Integrating machine learning with electronic health record data to facilitate detection of prolactin level and pharmacovigilance signals in olanzapine-treated patients

Xiuqing Zhu1,2†, Jinqing Hu1,2†, Tao Xiao1,3, Shanqing Huang1,2, Dewei Shang1,2* and Yuguan Wen1,2*

1Department of Pharmacy, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, China, 2Guangdong Engineering Technology Research Center for Translational Medicine of Mental Disorders, Guangzhou, China, 3Department of Clinical Research, Guangdong Second Provincial General Hospital, Guangzhou, China

Background and aim: Available evidence suggests elevated serum prolactin (PRL) levels in olanzapine (OLZ)-treated patients with schizophrenia. However, machine learning (ML)-based comprehensive evaluations of the influence of pathophysiological and pharmacological factors on PRL levels in OLZ-treated patients are rare. We aimed to forecast the PRL level in OLZ-treated patients and mine pharmacovigilance information on PRL-related adverse events by integrating ML and electronic health record (EHR) data.

Methods: Data were extracted from an EHR system to construct an ML dataset in 672×384 matrix format after preprocessing, which was subsequently randomly divided into a derivation cohort for model development and a validation cohort for model validation (8:2). The eXtreme gradient boosting (XGBoost) algorithm was used to build the ML models, the importance of the features and predictive behaviors of which were illustrated by SHapley Additive exPlanations (SHAP)-based analyses. The sequential forward feature selection approach was used to generate the optimal feature subset. The co-administered drugs that might have influenced PRL levels during OLZ treatment as identified by SHAP analyses were then compared with evidence from disproportionality analyses by using OpenVigil FDA.

Results: The 15 features that made the greatest contributions, as ranked by the mean (|SHAP value|), were identified as the optimal feature subset. The features were gender_male, co-administration of risperidone, age, co-administration of aripiprazole, concentration of aripiprazole, concentration of OLZ, progesterone, co-administration of sulpiride, creatine kinase, serum sodium, serum phosphorus, testosterone, platelet distribution width, α-L-fucosidase, and lipoprotein (a). The XGBoost model after feature selection delivered good performance on the validation cohort with a mean absolute error of 0.046,
mean squared error of 0.0036, root-mean-squared error of 0.060, and mean relative error of 11%. Risperidone and aripiprazole exhibited the strongest associations with hyperprolactinemia and decreased blood PRL according to the disproportionality analyses, and both were identified as co-administered drugs that influenced PRL levels during OLZ treatment by SHAP analyses.

Conclusions: Multiple pathophysiological and pharmacological confounders influence PRL levels associated with effective treatment and PRL-related side-effects in OLZ-treated patients. Our study highlights the feasibility of integration of ML and EHR data to facilitate the detection of PRL levels and pharmacovigilance signals in OLZ-treated patients.

KEYWORDS
machine learning, prolactin, olanzapine, electronic health record, hyperprolactinemia, pharmacovigilance, XGBoost, SHAP

Introduction

Prolactin (PRL), a polypeptide hormone, is primarily synthesized in and secreted from the anterior pituitary gland, and plays multiple roles in lactation, reproduction, and organ homeostasis (1). PRL secretion is regulated by stimulatory factors like the thyrotropin-releasing hormone (TRH) and inhibitory factors like dopamine (DA) in the hypothalamus, and is influenced by alterations in both physiological (e.g., pregnancy, stress, and sleep states) and pathological conditions (e.g., pituitary disorders, central nervous system disorders, and systemic diseases) (2, 3). Hyperprolactinemia is commonly defined as the condition of a sustained increase in PRL up to that of a fasting level (at least 2 h after waking) of above 20 ng/mL (~424 mIU/L) in men, and above 25 ng/mL (~530 mIU/L) in women (4). It has been found to be associated with an increased risk of many diseases, such as cardiovascular mortality in males (5), cancer (6), bone loss, and fractures (7). In particular, psychiatric patients with hyperprolactinemia usually exhibit short-term sexual dysfunction, amenorrhea or galactorrhea, and long-term sequelae such as osteoporosis (8). Recently, a nationwide study in Finland demonstrated that the long-term use of PRL-increasing antipsychotics is significantly associated with the increased risk of breast cancer in females with schizophrenia (9). Studies in vivo and in vitro have revealed that hyperprolactinemia-inducing antipsychotics can prompt precancerous lesions to progress to cancer via activating JAK-STAT5 (10).

A large group of drugs, including psychotropic drugs like antipsychotics, have the potential to cause the hypersecretion of PRL, which is the most common pharmacological cause of hyperprolactinemia (3, 11). In both short- and long-term toxicological studies with rodents, the drug-induced mechanisms of hypo- and hyperprolactinemia commonly involve the dopaminergic system (12). For example, Kunimatsu et al. (13) demonstrated that chronic hyperprolactinemia and maintained corpora lutea causing the decrease of bone density are commonly inducible in female rats undergoing long-term treatment with antipsychotics haloperidol and chlorpromazine (i.e., the DA D2 receptor antagonists). The affinity for DA D2 receptors, the penetration of the blood–brain barrier (BBB), and the dose required to adequately occupy cerebral D2 receptors play major roles in the hyperprolactinemic effects of antipsychotics and other xenobiotics (14). Serotonin (5-HT), which serves as an indirect modulator, also has a stimulatory role in PRL secretion in both the hypothalamus and the pituitary, probably mediated via the stimulation of PRL-releasing factors (15).

Olanzapine (OLZ), an atypical antipsychotic drug, has an intermediary binding affinity for DA D2 receptors, thereby inducing a moderate and dose-dependent elevation of PRL levels (15, 16). It also exerts antipsychotic effects and induces weight gain by blocking the 5-HT2A and 5-HT2c receptors, respectively (16, 17). Thus, the antagonism of OLZ toward the 5-HT2c receptor might partly explain its moderate PRL-elevating tendency (18, 19). In this regard, some gene polymorphisms in DA D2 and 5-HT2c receptors (e.g., DRD2 and 5-HT2A) have been found to affect PRL levels after OLZ administration (20). A logistic regression analysis of only 10 variables revealed that other risk factors, such as gender, dose, and fasting glucose levels, are also significantly correlated with elevated PRL levels in patients taking OLZ (21). Nevertheless, few studies have investigated the factors influencing PRL levels in OLZ-treated patients in light of multi-dimensional electronic health record
(EHR) data. In addition, Wu et al. (19) reported that elevated PRL levels were significantly associated with sexual dysfunction in patients with schizophrenia who had received OLZ treatment. A previous study revealed the alterations in mitochondria of the rat spermatocytes after experimental hyperprolactinemia (22). Recently, an in vivo animal study by Khalaf et al. (23) demonstrated the role of ovarian mitochondrial dysfunction and oxidative stress in ovarian toxicity induced by antipsychotics. On the other hand, the findings by Chen et al. (24) revealed that changes in PRL levels in the course of OLZ treatment are closely correlated with improvement in positive symptoms of schizophrenia, indicating that the PRL level of serum is a useful biological marker for predicting the effectiveness of antipsychotics (25, 26). Hence, monitoring PRL levels during OLZ treatment is vital to minimize the risk of PRL-related adverse events and maximize the response to treatment by antipsychotics.

Interest in Artificial Intelligence (AI)-assisted pharmacovigilance has grown in recent years (27). Within the field of AI, machine learning (ML) is a data-driven computational methodology increasingly applied for predictions of the post-marketing side-effects of drugs (28). The EHR is a source of data for detecting such adverse drug reactions (ADRs) due to its advantages of housing a collection of accurate, detailed, and abundant information on patients (28, 29). For example, On et al. (30) developed ML models for eight types of chemotherapy-induced ADRs (e.g., the nausea–vomiting prediction model) by using EHR data. In addition, it has been demonstrated that ML algorithms allow for the prediction of responses to drug treatment (e.g., antidepressants and anti-cancer drugs) (31, 32) and disease outcomes (e.g., stroke) (33).

In this study, we use the eXtreme gradient boosting (XGBoost) algorithm, a well-known supervised ML algorithm widely used in medicine (34), to construct a model of PRL prediction associated with the side-effects and clinical effectiveness of OLZ by using EHR data. The objectives of this study are to i) develop an XGBoost model for the detection of PRL levels in OLZ-treated patients, and ii) identify multiple factors, particularly co-administered drugs, that may cause hypo- or hyperprolactinemia during OLZ treatment by using an interpretable ML method—the SHapley Additive exPlanations (SHAP) analysis (35). The results are then compared with evidence from real-world disproportionality analyses by using the pharmacovigilance analysis tool OpenVigil FDA (http://openvigil.pharmacology.uni-kiel.de/openvigilfda.php). This online tool uses the “openFDA” API of the US Food and Drug Administration (FDA) to access pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS) (36). The flowchart of this work is shown in Figure 1.

Materials and methods

Data source

Clinical data on inpatients during OLZ treatment in the latter half of 2018 were mined from the EHR system of the Affiliated Brain Hospital of Guangzhou Medical University in China. The independent ethics committee of the hospital approved the data collection and waived the requirement of informed consent owing to the retrospective nature of our analyses ([2021] No. 027). We obtained 672 PRL measurements of 393 inpatients who had received OLZ treatment, along with information on the patients’ demographic characteristics, diagnoses, history of disorders, and combined medications and biochemical analyses that were determined at the same time points as their PRL levels. Finally, 473 features were identified that, along with the label—PRL, formed the dataset for the ML tasks. A summary of these features is provided in Table 1.

Data preprocessing

Data preprocessing is vital for acquiring high-quality data for modeling. We first omitted the features that had more than 50% missing values and then imputed those with fewer than 50% missing values by using the k-nearest neighbor method (37). Subsequently, min–max normalization and one-hot encoding were applied to the continuous variables and the categorical variables, respectively. Finally, the labels were transformed into the logarithmic scale.

Model development and evaluation

The final dataset in 672×384 matrix format was generated after data preprocessing, and was subsequently randomly divided into a derivation cohort (80%) for model development and a validation cohort (20%) for model validation. The XGBoost algorithm with the default hyperparameter settings was chosen for the regression prediction task. The metrics used for model evaluation were the mean absolute error (MAE), mean squared error (MSE), root-mean-squared error (RMSE), and mean relative error (MRE) (%). They are defined as follows:

\[
MAE = \frac{1}{n} \sum_{i=1}^{n} |y_i - \hat{y}_i|
\]

\[
MSE = \frac{1}{n} \sum_{i=1}^{n} (y_i - \hat{y}_i)^2
\]
\[ RMSE = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (y_i - \hat{y}_i)^2} \]

\[ MRE \ (%) = \frac{1}{n} \sum_{i=1}^{n} \frac{(y_i - \hat{y}_i)}{\hat{y}_i} \times 100 \%
\]

Where \( y_i \) and \( \hat{y}_i \) are the predicted and the actual values, respectively.

**Optimal feature combination and interpretation**

Redundant and irrelevant features can increase the computation time, and negatively impact and reduce the learning accuracy of the models. This problem can be solved by feature selection (38). We used the mean absolute SHAP values (|SHAP value|) to illustrate the global importance of features (39). The sequential forward feature selection approach was then employed to generate the optimal feature subset (40). The general practices in this bottom-to-top search method involved starting with an empty feature subset, adding one feature out of the remaining features in each iteration (the order of addition depended on the feature importance calculated by the SHAP values: the more important the feature was, the greater was the precedence it had), and then evaluating the pros and cons of the generated feature subset by using 10-fold cross-validation on the derivation cohort. The optimal feature combination was obtained when “no considerable alteration” of the MAE values was observed in the test sets. Subsequently, SHAP plots were drawn to interpret the contributions of these features to the outputs of the model. Finally, the overall performance of models before and after
feature selection was compared on the validation cohort by using the abovementioned metrics.

Disproportionality analyses of PRL-related adverse events with antipsychotics

We focused on co-administered medications that may have an impact on the PRL levels during OLZ treatment. To this end, the results of our SHAP analyses were compared with real-world evidence from disproportionality analyses based on the relative reporting ratio (RRR), a frequentist method, offered by OpenVigil FDA. The RRR was calculated as follows (36):

\[
RRR = \frac{DE \times N}{E \times D}
\]

where \(N\) denotes the total number of reports, \(DE\), \(E\), and \(D\) denote the numbers of reports when both the drug was used and the event occurred, the drug was used, and the event occurred, respectively.

We used the RRR to compare the strength of associations among a given list of antipsychotics (including OLZ, risperidone, sulpiride, amisulpride, aripiprazole, clozapine, quetiapine, ziprasidone, paliperidone, and perphenazine) with the adverse events “blood prolactin increased,” “hyperprolactinemia,” and “blood prolactin decreased.” The drug with the largest RRR value indicated the most proportional reporting of the reaction for it. Stopping the administration of this drug was thus considered first.

Implementation

Data processing and modeling were conducted by using the libraries pandas, numpy, scipy, matplotlib, seaborn, missingno, sklearn, XGBoost, shap and palettable. All the ML tasks were implemented in Python by using the Jupyter notebook.

Results

Dataset overview

The final dataset consisted of 672 log-transformed PRL label values and 383 features (115 continuous features and 268 categorical features). Figure 2A shows the 110 continuous features with less than 50% missing values, represented by the
white lines in each column. Figures 2B, C show the frequency histograms and quantile–quantile (Q–Q) plots of the labels before and after log-transformation, respectively. They indicated that the distribution of the log-transformed PRL ranging from 0.44 to 1 was the most symmetric and normal. Table 2 shows the descriptions of the labels and partial features in our original data, without data preprocessing, derived from the EHR system.

### Feature selection and interpretation

Figure 3A presents the trend of evolution of the decline in the MAE in the training and test sets of the derivation cohort by using the forward feature selection strategy based on feature importance computed by using SHAP values. The top 15 features were identified as the optimal feature subset because the MAE declined imperceptibly with the addition of subsequent features. They were ranked according to the mean (|SHAP value|) as follows (Figure 3B): gender_male, co-administration of risperidone (Risperidone), age, co-administration of aripiprazole (Aripiprazole), concentration of aripiprazole (C_Aripiprazole), concentration of OLZ (C_O LZ), progesterone, co-administration of sulpiride (Sulpiride), creatine kinase (CK), serum sodium (Na), serum phosphorus (P), testosterone, platelet distribution width (PDW), $\alpha$-L-fucosidase (AFU), and lipoprotein (a) [Lp(a)]. Figure 3C shows the Pearson’s correlations between the log-transformed PRL and these features, and indicates no prominent multi-collinear relationships among the features. Figure 3D presents...
the direction of effects of a variable on the output of the model. The SHAP dependence plots of these features show how they affected the outputs of our model (Figure 4). They indicate that higher PRL levels were related to females as well as the concomitant use of risperidone and sulpiride, and co-administered aripiprazole might have caused lower PRL levels. The comparisons of the influences of these three co-administered antipsychotics on PRL levels in terms of the gender of patients taking OLZ, based on the original data derived from the EHR system, are presented in Figure 5.

**Comparison of the performance of models**

An overall comparison of the performance of models before and after feature selection is listed in Table 3. Among them, the XGBoost model after feature selection had better predictive performance, with lower values of the MAE, MSE, RMSE, and MRE. The lack of clear patterns and the symmetrical distribution of the residuals indicated that our proposed XGBoost model after feature selection was suitable for fitting the data in the validation cohort (Figures 6A, B). Figure 6C shows that 47.41% and 68.89% of the predicted values were within ranges of ±30% and ±50% of the actual values, respectively.

**Disproportionality measures for antipsychotics and PRL-related adverse events**

Table 4 shows comparisons of the disproportionality measures for the 10 antipsychotics and PRL-related adverse events. Risperidone, paliperidone, and amisulpride were the top three antipsychotics associated with the risk of increased PRL concentration in the blood and hyperprolactinemia according to their RRR values. Similarly, aripiprazole exhibited the strongest association with decreased PRL content in blood, indicating that its use may protect patients taking OLZ from hyperprolactinemia.

**Discussion**

ML techniques have been successfully and widely applied to multiple fields in medicine, such as cancer diagnostics (41),

---

**Table 2** The descriptions of labels and partial features before data preprocessing.

| Categorical data                  | Description (the total number of input-output data pairs is 672) |
|-----------------------------------|---------------------------------------------------------------|
| Gender                           | Distribution [n (%)]                                          |
| Diagnosis of schizophrenia       | Male 360 (53.57%)                                             |
| Smoking history                   | Yes 327 (48.66%)                                              |
| Risperidone                      | Yes 90 (13.39%)                                               |
| Paliperidone                      | Yes 101 (15.03%)                                              |
| Amisulpride                       | Yes 6 (0.89%)                                                 |
| Sulpiride                         | Yes 20 (2.98%)                                                |
| Aripiprazole                      | Yes 24 (3.57%)                                                |
|                                    | Yes 36 (5.36%)                                                |
| Continuous data                   | Values [median (min-max)] Missing [n (%)]                     |
| PRL (mIU/L)                       | 708.19 (50.38–7216.28) 0 (0%)                                 |
| Age (years)                       | 45 (12–91)                                                    |
| BW (kg)                           | 61.35 (37–104)                                                |
| Daily dose of OLZ (mg)            | 15 (1.25–30)                                                  |
| ALT (U/L)                         | 18 (3–399)                                                    |
| C_Aripiprazole (ng/mL)            | 0 (0–647.37)                                                  |
| C OLZ (ng/mL)                     | 30.44 (2.14–127.31)                                           |
| Progesterone (ng/mL)              | 0.6 (0.3–77.8)                                                |
| Testosterone (mmol/L)             | 8.74 (0.35–59.33)                                             |
| CK (U/L)                          | 79.5 (16–1473)                                                |
| Na (mmol/L)                       | 140.5 (121.0–146.5)                                           |
| P (mmol/L)                        | 1.24 (0.62–2.90)                                              |
| AFU (U/L)                         | 27.15 (6–70)                                                  |
| Lp(a) (mg/L)                      | 163.7 (3.2–1052.6)                                            |
| PDW (%)                           | 15.8 (7.8–20.7)                                               |

Zhu et al. 10.3389/fendo.2022.1011492
FIGURE 3
(A) The evolution of the performance of XGBoost models on the derivation cohort based on different compositions of the feature set. (B) The ranking by importance of the top 15 features according to the mean (|SHAP value|). (C) Heat map of the correlations between the log-transformed PRL and the selected features as analyzed by Pearson’s correlation coefficient. (D) The SHAP summary plot of the top 15 features. The red (blue) dots denote the high (low) values of the features. The high (low) SHAP values of the features denote their high (low) log-transformed PRL values.

FIGURE 4
The SHAP dependence plots of the top 15 features. The SHAP values that exceeded zero represent high log-transformed PRL values, and vice versa.
treatment outcome predictions in patients with first-episode psychosis (42), and exploration of risk factors for the use of direct coercive measures in offender patients with schizophrenia spectrum disorders (43). AI-assisted pharmacovigilance has made large advancements but is still in its infancy. Chandak et al. (44) used ML to identify adverse drug effects posing increased risk to women based on public databases. We proposed a novel strategy that integrated ML with real-world clinical data of representative Chinese patient populations to advance AI-assisted pharmacovigilance studies. To the best of the authors’ knowledge, this is the first study to forecast the PRL level in OLZ-treated patients and mine pharmacovigilance information on PRL-related adverse events by integrating ML and EHR data. We used the XGBoost algorithm to construct an accurate model of PRL prediction that uses only two demographic characteristic predictors (i.e., gender_male and age), five predictors of drug information (i.e., risperidone, aripiprazole, C_Aripiprazole, C_OLZ, and sulpiride), and eight predictors of biochemical metrics [i.e., progesterone, CK, Na, P, testosterone, PDW, AFU, and Lp(a)]. This helps better understand these confounders that influence the PRL levels in OLZ-treated patients. They were found to be associated with the effectiveness of treatment and PRL-related side-effects.

The XGBoost algorithm, an ensemble learning method under the gradient boosting framework, is a scalable and distributed gradient-boosted decision tree ML library that allows for parallel tree boosting in both the classification and the regression tasks. It thus provides fast and accurate solutions for many problems in data science (45). It is generally considered to be a “black-box” model that loses the interpretability of the relationships between the inputs and the outputs of the models (46). In this study, we computed feature importance of the black-box XGBoost model by using the SHAP library, which used the SHAP values from game theory to estimate the contribution of each feature to the prediction in a model-agnostic manner (47). Furthermore, we drew more plots of interpretation, such as the SHAP summary plot and SHAP dependence plots, to show the general direction of influence and distributions of the SHAP outputs of each feature in the XGBoost model (48). In particular, our SHAP dependence plots demonstrated a non-linear relationship between C_OLZ and PRL, namely, a prominent trend of increase in the log-transformed PRL was observed as the normalized C_OLZ ranged from zero to approximately 0.4, and the trend of subsequent increase was not apparent. Moreover, we found that the log-transformed PRL was positively correlated with the range of the normalized C_OLZ from approximately 0.2 to 0.8 (corresponding to the C_OLZ ranging from approximately 25.03 ng/mL to 100.14 ng/mL). This range is close to the recommended therapeutic reference range (i.e., 20–80 ng/mL) and the laboratory alert level (i.e., 100 ng/mL) of OLZ according to the latest consensus-based guidelines of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP)-Therapeutic Drug Monitoring (TDM) expert group (49). On the other hand, typical PRL levels with regard to the etiology of drugs are 25–100 ng/mL (approximately 530–2120 mIU/L) (50), which is broadly in line with our PRL measurements of OLZ-treated patients (see Figure 2B). Severe drug-related hyperprolactinemia (commonly defined as PRL values above 100 ng/mL), in the context of 100–250 ng/mL (approximately 2120–5300 mIU/L) and > 250 ng/mL (> ~5300 mIU/L), were found to occur in ~30% and ~5% of the cases (particularly with antipsychotics).

| XGBoost models | MAE   | MSE   | RMSE  | MRE (%) |
|---------------|-------|-------|-------|---------|
| Before feature selection | 0.046 | 0.0043 | 0.065 | 18      |
| After feature selection   | 0.046 | 0.0036 | 0.060 | 11      |
respectively (50, 51). The aforementioned findings show that PRL may be a potential biological correlate for predicting the therapeutic effectiveness of OLZ and its PRL-related side-effects as well as their severity.

We also identified multiple confounders that might have influenced the PRL levels. They involved pathophysiological and pharmacological factors. The most important one was gender, i.e., females had more elevated RPL levels than males. A possible explanation for this is that females were more affected by antipsychotic-induced hyperprolactinemia than males (52). Likewise, our study revealed age-related changes in PRL levels, indicating that age is important because concomitant drug use and illnesses such as hypothyroidism and the degeneration of the ovarian secretion function, may be common in elderly populations (53, 54). Other hormones, including progesterone and testosterone, were also demonstrated to have effects on the PRL level. PRL commonly works antagonistically with estrogen and testosterone. It can inhibit the secretion of gonadotropin-releasing hormone by modulating the dopaminergic pathway, and thus may reduce testosterone levels associated with hypogonadism (55). It also acts directly on the granulosa cells of Graafian follicles to stimulate the release of progesterone and suppress estradiol production (56). The results indicated that hormone replacement (estrogen or testosterone) therapy may be an alternative pharmacological treatment strategy for hyperprolactinemia (57, 58). However, this strategy for antipsychotic-induced hyperprolactinemia is not recommended based on the latest evidence from network meta-analyses (59). PDW directly reflects the variability in platelet size, is considered to be an indicator of platelet activation and function, and is thus related to the extent of coronary artery disease (60). There are discrepancies in findings among some studies regarding the effects of PRL on platelet activation. Previous studies have demonstrated that hyperprolactinemia can cause adenosine diphosphate (ADP)-stimulated platelet activation, particularly in patients treated with antipsychotics. This might explain the increased risk for venous thromboembolism among them (61, 62). By contrast, Reuwer et al. (63) have suggested that PRL does not affect platelet aggregation or secretion in humans. Wahlberg et al. (64) found that PRL affected platelets in hyperprolactinemic patients in an indirect inhibitory way, indicating that it might TABLE 4 Relative reporting ratios (RRR) of prolactin (PRL)-related adverse events for a given list of antipsychotics.

| Antipsychotics | Blood prolactin increased | Hyperprolactinemia | Blood prolactin decreased |
|----------------|----------------------------|--------------------|---------------------------|
| Olanzapine     | 17.370                     | 13.760             | 10.561                    |
| Risperidone    | 44.788                     | 104.973            | 9.546                     |
| Sulpiride      | NAN                        | NAN                | NAN                       |
| Amisulpride    | 77.880                     | 51.690             | 0                         |
| Aripiprazole   | 11.205                     | 11.822             | 45.908                    |
| Clozapine      | 7.576                      | 3.613              | 2.567                     |
| Quetiapine     | 8.487                      | 6.665              | 2.185                     |
| Ziprasidone    | 23.303                     | 10.334             | 5.697                     |
| Paliperidone   | 103.214                    | 95.116             | 13.100                    |
| Perphenazine   | 7.838                      | 16.499             | 0                         |

Sulpiride is not approved for marketing in the United States by the FDA, and therefore was not found in the openFDA’s names of substances.
have a protective role in thromboembolic disease. The positive correlation between PDW and the log-transformed PRL in our study suggests that hyperprolactinemia in OLZ-treated patients might be associated with the increased risk of thromboembolic events because PDW increases during platelet activation (65). Moreover, PRL may have direct effects on the metabolism of lipids—for example, reducing lipoprotein lipase activity in the human adipose tissue (66). Nevertheless, the positive correlation between the log-transformed PRL and Lp(a) in OLZ-treated patients, which has not been reported in any previous study to the best of our knowledge, indicates that increased cardiovascular risk in OLZ-treated patients with hyperprolactinemia should be the focus of research in this context, especially in males (5), as Lp(a) is an independent marker of cardiovascular risk (67). Our study also revealed the negative correlation between the log-transformed PRL and Na. This result is in line with that of a previous study suggesting that serum PRL may participate in sodium retention (68). CK, P, and AFU also played contributory roles in the log-transformed PRL levels, although few past studies have revealed the detailed mechanisms underlying their relationships. They possibly involve other physiological processes, such as bone mineral liberation and glycoprotein metabolism (69, 70).

In addition to pathophysiological factors, the concomitant use of risperidone, aripiprazole, and sulpiride were identified as the top three pharmacological contributors to the effects of PRL levels in OLZ-treated patients. These findings are largely consistent with our disproportionality analyses of PRL-related adverse events with antipsychotics, which suggest that risperidone should be discontinued first in OLZ-treated patients with hyperprolactinemia, and that the use of aripiprazole may protect them from this adverse event. Therefore, our study has highlighted the feasibility of AI-based pharmacovigilance detection in resource-limited settings by using EHR as a source of data. In short, ML and EHR data can partner to identify PRL-related symptoms that may occur with borderline or normal standardized PRL values while maintaining clinical stabilization (76). Notably, an abnormally low PRL level after switching to aripiprazole might occur, and this is a potential warning sign of a psychotic rebound. Routinely monitoring PRL levels may help avoid such a rebound (77). Eftekhar et al. (78) reported that oxidative stress and mitochondrial dysfunction played key roles in liver injury caused by OLZ, indicating that antioxidants, particular the nanosamples is needed to improve the model generalization capability of the model. Second, although our findings were in accordance with previous reports demonstrating no influence of CYP2D6 variation on PRL levels in antipsychotic-induced hyperprolactinemia (83), some candidate genes associated with changes in PRL were not included in our study. For example, DRD2 may influence the susceptibility to hyperprolactinemia associated with OLZ treatment (84). Genetic associations of alterations in PRL in OLZ-treated patients may warrant further exploration. The confounding factors influencing the sex differences of pharmacovigilance signals on PRL-related adverse events and the pharmacogenetic mechanisms to explain these sex risks may be our future works.

Conclusions

In this study, we constructed an ML-based model of PRL prediction in OLZ-treated patients by using the XGBoost algorithm and EHR data. Based on SHAP analyses, we also identified multiple pathophysiological and pharmacological confounders that influence PRL levels as tightly related to the effectiveness of treatment and PRL-related side-effects in OLZ-treated patients. Furthermore, our work suggests the feasibility of AI-based pharmacovigilance detection by using EHR as a source of data. In short, ML and EHR data can partner to facilitate the detection of PRL levels and pharmacovigilance signals in OLZ-treated patients.
Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the independent ethics committee of the Affiliated Brain Hospital of Guangzhou Medical University. Written informed consent from the participants’ legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

DS and YW together conceived and designed the study. XZ wrote the original draft preparation. TX and SH performed the data collection. JH conducted the data analyses. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Guangzhou municipal key discipline in medicine (2021-2023), Guangzhou Municipal Science and Technology Project for Medicine and Healthcare (grant numbers 2020A011047 and 2020A011016), Natural Science Foundation of Guangdong Province (grant numbers 2018A0303130074 and 2021A1515011325), Guangdong Provincial Hospital Pharmaceutical Research Fund (grant number 2022A22) and Science and Technology Plan Project of Guangdong Province (grant number 2019B030316001).

Acknowledgments

We thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiol Rev (2000) 80(4):1523–631. doi: 10.1152/physrev.2000.80.4.1523
2. Egli M, Leeners B, Kruger TH. Prolactin secretion patterns: basic mechanisms and clinical implications for reproduction. Reproduction (2010) 140(5):643–54. doi: 10.1530/REP-10-0033
3. Torre DL, Falorni A. Pharmacological causes of hyperprolactinemia. Ther Clin Risk Manage (2007) 3(5):929–51.
4. Halbreich U, Kinon BJ, Gilmore JA, Kahn LS. Elevated prolactin levels in patients with schizophrenia: mechanisms and related adverse effects. Psychoneuroendocrinology (2003) 28 Suppl 1:53–67. doi: 10.1016/S0306-4530(02)00112-9
5. Krogh J, Selmer C, Torp-Pedersen C, Gislason GH, Kistorp C. Hyperprolactinemia and the association with all-cause mortality and cardiovascular mortality. Horm Metab Res (2017) 49(6):411–7. doi: 10.1055/s-0043-107243
6. Berinder K, Akre O, Granath F, Hulting AL. Cancer risk in hyperprolactinemia patients: A population-based cohort study. Eur J Endocrinol (2011) 165(2):209–15. doi: 10.1530/EJE-11-0076
7. di Filippo L, Doga M, Resmini E, Giustina A. Hyperprolactinemia and bone. Pituitary (2020) 23(3):314–21. doi: 10.1007/s11110-020-01041-3
8. Holt RJ. Medical causes and consequences of hyperprolactinaemia. A Context Psychiatrists J Psychopharmacol (2008) 22(2 Suppl):28–37. doi: 10.1177/0269881107087951
9. Taipale H, Solmi M, Lahteenvuori M, Tankanen A, Correll CU, Tiitonen J. Antipsychotic use and risk of breast cancer in women with schizophrenia. A nationwide nested case-control study in Finland. Lancet Psychiatry (2021) 8 (10):883–91. doi: 10.1016/S2215-3966(21)00241-8
10. Johnston AN, Bu W, Hein S, Garcia S, Camacho L, Xue L, et al. Hyperprolactinemia-inducing antipsychotics increase breast cancer risk by activating JAK-STAT5 in precancerous lesions. Breast Cancer Res (2018) 20 (1):42. doi: 10.1186/s13058-018-0969-z
11. Milano W, Collett C, Capasso A. Hyperprolactinemia induced by antipsychotics: from diagnosis to treatment approach. Endocr Metab Immune Disord Drug Targets (2017) 17(1):38–55. doi: 10.2174/1871530317666170424102332
12. Hangreaves A, Harlman J. Preclinical risk assessment of drug-induced hypo- and hyperprolactinemia. J Appl Toxicol (2011) 31(7):599–607. doi: 10.1002/jat.1725
13. Kunimatsu T, Kimura J, Funabashi H, Inoue T, Seki T. The antipsychotics haloperidol and chlorpromazine increase bone metabolism and induce osteopenia in female rats. Regul Toxicol Pharmacol (2010) 58(3):360–8. doi: 10.1016/j.yrtph.2010.08.001
14. Vouci V, Medvedovici A, Ranetti AE, Rădulescu FS. Drug-induced hypo- and hyperprolactinemia: mechanisms, clinical and therapeutic consequences. Expert Opin Drug Metab Toxicol (2013) 9(8):955–68. doi: 10.1517/17425255.2013.791283
15. Pesakens J, Pani I, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: A comprehensive review. CNS Drugs (2014) 28(5):421–53. doi: 10.1007/s40263-014-0157-3
16. Bhana N, Foster RH, Olney R, Plokker GL, Olaxpine: an updated review of its use in the management of schizophrenia. Drugs (2001) 61(1):111–61. doi: 10.2165/00003495-200161010-00011
large prospective study. *Platelets* (2010) 21(7):508–14. doi: 10.3109/09537040.2010.494743

61. Anafogulu I, Ertorer ME, Koozoglu I, Unal B, Haydardeoglu FE, Bakiner O, et al. Macroprolactinemia, like hyperprolactinemia, may promote platelet activation. *Endocrine* (2010) 37(2):294–300. doi: 10.1007/s12020-009-9304-x

62. Wallaschofski H, Eigenthaler M, Kiefer M, Donné M, Hentschel B, Gertz HJ, et al. Hyperprolactinemia in patients on antipsychotic drugs causes ADP-stimulated platelet activation that might explain the increased risk for venous thromboembolism: pilot study. *J Clin Psychopharmacol* (2003) 23(5):479–83. doi: 10.1097/01.jcp.0000088914.24613.51

63. Reuwer AQ, Nieuwland R, Fernandez J, Goffin V, van Tiel CM, Schaap MC, et al. Prolactin does not affect human platelet aggregation or secretion. *Thromb Haemost* (2009) 101(6):1119–27. doi: 10.1161/51567-5688(09)70307-1

64. Wahlberg J, Tillmar L, Ekman B, Lindahl TL, Landsberg E. Effects of prolactin on platelet activation and blood clotting. *Scand J Clin Lab Invest* (2013) 73(3):221–8. doi: 10.3109/00365513.2013.765963

65. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tiskopoulou F, Labrianou I. Platelet distribution width: A simple, practical and specific marker of activation of coagulation. *Hippokratia* (2010) 14(1):28–32.

66. Ling C, Svensson L, Odén B, Weidégård B, Edén B, Edén S, et al. Identification of functional prolactin (PRL) receptor gene expression: PRL inhibits lipoprotein lipase activity in human white adipose tissue. *J Clin Endocrinol Metab* (2003) 88(4):1804–8. doi: 10.1210/jc.2002-021137

67. Seedi R, Frohlich J. Lipoprotein (a), an independent cardiovascular risk marker. *Clin Diabetes Endocrinol* (2016) 2:7. doi: 10.1186/s40482-016-0024-x

68. Hansson KF, Torjesen PA. Increased serum prolactin in diabetic ketoacidosis; correlation between serum sodium and serum prolactin concentration. *Acta Endocrinol (Copenh)* (1977) 85(2):372–8. doi: 10.1530/acta.0.0850372

69. Pahura DN, DeLuca HF. Stimulation of intestinal calcium transport and bone calcium mobilization by prolactin in vitamin D-depleted rats. *Science* (1981) 214(4524):1038–9. doi: 10.1126/science.7302575

70. Jayakumar PG, Arunakaran J, Aruldas MM, Govindaraju P. Role of prolactin on epidermal glycoprotein metabolism in matured monkeys, macaca radiata: specific activities of glycosyltransferases and glycosidases. *Indian J Exp Biol* (1992) 30(11):1075–8.

71. Liang L, Hu J, Sun G, Hong N, Wu G, He Y, et al. Artificial intelligence-based pharmacovigilance in the setting of limited resources. *Drug Sci* (2022) 45(15):1–9. doi: 10.1007/140264-022-01170-7

72. Stojkovic M, Radmanovic B, Jovanovic M, Janic V, Muric N, Ristic DI. Risperidone induced hyperprolactinemia: From basic to clinical studies. *Front Psychiatry* (2022) 13:87470S. doi: 10.3389/fpsyt.2022.87470S

73. Ruecke C, Starr KR, Reavill C, Fenwick S, Deadman K, Jones DN. Effects of the atypical antipsychotics olanzapine and risperidone on plasma prolactin levels in male rats: A comparison with clinical data. *Psychopharmacol (Berl)* (2006) 184(1):107–14. doi: 10.1007/s00213-005-0230-1

74. Grigg J, Worsley R, Thew C, Gurvich C, Thomas N, Kulkarni J. Antipsychotic-induced hyperprolactinemia: synthesis of world-wide guidelines and integrated recommendations for assessment, management and future research. *Psychopharmacol (Berl)* (2017) 234(22):3279–97. doi: 10.1007/s00213-017-4730-6

75. Rustgs MM, Alabbaei AY, Nelson LA. Guidance on the treatment of antipsychotic-induced hyperprolactinemia when switching the antipsychotic is not an option. *Am J Health Syst Pharm* (2021) 78(10):862–71. doi: 10.1093/ahjp/ zxab065

76. Barata PC, Santos MJ, Melo JC, Maia T. Olanzapine-induced hyperprolactinemia: two case reports. *Front Pharmacol* (2019) 10:846. doi: 10.3389/fphar.2019.00846

77. Jen YW, Huang TJ, Chan HY, Haieh MH, Liu CC, Liu CM, et al. Abnormally low prolactin levels in schizophrenia patients after switching to aripiprazole in a randomized trial: A biomarker for rebound in psychotropic symptomol BMC Psychiatry (2020) 2015:552. doi: 10.1186/s12888-020-02957-7

78. Eftekhari A, Azarny Z, Parvipeur G, Eghbal MA. Involvement of oxidative stress and mitochondrial/fyosomal cross-talk in olanzapine cytotoxicity in freshly isolated rat hepatocytes. *Xenobiota* (2016) 46(4):369–79. doi: 10.1039/c5xb00752f

79. Omran B, Baek KI. Nanoantioxidants: pioneer types, advantages, limitations, and future insights. *Molecules* (2021) 26(22):7031. doi: 10.3390/molecules26227031

80. Khalil I, Yehya WA, Etteherieh AE, Alhadi AA, Dezfooli SM, Julkaphi NM, et al. Nanoantioxidants: recent trends in antioxidant delivery applications. *Antioxid (Basel)* (2019) 9(1):24. doi: 10.3390/antiox9010024

81. Kabiri M, Kamalinejad M, Bioos S, Shariat M, Sohrabvand F. Comparative study of the effects of chaminol (matriaria chamomilla L) and cabergoline on idiopathic hyperprolactinemia: A pilot randomized controlled trial. *Iran J Pharm Res* (2019) 18(3):1612–21. doi: 10.22037/ipj.2019.1100758

82. Kokol P, Kokol M, Zagoranski S. Machine learning on small size samples: a synthetic knowledge synthesis. *Sci Prog* (2022) 105(1):938. doi: 10.1177/003685042111029777

83. Calafato MS, Austin-Zimmerman I, Thygesen JH, Sairam M, Metastasio A, et al. Machine learning on small size samples: a synthetic knowledge synthesis. *Sci Prog* (2022) 105(1):938. doi: 10.1177/003685042111029777

84. Houston JP, Fijal B, Heinloth AN, Adams DH. Genetic associations of clozapine and quetiapine on olanzapine-induced disturbances in mitochondrial/lysosomal cross-talk in olanzapine cytotoxicity in freshly isolated rat hepatocytes. *Xenobiota* (2016) 46(4):369–79. doi: 10.1039/c5xb00752f

85. Zhu et al. 10.3389/fendo.2022.1011492

86. Calafato MS, Austin-Zimmerman I, Thygesen JH, Sairam M, Metastasio A, Marston L, et al. The effect of CYP2D6 variation on antipsychotic-induced hyperprolactinemia: A systematic review and meta-analysis. *Pharmacogenom J* (2020) 20(5):629–37. doi: 10.1007/s12928-019-0142-9

87. Houston JP, Fijal B, Heinloth AN, Adams DH. Genetic associations of prolactin increase in olanzapine/flupentixol combination-treated patients. *Psychiatry Res* (2016) 175(1-2):171–2. doi: 10.1016/j.psychres.2009.06.014