Duke University School of Medicine

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Predictive Modeling of Mortality in Invasive Talaromycosis Infection of HIV Patients

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INTRODUCTION

- Talaromycosis (penicilliosis) is an invasive fungal infection endemic in Southeast Asia and is a major cause of death in patients with advanced HIV disease.
- We recently demonstrated in the IVAP trial the superiority of Amphotericin B Deoxycholate over Itraconazole with regard to 24 week mortality, clinical response, and blood fungal clearance.
- Here, we built a predictive model and identified candidate surrogate markers of mortality in invasive talaromycosis, using the data from the IVAP trial

METHODS

- The IVAP trial enrolled 440 patients with talaromycosis across 5 hospitals in Vietnam from October 2012 to December 2015. 219 patients received Amphotericin B treatment and 221 patients received Itraconazole treatment during the first 14 days after randomization. Serial blood fungal colony-forming units were quantified until clearance over 24 weeks.

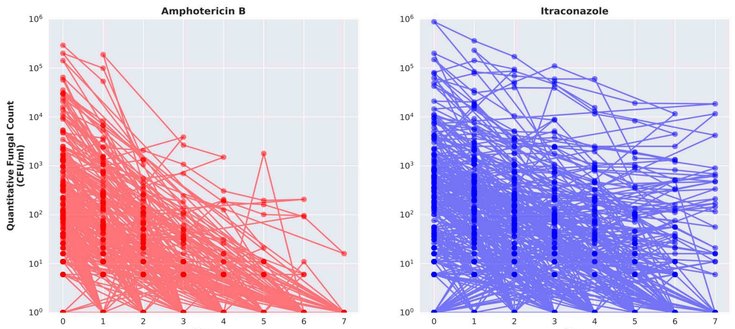


Figure 1. The fungal counts in blood at the first week of treatment

- Figure 2 and 3 showed three main patterns of early fungal clearance dynamics in individual patients. We summarized the dynamics using a double exponential regression model and compared it with a standard linear model with respect to model quality via Akaike information criterion (AIC).

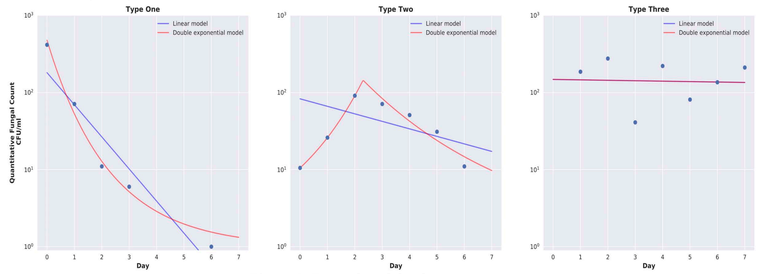


Figure 2. Examples of the three patterns

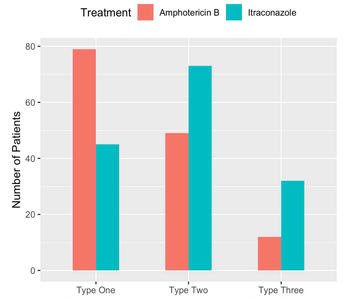


Figure 3. patterns versus number of patients

- Double exponential model:

$$\log(\text{fungal load} + 1) = \begin{cases} a * \exp\left(\frac{\text{time} - c}{bl}\right), \text{time} < c \\ a * \exp\left(\frac{\text{time} - c}{-br}\right), \text{time} \geq c \end{cases}$$

a is the peak value of fungal count within the first week,
c is the days to reach the maximum fungal count,
bl is the reciprocal of growth constant,
br is the reciprocal of decay constant(Figure 4).

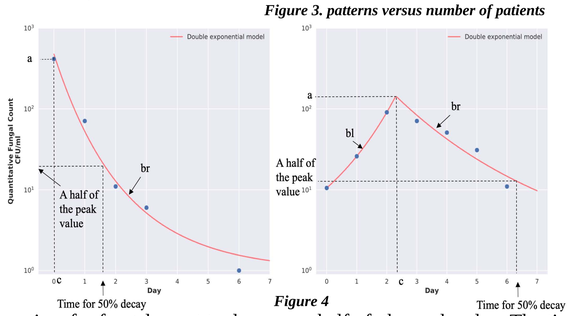


Figure 4

- We proposed a new predictor named **time for 50% fungal decay**, i.e., time for fungal count to decrease a half of the peak value. The time to 50% fungal decay is calculated from the double exponential model.
- A cox proportional hazard model landmarked at the 7th day was built, including a binary covariate (whether time for 50% fungal decay is larger than the median value) adjusted by age, antifungal treatment, antiretroviral status, IVDU, baseline CD4 count, fungal count at enrollment, and dyspnea requiring oxygen. The first week is the time-period used to fit a double exponential model and predict time for 50% fungal decay.

RESULTS

- The double exponential model performed better than the linear model. The mean AIC of the double exponential model is 29.16 (95% CI: 23.11 to 35.20) and the mean AIC of the linear model is 55.95 (96% CI: 52.24 to 59.67)
- The median time to 50% fungal decay is 1.97 days of all 290 patients. Cumulative mortality is significantly higher in patients with >1.97 days to 50% fungal decay compared to those with ≤1.97 days to 50% fungal decay (p<0.001, log-rank test, Figure 5).
- The median time to 50% fungal decay from the double exponential model is a significant cut-off between high risk and low risk of mortality, adjusted by the covariates. Patients with >1.97 days to 50% fungal decay have 4.23 times higher risk of mortality than patients with ≤1.97 days to 50% fungal decay (p=0.004, 95% CI: 1.60 to 11.19, Figure 6)

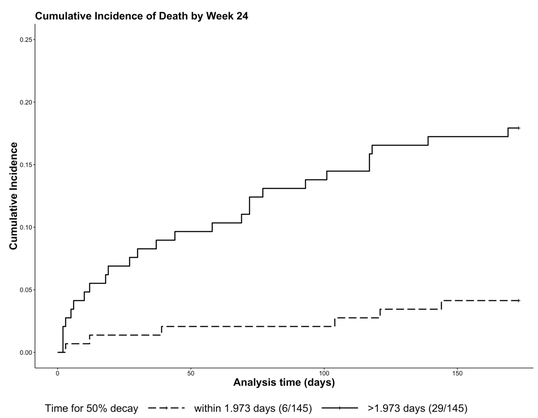


Figure 5. Cumulative incidence curve by median of time to 50% fungal decay

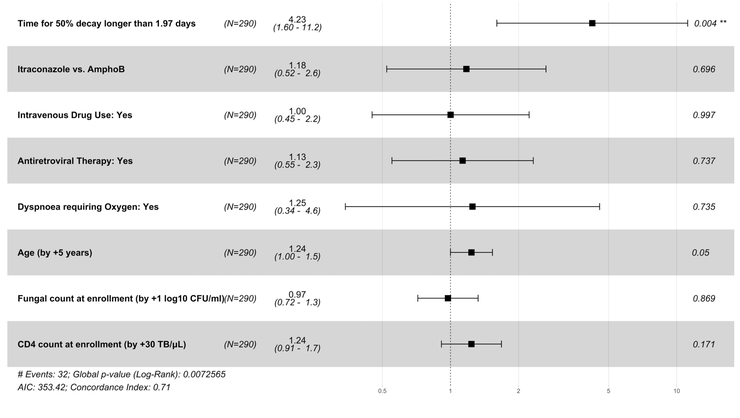


Figure 6. Hazard ratio in the cox proportional hazard model

- The median time for 50% decay of the patients receiving Itraconazole treatment is 3.19 days, and that of the patients receiving Amphotericin B treatment is 1.01 days.
- Patients receiving the same treatment were divided into two strata by the median time for 50% decay (Figure 7). In the Itraconazole group, the mortality in patients with >3.19 days for 50% decay is higher than that in patients with ≤ 3.19 days to 50% decay (p=0.01). But in the Amphotericin B group, the two mortality curves stratified by the median time for 50% decay are not significantly different (p=0.2, log-rank test).
- In the Itraconazole arm, older age (+5 years) and >3.19 days to 50% fungal decay were significant predictors of mortality, HR=1.38, 95% CI: 1.08 to 1.78, p=0.01 and HR=5.07, 95%CI: 1.64 to 15.68, p=0.005, respectively. In the Amphotericin B arm, >1.01 days for 50% decay was not a significant predictor of mortality (HR=2.54, 95% CI: 0.62 to 10.45, p=0.20). But a delay in days to start fungal clearance was a significant predictor of mortality in the Amphotericin B arm, adjusted by the same covariates above (p-value is 0.009, HR of 1 day increment was 1.35, 95% CI: 1.08 to 1.70)

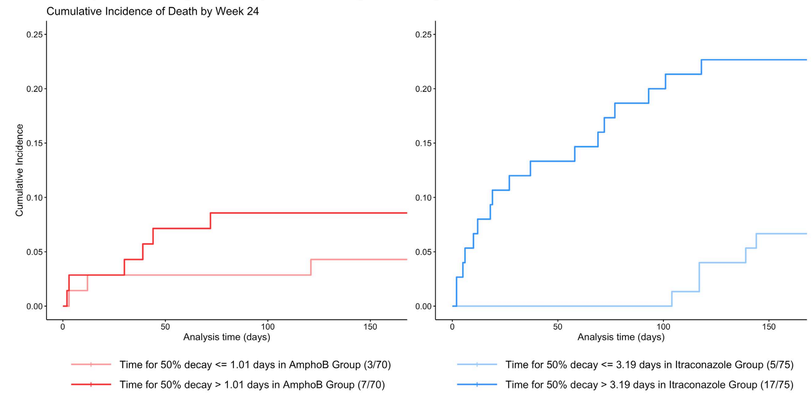


Figure 7. Mortality curve by median time to 50% fungal decay in each treatment group

CONCLUSIONS

- The double exponential model performs better than the linear model, and captures more information of the early fungal clearance dynamics.
- The median time to 50% fungal decay (1.97 days) from the double exponential model is a significant cut-off between high risk and low risk of 24 week mortality and can potentially be used as outcome measures for early phase clinical trials to efficiently assess novel therapeutic strategies for HIV-associated talaromycosis.
- In the Itraconazole group, the median time to 50% fungal decay (3.19 days) is a significant cut-off between high and low risk of mortality. In the Amphotericin B group, the median time for 50% decay (1.01 days) is not a significant cut-off, but a delay in days to start fungal clearance is a significant predictor of mortality.