Poster #MSR6

A Multi-state Framework for Analyzing Outcomes in Diffuse Large B-cell Lymphoma Treated with Autologous Hematopoietic Stem Cell Transplant

Deepa Jahagirdar,[1] Jonas Häggström,[2] Marco Ghiani,[3] Grammati Sarri,[4] Anupama Vasudevan[2]
[1]Cytel, Ottawa, Ontario, Canada; [2]Cytel, Cambridge, MA, US; [3]Cytel, Berlin, Germany; [4]Cytel, London, United Kingdom

Background

- Hematopoietic stem cell transplant (HSCT) is a key therapeutic strategy for patients with high-risk or stable diffuse large B-cell lymphoma (DLBCL).
- Multi-state Markov models are widely applied in oncology and neurology to characterize disease progression, including transitions such as remission and relapse.
- These models provide valuable insights into complex clinical pathways and enhance the accuracy of patient outcome predictions.
- Unlike traditional survival analyses, multi-state Markov models enable detailed exploration of the timing and dynamic sequence of clinical events.
- This approach generates a deeper understanding of disease dynamics, informing cost-effectiveness evaluations and guiding healthcare policy decisions in health technology assessment.

Objective

- The objective of this study was to apply multi-state Markov modeling in DLBCL to identify key clinical transitions and timing, generating insights that inform cost-effectiveness evaluations and support regulatory decision-making.

Methods

Data Source

- The data set was collected by the Center for International Blood and Marrow Transplant Research (CIBMTR).
- CIBMTR is supported primarily by the Public Health Service U24CA076518 from the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, 75R60222C00011 from the Health Resources and Services Administration; N00014-23-1-2057 and N00014-24-1-2507 from the Office of Naval Research; NMDP; and the Medical College of Wisconsin.[1]

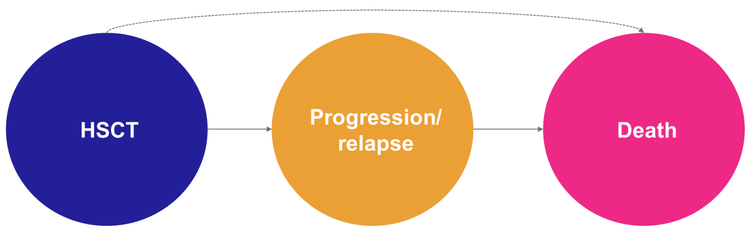
Cohort

- The cohort included adults aged 18 years and older with primary refractory, chemo-sensitive DLBCL who underwent autologous HSCT between 2003 and 2018.

Analysis

- A multi-state Markov model was applied, including transitions between three states as shown in Figure 1.

Figure 1. Summary of transitions between states



Abbreviation: HSCT, hematopoietic stem cell transplant

- Exact transition times were assumed to be non-informative; however, exact times were used for death.
- The probabilities of being in each state at a given time, conditional on being in another state at a previous time, was estimated using the transition probability matrix (i.e., the observed transitions between states).
- The models were adjusted for age (below or above age 50 years) and sex.
- Analyses were performed using R, utilizing the msm package for modeling.[2]

Results

- In total, 170 patients were considered for analysis.
- The median (range) age was 54 (20 to 77) years.
- A greater percentage of the patients were males (65%) vs females (35%).
- One patient was excluded because they were observed to relapse and experience death on the same day.

The observed transitions included:

21 Patients who died without relapse

65 Patients who died after relapse

16 Patients who relapsed without death

81 Patients who relapsed after HSCT

- The longest sojourn time was in the HSCT state without progression/relapse (Table 1).
- Patients who progressed/relapsed were almost three times more likely to die, compared with the remaining patients who were progression free, post HSCT.
- Patients spent more than twice as long in the HSCT state than in the state of progression.

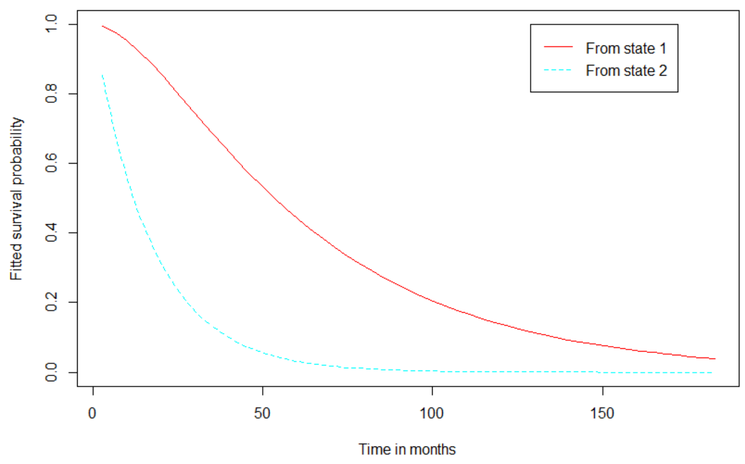
Table 1. Transition hazard intensities and sojourn times

State	Hazard intensity* (95% CI)	Mean number of months** (95% CI)
HSCT recovery		50 (41, 61)
HSCT → progression	0.02 (0.016, 0.02)	
Progression/relapse		17 (14, 22)
Progression/relapse → death	0.057 (0.05, 0.07)	

*Instantaneous risk of transition to the next state in a given month
**Sojourn time = mean number of months spent in a given state, or 1/hazard intensity
Abbreviations: CI, confidence interval; HSCT, hematopoietic stem cell transplant

- Patients aged ≥50 years were approximately twice as likely to progress/relapse compared with patients aged ≤49 years.
  - Adjusted hazard ratio (HR): 1.94 (95% confidence interval [CI]: 23, 3.07)
- Patients aged ≥50 years were three times as likely to experience death after progression/relapse than patients aged ≤49 years.
  - Adjusted HR: 2.86 (95% CI: 1.65, 4.97)
- Females were less than half as likely as males to progress/relapse.
  - Adjusted HR: 0.42 (95% CI: 0.27, 0.65)
- Females were less than half as likely as males to die once they progressed/relapsed.
  - Adjusted HR: 0.50 (95% CI: 0.29, 0.84)
- At 60 months (five years), survival was generally low. (Figure 2).

Figure 2. Overall survival by state



- Five-year survival probabilities were low among those who had progressed (Table 2).
- Approximately one-half of subjects in the HSCT state were expected to have progressed, while one-third of subjects were expected to have remained progression free.
- Among those who had progressed, almost all (0.97) were expected to have died.

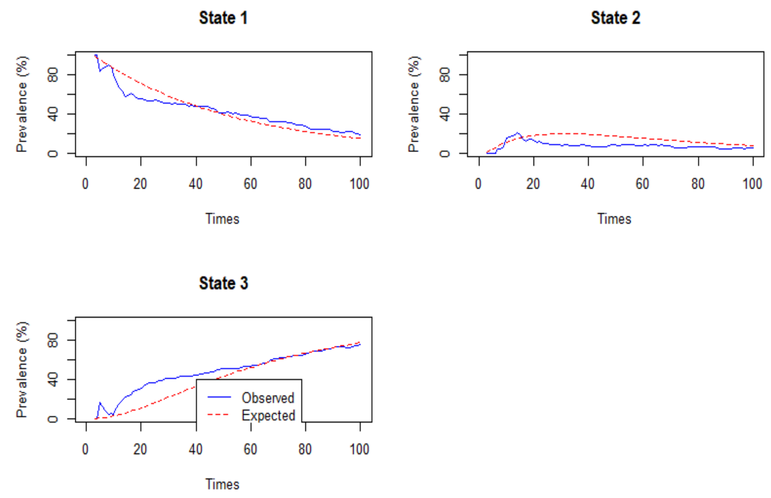
Table 2. Five-year transition probabilities

	HSCT	Progression	Death
HSCT	0.30	0.14	0.56
Progression	0	0.03	0.97
Death	0	0	1

Abbreviation: HSCT, hematopoietic stem cell transplant

- Model fit was assessed by comparing observed versus expected prevalences over time, within each state. (Figure 3).
- Comparing observed versus expected prevalences suggests relatively good model fit.
- The flexibility of the model to capture changes in the first 10 months could be improved as a next step.

Figure 3. Observed versus expected (modeled) prevalence of patients at each month*



*State 1 = HSCT; state 2 = progression; state 3 = death
Abbreviation: HSCT, hematopoietic stem cell transplant

Conclusions

- Patients spent more than twice as long in the post-HSCT state without progression, compared with in a relapse state before death.
- Once relapsed, the five-year survival probability was low with 0.97 patients expected to progress to death.
- Multi-state Markov models effectively capture the dynamic clinical pathways in DLBCL, providing estimates of progression and mortality risks, as well as time spent in each disease state.
- These insights are valuable for guiding post-HCST surveillance and treatment strategies, and have important implications for cost-effectiveness analysis, health technology assessment, and regulatory decision-making.

References

1. Bal S, et a;. Outcomes of Autologous Hematopoietic Cell Transplantation in Diffuse Large B Cell Lymphoma Refractory to Firstline Chemoimmunotherapy. Transplant Cell Ther. 2021;27(1):55.e1-55.e7;
2. Jackson, C. (2011). Multi-State Models for Panel Data: The msm Package for R. Journal of Statistical Software, 38(8), 1–28.

Disclosures

This study was investigator initiated and received no funding. All authors are employees of Cytel, Inc.