SAS GLOBAL FORUM 2019

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Background: HIV infected ART naive patients may experience many intermediate events including between-event transition throughout the duration of their follow up. Through modeling these transitions, we can get a deeper understanding of HIV disease process and progression and factors that influence disease process and progression pathway. In this work, we present transition-specific parametric multi-state models to describe HIV disease process and progression.

Methods: The data is from an ongoing prospective cohort study conducted amongst adult women who were HIV-infected in KwaZulu-Natal, South Africa. Participants were enrolled into the acute HIV Infection phase, and then followed up during chronic infection and up to ART initiation.

Results: Transition specific distributions for multi-state models, including a variety of accelerated failure time (AFT) and proportional hazards models (PH), were presented and compared in this study. The analysis revealed that women enrolling with lower CD4 count (sever and advanced disease stage) had a far lower chance on immune recovery, and a considerably higher chance of immune deterioration compared to those women enrolling with a CD4 count greater than 350 (mild and normal disease stage). Our analyses also revealed that middle age, higher educational levels, higher scores for red blood cell counts, higher mononuclear scores, higher granulocytes scores and higher physical health score, all had a significant effect on a shortened time to immunological recovery, while women with many sex partners, higher viral load and larger family size had a significant effect on accelerating time to recurrence.

Conclusion: Multi-state modelling of transition specific distributions offers a flexible tool for the study of demographic and clinical characteristics affects on entire disease progression pathway. It is hoped that the article will help applied researchers to familiarize with the models and including interpretation of results.

Background Continued

➢ Multi-state is very useful for giving a better understanding of HIV disease process and progression over time.
➢ Most methodological developments have generally focused on semi-parametric as the fundamental framework of the multi-state model.
➢ The basis of this paper is the modeling of time to sequential adverse events of HIV/AIDS, using transition specific parametric distributions for multi-state models.

Data

➢ CAPRISA 002, 004 and 008 massive datasets
➢ They are ongoing prospective cohort study in KZN, Durban, South Africa.

Factor Analyses of Clinical Parameters

White blood cell parameters
- F1: Granulocytes comp
- F2: Mononuclear comp
- F3: Eosinophils comp
- Red blood cell parameters
- F1: Hb&H comp
- F2: RBC indices comp
- Blood Chemistry
- F1: Liver abnormality comp
- F2: Electrolyte comp

81% 77% 85%
Modeling Sequential Adverse Events of HIV/AIDS: Transition-Specific Parametric Multi-state Model
Zelalem Dessie¹, Temesgen Zewotir¹, Henry Mwambi¹ and Delia North¹
¹University of KwaZulu-Natal, South Africa

Data Continued

Multi-State Model Continued

The transitions are to be modelled by a four-state multi-state model.

Transition probabilities between two states, \( i \) and \( j \), relative to the given process history, are defined as

\[
P_{ij}(s, t) = P(Y(t) = j | Y(s) = i, H_s) \quad \text{for } i, j \in S \text{ and } s, t \in T
\]

The implementation was carried out using:

\[\text{Proc NLMIXED}...\]
Multi-State Model Continued

We also calculated and plotted the transition probabilities using :

Results and discussion

Estimated Transition Probability

- Women enrolling with lower CD4 count (sever and advanced disease stage) had a far lower chance on immune recovery
- It has a higher chance of immune deterioration compared to those women enrolling with a CD4 count greater than 350 (mild and normal disease stage)

Model Selection

- The best fitting model for transition 1 was found to be the Log-Normal model
- The best fitting model for transition 2, 4, 5 and 6 was found to be the Log-logistic model
- The best fitting model for transition 5 and 6 was found to be the Weibull model

Results Continued

Transition-Specific Parametric Multi-state Results

<table>
<thead>
<tr>
<th>Variables</th>
<th>Transition 1: Severe to Advanced</th>
<th>Transition 2: Advanced to Mild</th>
<th>Transition 3: Mild to Normal</th>
<th>Transition 4: Normal to Mild</th>
<th>Transition 5: Mild to Advanced</th>
<th>Transition 6: Advanced to Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Load</td>
<td>0.12(0.04, 0.21)</td>
<td>0.07(0.03, 0.17)**</td>
<td>0.03(0.00, 0.20)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
</tr>
<tr>
<td>TB No</td>
<td>0.22(0.31, 0.43)**</td>
<td>0.32(0.22, 0.46)</td>
<td>0.24(0.16, 0.35)</td>
<td>0.26(0.18, 0.35)</td>
<td>0.26(0.18, 0.35)</td>
<td>0.26(0.18, 0.35)</td>
</tr>
<tr>
<td>Marital Status: Married</td>
<td>0.14(0.37, 0.65)</td>
<td>0.12(0.10, 0.33)</td>
<td>0.06(0.16, 0.29)</td>
<td>0.02(0.23, 0.41)</td>
<td>0.13(0.56, 0.71)</td>
<td>0.06(0.29, 0.41)</td>
</tr>
<tr>
<td>Marital Status: Never Married</td>
<td>0.12(0.14, 0.20)**</td>
<td>0.04(0.10, 0.20)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
</tr>
<tr>
<td>Education: 9-10 Grade</td>
<td>0.04(1.0, 1.0)</td>
<td>0.08(0.16, 0.32)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
</tr>
<tr>
<td>Education: &gt;11 Grade</td>
<td>-0.07(1.0, 1.0)</td>
<td>-0.06(0.21, 0.32)</td>
<td>-0.16(0.45, 0.12)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
</tr>
<tr>
<td>Age, Cat:23-39</td>
<td>0.11(0.74, 0.39)</td>
<td>-0.21(0.44, 0.01)</td>
<td>0.00(0.26, 0.16)</td>
<td>0.13(0.35, 0.08)</td>
<td>0.06(0.04, 0.12)</td>
<td>0.01(0.50, 0.97)</td>
</tr>
<tr>
<td>Age, Cat:&gt;40</td>
<td>0.16(0.03, 0.29)**</td>
<td>-0.52(0.95, 0.06)</td>
<td>0.46(0.81, 0.10)</td>
<td>0.18(0.89, 0.17)</td>
<td>0.06(0.13, 0.56)</td>
<td>0.43(0.19, 1.16)</td>
</tr>
<tr>
<td>Sex: Female</td>
<td>-0.10(0.18, 0.02)**</td>
<td>0.10(0.04, 0.06)</td>
<td>0.02(0.31, 0.26)</td>
<td>0.00(0.26, 0.18)</td>
<td>0.16(0.05, 0.41)</td>
<td>0.36(0.03, 0.72)**</td>
</tr>
<tr>
<td>Independent Score</td>
<td>0.02(0.05, 0.09)</td>
<td>0.01(0.03, 0.03)</td>
<td>0.02(0.04, 0.01)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
</tr>
<tr>
<td>Social relationship</td>
<td>0.01(1.0, 1.0)</td>
<td>0.04(0.03, 0.03)</td>
<td>0.06(0.03, 0.06)</td>
<td>0.03(0.01, 0.06)</td>
<td>0.02(0.00, 0.04)</td>
<td>0.05(0.10, 0.10)</td>
</tr>
<tr>
<td>Physical Health Score</td>
<td>-0.13(0.23, 0.03)**</td>
<td>-0.01(0.05, 0.04)</td>
<td>-0.31(0.16, 0.46)**</td>
<td>0.18(0.23, 0.33)</td>
<td>-0.04(0.08, 0.11)</td>
<td>0.02(0.00, 0.04)</td>
</tr>
<tr>
<td>Psychological Score</td>
<td>0.10(0.01, 0.20)</td>
<td>0.08(0.04, 0.13)</td>
<td>0.05(0.06, 0.14)</td>
<td>0.16(0.10, 0.20)**</td>
<td>0.00(0.04, 0.11)**</td>
<td>0.07(0.00, 0.14)**</td>
</tr>
<tr>
<td>Liver Abn Comp</td>
<td>0.01(0.18, 0.18)</td>
<td>0.11(0.03, 0.20)**</td>
<td>0.05(0.13, 0.02)</td>
<td>0.04(0.05, 0.10)</td>
<td>0.01(0.06, 0.08)</td>
<td>0.02(0.12, 0.38)</td>
</tr>
<tr>
<td>RBC indices</td>
<td>0.01(0.11, 0.25)</td>
<td>0.09(0.01, 0.17)</td>
<td>0.07(0.15, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
<td>0.00(0.00, 0.00)</td>
</tr>
<tr>
<td>Platelets comp</td>
<td>0.13(0.22, 0.20)</td>
<td>0.06(0.15, 0.00)**</td>
<td>0.02(0.15, 0.00)**</td>
<td>0.12(0.11, 0.32)</td>
<td>0.04(0.05, 0.04)</td>
<td>0.23(0.10, 0.41)**</td>
</tr>
<tr>
<td>Monocytes comp</td>
<td>0.08(0.38, 0.03)</td>
<td>-0.39(0.25, -0.12)**</td>
<td>-0.27(0.34, -0.19)**</td>
<td>0.51(0.13, 0.26)</td>
<td>0.29(0.02, 0.00)</td>
<td>0.27(0.13, 0.42)**</td>
</tr>
</tbody>
</table>

Example of Interpretation

- The viral load of a woman in the study increases, the time from advanced to mild stages of the disease decelerated by a factor of 0.90 ($\text{Time Ratio} = e^{0.11} = 0.90$)
- The time from mild to normal disease stages of non TB co-infected women, was accelerated by a factor of 1.68 ($\text{Time Ratio} = e^{0.32} = 1.68$), as compared to TB co-infected
Results Continued

✓ These comparisons showed the overall good performances of parametric transition specific multi-state model in terms of fit for the transition probabilities

Future Direction

✓ In future work, we plan to conduct complex statistical models such as multivariate structural equation model of ordinal clinical state, viral load and QOL of a patient on some relevant factor, covariates and latent variables

Reference


