Predictors of Adverse Events and Determinants of the Voriconazole Trough Concentration in Kidney Transplantation Recipients

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Introduction

Invasive fungal infections are a feared complication. The 12-week survival rates of this infection were only about 60%. Furthermore, 22.1% of the survivors experienced graft loss because of this terrible infection. Voriconazole is recommended as primary therapy for invasive aspergillosis. However, voriconazole exhibits nonlinear pharmacokinetics.

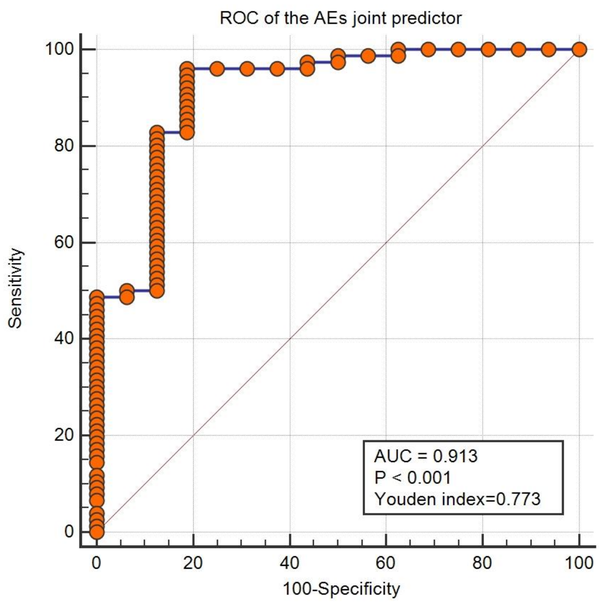
Methods

From January 1, 2016, to December 31, 2019, hospitalization renal recipients were eligible to enroll in the study. Inclusion criteria and exclusion criteria were listed. The statistic approach of two main outcomes was as follows: (1) Analyze the predictors significantly affected the occurrence of the adverse events by binary logistic regression. (2) Analyze the determinations of voriconazole trough concentration by multiple linear regression.

Results

A total of 93 eligible patients was satisfied with the inclusion criteria, and we finally collected 213 voriconazole trough concentration values. 77 (82.80%) of them had occurred the adverse events. Predictors of the adverse events were voriconazole trough concentration (H.R.:2.614; P=0.016), cytochrome P450 2C19(CYP2C19), and hemoglobin (H.R.:0.181; P=0.005). The predictive power of these three factors was 91.30%.Meanwhile, voriconazole trough concentration in population with phenotype of CYP2C19 intermediate metabolizer was 1.23 mg/L (P < 0.001) lower in average than those with phenotype of CYP2C19 poor metabolizer. Synchronously, it would decrease by 1.521 mg/L (P < 0.001) in individuals with CYP2C19 normal metabolizer approximately. It would also decrease because of a higher count of blood platelet(P=0.004) and concomitant use of the ilaprazole(P=0.001). While on the contrary, it would increase due to the factor of hemoglobin (P<0.001).

FIGURE 1. Receiver operating characteristic (ROC) curve for predicting adverse events.



Objectives

The purpose of this study is to identify predictors of the occurrence of adverse events and to determine the magnitude of serum voriconazole trough concentration in kidney transplantation recipients.

FIGURE 2. Distinction of voriconazole trough concentration in different group.

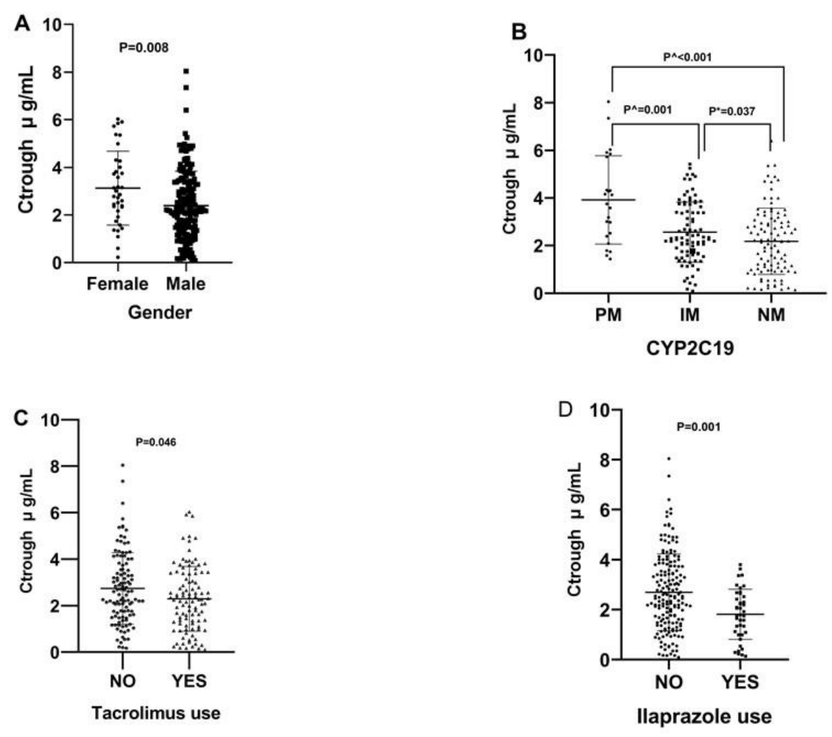
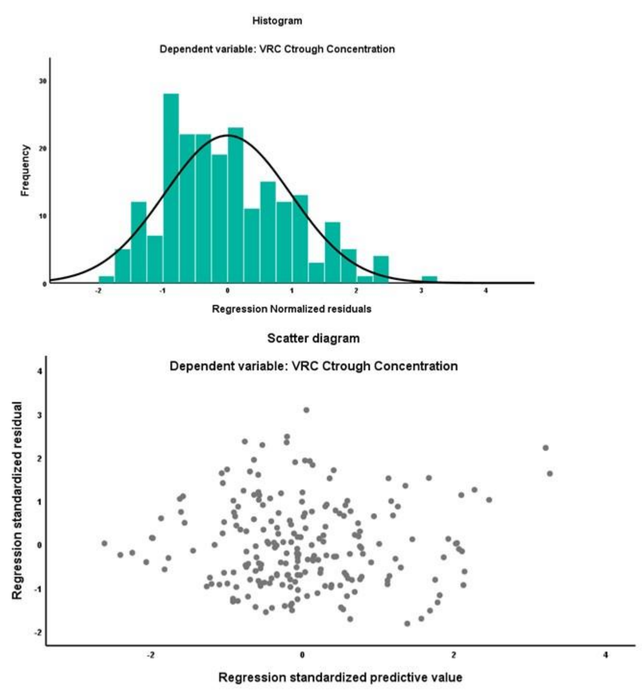


FIGURE 3. Histogram of residual distribution and Scatter diagram of residual distribution. Residuals are normally distributed; The residual distribution is between minus 2 and 2. Both demonstrate that the linear regression model fits well.



Conclusions

The phenotype of CYP2C19, hemoglobin, platelet count and concomitant use of drugs were perfect predictors of the adverse events and biologically plausible modulators of the magnitude of voriconazole trough concentration. If we can consider these factors during voriconazole use, we can likely maximize the treatment effect and minimize adverse events.

Declaration： The authors declare no conflict of interest.