Am J Transl Res 2025;17(11):9076-9083
www.ajtr.org /ISSN:1943-8141/AJTR0167491

Original Article

Combinatorial classification model for predicting antipsychotic-induced hyperprolactinemia risk

Zhenhua Wang[1], Jing Li[2], Yajuan Le[1], Haiying Jin[1], Xiaocong Fei[1], Haizhi Chen[1]

[1]Department of Psychiatry, Huzhou Third Municipal Hospital, The Affiliated Hospital of Huzhou University, Huzhou 313000, Zhejiang, China; [2]Department of Party and Government Comprehensive Office, Center for Disease Control and Prevention of Huzhou City, Huzhou 313000, Zhejiang, China

Received July 16, 2025; Accepted November 5, 2025; Epub November 15, 2025; Published November 30, 2025

Abstract: Objectives: To develop a risk prediction model for antipsychotic-induced hyperprolactinemia in female patients with schizophrenia. Methods: A total of 200 female patients with first-episode schizophrenia who underwent antipsychotic monotherapy at Huzhou Third Municipal Hospital from February 2022 to December 2023 were enrolled in this study. Venous blood samples were collected before treatment to measure thyroid function, cortisol, and sex hormones. Based on the levels of prolactin (PRL) and macroprolactin (MPRL) after four weeks of treatment, patients were divided into two groups: the hyperprolactinemia group (n = 92) and the macroprolactinemia group (n = 108). Baseline clinical data were compared between groups, and a risk prediction model was constructed and evaluated using receiver operating characteristic (ROC) analysis, calibration curves, and decision curve analysis (DCA). External validation was performed in an independent cohort of 57 patients with schizophrenia admitted between January and July 2024. Results: Univariate and multivariate analyses identified body mass index (BMI), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and cortisol as significant predictors of antipsychotic-induced hyperprolactinemia ($P < 0.05$). The ROC curve showed an area under the curve (AUC) of 0.838 for the modeling cohort, with specificity and sensitivity of 0.896 and 0.635, respectively. Internal and external verification yielded AUCs of 0.852 and 0.689, with specificities/sensitivities of 0.903/0.759 and 0.677/0.615, respectively. The calibration curve demonstrated good alignment with the ideal curve, and DCA indicated the model provided superior net clinical benefit. Conclusions: The proposed model accurately predicts the risk of antipsychotic-induced hyperprolactinemia in female patients with schizophrenia, offering a valuable tool for early clinical risk assessment.

Keywords: Antipsychotic drugs, hyperprolactinemia, schizophrenia, prediction model

Introduction

Schizophrenia is a chronic, severe, and disabling mental illness primarily treated with antipsychotic drugs [1, 2]. While antipsychotics are essential for symptom control, they frequently induce elevated serum prolactin (PRL) levels. However, only some patients develop clinically significant hyperprolactinemia (HPRL), whereas others exhibit asymptomatic elevation-termed macroprolactinemia - which does not need prolactin-lowering therapy [3-5]. Risperidone is a widely used atypical antipsychotic drug, commonly prescribed for both acute and chronic schizophrenia. However, due to patients' limited self-care abilities, relying solely on clinical manifestations may delay diagnosis and treatment in those with true HPRL requiring intervention. Conversely, the absence of macroprolactin (MPRL) testing may lead to unnecessary treatment in asymptomatic patients, potentially causing excessive suppression of monomeric PRL and subsequent gonadal or luteal insufficiency, resulting in clinical misdiagnosis and overtreatment [6]. Therefore, early prediction and accurate identification of HPRL caused by antipsychotics are particularly important.

According to the neuroendocrine theory, PRL secretion is primarily regulated by the hypothalamic-pituitary-gonadal (HPG) axis [7], with additional modulation by the hypothalamic-pituitary-thyroid (HPT) and hypothalamic-pituitary-adrenal (HPA) axes. These neuroendocrine axes not only regulate their respective target glands but also interact through complex inter-

https://doi.org/10.62347/RJWI9610

axis feedback mechanisms [8]. Based on this regulatory framework, the present study incorporated MPRL detection to accurately distinguish true HPRL induced by antipsychotics and established an early prediction model grounded in neuroendocrine regulation. This model aims to guide individualized antipsychotic therapy, improve treatment adherence, reduce disease recurrence, and ultimately alleviate the burden on families and society.

Materials and methods

Subjects

This study enrolled 200 female patients with first-episode schizophrenia admitted to Huzhou Third Municipal Hospital between February 2022 and December 2023. All participants received risperidone monotherapy for a 4-week observation period. Venous blood samples were collected before treatment to measure thyroid function, cortisol, and sex hormone levels. The dataset was randomly divided into a modeling cohort (n = 140) and an internal verification cohort (n = 60) at a ratio of 7:3.

Inclusion criteria: (1) Diagnosis of schizophrenia confirmed by at least two attending psychiatrists according to the *International Classification of Diseases, 10th Revision* (ICD-10), with a Positive and Negative Syndrome Scale (PANSS) score ≥ 60; (2) Regular menstrual cycles and normal baseline PRL levels; (3) Age ≥ 18 years.

Exclusion criteria: (1) Presence of organic brain disorders, affective disorders, or other psychiatric conditions; (2) Severe physical illnesses or conditions that could interfere with assessments; (3) History of substance abuse or dependence within the past year; (4) Use of antipsychotics, mood stabilizers, antiepileptics, or other drugs that could affect PRL levels within the past six months; (5) Pregnancy or breastfeeding.

For external validation, clinical data from an additional 57 patients with schizophrenia ad mitted between January and July 2024 were collected using identical inclusion and exclusion criteria. This study was approved by the Ethics Committee of Huzhou Third Municipal Hospital, the Affiliated Hospital of Huzhou University. Informed consent was obtained from all patients.

Implementation steps

(1) Clinical and demographic data were collected, including age, parity, menstrual status, BMI, and disease duration. The total treatment observation period lasted 4 weeks. (2) All patients received monotherapy with a single antipsychotic agent (excluding aripiprazole). Drug dosages were titrated to therapeutic levels within the first 2 weeks, and no additional endocrine medications were administered. Fasting venous blood samples (5 mL) were collected in the morning prior to treatment. To minimize hormonal fluctuations, blood sampling was performed outside the menstrual period and 2-4 days before or after menstruation. Serum PRL, MPRL, thyroid function [free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH)], cortisol, and sex hormones [luteinizing hormone (LH), follicle stimulating hormone (FSH), and sex hormone-binding globulin (SHBG)] were measured. Baseline differences in these indices between the hyperprolactinemia and macroprolactinemia groups were analyzed, and significant predictors were subsequently used to establish a risk prediction model.

Construction and verification of the model

The model was constructed using R (v4.4.1). All patients were randomly divided into a modeling cohort (n = 140) and an internal verification cohort (n = 60) in a 7:3 ratio. The modeling cohort data were utilized to construct the prediction model, while the internal verification cohort data were utilized to evaluate its predictive performance. The dependent variable was antipsychotic-induced hyperprolactinemia. Model performance was assessed in both internal and external validation cohorts, calculating accuracy, sensitivity, specificity, recall rate, precision, and the area under the receiver operating characteristic curve (AUC). A combined classification model was established using the “rms” package in R software. Model discrimination, calibration, and clinical utility were evaluated through ROC analysis, calibration plots, and decision curve analysis, respectively.

Statistical methods

All statistical analyses were conducted with using SPSS 23.0 software. Quantitative vari-

Table 1. Comparison of training set data between the two groups of patients

Index	Hyperprolactinemia group (n = 63)	Macroprolactinemia group (n = 77)	t/χ^2	*P*
Age (year, $\bar{x}\pm s$)	31.25±5.71	34.22±6.38	-2.871	0.005
Parity			1.087	0.581
0	28	36		
1	20	28		
≥2	15	13		
Menstruation			1.327	0.515
Less flow	46	51		
More flow	4	9		
Moderate flow	13	17		
BMI (kg/m^2, $\bar{x}\pm s$)	20.84±2.08	22.02±2.30	-3.132	0.002
Course of dieses (month, $\bar{x}\pm s$)	11.95±3.39	12.17±3.60	-0.364	0.717
FT3 (pmol/L)	3.50±0.84	3.38±1.01	0.767	0.445
FT4 (pmol/L)	13.83±1.13	14.33±1.55	-2.124	0.035
TSH (μU/mL)	1.74±0.66	1.48±0.65	2.336	0.021
Cortisol (nmol/L, $\bar{x}\pm s$)	331.81±82.27	256.45±54.25	6.498	<0.001
LH (mU/mL, $\bar{x}\pm s$)	7.69±2.23	8.23±2.76	-1.256	0.211
FSH (mU/mL, $\bar{x}\pm s$)	6.80±2.50	6.57±1.91	0.610	0.543
SHBG (ng/mL, $\bar{x}\pm s$)	223.10±25.34	216.47±24.11	1.582	0.116
Risperidone blood concentration (ng/mL)	28.17±2.76	27.96±2.85	0.452	0.652

Tips: FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone; LH: luteinizing hormone; FSH: follicle stimulating hormone; SHBG: sex hormone binding globulin.

Table 2. Variable assignment

Index	Description of valuation
Age	Actual value entry
BMI	Actual value entry
FT4	Actual value entry
TSH	Actual value entry
Cortisol	Actual value entry

BMI: Body Mass Index; FT4: free thyroxine; TSH: thyroid stimulating hormone.

ables were expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared between groups using the independent-samples t-test. Categorical variables were expressed as counts and percentages, and analyzed using the chi-square tests (χ^2) test. Repeated measurements over time were evaluated using repeated-measures analysis of variance (ANOVA) followed by LSD-t test. Multivariate logistic regression was employed to identify independent predictors of antipsychotic-induced hyperprolactinemia in schizophrenic patients. A *P* value < 0.05 was considered statistically significant.

Results

Univariate and multivariate regression analyses of independent risk factors for antipsychotic-induced hyperprolactinemia

Based on MPRL and PRL levels, patients in the training set were categorized into a hyperprolactinemia group (n = 63) and a macroprolactinemia group (n = 77). In univariate analysis, significant differences were observed between the hyperprolactinemia and macroprolactinemia groups in age, BMI, FT4, TSH and cortisol (all $P < 0.05$), whereas no significant differences were observed in the remaining variables ($P > 0.05$) (**Table 1**).

Variables identified as significant in univariate analysis, including age, BMI, FT4, TSH and cortisol were subsequently entered as independent variables in a multivariate logistic regression analysis. The occurrence of antipsychotic-induced hyperprolactinemia (coded as 0 for macroprolactinomas and 1 for hyperprolactinemia) served as the dependent variable in the logistic analysis, as shown in **Table 2**.

Table 3. Multivariate logistic regression analysis

Index	*B*	SE	Wald	*P*	OR	95% CI
Age	-0.064	0.035	3.365	0.067	0.938	0.876-1.004
BMI	-0.330	0.105	9.795	0.002	0.719	0.585-0.884
FT4	-0.385	0.168	5.225	0.022	0.681	0.490-0.947
TSH	0.744	0.357	4.350	0.037	2.105	1.046-4.237
Cortisol	0.018	0.004	23.420	<0.001	1.018	1.011-1.026
Constant	7.908	3.415	5.362	0.021	2717.903	-

BMI: Body Mass Index; FT4: free thyroxine; TSH: thyroid stimulating hormone.

Table 4. Comparison of modeling cohort and internal verification cohort data

Index	Modeling cohort (n = 140)	Internal verification cohort (n = 60)	*t*	*P*
BMI	21.49±2.27	21.25±2.20	0.690	0.491
FT4	14.11±1.39	14.12±1.24	-0.085	0.933
TSH	1.59±0.66	1.55±0.69	0.427	0.670
Cortisol	290.36±77.74	312.95±92.75	-1.774	0.078

BMI: Body Mass Index; FT4: free thyroxine; TSH: thyroid stimulating hormone.

Multivariate logistic regression analysis identified BMI, FT4, TSH, and cortisol as independent predictors for antipsychotic-induced hyperprolactinemia in schizophrenic patients ($P < 0.05$). The prediction equation was developed: Y = 7.908 - 0.330 × BMI - 0.385 × FT4 + 0.744 × TSH + 0.018 × Cortisol. Detailed statistical results are presented in **Table 3**.

Construction and verification of the predictive model

Statistical comparison revealed balanced baseline characteristics between the training and validation cohorts ($P > 0.05$, **Table 4**).

Based on the four independent predictors identified (BMI, FT4, TSH, and cortisol), a combinatorial classification model was constructed to predict the risk of antipsychotic-induced hyperprolactinemia using the modeling cohort data (**Figure 1**). For instance, a patient with a BMI of 19 kg/m^2, FT4 of 13 pmol/L, TSH of 2 μU/mL, and cortisol of 300 nmol/L, the corresponding nomogram scores would be approximately 36, 34, 19, and 49 points. The total score of 138 points corresponds to a predicted hyperprolactinemia risk of about 69%.

ROC curve analysis showed that the model achieved an AUC of 0.838 (95% CI: 0.774-0.902) in the modeling cohort, with a specificity of 0.896 and sensitivity of 0.635. In the internal verification cohort, the AUC was 0.852 (95% CI: 0.751-0.965), with specificity of 0.903 and sensitivity of 0.759. Calibration curve analysis indicated that the nomogram's predicted probabilities closely aligned with the ideal reference curve, indicating excellent calibration. DCA revealed that the model provided a greater net benefit than the two extreme strategies (treating all or none), indicating strong practical utility (**Figure 2**).

To externally validate the model, clinical data from 57 schizophrenia patients admitted between January and July 2024 were analyzed. The model demonstrated robust discriminatory power, with an AUC of 0.689 (95% CI: 0.550-0.827), with sensitivity of 61.5% and specificity of 67.7%. Further calibration analysis revealed close alignment between predicted and observed outcomes, suggesting high clinical reliability. Notably, the model's net benefit surpassed both extreme scenarios (e.g., treating all or none), supporting its clinical utility (**Figure 3**).

Discussion

Schizophrenia is a chronic and severe psychiatric disorder with a complex pathogenesis, challenging treatment, and high relapse rate, imposing a significant psychological and economic burden on patients and their families [9, 10]. In female patients, elevated serum prolactin (PRL) can lead to menstrual irregularities, galactorrhea, and infertility, severely affecting their life quality [11, 12]. Therefore, it is essential to identify risk factors for antipsychotic-induced hyperprolactinemia in female patients

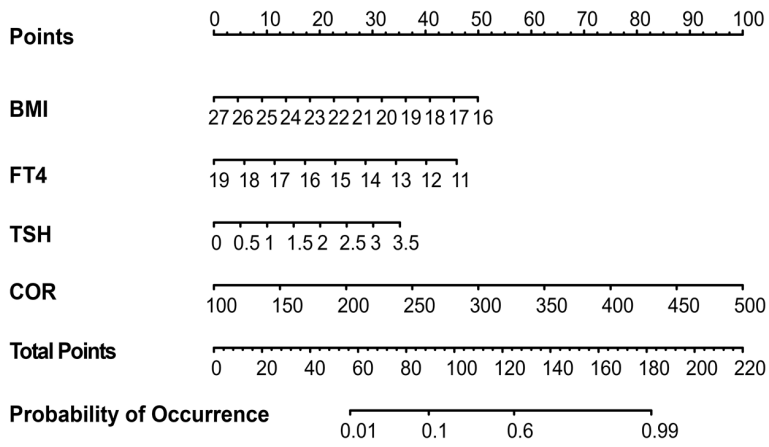

Figure 1. Nomogram (combinatorial classification model). BMI: Body Mass Index; FT4: free thyroxine; TSH: thyroid stimulating hormone; COR: cortisol.

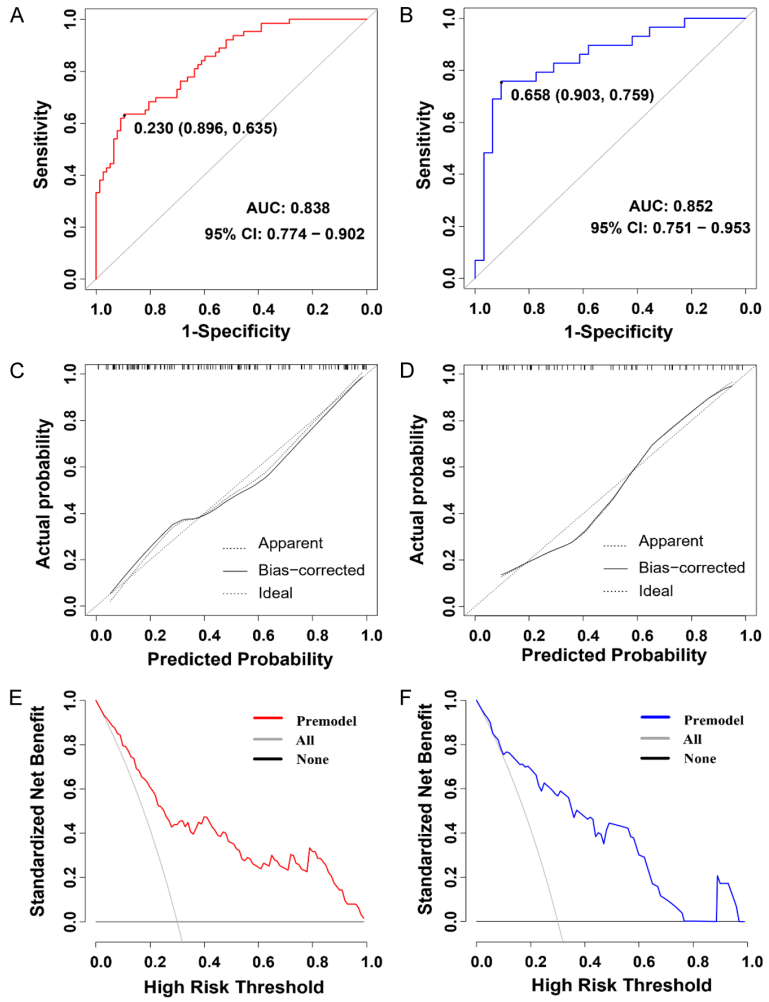

Figure 2. Model validation. A. ROC curve of the combinatorial classification model in the modeling cohort; B. ROC curve of the combinatorial classification model in the internal verification cohort; C. Calibration curve of the modeling cohort; D. Calibration curve of the internal verification cohort; E. Decision curve of the modeling cohort; F. Decision curve of the internal verification cohort.

with schizophrenia and construct a risk prediction model to facilitate early intervention.

PRL is synthesized and secreted by lactotroph cells in the anterior pituitary gland, regulated by hypothalamic dopamine (an inhibitory hormone) and prolactin-releasing hormone [13]. Abnormal serum PRL levels result in HPRL. As clinical research on HPRL progresses, MPRL has been recognized as a significant contributor to apparent HPRL, complicating clinical diagnosis [14]. MPRL typically consists of high-molecular-weight PRL complexes - mainly tetramers or PRL bound to immunoglobulins - with limited biological activity and minimal impact on the endocrine system, including the HPA axis [15, 16]. Additionally, classical antipsychotics are well-established inducers of HPRL [17, 18], therefore, monitoring serum PRL and identifying patients at high risk for true HPRL are essential components of safe and effective antipsychotic therapy.

Logistic regression analysis further confirmed that BMI, FT4, TSH, and cortisol were significant predictors of antipsychotic-induced hyperprolactinemia. Adipose tissue serves as the second-largest source of PRL production in the human body. The results of this study show that patients with HPRL exhibited lower BMI, possibly because elevated PRL suppresses lipid storage and adipokine synthesis. Additionally, the hyperprolactinemia group showed higher TSH and lower FT4 levels. This finding may reflect the influence of antipsychotic

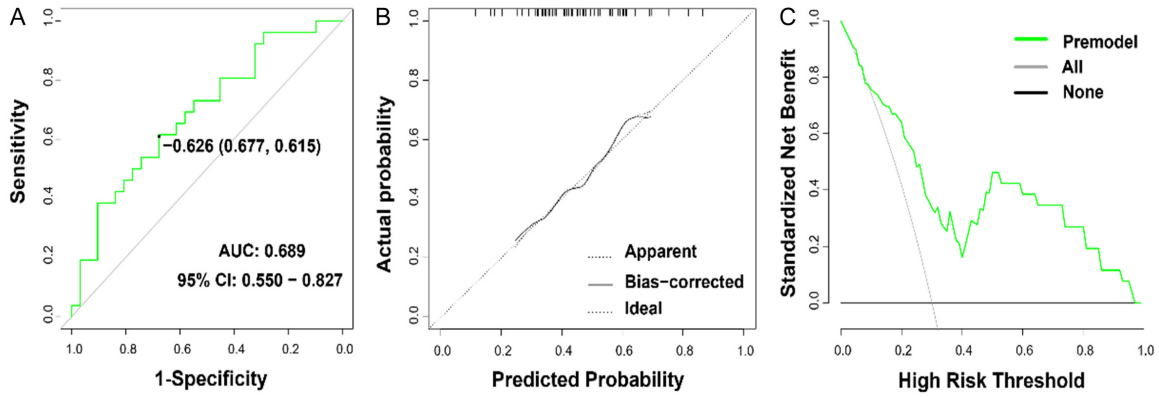

Figure 3. External verification of the model. A. ROC curve of the combinatorial classification model in the external verification cohort; B. Calibration curve of the external verification cohort; C. Decision curve of the external verification cohort.

medications, through their effects on neurotransmitter metabolism, on thyroid hormone levels [19, 20]. The HPT axis and the HPG axes are two major endocrine systems under pituitary control, functioning through closely interrelated feedback mechanisms. Thyrotropin-releasing hormone (TRH) secreted by the hypothalamus not only stimulates TSH secretion but also promotes PRL release [21]. Thus, any disturbance in this balance can elevate PRL levels, contributing to hyperprolactinemia. Endocrine hormone secretion is modulated by neurotransmitters, and antipsychotic drugs can interfere with the thyroid regulation via 5-hydroxytryptamine (5-HT) and dopamine receptor pathways. Their inhibitory effect is partly mediated through the interaction between 5-HT_2 receptors and FT4 levels [22]. Most antipsychotics exhibit potent antagonism of dopamine D_2 and 5-HT_2 receptors, leading to decreased FT4 levels [23]. Additionally, their α_1-adrenergic receptor antagonism enhances sedative effects and indirectly influences thyroid function. In hyperprolactinemia, elevated PRL levels exert negative feedback on dopamine neurons in the hypothalamus, stimulating the activity of α-endorphin neurons. This inhibits the synthesis and release of GnRH, reducing gonadotropin levels and diminished pulsatile release. As a result, the positive feedback of estrogen is disrupted, leading to anovulation and menstrual irregularities [24, 25]. Cortisol (Cor), the terminal hormone of the HPA axis, also plays a role. Clinical trials have shown that baseline Cor levels are elevated in patients with schizophrenia across different disease stages [26, 27]. Some researchers suggest that antipsychotic medications can increase plasma Cor levels in patients, possibly due to HPA axis dysregulation in individuals with HPRL [28]. Collectively, these findings suggest that age, BMI, FT4, TSH and cortisol collaboratively modulate the risk of antipsychotic-induced hyperprolactinemia in patients with schizophrenia.

Nomograms are widely used in medical research to quantitatively estimate disease risk and guide personalized treatment decisions [29, 30]. Studies have shown that a nomogram can effectively improve prediction accuracy by integrating multiple clinical indicators and biomarkers [31]. The present study demonstrated excellent performance, with an AUC of 0.838 in the modeling cohort, with specificity and sensitivity of 0.896 and 0.635, respectively. The calibration curve of the nomogram closely aligned with the ideal reference line, indicating strong agreement between predicted and observed probabilities. Additionally, the decision curve analysis showed that the model provided greater net clinical benefits than the reference line, indicating robust discriminative power and practical utility. Both internal and external verifications confirmed the strong predictive performance of the nomogram. This is consistent with prior studies emphasizing that rigorous model validation is essential for assessing stability and generalizability [32]. Thus, the combinatorial classification model established in this research is reliable and clinically practical, capable of early identification of true hyperprolactinemia and positively impacting patient prognosis.

The model established in this study has a good application prospect. It provides clinicians with

a reliable tool to optimize antipsychotic selection and formulate personalized treatment plans, thereby reducing the incidence of hyperprolactinemia and its complications, enhancing patients' treatment compliance and quality of life. Moreover, this approach can facilitate the optimization of antipsychotic drug development and advance the implementation of personalized psychiatry.

Nevertheless, this study has certain limitations. Owing to the limited sample size and single-center design, the external validation did not include data from other medical institutions, which may limit the representativeness of the validation cohort. Therefore, the predictive accuracy of this model across different populations needs to be further verified through large-scale, multicenter clinical studies.

Conclusion

In summary, BMI, FT4, TSH, and cortisol are independent factors influencing antipsychotic-induced hyperprolactinemia in patients with schizophrenia. Early evaluation of these parameters can facilitate the identification of high-risk individuals and support more accurate medication plans. Future research should further explore the roles of gene polymorphisms and epigenetic mechanisms in drug-induced hyperprolactinemia to deepen understanding of its pathogenesis and optimize prevention and treatment approaches.

Acknowledgements

This work was supported by Zhejiang Province Medical and Health Science and Technology Plan Project (2022KY1225).

Disclosure of conflict of interest

None.

Address correspondence to: Zhenhua Wang, Department of Psychiatry, Huzhou Third Municipal Hospital, The Affiliated Hospital of Huzhou University, No. 2088 Tiaoxi East Road, Wuxing District, Huzhou 313000, Zhejiang, China. Tel: +86-0572-2132318; E-mail: wzh2lj@163.com

References

[1] Lu Z, Sun Y, Zhang Y, Chen Y, Guo L, Liao Y, Kang Z, Feng X and Yue W. Pharmacological treatment strategies for antipsychotic-induced hyperprolactinemia: a systematic review and network meta-analysis. Transl Psychiatry 2022; 12: 267.

[2] Solmi M, Seitidis G, Mavridis D, Correll CU, Dragioti E, Guimond S, Tuominen L, Dargél A, Carvalho AF, Fornaro M, Maes M, Monaco F, Song M, Il Shin J and Cortese S. Incidence, prevalence, and global burden of schizophrenia-data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. Mol Psychiatry 2023; 28: 5319-5327.

[3] Zhu Y, Zhang C, Siafis S, Zhuo K, Zhu D, Wu H, Liu D, Jiang K, Wang J, Leucht S and Li C. Prolactin levels influenced by antipsychotic drugs in schizophrenia: a systematic review and network meta-analysis. Schizophr Res 2021; 237: 20-25.

[4] Doğan Bulut S, Bulut S, Tüzer V, Ak M, Ak E, Kisa C, Aydemir Ç and Göka E. The effects of prolactin-raising and prolactin-sparing antipsychotics on prolactin levels and bone mineral density in schizophrenic patients. Noro Psikiyatr Ars 2014; 51: 205-210.

[5] Yao K, Yang L, Zhang Q, Li C, Tian H and Zhuo C. Aripiprazole alleviates the high prolactin levels induced by amisulpride via distinct molecular mechanisms: a network pharmacology and molecular docking study. BMC Psychiatry 2025; 25: 373.

[6] Goh KK, Chen CH and Lu ML. Evaluating the efficacy of metformin in reducing hyperprolactinemia among patients with schizophrenia: a meta-analysis of randomized controlled trials. J Psychopharmacol 2025; 39: 815-824.

[7] Matuszewska A, Kowalski K, Jawień P, Tomkalski T, Gaweł-Dąbrowska D, Merwid-Ląd A, Szeląg E, Błaszczak K, Wiatrak B, Danielewski M, Piasny J and Szeląg A. The Hypothalamic-Pituitary-Gonadal axis in men with schizophrenia. Int J Mol Sci 2023; 24: 6492.

[8] Haidenberg-David F, Sidauy-Adissi J, Moscona-Nissan A, Jonguitud-Zumaya E, Fugarolas-Morinelli M, Martinez-Mendoza F, Taniguchi-Ponciano K, Marrero-Rodríguez D and Mercado M. Overview of hyperprolactinemia: general approach and reproductive health implications. Arch Med Res 2024; 55: 103102.

[9] Javitt DC. cognitive impairment associated with schizophrenia: from pathophysiology to treatment. Annu Rev Pharmacol Toxicol 2023; 63: 119-141.

[10] Takeda T, Umehara H, Matsumoto Y, Yoshida T, Nakataki M and Numata S. Schizophrenia and cognitive dysfunction. J Med Invest 2024; 71: 205-209.

[11] Glezer A, Garmes HM, Kasuki L, Martins M, Elias PCL, Nogueira VDSN, Rosa-E-Silva ACJS, Maciel GAR, Benetti-Pinto CL and Nácul AP.

Hyperprolactinemia in women: diagnostic approach. Rev Bras Ginecol Obstet 2024; 46: e-FPS04.

[12] Benetti-Pinto CL, Nácul AP, Rosa E Silva ACJ, Maciel GAR, Dos Santos Nunes Nogueira V, Elias PCL, Martins M, Kasuki L, Garmes HM and Glezer A. Hyperprolactinemia in women: treatment. Rev Bras Ginecol Obstet 2024; 46: e-FPS05.

[13] Lopez-Vicchi F, De Winne C, Brie B, Sorianello E, Ladyman SR and Becu-Villalobos D. Metabolic functions of prolactin: physiological and pathological aspects. J Neuroendocrinol 2020; 32: e12888.

[14] Che Soh NAA, Yaacob NM, Omar J, Mohammed Jelani A, Shafii N, Tuan Ismail TS, Wan Azman WN and Ghazali AK. Global prevalence of macroprolactinemia among patients with hyperprolactinemia: a systematic review and meta-analysis. Int J Environ Res Public Health 2020; 17: 8199.

[15] Zhenhua W, Haizhi C, Jing L, Xiaocong F, Jianhua L, Jianjun L, Lilei L and Haiying J. Occurrence of macroprolactinemia in schizophrenia patients treated with risperidone or amisulpride. Asia Pac Psychiatry 2022; 14: e12469.

[16] Krysiak R, Kowalcze K and Okopień B. Macroprolactinemia attenuates the impact of levothyroxine on hypothalamic-pituitary-thyroid axis activity and thyroid autoimmunity in women with autoimmune hypothyroidism. J Clin Pharmacol 2020; 60: 1496-1501.

[17] Lu Z, Sun Y, Zhang Y, Chen Y, Guo L, Liao Y, Kang Z, Feng X and Yue W. Pharmacological treatment strategies for antipsychotic-induced hyperprolactinemia: a systematic review and network meta-analysis. Transl Psychiatry 2022; 12: 267.

[18] Ruljancic N, Bakliza A, Vuk Pisk S, Geres N, Matic K, Ivezic E, Grosic V and Filipcic I. Antipsychotics-induced hyperprolactinemia and screening for macroprolactin. Biochem Med (Zagreb) 2021; 31: 010707.

[19] Chen J, Ge H, Liu N, Li Y, Dong Y, Wang X, Xun Z and Li S. Sex-specific differences in the relationship between thyroid hormones and neurocognition in schizophrenia: a large-scale cross-sectional study. Psychoneuroendocrinology 2025; 172: 107249.

[20] Jiang QH and Gong WD. Correlation analyse between thyroid hormone levels and severity of schizophrenia symptoms. World J Psychiatry 2025; 15: 100880.

[21] Wang Z, Li J, Chen H, Jin H, Wang S and Hu X. The correlation between DRD_2 and COMT gene polymorphisms, HPT and HPG axes functions, and antipsychotic drug-induced hyperprolactinemia and macroprolactinemia. Neuropsychiatr Dis Treat 2025; 21: 1011-1017.

[22] Razakarivony O, Newman-Tancredi A and Zimmer L. Towards in vivo imaging of functionally active 5-HT_{1A} receptors in schizophrenia: concepts and challenges. Transl Psychiatry 2021; 11: 22.

[23] Gaitonde SA, Avet C, de la Fuente Revenga M, Blondel-Tepaz E, Shahraki A, Pastor AM, Talagayev V, Robledo P, Kolb P, Selent J, González-Maeso J and Bouvier M. Pharmacological fingerprint of antipsychotic drugs at the serotonin 5-HT_{2A} receptor. Mol Psychiatry 2024; 29: 2753-2764.

[24] Keen F, Chalishazar A, Mitchem K, Dodd A and Kalhan A. Central hypothyroidism related to antipsychotic and antidepressant medications: an observational study and literature review. Eur Thyroid J 2022; 11: e210119.

[25] Khoodoruth MAS, Abdo AKA and Ouanes S. Quetiapine-induced thyroid dysfunction: a systematic review. J Clin Pharmacol 2022; 62: 20-35.

[26] Kogler L, Wang R, Luther T, Hofer A, Frajo-Apor B and Derntl B. Cortisol in schizophrenia spectrum disorders: a comprehensive meta-analysis. Front Neuroendocrinol 2025; 77: 101186.

[27] Inova A, Birkenæs V, Quintana DS, Ormerod MBEG, Ueland T, Ueland T, Djurovic S, Andreassen O, Steen NE and Aas M. Cortisol and C-reactive protein (CRP) regulation in severe mental disorders. Psychoneuroendocrinology 2025; 172: 107272.

[28] Burghardt KJ, Mando W, Seyoum B, Yi Z and Burghardt PR. The effect of antipsychotic treatment on hormonal, inflammatory, and metabolic biomarkers in healthy volunteers: a systematic review and meta-analysis. Pharmacotherapy 2022; 42: 504-513.

[29] Zhang C, Dong N, Xu S, Ma H and Cheng M. Identification of hub genes and construction of diagnostic nomogram model in schizophrenia. Front Aging Neurosci 2022; 14: 1032917.

[30] Hou M, Wu Y, Xue J, Chen Q, Zhang Y, Zhang R, Yu L, Wang J, Zhou Z and Li X. A predictive model for readmission within 1-year post-discharge in patients with schizophrenia. BMC Psychiatry 2024; 24: 573.

[31] Wu J, Zhang H, Li L, Hu M, Chen L, Xu B and Song Q. A nomogram for predicting overall survival in patients with low-grade endometrial stromal sarcoma: a population-based analysis. Cancer Commun (Lond) 2020; 40: 301-312.

[32] Lee SW, Jang J, Seo WY, Lee D and Kim SH. Internal and external validation of machine learning models for predicting acute kidney injury following non-cardiac surgery using open datasets. J Pers Med 2024, 14: 587.