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Construction of a Prediction Model for Voriconazole-Induced Hepatotoxicity Based on Mixed-Effects Random Forest

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Abstract. Voriconazole is a second-generation triazole antifungal agent with strong antifungal activity against a variety of clinically significant pathogens. Controlling blood concentrations within guideline limits through blood concentration monitoring can reduce the probability of hepatotoxicity in patients with voriconazole. However, statistical analysis based on real-world data found that there were still several patients who had blood concentration monitoring developed voriconazole induced hepatotoxicity. Therefore, it has important clinical significance to predict whether hepatotoxicity will occur in patients who meet the guidelines for voriconazole plasma concentration requirements. In this study, based on real-world data, the mixed-effects random forest was used to analyze the electronic medical record data of patients who met the guidelines for voriconazole blood concentration requirements during hospitalization, and a predictive model was constructed to predict whether patients would develop hepatotoxicity within 30 days after using voriconazole.

Keywords. Voriconazole, hepatotoxicity, real-world study, mixed-effect random forest, prediction model

1. Introduction

Voriconazole is a second-generation triazole antifungal agent with strong antifungal activity against a variety of clinically important pathogens, including aspergillus and candida [1]. Voriconazole exhibits non-linear pharmacokinetics, and its metabolism is related to multiple factors, and the reduced efficacy or toxicity of voriconazole may be related to its blood levels [2,3]. Therefore, therapeutic drug monitoring (TDM) is recommended for optimizing the therapeutic effect of voriconazole and reduce its side effects [1]. However, there are still studies showing that even patients whose voriconazole plasma trough concentration is within the recommended range of guidelines will still experience hepatotoxicity, adjusting the drug dose and reducing the plasma trough concentration can alleviate the patient's hepatotoxicity, but cannot cure it [4,5]. Therefore, identifying risk factors for predicting whether voriconazole patientswith

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TDM will develop hepatotoxicity and constructing a corresponding predictive model can help clinicians to better use voriconazole for the treatment of invasive mycosis.

With the widespread use of voriconazole, a large number of real-world data on patients taking voriconazole have been accumulated in various medical institutions. Compared with ideal clinical trials, real-world data can generate real-world evidence that better reflects real-world drug treatment response [6]. In recent years, the progress of machine learning and artificial intelligence technology has provided new strategies for real-world research, which can better mine the information in real-world data to perform various tasks including detection of adverse drug reactions [7].

In this study, the real-world electronic medical record data of voriconazole patients who received TDM was extracted and analyzed through machine learning methods. A model was built to predict occurrence of hepatotoxicity within 30 days after drug administration, which could help improving the clinical management of voriconazole.

2. Methods

2.1. Data collection and pre-processing

Data were collected from the Zhejiang Laboratory's multi-center intelligent medical information platform. Adult patients with voriconazole administration who were hospitalized in a large hospital from July 2017 to October 2020 and had liver function test results within two weeks before the first dose were included in this study. The demographic information, the history of voriconazole-related diseases, the use of voriconazole from 14 days before the beginning of each observation period to the end of each observation period, the results of laboratory tests, other medication and the surgical procedures of included patients were extracted for further analysis, the observation period refers to the continuous treatment of voriconazole in patients.

The extracted data were further processed with following steps:

- For features with missing values, when the proportion of the missing value is more than 50%, the feature is removed from this study. While the proportion of the missing value is less than 50%, the feature is imputed with the latest eigenvalue of the same patient or the median / mode of the normal value of the feature in the whole hospital. Features that cannot be imputed will be removed from this study.
- In this study, the occurrence of hepatotoxicity was judged according to the results of liver function test, so the time point of the first voriconazole administration during the observation period and the time point of each subsequent liver function test were taken as the predicted time point of this study.
- The extracted patient data were converted into the dose and days of voriconazole administration, the average/mode of laboratory test results, and whether there exists operation process and drug exposure occurred between each predicted time point and the previous one. For the first time point of each observation period, the conversion was based on the data between the first dose and 14 days before the first dose.
- Finally, this study extracted the relevant test results of patients during hospitalization, and calculated whether hepatotoxicity occurred within 30 days after each liver function test in each observation window according to the

definition of drug-induced liver injury defined by the European Association for the Study of the Liver [8], which was used as the outcome index of this study for modeling and analysis.

2.2. Feature selection

Due to the large number of features involved in this study, the information value (IV) was used to evaluate and screen the importance of each feature for predictive model construction. IV is a measure used to quantify the predictive power of independent variables when used to predict outcome events. We set three different thresholds 0.01, 0.05 and 0.1 for feature selection and three different feature sets of IV>0.01, IV>0.05, and IV>0.1 were obtained for subsequent analysis

2.3. Model construction and evaluation

As the data analyzed in this study belong to repeated measurement data, the use of mixed effect model for analysis and modeling can effectively make use of the correlation between multiple measurement results of the same patient [9]. Considering the potential nonlinear relationship, the mixed effect random forest model (MERF) [10] was chosen for this study, which is defined as following equation (1):

$$y_i = f(x_i) + b_i + e_i, b_i \sim N(0, B) \quad (1)$$

Where i is every patient in this cohort; y_i is whether patient i has hepatotoxicity within 30 days; x_i is the characteristic matrix of patient i used for analysis and modeling; $f(x_i)$ is a conventional random forest model; b_i is the random effect coefficient of each patient i, which obeys the distribution $N(0, B)$, where B is the parameter learned from the training data; e_i is the random noise of each patient i, which obeys the same distribution. The parameters of the model are obtained by self-help sampling and iterative training.

We use average precision, recall and f1 scores from 5-fold cross validation for model evaluation. Samples with top 28.1% of predicted probability are categorized as positive samples with reference to the proportion of positive samples in the study cohort.

3. Results

3.1. Results of data processing and feature selection

According to the process of data collection and processing in section 2.1, this study finally obtains 7929 prediction points, and the data overview for analysis is shown in Table 1. Through feature selection based on IV, according to different thresholds, three different feature sets including 147, 35, 19 features are obtained, which are IV > 0.01, IV > 0.05 and IV > 0.1, respectively.

Table 1. An overview of the data used for analysis and modeling in this study

Feature Type	Feature Overview
Predictive time point	7929 predictive time point in total, of which 2229 occurred hepatotoxicity within 30 days after voriconazole administration.
Demography	Age (19-92, Mean: 54.05, Median: 55.00) of included patients.

Voriconazole drug administration	The total dose (0-83600, Mean: 888.50, Median: 400.00) and daily dose (0-1200, Mean: 325.60, Median: 400.00) of voriconazole exposure between the current predicted time point and the previous one.
Condition	Medical history of organ transplant (4268), liver disease (1455) including cirrhosis, failure, and tumor, lung disease (4115) including pulmonary infection and pneumonia, and other diseases related to voriconazole (981).
Procedure	Whether a surgical process occurs between the current predicted time point and the previous one, a total of 276 surgical procedures were included.
Drug exposure	Whether the drug exposure of a drug occurred between the current predicted time point and the previous one, a total of 280 drug according to their active components were included.
Laboratory examination	Summary of each laboratory examination between the current predicted time point and the previous one, a total of 407 laboratory examination were included.

3.2. Model construction and evaluation

Supported vector machine (SVM), logistic regression (LR), random forest (RF) and MERF models were constructed for each feature sets, respectively. The performance of different models constructed with different feature sets were summarized in Figure 1.

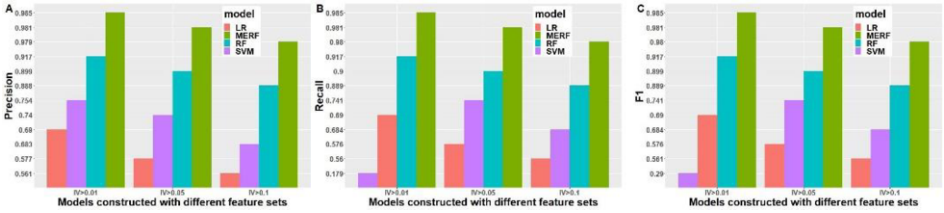

Figure 1. Precision (A), recall (B) and F1 (C) of models constructed with different feature sets.

4. Discussion

The comparison results of the model performance in figure 1 indicate that the prediction performance of the LR model is poor, suggesting that there is non-linear relationship between the features used in model training. The MERF model has the best prediction performance, indicating that on the basis of the RF model, adding the mixed effect can better mine the information in the repeated measurement data. When using IV for feature screening, the feature set filtered by threshold 0.01 in this study can get better results, however, the improvement compared with models constructed with feature set filtered by threshold 0.05 or 0.1 is limited. Therefore, in clinical use, the MERF model trained by the feature set with IV > 0.1 can be considered.

The MERF model trained by the feature set with IV >0.01 showed the best performance, with a precision of 0.985, a recall of 0.985 and a F1 of 0.985, indicating that the model can effectively predict the occurrence of hepatotoxicity within 30 days after the use of voriconazole in the current cohort. However, the current study cohort comes from a single institution, so the current research results need to be further evaluation in multi centers, combined with lifelong learning, transfer learning and other techniques to optimize the generalization ability of the model, so that the model can provide better assistant decision-making for clinical voriconazole drug management.

5. Conclusions

Based on the real-world data from the multi-center intelligent medical information platform of Zhejiang Laboratory, this study extracted the repeated measurement data of patients who used voriconazole and received TDM during hospitalization, constructed a mixed-effect random forest model to predict the occurrence of hepatotoxicity within 30 days, and evaluated the prediction performance of the model by 5-fold cross-validation. Compared with the logical regression, support vector machine and random forest models without considering the mixed effect, the mixed effect random forest model can better mine and analyze the repeated measurement data in this study, and assist better management of voriconazole.

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