Introduction

Background

Leukemia is a cancer of the blood that consists of numerous subtypes based on the type of blood cells infected and the rate of differentiation. A slower-growing leukemia is classified as acute. A standard treatment for acute leukemia is a bone marrow transplant (BMT). BMTs can be allogeneic, meaning a patient receives cells from a donor, or autologous, where the patient is its own donor. The ultimate goal of a BMT is for successful engraftment of healthy stem cells into a host and an increase in platelet counts. Studies show that the success of a BMT can depend on various factors known at the time of transplantation, such as the age and sex of the patient and/or donor, the stage of the initial disease, and the time elapsed since disease diagnosis. As the patient undergoes post-transplantation experiences, the ultimate prognosis may change due to unpredictable events, such as the occurrence of acute graft-versus-host disease (aGVHD) or the recovery of platelet counts. A transplant is considered unsuccessful if a patient relapses or passes away during remission.

The analyzed study data were collected to gather information on certain characteristics of patients and donors, as well as events during the transplant process, to determine whether risks of relapse or death are predictable. The study was conducted at four hospitals in the United States and Australia, and included 137 patients who received a radiation-free conditioning regimen of oral Busulfan and intravenous cyclophosphamide. The researchers assessed and noted various factors such as patient and donor age and sex, cytomegalovirus (CMV) immune status, wait time from diagnosis to transplant, disease group, FAB classification, and prophylactic use of methotrexate. Disease group refers to a classification of acute lymphoblastic leukemia (ALL), and high- and low-risk acute myelocytic leukemia (AML). FAB classification grades leukemia subtypes based on affected cells. For the purposes of this analysis, a grade of 4, 5, or AML will be categorized as one group and the other subtypes will be grouped together separately. These variables will henceforth be referred to as baseline characteristics or factors. Patients were followed until the end of the study or death.

Previous studies have suggested that the patient's CMV status may be associated with morbidity and mortality. Patients who are positive for CMV may have a higher risk of complications such as GVHD, increased rates of infections, and organ damage. However, the use of immunosuppressive therapy, like methotrexate, to prevent GVHD can further increase the risk of CMV reactivation, leading to a higher risk of mortality. Therefore, understanding how a patient's CMV status affects BMT outcome is crucial for predicting the risk of death or relapse.

Objective

The objective of this study is to investigate disease-free survival in patients who have undergone a BMT for leukemia. In particular, the study seeks to estimate the disease-free survival time for enrolled patients, compare patients in different disease groups or FAB classifications with respect to available baseline measurements, and determine if any of the measured baseline variables are associated with differences in disease-free survival. Furthermore, the study aims to explore the relationship between the occurrence of aGVHD after transplantation and disease-free survival, as well as investigate whether aGVHD is an important prognostic event. Moreover, the study will examine whether prophylactic use of methotrexate, an immunosuppressant, is associated with an increased or decreased risk of developing aGVHD, and assess the impact of the recovery to normal platelet levels on disease-free survival and relapse risk. The findings of this study will provide valuable insights into the factors affecting disease-free

survival in patients with acute leukemia who have undergone a BMT, which can inform clinical decision-making and ultimately improve patient outcomes.

Dataset

The dataset includes information on 137 patients who underwent allogeneic BMTs as treatment for acute leukemia. The variables in the dataset include patient identification, time variables (in days) until death or the end of study, wait time until transplant, onset of aGVHD, and recovery to normal platelet levels, as well as indicator variables of death, relapse, disease-free survival, development of aGVHD, recovery to normal platelet level, and prophylactic use of methotrexate. The dataset also includes disease subtype by morphologic FAB classification, disease classification (including ALL, and high- or low-risk AML), patient age, sex, and CMV status, donor age, sex, and CMV status, and recruitment center. The dataset provides information that can be used to explore factors associated with patient prognosis following BMT.

Methods

In these analyses, for all statistical tests performed, we utilized a Type I error rate of 0.1. This was done to account for low statistical power associated with a low sample size, which decreases our ability to detect effect measure estimates under a certain level. Thus, increasing the Type I error rate decreases chances of falsely rejecting statistical hypotheses.

Question 1

To best provide an estimate of disease-free survival time for patients enrolled in this study and summarize the main characteristics of this study, we first calculated the estimated median time of disease-free survival. This was calculated based on a survival function using the disease-free survival indicator, which categorized individuals based on whether they died or relapsed, or if they were alive and disease-free. Accordingly, we used the time until relapse, death, or end of study (in days) as the time variable to calculate survival estimates and cumulative hazards. We fit a Kaplan-Meier curve and Nelson-Aalen model to estimate the probability of survival after 2 years or 730 days. Due to conflicting evidence of what characteristics influence disease-free survival, and the nature of an exploratory analysis, we decided to not initially adjust for any other characteristics to reduce the possibility of skewing, and to be able to compare this unadjusted model to further analyses. All estimates and probabilities were calculated with their respective 90% confidence intervals.

Question 2

In order to assess how baseline characteristics differed by disease subtype (FAB grade) and classification (ALL, and low- and high-risk AML), we created a descriptive characteristics table. The distributions of the numeric variables (the patient's age, the donor's age, and the wait time until transplant) were assessed. The age variables were normally distributed, but the distribution of the variable for wait time until transplant was skewed to the right. Thus, the mean and standard deviation of the patient and donor age were calculated, and the median and interquartile range of the wait time variable were calculated. For the categorical variables (patient and donor sex, patient and donor CMV status, and prophylactic use of methotrexate), the number and percentage of participants who were male, CMV+, and had a history of prophylactic use of methotrexate were reported, respectively.

Question 3

To determine whether any of the measured baseline variables were associated with differences in disease-free survival, we created a survival function using the entire dataset, and the disease-free survival indicator and the time until relapse, death or end of study in days as the time variable. We fit a Cox proportional model for each variable independently using the disease-free survival indicator, which categorized individuals based on whether they died or relapsed, or if they were alive and disease-free to determine if the adjusted effect of the individual variable was significant. These individual analyses would provide insight into which variables would be needed to develop an adjusted model. Additionally, we conducted a similar analysis adjusting for all baseline variables. We wanted to determine whether any of the baseline variables were significant, while also adjusting for the other baseline variables as an unadjusted model was already presented earlier. For any baseline variables that were borderline significant, we conducted an ANOVA test to determine whether removing that variable would actually be significant with differences in disease-free survival. Wald tests were conducted to assess significance at an alpha level of 0.1.

Question 4

To evaluate the impact of occurrence of aGVHD on disease-free survival and risk of relapse, we constructed a new variable to account for the time-varying effect of aGVHD in the study. We considered this method because, if a patient were to develop aGVHD earlier in the study, there is more of a chance that it would impact survival and relapse compared to aGVHD diagnosed closer to study endpoint. In assessing disease-free survival, every patient who developed aGVHD was split into two groups and was given a survival status in the time period before development of aGVHD and after. In assessing risk of relapse, every patient who developed aGVHD was split into two groups and was given a relapse status in the time period before development of aGVHD and after. Thereafter, we created survival objects utilizing the new cut-off points. We then fit a Cox proportional hazard model involving the effect of aGVHD on disease-free survival and another on relapse status.

Question 5

To evaluate the effect that baseline characteristics had on disease-free survival among patients who developed aGVHD, the data were subsetted to only those who developed aGVHD. We created a survival function using the disease-free survival indicator and the time until relapse, death, or end of study in days as the time variable. This survival object was fit to a Cox proportional hazards model that included all baseline measurements. Adjusted models were included for this analysis because an unadjusted analysis was previously reported, and the adjusted models would give us information about the unconfounded hazard ratios. Wald tests were then used to assess significance at an alpha level of 0.1.

Question 6

To evaluate whether the administration of methotrexate is associated with increased or decreased risk of developing aGVHD, we created a survival object looking at time from transplant to development of aGVHD, and aGVHD status. Before creating a survival model, we considered additional variables that may be related to risk of developing aGVHD. Delayed engraftment may be associated with delayed aGVHD and thus, time until recovery of platelet counts may be associated with both aGVHD development and methotrexate status. With respect to disease groups, patients with ALL have lower levels of lymphocytes compared to patients with AML, which would impact the host cells' abilities to

activate an immune response against donor cells, so that variable will be included in the model. One's immune system deteriorates as age increases, providing justification to include both host and donor age in the model. It is thought that a sex-mismatched BMT will engraft better. For the aforementioned connections of engraftment to aGVHD, both host and donor sex will be included in the model. CMV is a viral infection, which can stay latent for long periods of time. If a host has CMV and donor cells have never encountered it, this may be enough to trigger and reactivate the infection. If a donor has CMV, there is a chance of transference to the host. In both cases, this would ramp up the immune system and increase risks of aGVHD, and thus should be adjusted for.

We fit a Cox proportional hazard model involving the dichotomous effect of methotrexate on development of aGVHD, adjusting for continuous time until platelet recovery, categorical disease group, continuous donor and host age, dichotomous donor and host sex, and dichotomous donor and host CMV status.

Question 7

To evaluate the impact of recovery of normal platelet levels on disease-free survival and risk of relapse, we constructed a new variable to account for the time-varying effect of recovery of normal platelet levels in the study. We considered this method because, if a patient were to recover their platelet levels earlier in the study, there is an increased likelihood of survival and relapse impacts compared to recovery of platelet levels near the end of the study. In looking at disease-free survival, every patient who recovered to normal platelet levels was split into two groups and was given a survival status in the time period before recovering to normal platelet levels and after. In looking at risk of relapse, every patient who recovered to normal platelet levels was split into two groups and was given a relapse status in the time period before recovering to normal platelet levels and after. We then created survival objects using the new cut-off points, and fit Cox proportional hazard models involving the effect of recovering of normal platelet levels on disease-free survival and another on relapse status.

Results and Discussion

Question 1

Among all patients enrolled in the study, the median disease-free survival time is 481 days, with an associated 90% confidence interval (383, 677). The estimated probability of disease-free survival after 2 years is 0.42, with a 90% confidence interval of (0.35, 0.49). The fitted Kaplan-Meir survival curve is presented in Figure 1, while the Nelson-Aalen cumulative hazard estimate can be seen in Figure 2.

Question 2

The calculated descriptive statistics are displayed in Table 1. For disease subtype, the proportion of males was higher for those with patients with an FAB grade of 4 or 5 and AML, compared to those who were classified as otherwise, as well as their respective donors. The proportion of those who were CMV positive was also higher for patients with an FAB grade of 4 or 5 and AML, compared to those who were classified as otherwise, as well as their respective donors. Both patient and donor mean age were similar between the groups. Those with an FAB grade of 4 or 5 and AML were more likely to have a history of prophylactic use of methotrexate. Additionally, the median wait time until transplant was slightly higher for those with an FAB grade of 4 or 5 and AML. Patients with an FAB grade of 4 or 5 and

AML were more likely to be male, CMV positive, have a history of prophylactic use of methotrexate, and have a slightly longer waiting time for a transplant.

For disease classification, patient and donor age and sex were similar across classifications. The percentage of patients who were CMV positive was lower for those with ALL. Donor CMV status was similar across groups. The median wait time until transplant was much lower for those with low-risk AML. A history of prophylactic use of methotrexate was also consistent across groups.

Question 3

Only the baseline characteristics that reported differences in disease-free survival among all patients will be reported here. After fitting a Cox proportional hazard model for each individual characteristic, at an alpha level of 0.10, the only characteristics that showed significant differences in disease-free survival were disease subtype and disease group. Among all enrolled patients, we estimate the hazards of death for those with a FAB grade of 4 or 5 and AML to be 1.89 (90% CI: 1.31, 2.73) times that of those without. Given our p-value of 0.00427, we reject the null hypothesis that the hazard of death does not vary by disease subtype at the 0.1 significance level. Similarly, we estimate the hazards of death for those with low risk AML to be 0.56 (90% CI: 0.35, 0.90) times that of those with ALL. Given our p-value of 0.0457, we reject the null hypothesis that the hazard of death does not vary by disease group when comparing those with low risk AML and those with ALL at the 0.1 significance level. Additionally, we reject the null hypothesis that the hazard of death does not vary by disease group (p-value = 0.001). Prophylactic use of Methotrexate also showed a borderline significant difference in disease-free survival (p-value = 0.0944), but we needed to conduct further analysis to determine whether it was actually significant. After conducting an ANOVA test to determine whether removing prophylactic use, while adjusting for disease subtype and group, made a difference in disease-free survival, we failed to reject the null hypothesis that hazard of death does not vary by history of prophylactic use of methotrexate (p-value = 0.1617).

After fitting a Cox proportional hazard model that adjusted for all baseline characteristics, at an estimated alpha level of 0.10, the only characteristics that showed significant differences in disease-free survival were disease subtype and disease group. Among all enrolled patients, we estimate the hazards of death for those with a FAB grade of 4 or 5 and AML to be 2.23 (90% CI: 1.40, 3.55) times that of those without, adjusting for all baseline characteristics. Given our p-value of 0.00450, we reject the null hypothesis that the hazard of death does not vary by disease subtype at the 0.1 significance level. Similarly, adjusting for all baselines characteristics, we estimate the hazards of death for those with low-risk AML to be 0.35 (90% CI: 0.19, 0.64) times that of those with ALL. Given our p-value of 0.00414, we reject the null hypothesis that the hazard of death does not vary by disease group when comparing those with low-risk AML and those with ALL at the 0.1 significance level. We conducted subsequent ANOVA tests to validate that disease group and subtype were the only characteristics that showed significant differences in disease-free survival, while adjusting for all baseline characteristics. We tested adjusted models and removed baseline characteristics one by one. The results rejected the null hypothesis that hazard of death does not vary by disease group (p-value = 0.0499) and subtype (p-value < 0.001).

Together, these analyses provided evidence that disease subtype and disease group were the only baseline characteristics that showed a difference in disease-free survival.

Question 4

We estimate that the hazard of death comparing patients who developed aGVHD is 2.43 when compared to patients who did not develop aGVHD (90% CI: 1.70, 3.47). Given our p-value < 0.001, we reject the null hypothesis that the survival probability does not differ by aGVHD status in favor of the alternative hypothesis at the 0.1 significance level. Thus, there is evidence that the hazard of death differs by aGVHD status, with a higher hazard in those who developed aGVHD. This can further be seen in Figure 3 displaying survival status throughout the study of patients with and without aGVHD.

We estimate that the hazard of relapse comparing patients who developed aGVHD is 1.26 when compared to patients who did not develop aGVHD (90% CI: 0.70, 2.26). Given our p-value of 0.519, we fail to reject the null hypothesis that the risk of relapse does not differ by aGVHD status at the 0.1 significance level. This can further be seen in Figure 4 displaying risk of relapse throughout the study of patients with and without aGVHD.

From these results, aGVHD is associated with a lower survival probability/higher hazard of death, and is not significantly associated with a decreased risk of relapse. Thus, we can conclude that aGVHD is an important prognostic factor in determining the probability of survival after transplantation, but not in determining risk of relapse.

Question 5

Only the baseline characteristics that reported significant differences in disease-free survival will be reported here. The baseline factors that showed significant difference in disease-free survival among those who developed aGVHD were the age of the donor, prophylactic use of methotrexate, and wait time for transplantation. Among those who developed aGVHD, we estimate the hazards of death for those whose BMT donors were a given age to be 1.12 (90% CI: 1.01, 1.24) times that of those whose BMT donors were one year younger, adjusting for all other baseline measurements. Given our p-value of 0.0745, we reject the null hypothesis that the hazard of death does not vary by the donor's age at the 0.1 significance level. Among those who developed aGVHD, we estimate the hazards of death for those who have a history of prophylactic use of methotrexate to be 9.10 (90% CI: 1.94, 42.63) times that of those who do not have a history of prophylactic use of methotrexate, adjusting for all other baseline measurements. Given our p-value of 0.0187, we reject the null hypothesis that hazard of death does not vary by history of prophylactic use of methotrexate at the 0.1 significance level. Among those who have developed aGVHD, we estimate the hazards of death for those who have a given wait time until BMT to be 1.00 (90% CI: 1.00, 1.00) times that of those whose wait time was one day less, adjusting for all other baseline measurements. Given our p-value of 0.0965, we reject the null hypothesis that the hazard of death does not vary by wait time until BMT at the 0.1 significance level. Table 3 displays full results for all baseline characteristics.

Question 6

We estimate that the hazard of aGVHD, adjusting for time to platelet count recovery, donor age, donor sex, donor CMV status, host age, host sex, host CMV status, and disease group comparing patients who received methotrexate is 0.45 compared to patients who did not receive methotrexate (90% CI: 0.19, 1.07). Given our p-value of 0.1297, we fail to reject the null hypothesis that the risk of developing aGVHD does not vary by methotrexate administration at the 0.1 significance level. This can further be seen in Figure 5 displaying the probability of aGVHD development from time of transplant of patients who received and patients who did not receive methotrexate.

Question 7

We estimate that the hazard of death is 0.61 for individuals with recovery of normal platelet levels than individuals without recovery of normal platelet levels (90% CI: 0.39, 0.95). Given our p-value of 0.0654, we reject the null hypothesis that the association differs by status of recovery to normal platelet levels at the 0.1 significance level. We can conclude that there is evidence that the recovery of normal platelet levels is associated with improved disease-free survival. This can further be seen in Figure 6 displaying survival status throughout the study of patients who did or did not experience recovery of platelet levels.

We estimate that the hazard of risk of relapse is 1.98 for individuals with recovery of normal platelet levels versus individuals without recovery of normal platelet levels (90% CI: 0.75, 5.24). Given our p-value of 0.247, we fail to reject the null hypothesis that the association differs by status of recovery to normal platelet levels at the 0.1 significance level. We did not find evidence that the recovery of normal platelet levels is associated with a decreased risk of relapse. This can further be seen in Figure 7 displaying risk of relapse throughout the study of patients who did or did not experience recovery of platelet levels.

From these results, recovery of normal platelet levels is associated with a higher survival probability/lower hazard of death, and is not significantly associated with a decreased risk of relapse.

Implications of Findings

We found that the type of acute leukemia a patient is diagnosed with, the development of aGVHD, and the return to normal platelet levels all have a significant impact on rates of disease-free survival after a BMT. We did not find an association between aGVHD development or platelet recovery on risk of relapse. Additionally, we did not find an association between prophylactic use of methotrexate on the development of aGVHD. These findings have multiple implications. A patient's prognosis and probability of survival may be determined through their initial diagnosis, and decreased if they develop aGVHD or increased if their platelet counts return to normal. Although methotrexate is given as an immunosuppressant to prevent the development of aGVHD, it may not be as effective as clinicians think. Medications to improve engraftment and platelet counts may help to increase survival probability in these patients.

Limitations

Our study had limitations which need to be considered when interpreting these results. The study data only contained data on 137 patients, which is relatively small to make clinical decisions from. For this reason, there may be limited generalizability of our findings. Additionally, the patients reigned from hospitals in high-income countries where medical resources are more plentiful, and access to care easier. Thus, our findings can only be generalized to persons from similar resource settings. Moreover, we do not have data on the human leukocyte antigen (HLA) type of the donor and the patient. Optimally, a donor's HLA type would be matched as best as possible with the patient's for increased chances of engraftment and survival. However, lacking these data, we cannot conclude whether low rates of survival were due to this fact. Furthermore, we do not have data on CD3 and CD34 levels. CD3 is a marker for T-cells or an immune response and CD34 is a marker for stem cells. Some studies demonstrate that higher levels of CD3 and CD34 in the patient inhibits successful engraftment and can lead to aGVHD development. Thus, differences in aGVHD development and platelet recovery levels may be a result of these levels.

Tables

Table 1: Descriptive statistics of baseline characteristics differentiated between disease subtype and disease classification

	Disease Subtype		***Disease Classification***		
Baseline Characteristics	***FAB[1] grade 4 or 5***	***Otherwise***	***Acute Lymphoblastic Leukemia***	***Acute Myelocytic Leukemia (Low Risk)***	***Acute Myelocytic Leukemia (High Risk)***
Patient					
Sex: Male[2] (n, %)	24, 53.30	56, 60.9	26, 68.40	30, 55.60	24, 53.30
Age (mean, SD)	27.89, 9.81	28.60, 9.48	24.42, 7.30	29.41, 8.76	30.44, 11.22
CMV Status: Positive[2] (n, %)	24, 53.30	44, 47.80	15, 39.40	26, 48.10	27, 60.0
Donor					
Sex: Male[2] (n, %)	30, 66.70	58, 63.00	26, 68.40	34, 63.0	28, 62.20
Age (mean, SD)	26.96, 11.13	29.00, 9.67	26.79, 8.93	28.07, 9.24	29.93, 12.06
CMV Status: Positive[2] (n, %)	14, 31.10	44, 47.80	17, 44.70	22, 40.70	19, 42.20
Wait time for transplant (median, IQR)	150, 105	180, 130	199.50, 333	120, 90	210, 135
Prophylactic use of Methotrexate, yes[2] (n, %)	8, 17.80	32, 34.80	17, 44.70	12, 22.20	11, 24.40

1 = French-American-British classification
2 = This term represents the number and proportion of the population that has this designation

Table 2: Cox Proportional Hazard Model and Statistics per Baseline Characteristics

	Model with Individual Characteristic		***Full Model With All Characteristics***	
Characteristic	***Hazard Ratio (90% Confidence Interval)***	***p-value[1]***	***Hazard Ratio (90% Confidence Interval)***	***p-value[1]***
Disease Subtype	1.89 (1.31, 2.73)	**0.00427**	2.23 (1.40, 3.55)	**0.00450**
Disease Group[2]		**0.001**		
Low Risk AML[3]	0.56 (0.35, 0.90)	**0.0457**	0.35 (0.19, 0.64)	**0.00414**
High Risk AML[3]	1.47 (0.95, 2.28)	0.1516	0.83 (0.45, 1.51)	0.60545
Donor				
Sex	0.99 (0.68, 1.44)	0.97	1.03 (0.69, 1.54)	0.89036
Age	1.01 (0.99, 1.04)	0.252	1.00 (0.97, 1.03)	0.90651
CMV Status	1.05 (0.73, 1.51)	0.836	0.95 (0.63, 1.43)	0.84600
Patient				
Sex	0.79 (0.55, 1.15)	0.301	0.90 (0.60, 1.33)	0.65053
Age	1.01 (0.99, 1.03)	0.338	1.01 (0.98, 1.05)	0.49601
CMV Status	1.17 (0.81, 1.68)	0.482	0.94 (0.62, 1.43)	0.81176
Time Until Transplant	0.99 (0.99, 1.00)	0.791	1.00 (1.00, 1.00)	0.38424
Prophylactic Use of Methotrexate	1.49 (1.01, 2.20)	**0.0944**	1.34 (0.88, 2.03)	0.25099

1 = bolded terms represent significant characteristics for $\alpha = 0.1$
2 = Reference group is those with acute lymphoblastic leukemia.
3 = Acute Myelocytic Leukemia (AML)

Table 3: Hazard Ratios and 90% Confidence Intervals of baseline characteristics for disease-free survival among those who developed aGVHD

	Estimated Hazard Ratio	***90% Confidence Interval***	***p-value[1]***
Patient			
Sex	0.86	0.26, 2.84	0.8326
Age	0.98	0.89, 1.08	0.7332
CMV Status	0.47	0.13, 1.74	0.3423
Donor			
Sex	0.79	0.21, 2.96	0.7659
Age	1.12	1.01, 1.24	**0.0745**
CMV Status	1.96	0.60, 6.42	0.3507
Wait Time For Transplant	1.001	1.00, 1.002	**0.0965**
Prophylactic Use Of Methotrexate	9.01	1.94, 42.63	**0.0187**
Disease Subtype (FAB = 4 or 5)[2]	1.51	0.31, 7.37	0.6714
Disease Classification			
AML Low Risk[3]	3.37	0.45, 25.41	0.3233
AML High Risk[3]	11.67	0.99, 136.30	0.1001

1 = bolded terms represent significant characteristics for $\alpha = 0.1$
2 = The comparison group is those with an FAB grade that is NOT 4 or 5
3 = The comparison group is those with Acute Lymphoblastic Leukemia

Figures

Question 1

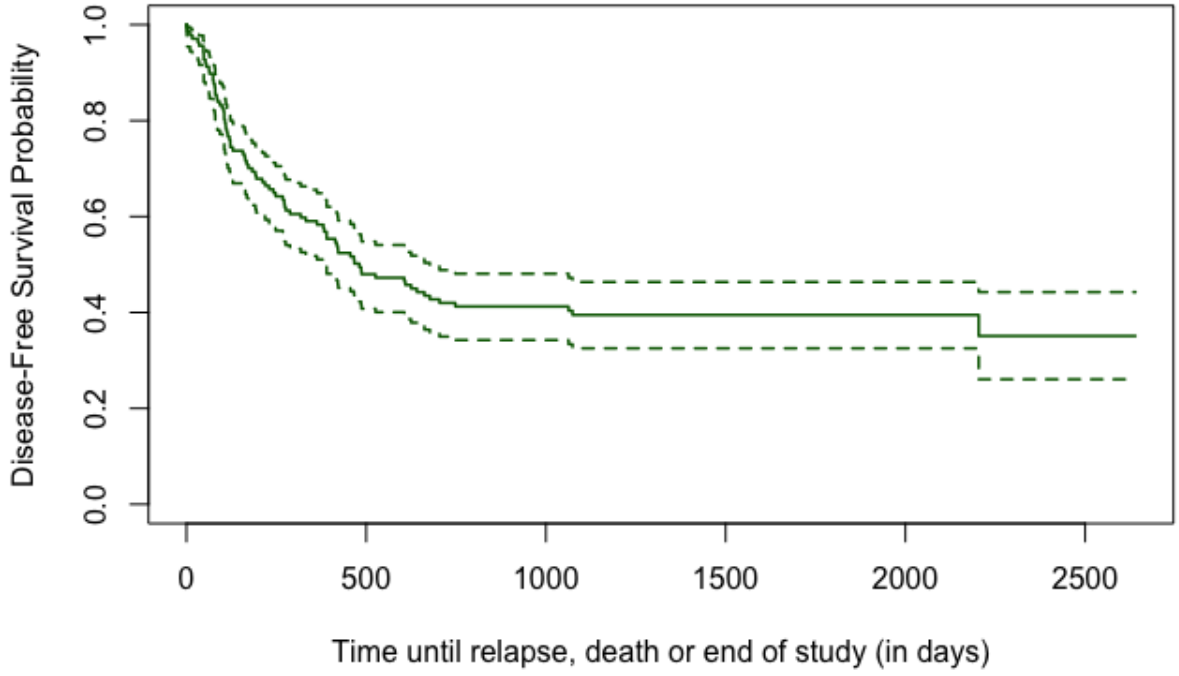

Figure 1: Kaplan Meier curve displaying disease-free survival probability over the course of the study. Dotted lines represent 90% confidence intervals.

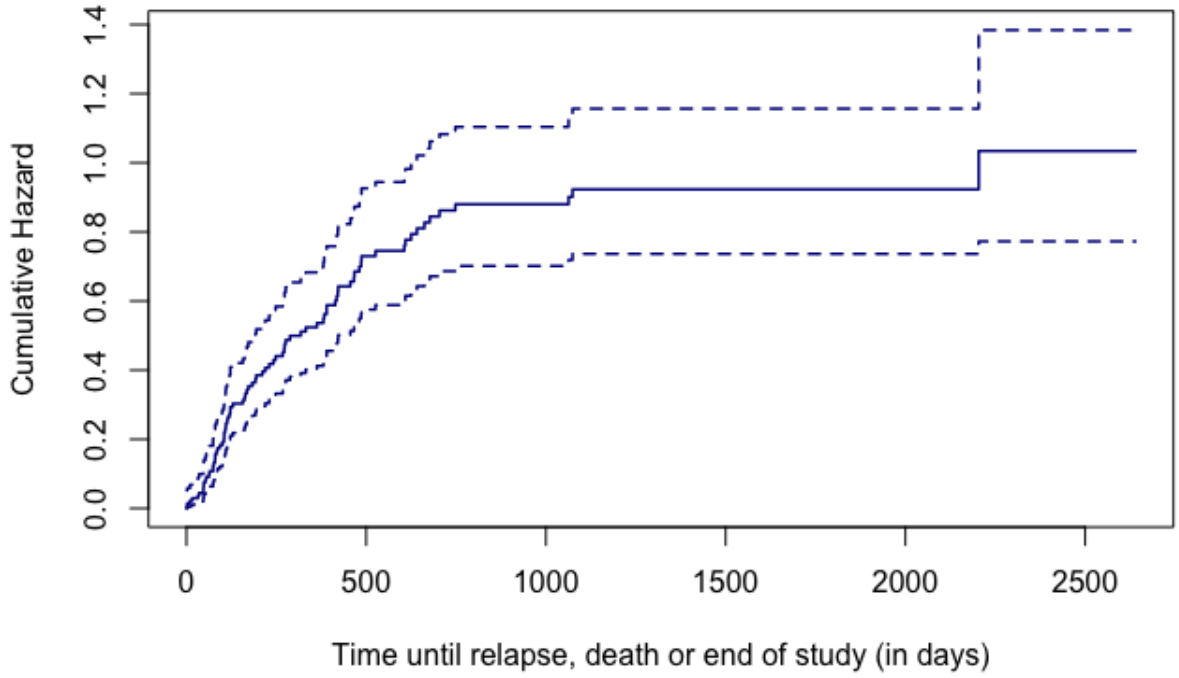

Figure 2: Nelson-Aalen curve displaying cumulative hazard over the course of the study. Dotted lines represent 90% confidence intervals.

Question 4

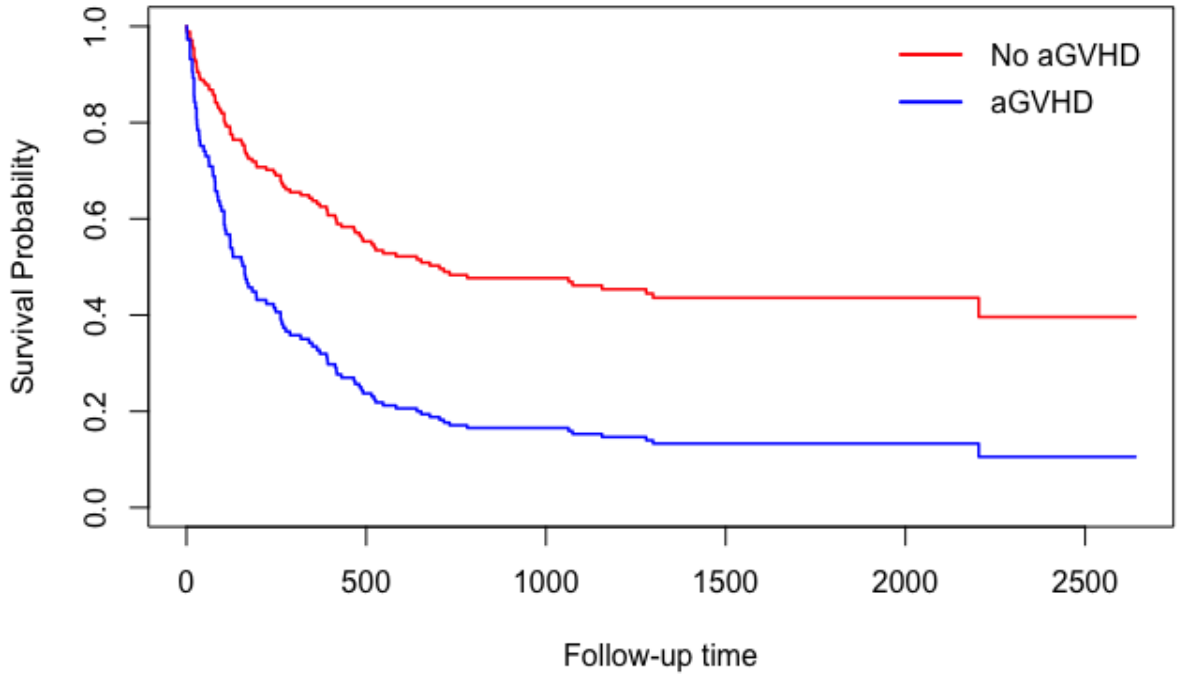

Figure 3: Kaplan Meier curve displaying the probability of disease-free survival amongst patients who developed aGVHD versus those who did not.

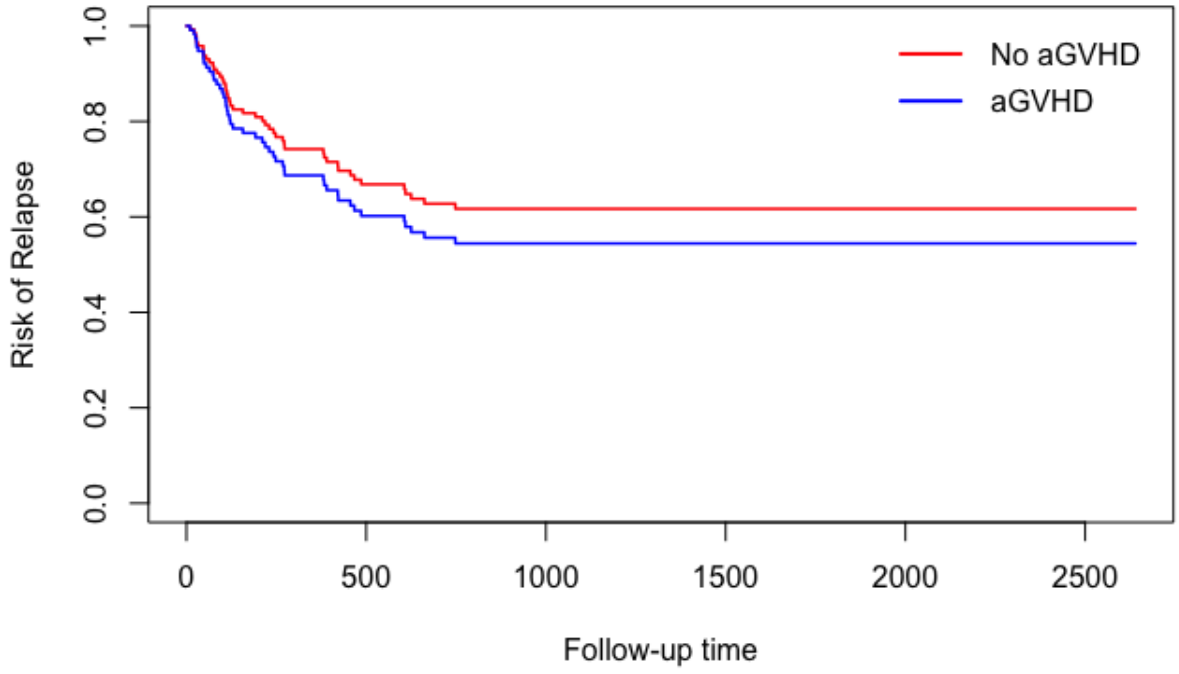

Figure 4: Kaplan Meier curve displaying the probability/risk of relapse amongst patients who developed aGVHD versus those who did not.

Question 6

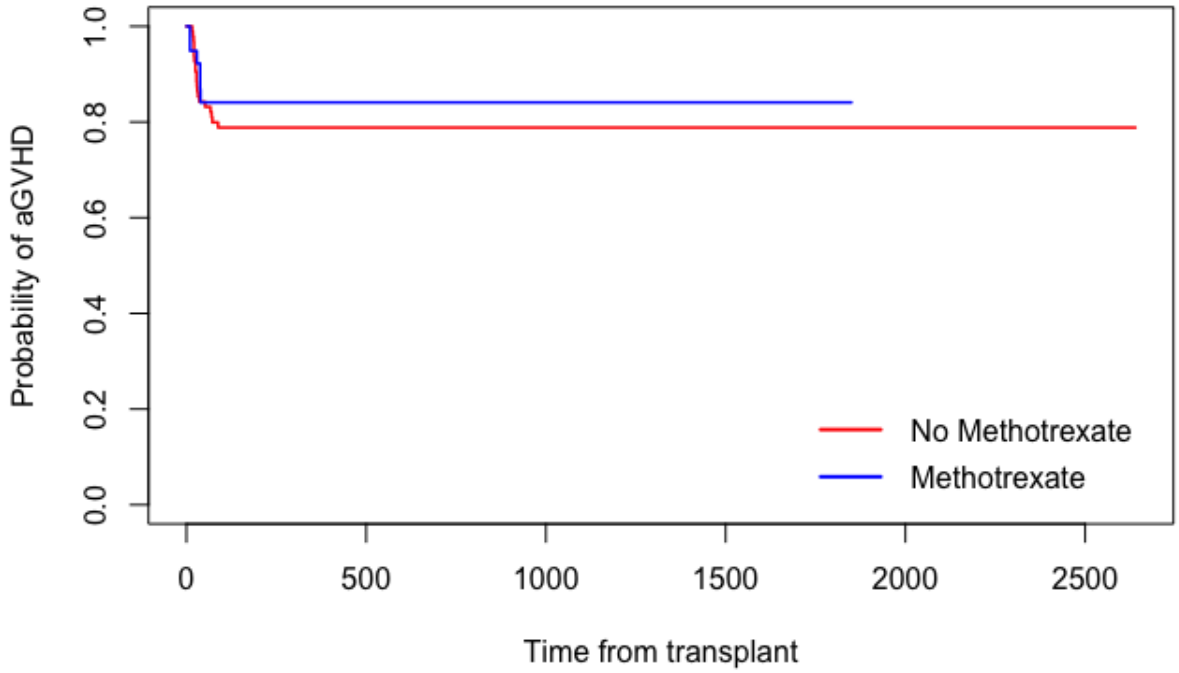

Figure 5: Kaplan Meier curve displaying the probability of developing aGVHD in patients who were given methotrexate versus those who were not.

Question 7

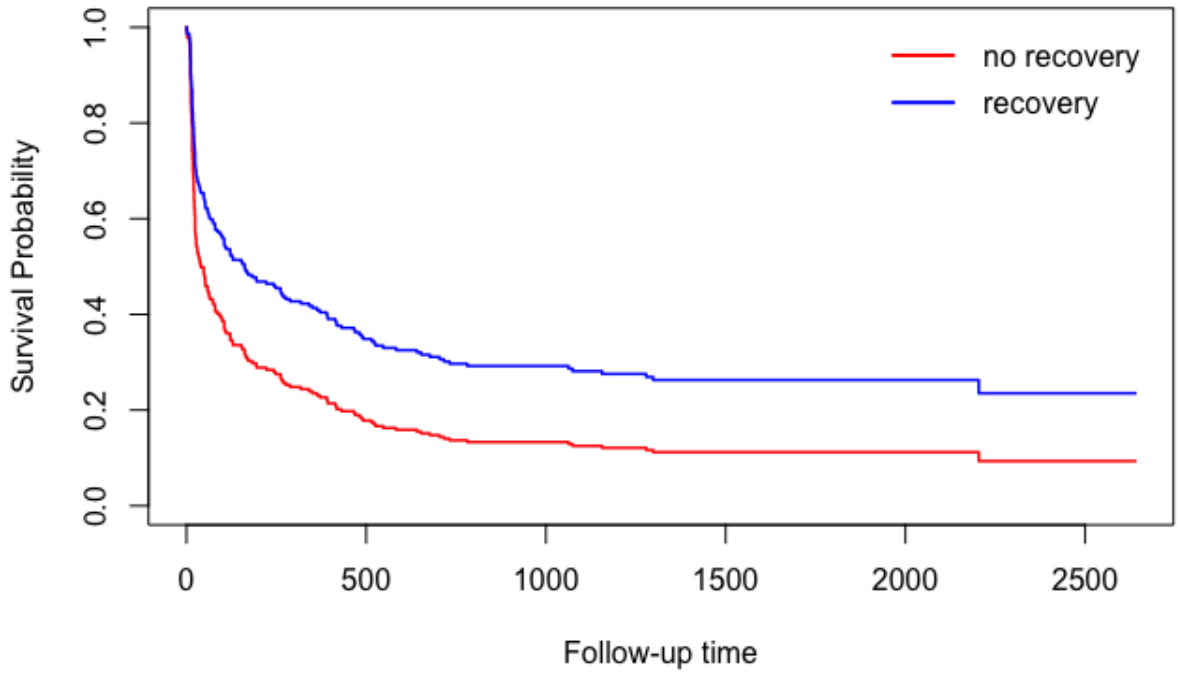

Figure 6: Kaplan Meier curve displaying the probability of disease-free survival between patients who recovered platelets to normal levels versus those who did not

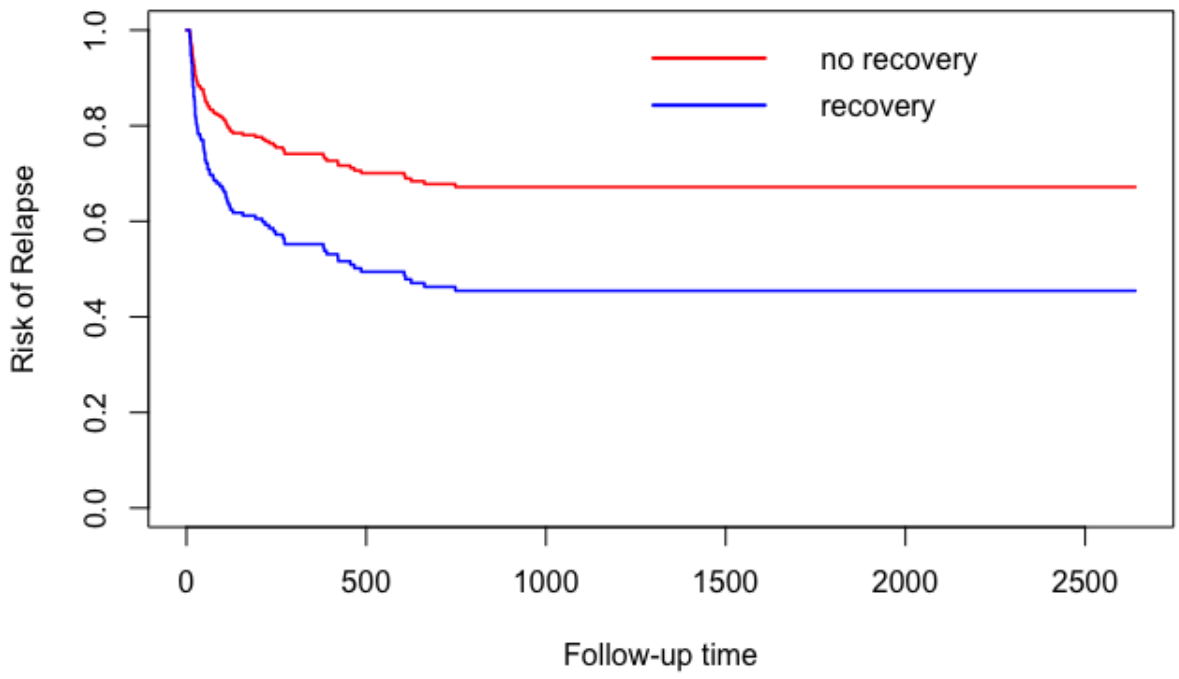

Figure 7: Kaplan Meier curve displaying the probability/risk of relapse between patients who recovered platelets to normal levels versus those who did not