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Design and Application of Multi-Center Clinical Research Platform for Phenotyping of Voriconazole Hepatotoxicity

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Abstract. We introduce a phenotyping pipeline for voriconazole hepatotoxicity based on a multi-center clinical research platform. Using the platform's queue construction, feature generation, and feature screening functions, 52 features were obtained for model training. The prediction model of voriconazole hepatotoxicity was obtained by using the model training and evaluation functions of the platform. Important risk factors and protection factors of the model were listed.

Keywords. Multi-center clinical research platform, voriconazole hepatotoxicity, phenotyping, electronic medical records

1. Introduction

Voriconazole is a broad-spectrum triazole antifungal drug with broad antibacterial spectrum, strong antibacterial activity and high oral bioavailability. According to the guidelines for drug induced liver injury (DILI), the clinical manifestations are usually non-specific [1]. Only some hepatic biochemical indicators increased to varying degrees.

In this paper, a multi-center clinical research platform was built, and the application of voriconazole hepatotoxicity phenotyping was initially explored. Through the data analysis provided by the platform, the final features are screened from the candidates.

2. Methods

The functional modules of the platform are divided into the following steps: The cohort construction module provides multi-dimensional cohort condition construction; feature generation supports flexible definition and generation of features; feature screening module provides a variety of feature screening methods; model training and evaluation module provides a variety of machine learning methods.

The data who had taken voriconazole came from the EHR database of the First Affiliated Hospital of Zhejiang University School of Medicine from 2010 to 2020.

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IV screening and AIC feature screening methods were used. And a LR model was chosen for prediction. Another approach to model interpretation is the Shapley Additive Explanations (SHAP) method, which interprets the predicted values of the model as the sum of the attributive values for each input feature.

3. Results

11599 observation windows were selected as cohort samples. The study extracted 10386 kinds of characteristics, including 2 kinds of basic information (age and gender), 4173 kinds of diagnosis, 400 kinds of surgery, 3169 kinds of abnormal detection, 2585 kinds of medication, and 10342 kinds of symptoms. Among IV value screening and AIC feature screening, 32 were characterized by abnormal test items, 19 were medication records, and 1 was basic patient information.

4. Discussion

According to the OR value and the results of the SHAP method, we can see that "the degree of jaundice in the specimen", "high-density lipoprotein-C", "serum ammonia", "magnesium isocyanate", "balliximab" and "dicyclic alcohol" were important risk factors. Contrarily, the medication records of "tibivudine", "montmorillonite", "chlorhexidine tinidazole" and "medium-long chain fat milk" were important protective factors.

Based on the platform, this model can screen out patients with missing liver function test but high risk of voriconazole hepatotoxicity in the EHR system. Doctors can review these patients' EHRs to determine a final diagnosis. In addition, the phenotypic mining process presented in this paper can also be applied to other diseases.

5. Conclusions

This study completed the design and development of a multi-center clinical research platform. Based on this platform, phenotyping of Voriconazole hepatotoxicity was conducted by using the EHR data except liver function detection. In the future, long-term follow-up management of patients is needed to further support prospective studies.

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