metabolic capacities were classified as the control group, whereas those with abnormal metabolism capacity were designated the case group. Abnormal metabolism of psychotropic drugs refers to genetic variations or polymorphisms that influence drug metabolism at the genetic level. These variations impact the activity, expression or function of drug metabolic enzymes, thereby leading to abnormal drug metabolism (22).

To identify clinical indicators associated with drug metabolism, uni- and multivariate analyses on the total dataset were performed. Univariate analyses were conducted using the unpaired two-independent sample t-tests for continuous variables and χ^2 tests for categorical variables. Multivariate analyses were performed using three multivariable logistic regression models to investigate the association between clinical indicators and psychotropic drug metabolism. Clinical indicators that were not significant according to χ^2 test or multivariable logistic regression were excluded from subsequent analyses.

In the training dataset, significant clinical indicators were rescreened to identify potential risk factors. The associations between risk factors and differences in drug metabolism were validated using the validation dataset. A schematic overview of the study design is shown in Fig. 1.

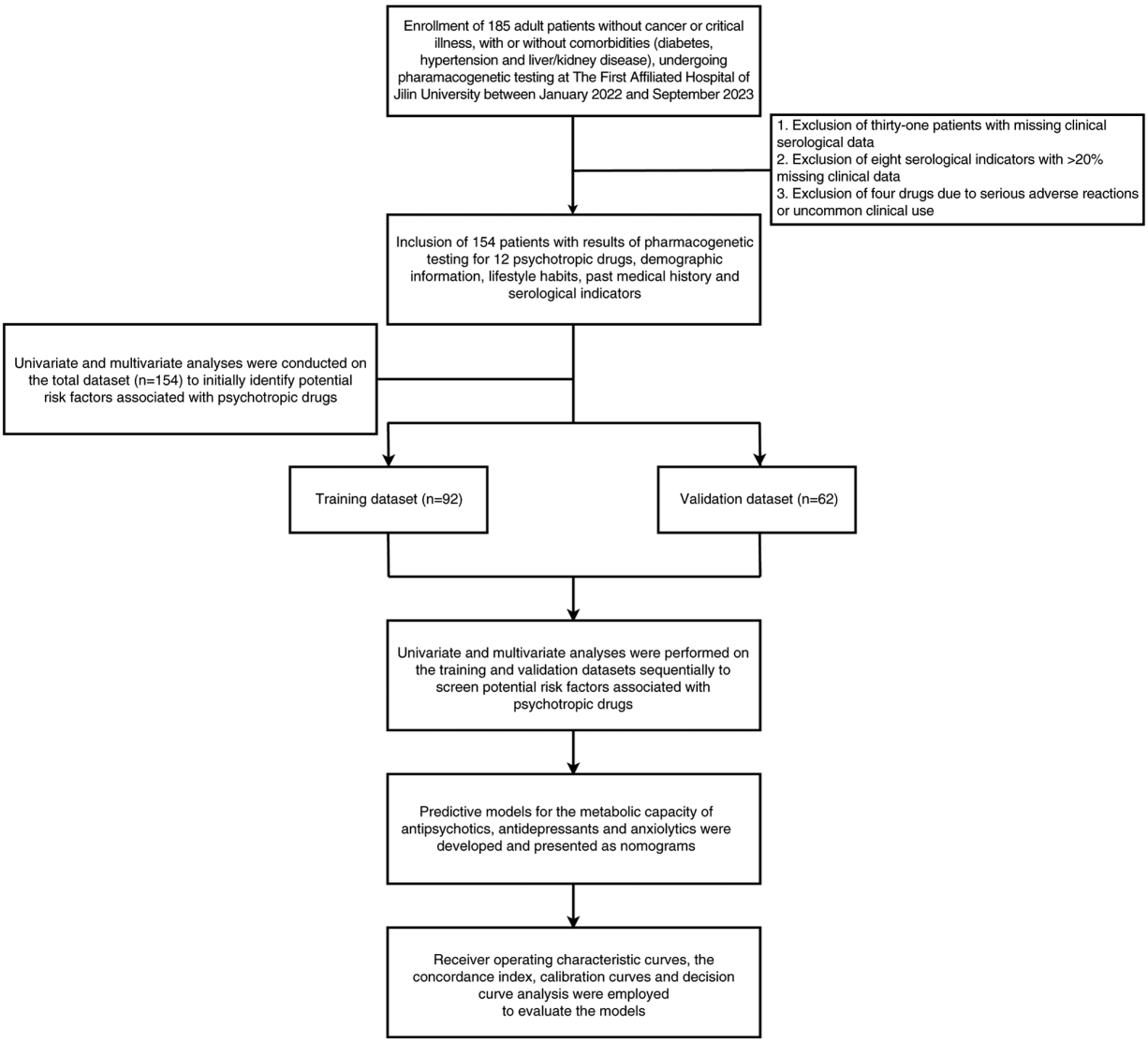

Figure 1. Overview of the study design.

Statistical analysis. Data are presented as the mean ± SD. In the preliminary analysis of the data, the unpaired two-independent sample t-tests were used to compare continuous variables, whereas the categorical variables were assessed using χ^2 or Fisher's exact test, as appropriate. Potential risk factors associated with abnormal psychotropic metabolism were further evaluated via three multivariable binary logistic regression models, with adjustments for two covariates (age and sex). Model 1 used binary logic regression to evaluate the association between each clinical indicator and the metabolic capacity of psychotropic drugs. In Model 2, variables that exhibited statistical significance were selected for multivariable logistic regression analysis. In Model 3, all clinical indicators were included in a multivariable binary logistic regression analysis. $P<0.05$ was considered to indicate a statistically significant difference. All analyses were conducted in R (version 4.1.2, http://www.R-project.org/) and SPSS (version 26, IBM Corp.).

Establishment and evaluation of predictive models. Variables that were identified as statistically significant were incorporated into the final multivariable model. To display the results of the logistic regression, the coefficients that were obtained from the multivariable analysis were used as weights to develop a nomogram, which facilitates the practical application of the model in evaluating the probability of abnormal drug metabolism. The performance of the predictive model was evaluated via receiver operating characteristic curves, the concordance index, calibration curves and decision curve analysis (DCA). The R packages used were 'rms' (version 6.7-0, http://cran.r-project.org/web/packages/rms), 'pROC' (version 1.18.4, http://cran.r-project.org/web/packages/pROC), and 'rmda' (version 1.6, http://cran.r-project.org/web/packages/rmda).

Results

Demographic and clinical characteristics of the patients. A total of 154 patients with clinical information and pharmacogenetic testing results were included. The sociodemographic characteristics of the study sample are shown in Tables SI-III. Metabolic capacities for various psychotropic drugs were estimated based on pharmacogenetic testing (Table SIV). The

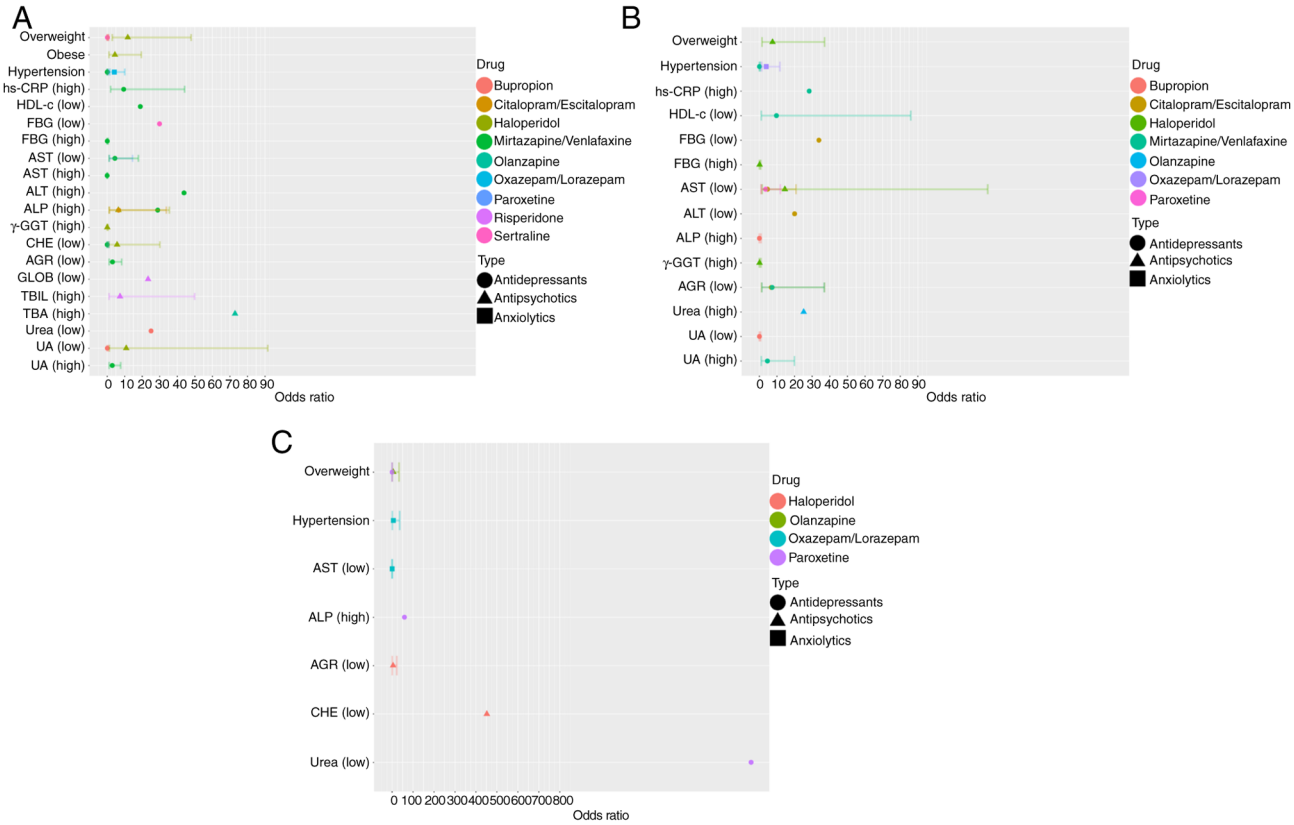

Figure 2. Multivariate logistic regression analysis was used to analyse association between clinical information, serological indicators and the metabolic capacity of psychotropic drugs. Multivariate logistic regression analysis results for (A) total, (B) training and (C) validation dataset. hs-CRP, hypersensitive C-reactive protein; HDL-c, high-density lipoprotein cholesterol; FBG, fasting blood glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; CHE, cholinesterase; AGR, albumin to globulin ratio; GLOB, globulin; TBIL, total bilirubin; TBA, total bile acid; UA, uric acid.

majority of patients exhibited normal metabolic capacities for haloperidol (n=97; 63.0%), olanzapine (n=138; 89.6%), risperidone (n=148; 96.1%), citalopram/escitalopram (n=137; 89.0%), sertraline (n=141; 91.6%), and mirtazapine/venlafaxine (n=90; 58.4%). However, a notable proportion of the patients displayed abnormal metabolism for bupropion (n=107; 69.5%), paroxetine (n=72; 46.8%), and oxazepam/lorazepam (n=120; 77.9%).

Preliminary identification of clinical indicators associated with the ability to metabolize psychotropic drugs via univariate analysis. Univariate analyses revealed clinical indicators that were significantly associated with the ability to metabolize psychotropic drugs in the total dataset (Tables SI-SIII). These indicators included BMI, hypertension, diabetes, hs-CRP, FBG, triglyceride, AST, ALT, γ-GGT, CHE, prealbumin, unconjugated bilirubin and creatinine.

Screening of potential risk factors associated with the ability to metabolize psychotropic drugs via multivariate analysis. To investigate the independent risk factors associated with abnormal drug metabolism, multivariate analyses were conducted on the total dataset (Fig. 2A; Tables SV-XIII). The multivariate analyses revealed associations between clinical indicators and abnormal metabolism of psychotropic drugs. For antipsychotics, metabolic abnormality was significantly associated with BMI and ALP, γ-GGT, CHE and UA levels for haloperidol, TBA levels for olanzapine and GLOB and TBIL levels for risperidone. For antidepressants, metabolic abnormality was significantly associated with BMI and ALP levels for citalopram/escitalopram, BMI and FBG levels for sertraline, urea and UA levels for bupropion, hypertension and AST and CHE levels for paroxetine and hs-CRP, FBG, HDL-c, AST, ALT, ALP, CHE and UA levels, as well as AGR and hypertension, for mirtazapine/venlafaxine. For anxiolytics, abnormal metabolism of oxazepam/lorazepam was associated with hypertension. These findings were based on analyses conducted for individual drugs rather than drug combinations.

To verify the predictive ability, potential risk factors were screened in the training dataset and association between these factors and drug metabolism were assessed in the validation dataset (Fig. 2B and C; Tables SXIV-SXXXI). AGR, CHE, urea and UA emerged as candidate risk factors via χ^2 test or binary logistic regression in the total and training dataset, whereas BMI, hypertension, AST and ALP were significant indicators via both χ^2 test and binary logistic regression in the validation dataset.

The multivariate analyses revealed several factors related to the abnormal metabolism of psychotropic drugs. Overweight individuals had significantly increased risk of abnormal metabolism of haloperidol (OR, 7.493, 95% CI: 1.516-37.027), with an increased risk also observed when CHE levels were decreased (OR, 5.668, 95% CI: 1.068-30.085). Similarly, overweight status was also associated with abnormal metabolism of olanzapine (OR, 5.863, 95% CI: 1.026-33.501). Moreover, a

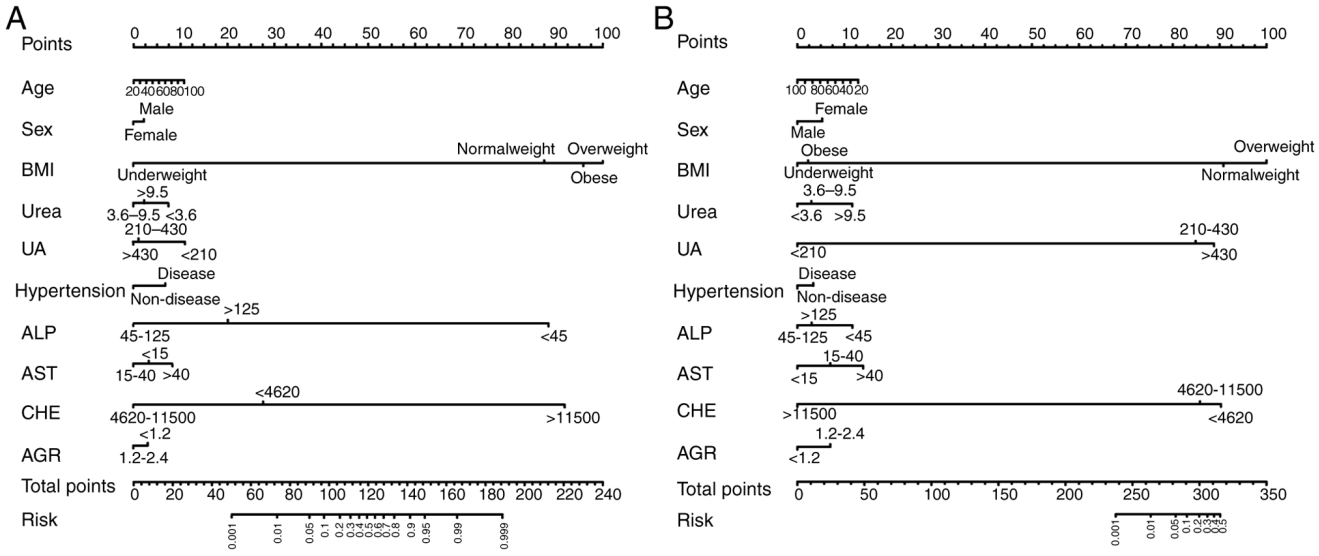

Figure 3. Nomograms for predicting the metabolic capacities of antipsychotics. (A) Haloperidol. (B) Olanzapine. BMI, body mass index; UA, uric acid; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CHE, cholinesterase; AGR, albumin to globulin ratio.

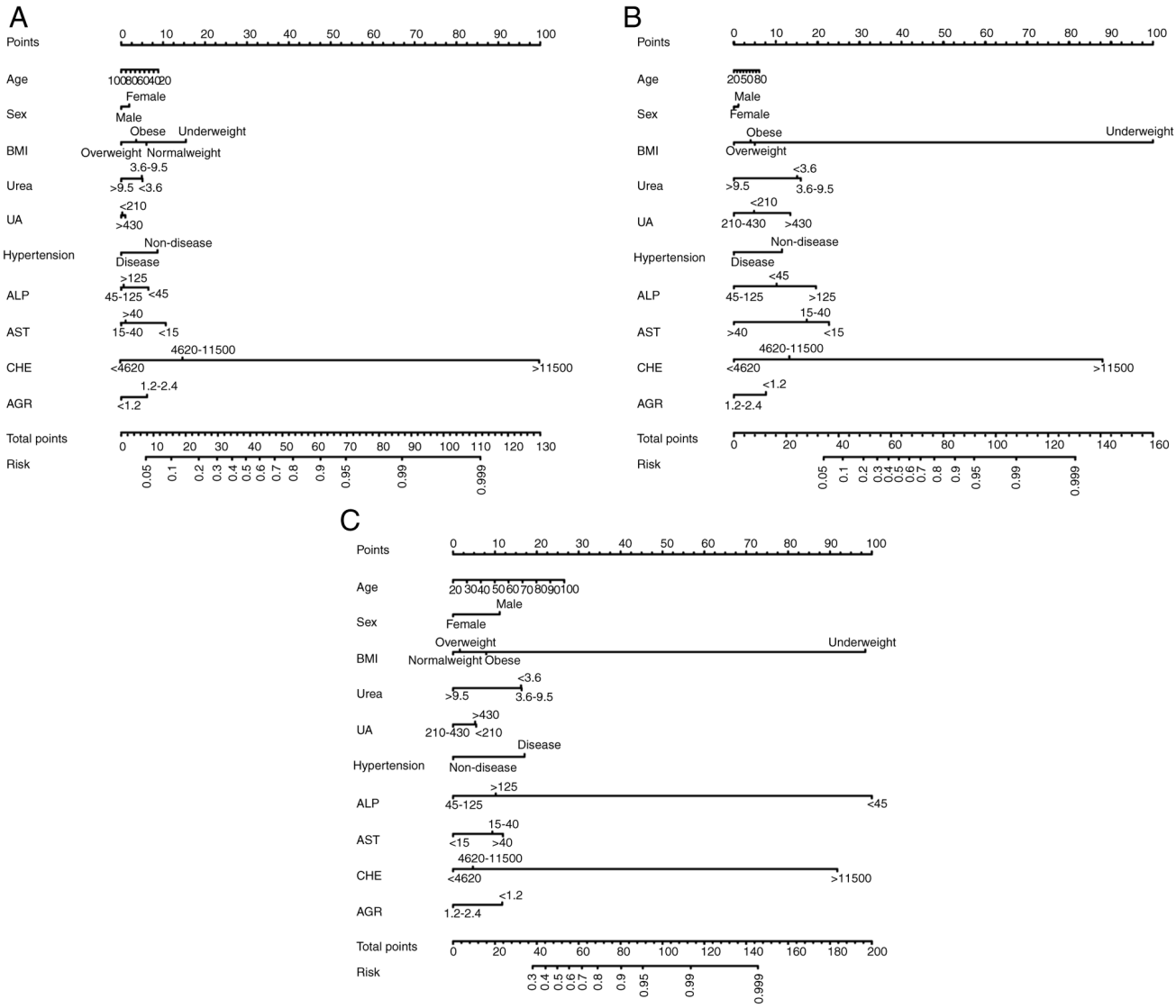

Figure 4. Nomograms for predicting the metabolic capacities of antidepressants and anxiolytics. (A) Paroxetine. (B) Mirtazapine/venlafaxine. (C) Oxazepam/lorazepam. BMI, body mass index; UA, uric acid; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CHE, cholinesterase; AGR, albumin to globulin ratio.

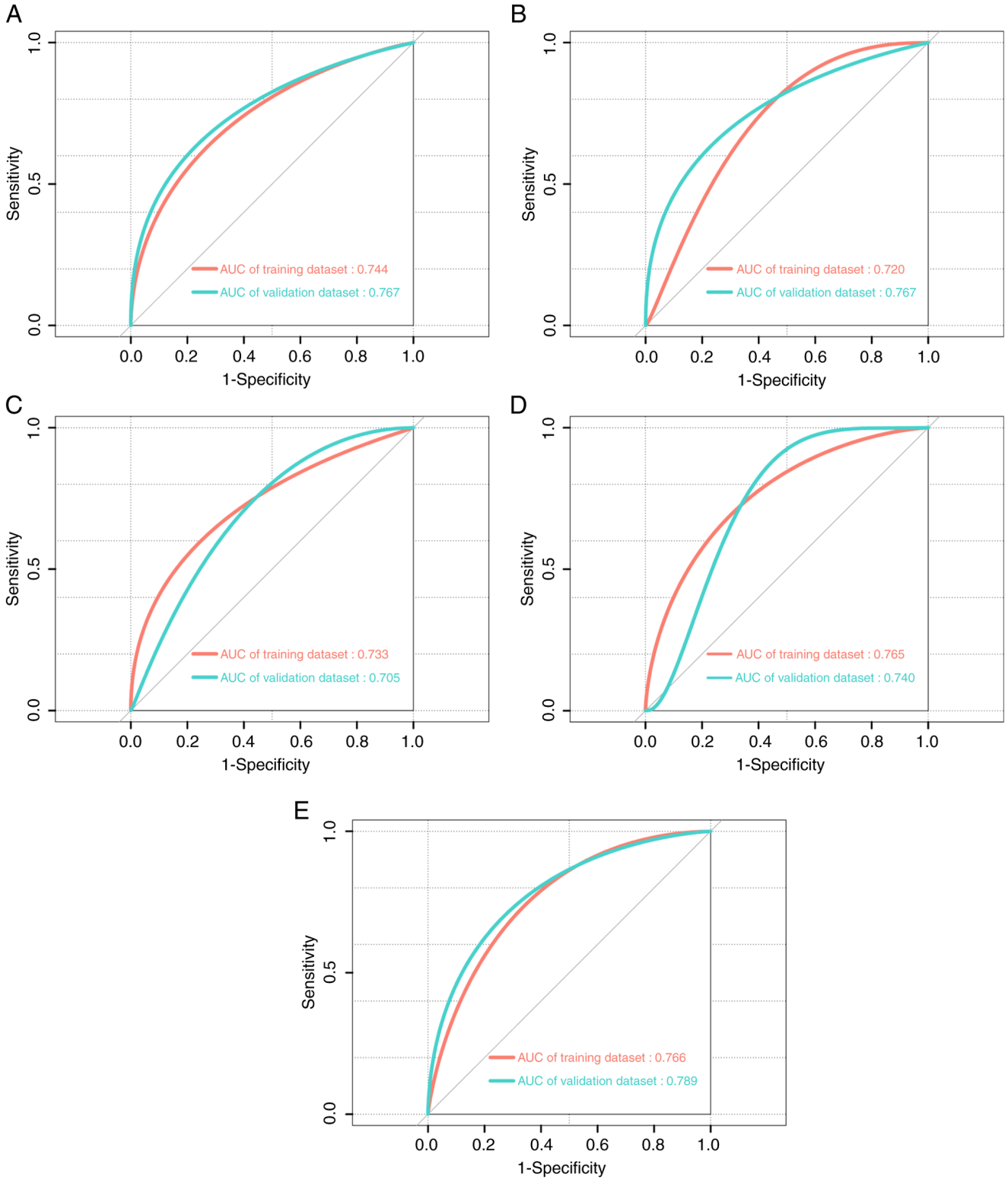

Figure 5. Evaluation of predictive models for the metabolic capacities of psychotropic drugs based on the training and validation datasets. (A) Haloperidol. (B) Olanzapine. (C) Paroxetine. (D) Mirtazapine/venlafaxine. (E) Oxazepam/lorazepam. AUC, area under the receiver operating characteristic curve.

decrease in the AST levels was identified as being a significant risk factor for abnormal metabolism of paroxetine (OR, 4.404, 95% CI: 1.335-14.533).

Hypertension was a risk factor for abnormal metabolism of oxazepam/lorazepam (OR, 3.878, 95% CI, 1.290-11.661) but paradoxically acted as a protective factor for abnormal metabolism of mirtazapine/venlafaxine (OR, 0.052, 95% CI: 0.01-0.278). Additionally, decreased levels of HDL-c (OR, 18.903, 95% CI: 1.301-274.721) and AGR (OR, 3.071, 95% CI: 1.139-8.281), as well as increased levels of UA (OR, 4.597, 95% CI: 1.059-19.962), were risk factors for abnormal metabolism of mirtazapine/venlafaxine. Furthermore, multivariable logistic regression analyses revealed significant associations between ALP and urea and abnormal metabolism of both antipsychotics and antidepressants.

Feature selection and development of individualized prediction models. Significant differences were observed in BMI, hypertension and ALP, AST, CHE, AGR, urea and UA levels between individuals with abnormal and normal metabolism. Using these significant factors, along with age and sex, prediction models were developed to assess the likelihood of abnormal metabolism for five psychotropic drugs (Figs. 3 and 4).

The nomogram of haloperidol highlighted BMI as the most influential factor in determining metabolic capacity, followed by CHE and ALP. By contrast, sex and AGR exhibited minimal effects on haloperidol metabolism. Similarly, the nomogram of olanzapine indicated that BMI plays a pivotal role in determining metabolic capacity, with CHE and UA also notably contributing, whereas hypertension and sex exerted a limited influence. In the nomograms of paroxetine, mirtazapine/venlafaxine and oxazepam/lorazepam, various factors were also found to influence drug metabolism. Specifically, in the case of paroxetine, CHE exhibited the most prominent impact, followed by BMI and AST, with sex and UA demonstrating limited effects. Similarly, the nomogram for mirtazapine/venlafaxine highlighted BMI as the primary influencing factor, followed by CHE and AST, whereas sex and age had minimal impacts. Finally, the nomogram for oxazepam/lorazepam indicated that ALP exhibited the greatest impact on metabolic capacity, followed by BMI and CHE, whereas UA and sex had limited impacts.

Performance evaluation of individualized prediction models. The developed models incorporated age, sex, BMI, hypertension, ALP, AST, CHE, AGR, urea and UA. For the 154 patients, the C-indices of the nomograms for haloperidol, olanzapine, paroxetine, mirtazapine/venlafaxine and oxazepam/lorazepam were 0.748, 0.733, 0.678, 0.734 and 0.751, respectively. Additionally, in the training dataset, the area under the receiver operating characteristic curve (AUC) values were 0.744, 0.720, 0.733, 0.765 and 0.766, respectively. In the validation dataset, AUC values for these drugs were 0.767, 0.767, 0.705, 0.740, and 0.789, respectively (Fig. 5). These results indicated that the models exhibited moderate predictive accuracy in predicting the abnormal metabolic capacity of psychotropic drugs. To assess model performance, calibration curves were used to evaluate the accuracy of the nomograms (Figs. S1 and S2). The predictive performance of the nomograms in both the training and validation datasets was moderately consistent with the actual results. In addition, DCA has also been widely used to evaluate the clinical utility of nomograms (23,24). As shown by the DCA, the nomograms demonstrated a notable positive net benefit for predicting the risk of abnormal metabolism capacity of psychotropic drugs, thus indicating their potential for clinical application (Fig. S3).

Discussion

The present study developed and validated innovative predictive models for assessing the metabolic capacity of psychotropic drugs based on clinical characteristics and serological indicators. These models provide a practical alternative to pharmacogenetic testing by offering greater accessibility, cost-effectiveness and time efficiency. Unlike genetic testing, which requires advanced technology and equipment, the present models rely on easily available clinical information, thus making them more suitable for routine clinical use. Each of the predictive models incorporated ten key variables that notably influence the metabolism of psychotropic drugs, including age, sex, BMI, hypertension, ALP, AST, CHE, AGR, urea and UA.

Elderly individuals are particularly susceptible to the side effects of psychotropic drugs due to physiological, pharmacokinetic and pharmacodynamic changes associated with age (25). As age increases, DNA hypermethylation typically occurs in the promoter region. This epigenetic change results in decreased expression levels of genes regulated by DNA methylation, including those involved in drug metabolism and distribution, such as cytochrome P450 (CYP) enzymes; these changes impair the metabolism of psychotropic drugs (26,27). Previous studies have demonstrated that age affects the clearance of escitalopram, whereas BMI affects the volume of distribution of escitalopram (28-30). The CYP450 enzyme family serves a central role in the metabolism of psychotropic drugs. Several studies have shown that genetic polymorphisms in CYP2C19, CYP2D6 and other genes are associated with antipsychotic medication concentrations in the blood (31-34). Although there is no significant sex-specific difference in CYP2C19 activity, it has been reported that female patients tend to exhibit increased CYP2D6 activity (35,36). Furthermore, patients with depression and certain types of anxiety disorder (such as generalized anxiety disorder) have a notably increased likelihood of concurrently developing hypertension (37). Additionally, variations in liver and renal function affect the pharmacokinetics of individuals (38,39). Depression is associated with an increase in oxidative stress and a decrease in antioxidant defences (40). Chaudhari *et al* (41) reported a negative association between serum UA levels and the intensity of depression, which may be attributed to the potent antioxidant properties of UA.

The present study established effective nomograms that display the impacts of risk factors on drug metabolism and effectively evaluate metabolic capacities for psychotropic drugs. These nomograms incorporate easily accessible clinical indicators, thereby enhancing their practicality and clinical utility. These nomograms predict the possibility of abnormal drug metabolism in patients, thus providing clinical decision-making references for the necessity of early screenings for psychiatric drug metabolism and pharmacogenetic testing. For patients with a low predicted likelihood of abnormal metabolism, pharmacogenetic testing can be deferred or cancelled, thus conserving both time and resources. Within-cohort validation demonstrated that the models possessed reasonable discriminatory and calibration abilities.

However, the present study had limitations. First, the retrospective study design and relatively small sample size may introduce a potential selection bias. Second, the estimated glomerular filtration rate, the main index for evaluating renal function, was not included in the logistic regression analysis due to the lack of available data in the retrospective study. Follow-up studies incorporating more appropriate variables are needed to refine the model and enhance its ability to assess abnormal drug metabolism. Third, although the robustness of nomograms was internally validated in the same population, external validation in populations from other regions and countries is lacking.

Multicentre studies with larger, more diverse populations are needed to validate and generalize the predictive models.

In conclusion, BMI, hypertension, ALP, AST, CHE, AGR, urea and UA serve key roles in distinguishing between normal and abnormal metabolism of antipsychotic drugs. Based on these associations, convenient, cost-effective, non-invasive, radiation exposure risk-free and simple prediction models were established. The nomograms constructed based on these models exhibited favourable diagnostic accuracy and calibration in distinguishing between normal and abnormal drug metabolism. To extend the applicability of these models and promote their use in diverse populations, further validation with data from different institutions is warranted.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SZ, XH and YJ analyzed the data and wrote the manuscript. PZ, JS and YJ conceived the study, supervised the research and edited the manuscript. All authors have read and approved the final manuscript. SZ and XH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The Ethical Standard Research Committee of the First Affiliated Hospital of Jilin University approved the present study (approval no. AF-IRB-032-06). The requirement for informed consent was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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