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

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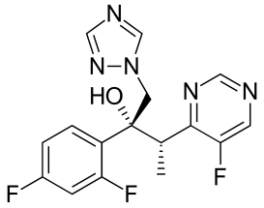
Introduction

- Voriconazole is a triazole antifungal agent with strong antifungal activity against a variety of clinically important pathogens
- Voriconazole exhibits non-linear pharmacokinetics, and its metabolism is related to multiple factors
- Hepatotoxicity is one of the most concerned adverse drug reactions
- Guidelines recommend the implementation of therapeutic drug monitoring and the control of plasma valley concentration within the range of 0.5-5.5mg/L

Voriconazole



Recommendation 5

The trough blood concentration of VRZ is recommended to be maintained above 0.5 mg·L^{-1} (1B, *strong recommendation, moderate quality of evidence*).

Summary of the Evidence

Patients whose VRZ trough blood concentration was ≤0.5 mg·L^{-1} exhibited a lower rate of treatment response (RR = 0.49, 95% CI: 0.29–0.81, moderate quality of evidence).[30]

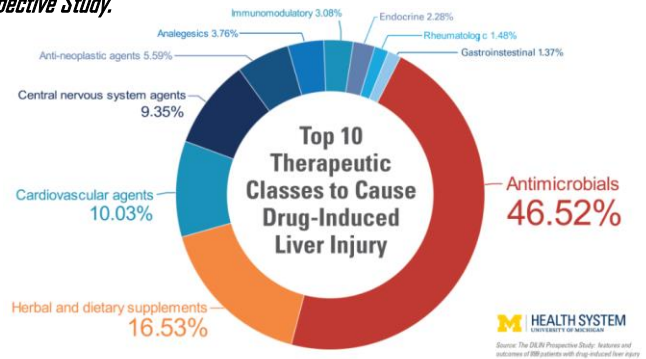
Recommendation 6

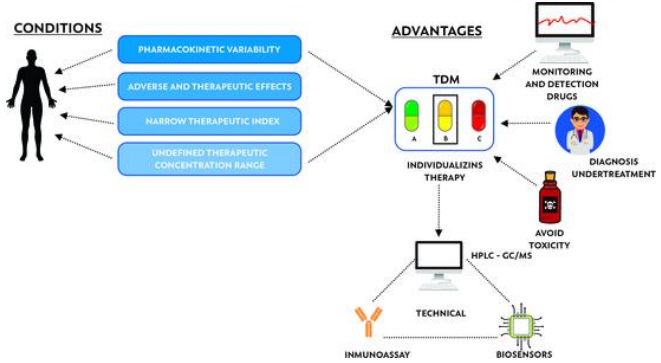
The trough blood concentration of VRZ is recommended to be maintained below 5 mg·L^{-1} for Chinese population (1B, *strong recommendation, moderate quality of evidence*).

Summary of the Evidence

Asian patients whose VRZ trough blood concentration was <5 mg·L^{-1} exhibited a lower rate of hepatotoxicity (RR = 0.34, 95% CI: 0.13–0.87, moderate quality of evidence).[30]

Features and outcomes of 899 patients with drug-induced liver injury DILIN Prospective Study.





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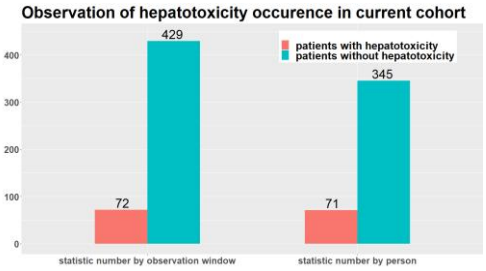
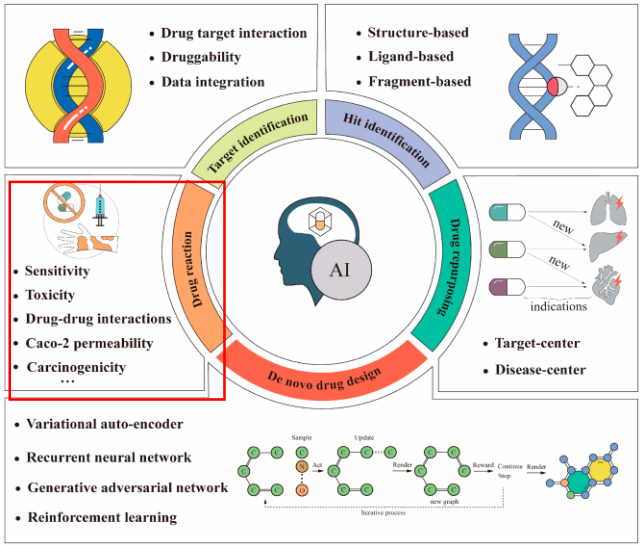
Introduction

- Several studies suggest that even patients whose voriconazole plasma trough concentration is within the recommended range of guidelines will still experience hepatotoxicity
- Compared with ideal clinical trials, real-world data can generate real-world evidence that better reflects real-world drug treatment response
- A large number of real-world data on patients taking voriconazole have been accumulated in various medical institutions
- Machine learning and artificial intelligence technology can better mine the information in real-world data to perform various tasks including detection of adverse drug reactions



- Framework for FDA's Real-World Evidence Program
- Use of Electronic Health Records in Clinical Investigations
- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
- Data Standards for Drug and Biological Production Submissions Containing Real-World Data
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
- Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products
- Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
- Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs



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Methods-Data collection and pre-processing

Cohort Definition

Multi-Centre Intelligent Medical Informatics Platform of Zhejiang Lab

Data of patients with voriconazole administration who were hospitalized in a large hospital from July 2017 to October 2020 were extracted (n = 8110)

Patient under 18 and without liver function test results within two weeks before the first voriconazole administration were excluded (n = 7808)

Patient who received TDM were included (n = 416)

Data Imputation

Proportion of missing values

<50%

≥50%

Imputation

Feature removed

imputation with the latest eigenvalue of the same patient or the median / mode of the normal value of the feature in the whole hospital

Imputation failed

Imputation finished

Prediction Time Definition

Observation window acquisition according to voriconazole administration

Prediction time point acquisition according to first administration and time of liver function test

Hepatotoxicity in 30 Days of each prediction time point was labeled according to EASL

Data Transformation

Data between current prediction time point and last one were summarized as feature for current prediction time point

For the first prediction time point, 14 days before the first time point were regarded as last time point

Occurrence of drug exposure, procedure and condition, average/mode value of numeric/category laboratory examination

Methods-Model Construction

Feature Selection

- Information value (IV) is one of the most useful technique to select important variables in a predictive model.
- We set three thresholds of IV for feature selection, which are 0.01, 0.05 and 0.1 respectively

$$IV = \sum (n_{non-event} - n_{event})/n_{all} \times WOE$$

$$WOE = \ln \frac{n_{non-event}}{n_{event}}$$

Model Construction

- Mixed effect model is suitable for repeated measurement data
- Considering the potential nonlinear relationship between selected features, mixed effect random forest (MERF) was chosen for model construction

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

Model Evaluation

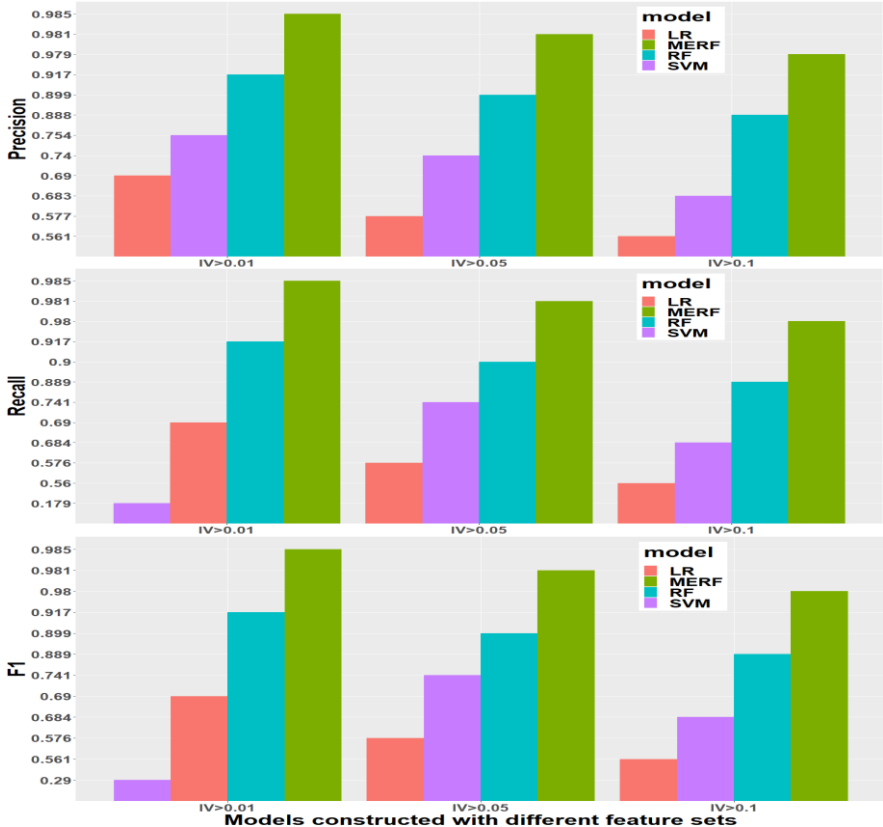
- Average precision, recall and f1 scores from 5-fold cross validation were used for model evaluation
- The performance of MERF model were compared with RF, LR, and SVM models.

Results

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.

Results

Feature Type \ Feature Set	IV>0.01	IV>0.05	IV>0.1
Demography	Age	Age	Age
Voriconazole drug administration	Total Dose and Daily Dose	Total Dose	/
Condition	4	2	/
Drug exposure	34	10	4
Laboratory examination	106	21	14
Total	147	35	19



Conclusion

- A model for predicting occurrence of hepatotoxicity within 30 days of patients who used voriconazole and received TDM during hospitalization was built based on EHR data
- The model considering mixed effects showed considerable performance according to internal 5-fold cross-validation and better performance than conventional machine learning models
- Further multi-center validation and generalization test is necessary to transfer current work into clinical use