Impact of Graft vs. Host Disease (GvHD) on Survival in Bone Marrow Transplant Patients

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Introduction:

Focus:

- Transplant patients treatment and their outcomes: GvHD and survival.

What is Graft vs. Host Disease?

- Condition in which donor cells attack the cells of the recipient.
- Occurs in 60-80% of allogeneic bone marrow and stem cell transplants.
- Classified into two categories: Acute and Chronic
- Acute occurs within 100 days, whereas Chronic occurs after approximately 100 days.

Introduction:
What is Graft vs. Host Disease?

Acute GvHD Within 100 days

- Skin: Rashes, Blisters, Peeling
- Liver: Jaundice (Yellowing of eyes and skin)
- Gastrointestinal: Abdominal pain, diarrhea, and blood in stool

Chronic GvHD After approx. 100 days

- Same symptoms as Acute GvHD with additional complications
- Such as:
- Eyes: dryness, vision changes
- Joints: muscle weakness, stiffness
- Lungs: shortness of breath, damage of lung tissue

Introduction:

What is Antihuman T-lymphocyte Immune Globulin (ATG)?

- Non human antibodies used in the depletion of human T-cells
- Administered after the chemotherapy regimen, allowing a regeneration of blood before transplant.
- ATG is primarily given to patients receiving allogeneic transplant from unrelated donors but in severe cases it is given to related recipients.
- Can suppress the immune response and maintain a tolerance of the donor cells after transplant.

Objectives:

Questions

- How does chronic GvHD affect survival rates?
- Does the impact of chronic GvHD on survival differ between patients with and without ATG?

Data Overview:
Overall Dataset

- A total of 125 patients were included with Acute Lymphoblastic Leukemia (ALL), Myelodysplastic Disease (MDS) and Acute Myelogenous Leukemia (AML) treated from 2011 to 2017.
    - Collected from the University of Iowa Hospital

Chronic GvHD	ATG		Total
	Yes	No	
Yes	50 (64.94%)	31 (64.58%)	81 (64.8%)
No	27 (35.06%)	17 (35.42%)	44 (35.20%)
Total	77	48	125

Data Overview:
Patient Characteristics

- 32 variables were used in the analysis.
- To compute the missing values for numerical data we used the median and for categorical data we used the mode.

- Variable Groups are:
  - Recipient and Donor Profiles (Blood Type, Age, etc.)
  - Severity of Cancer and Acute/Chronic GvHD (if applicable)
  - Treatment and Response observations and coefficients (KPS, HCT, CD_34, etc.)
  - Transplant Types and Risks associated (PBSC, Marrow, Disease Risk, etc.)

Methodology:
Survival Endpoints

- Survival Analysis is defined as a set of methods that are used to analyze data whereas the outcome variable is the time of occurrence of an event of interest.

Overall Survival:

$$Date\ of\ Last\ Contact\ - (Date\ of\ Transplant + 100)$$

Progression-Free Survival:

$$\begin{cases} Date\ of\ Relapse \\ Date\ of\ Death \end{cases} - (Date\ of\ Transplant + 100)$$

- Subjects who did not have the event of interest were treated as *censored* observations in the survival analysis.
- Censoring happened because the study ended before the event occurred.

Methodology:
Survival Methods

- Kaplan-Meier methods were used to obtain nonparametric estimates and plots of the Overall Survival (OS) and Progression-Free Survival (PFS) functions.
- A Cox Regression was used to compare with chronic and non chronic after adjusting for other factors that impacted survival.
- Mathematical model that expresses the hazard rate $\lambda(t; x)$ as a function of time t and predictor variables x.

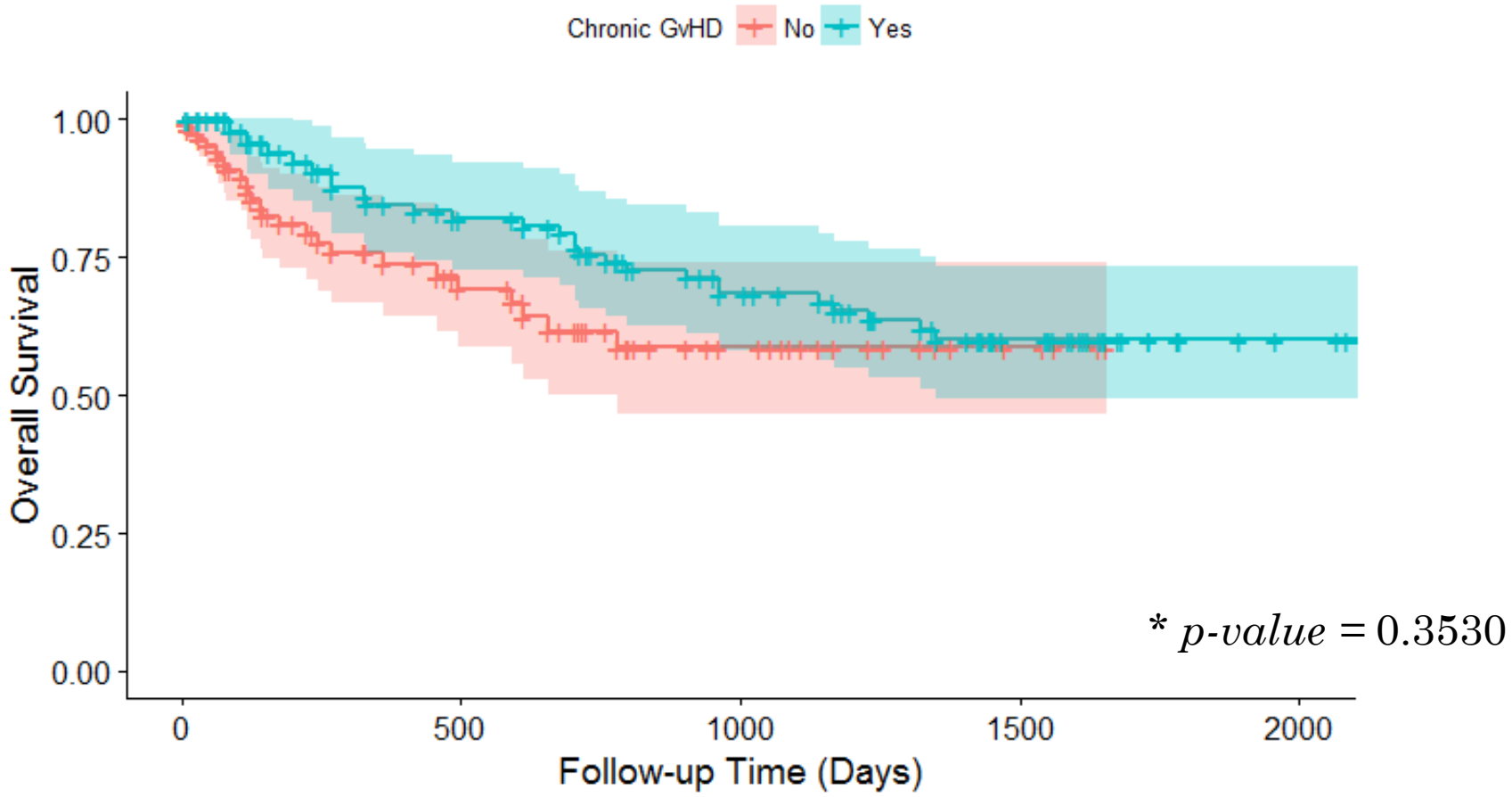
$$\lambda(t; x) = \lambda_0(t) e^{\{\beta_1 x_1 + \cdots + \beta_p x_p\}}$$

- Chronic disease was included in the model as a time dependent covariate.

Methodology:
Variable Selection

- Stepwise variable selection to identify important baseline variables to include in the Cox regression model.
- Stepwise selection iteratively included or excluded variables to select the best fitting model according to the Akaike Information Criterion (AIC).
- AIC is a quantitative metric that aims to strike a balance between model fit to the data and number of included variables.
- Smaller values indicate more desirable models.
- After variable selection, chronic GvHD and ATG were added.

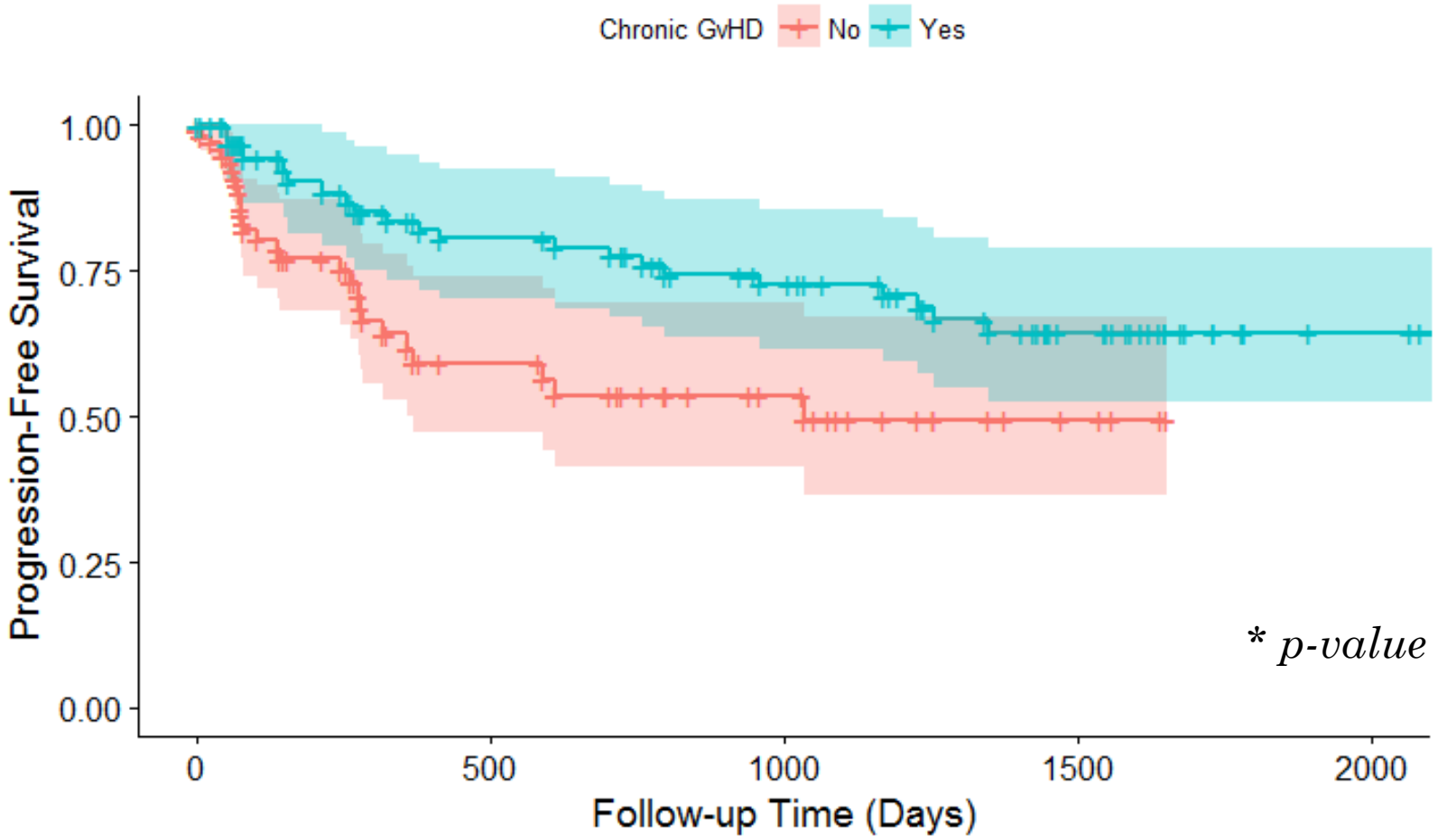
Graphs:
Overall Survival by Chronic GvHD



* *p-value* = 0.3530

Graphs:

Progression-Free Survival by Chronic GvHD



* $p\text{-}value = 0.0502$

Table: Multivariate Analysis
Overall Survival

Factor	Comparison	Hazard Ratio	95% CI	P-value
Acute GvHD*	1-unit increase	1.46	(1.11,1.91)	0.0065
Prep. Class*	RIC vs. Myeloablative	1.73	(0.90,3.31)	0.0991
Disease Risk*	1-unit increase	1.39	(0.94,2.05)	0.0992
Chronic GvHD w/o ATG	Yes vs. No	0.25	(0.09,0.70)	0.0083
Chronic GvHD w/ ATG	Yes vs. No	1.47	(0.95,1.96)	0.3120

* AIC Stepwise Selection

- The interaction p-value between chronic GvHD and ATG is 0.0040.

Table: Multivariate Analysis
Progression-Free Survival

Factor	Comparison	Hazard Ratio	95% CI	P-value
Acute GvHD*	1-unit increase	1.66	(1.26,2.19)	0.0003
Prep. Class*	RIC vs. Myeloablative	1.48	(0.73,2.98)	0.2736
Transplant Type*	Unrelated vs. Related	0.52	(0.21,1.25)	0.1450
Age at Transplant*	1-year increase	1.04	(1.01,1.06)	0.0097
Chronic GvHD w/o ATG	Yes vs. No	0.24	(0.08,0.70)	0.0088
Chronic GvHD w/ ATG	Yes vs. No	0.65	(0.29,1.47)	0.3060

* AIC Stepwise Selection

- The interaction p-value between chronic GvHD and ATG is 0.1207.

Conclusion:

- There was no significant statistical evidence to show that the impact of chronic GvHD on survival differs in patients with ATG. However, there was significant statistical evidence that the impact of chronic GvHD on survival differs without ATG.
- For patients without ATG, having chronic GvHD indicated a higher survival rate.

Postulation:

- Upon diagnosis of chronic GvHD it is possible that treatment regimen between patients without ATG was changed to deal with the situation. As such, these differ treatments could of affected the overall survivability.

Study Limitations:

- Our sample size was small.
- Required more in-depth analyses
- Lack of information, e.g. time of Acute Disease and time of transformation from limited to extensive in chronic GvHD.
- Lack of diversity, i.e. only one African American and Blood types
- Missing values in the data set
- Grouping variables was done due to small samples sizes in some of the levels

Future Research:

- Is there difference in overall survivability for Chronic GvHD depending on the type of cancer they have?
- Analyzing the Progression Free Survival in Chronic GvHD through the severity of None to Limited to Extensive.
- Doing the comparison between complete matches vs. partial matches in stem cell transplant patients.

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- Packages used in R: “survival”, “randomForest”, “dpylr”, “MASS”, “multcomp”, “lubridate”.

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Any Questions?