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Survival Analysis of Patients with Acute Myeloid Leukemia

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Master of Public Health

Biostatistics and Bioinformatics

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Survival Analysis of Patients with Acute Myeloid Leukemia

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B.S.

Wuhan University

2015

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Biostatistics and Bioinformatics

2017

Abstract

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By Yufan Chen

Background: Patients with primary refractory/relapsed acute myeloid leukemia (PRRA) usually have poor overall survival (OS) outcomes. This study examined and determined the effects of several risk factors associated with PRRA patients' OS. Sixty-seven patients and 4 different types of treatment were studied based on patients' characteristics.

Methods: Summarization of the demographic and clinical variables was calculated and provided in tabular form. Logistic regression was fitted to determine the risk factor associated with whether patients achieved the first complete remission (CR1). Survival analysis was performed to identify the risk factors associated with patients' OS. After univariate analysis, hazard ratio and p-value for each potential risk factor was calculated. Forward model selection was applied to determine the final multivariable Cox proportional hazard model. Kaplan-Meier curves, the supremum test for the proportional hazards assumption and the plots of the standardized scores process were obtained.

Results: Mean age of patients at diagnosis was 55. Patients who were alive at 1 year was the most important prognostic factor to determine whether patients achieved CR1 with odds ratio of 50 (p-value<0.0001). In the final Cox proportional hazard model, an positive bmt in CR2 (HR: 0.341, 95% CI: (0.138, 0.843)), an favorable Cytogenetics (HR: 0.629, 95% CI: (0.340, 1.163)), an ECOG PS 0-1 (HR: 0.272, 95% CI: (0.130, 0.569), re-induction treatment (HR: 0.440, 95% CI: (0.206, 0.938)) and re-induction and hypomethylating agents Combo treatment (HR: 0.247, CI: (0.108, 0.564)) were associated with patients' OS.

Conclusion: The overall survival for PRRA patients was dismal. In order to improve PRRA patients' overall survival, new and less toxic treatments as well as improving patients' general well-being and daily activities were crucial, as ECOG PS accounted for a large amount of patients' CR1 and OS. Further studies would be needed to find both new treatment strategies and other ways to provide better patients care.

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1. Introduction

Acute Myeloid Leukemia (AML) is a type of cancer characterized by the leukemic infiltration of the bone marrow, often leading to hematopoietic insufficiency and related symptoms such as thrombocytopenia and anemia [1]. AML accounts for only about 1.2% of total cancer deaths in the United States [2] and therefore is a relatively rare disease. However, its incidence rate is likely to go up with the growth of an aging population. The American Cancer Society estimates that there will be about 21,380 new cases of AML (mostly in adults) and about 10,590 deaths from AML in the United States for 2017 [3]. AML is a little more common in men than in women. According to the previous research, 35-40% of patients with AML under the age of 60 experience a complete response and 5-15% of AML patients over 60 years old. 5-10 months is the survival time for older people who lose to intensive chemotherapy [4]. Several risk factors other than aging have been found, but the specific cause of AML is still unknown.

After the most common and effective ("3+7") induction chemotherapy, 60-80% of younger adults (18 to 60 years old) experience complete remission (CR), in contrast, around 50% of older patients (over 60 years old) receive CR. The patients who fail to obtain first complete remission (CR1) are considered primary refractory or relapsed [5]. Those patients identified with either primary refractory or relapsed AML (PRRA) are often older, since the outcomes of older patients are prone to be worse with the increase of age. Besides, patients with PRRA are more likely to suffer from adverse cytogenetics, which has a strong influence on achievement of CR and OS [6]. There are several clinical factors that are associated with the complete remission and overall survival. Among those factors, adverse cytogenetics, age, white blood cell count and secondary leukemia are the most significant prognostic features that are able to predict the complete remission and overall survival [7]. Due to aging, adverse cytogenetics and many other reasons,

there is a lack of effective treatment for patients with PRRA, which leads to an unpromising overall survival (OS). As a result, PRRA has become a tough problem for treatment of AML [8].

The potential prognostic factors which are counted important in predicting complete remission and overall survival in this study include secondary AML, cytogenetics, Eastern Cooperative Oncology Group Performance Status (ECOG PS), types of relapsed treatment received and the presence of extramedullary disease. Myeloproliferative disease, or so-called secondary AML, usually has a worse prognosis than AML, which means a smaller probability to achieve a complete remission and positive overall survival. Secondary AML is typically associated with a high possibility of adverse cytogenetic disorders [9]. Cytogenetics is the single most important predictive factors in AML. Some abnormalities in cytogenetics can lead to favorable outcomes, but most of AML patients identified with an abnormal cytogenetics will be considered in risk group [10]. ECOG PS is the performance status score proposed by Eastern Cooperative Oncology Group (ECOG), which attempts to quantify the general well-being and daily activities of cancer patients. This measure is often used to assess the condition of cancer patients and is an important factor used to determine chemotherapy [11].

In this paper, survival analysis techniques identify the factors associated with improved overall survival. A categorical data analysis investigated the factors associated with complete remission based on a study conducted by Winship Cancer Institution, whose subjects are patients diagnosed with PRRA.

2. Methods

2.1 Data Collection

The data for analysis came from a retrospective study on AML patients conducted at Emory University Hospital. This study got the permission from the Emory Institutional Review Board. Those demographic and related clinical features such as age and gender were obtained from the electronic medical records. All these features will go through descriptive analysis and be included in descriptive table (table 1).

After one induction, whether a patient achieved the first complete remission (CR1) is recorded. If patients failed to obtain CR1 after one induction, they were classified as having primary refractory AML. If patients obtain CR1 after one induction and then relapsed afterwards, they were counted to have relapsed AML. AML that evolved from an antecedent hematological disorder or which was treatment-related in nature such as prior exposure to chemotherapy, radiation and environmental toxins was considered secondary AML. Presence and sites of extramedullary disease were documented. The fluorescent in-situ hybridization panel for recurrent cytogenetic abnormalities was performed as the test for normality of patients' cytogenetics. Bone marrow aspirate, biopsy and other tests (i.e. flow cytometry, evaluation of morphology, chromosome analysis) were performed, but the results of these tests were not used to build the predictive model for complete remission and overall survival.

Based on the information of patients' ECOG PS, age, treatment compliance and CMS, treatment decision for each patient was made. The initial induction chemotherapy was the standard "7+3" therapy, this typical "7+3" therapy consisted of 7 days of standard-dose cytarabine (100-200 mg/m2/day) and 3 days of anthracycline. Whether patients succeeded in responding to the treatment was assessed for each patient. The recommendation of the International Working Group

(IWG) was used as reference for the response criteria [12]. If patients were not able to respond to the standard treatment, they received re-induction with another chemotherapy system which was also based on anthracycline instead. As mentioned before, if patients failed to respond to the first induction treatment, they were considered as having primary refractory AML. Patients typically received consolidation of another 3 to 4 cycles of high-dose cytarabine, if they successfully responded to the first and second induction treatment. After chemotherapy, these two groups of patients were both monitored by the research team.

Based on the diagnosis of PRRA from initial induction chemotherapy and the patients' physical condition, they were given different follow up treatments. The following treatments were re-induction (most commonly fludarabine, high-dose cytarabine, and idarubicin [FLAG/Ida]), a hypomethylating agent (most commonly decitabine), just supportive care (no other treatment), or a clinical trial (combo of treatments).

2.2 Statistical Analysis Method

2.2.1 Descriptive Analysis

The descriptive table for patients' characteristics was firstly constructed. For continuous variables, the mean and standard deviation were summarized. For binary or categorical variables, the frequencies and percentage were presented. The descriptive statistics of risk factors were summarized in groups of patients who achieved complete remission and who did not separately.

2.2.2 Logistic Regression

Since the dependent variable had binary outcomes, a linear logistic regression model was fitted. The standard logistic function was used:

$$\sigma(t) = \frac{e^t}{e^t + 1} = \frac{1}{1 + e^{-t}}$$

Because a linear logistic regression was used here, t is a linear function of the independent variable X. The function of t can be expressed as:

$$t = \beta_0 + \beta_1 x$$

Then the logistic function can be written as a function of X:

$$f(x) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x)}}$$

f(x) is the probability of the dependent variable (outcome) getting a "successful" result. The univariate analysis was performed, the crude odds ratio and 95% confidence interval were calculated for each risk factor to present a general idea of the association between outcome and a single independent variable. If the odds for each risk factor is $e^{\beta_0 + \beta_1 x}$ then the odds ratio can be presented as $\frac{e^{\beta_0 + \beta_1 x_1}}{e^{\beta_0 + \beta_1 x_0}}$. All categorical variables were reference cell coded.

The multivariable analysis was also performed. Forward selection based on AIC was conducted to select the best linear logistic model to predict the outcome. The general forward selection procedure is as following:

Step 1: Univariate logistic model is fitted. The reduction in AIC from the intercept-only model to the current model is calculated. The risk factor that relatively reduces the AIC most is added to the model and will be included in the model for the following selection process.

Step 2: Based on the model selected from step 1, add the other risk factor to the model one at a time and calculate AIC value. As the step 1, the risk factor with the largest AIC reduction is added to the model.

Step 3: Repeat step 2 until there is no reduction in AIC when adding a risk factor. The model with the smallest AIC is the final model selected by forward selection.

The adjusted odds ratio for multivariable model effects were calculated using the final model selected by forward selection.

2.2.3 Cox Proportional Hazards model formulation

For survival analysis, estimated Kaplan-Meier survival curves were plotted for each level of risk factors to have a general perspective about overall survival of the patients with different risk factors and to serve as a check to the assumption of the proportional hazards assumption. The Cox proportional hazards model was constructed. Proportional hazard model always contains two parts: the underlying baseline hazard function, which describes how the risk of the event changes at the baseline level of covariates; and the effect parameter, which demonstrates the change of risk according to covariates. The form of hazard function for the Cox proportional hazard model is:

$$\lambda(t|X_i) = \lambda_0(t)\exp\left(\beta X_{i1} + \cdots + \beta X_{ip}\right) = \lambda_0(t)\exp(\beta X_i)$$

$\lambda(t|X_i)$ is the hazard rate given time t for subject i with covariate X_i. The local Wald test was performed to see if there any significant difference between different levels of covariates. The score test is equivalent to the log rank test here, which can give us some insights from nonparametric perspective.

Forward model selection was performed again for survival analysis. Adjusted hazard ratio was calculated for each risk factor in multivariable model. Local Wald tests were conducted for each variable in the final model and p-value were output.

2.2.4 Evaluate Assumptions

In fitting the Cox PH models, we assumed independence of censoring times to ensure reliable and unbiased survival estimates. We also assumed that censoring was non-informative, meaning that we assumed the reasons for censoring were not related to the medical condition of participants. Since the Cox PH model also assumes that the proportion to the hazard functions of two groups is always independent of time, Supremum test for proportional hazards assumption and the plots of the standardized score process were applied.

All the analyses were performed using SAS 9.4. The significance level was set to 0.05.

3. Results

3.1 Descriptive Analysis

The results of univariate analysis were shown in table 1. From the table, the mean age of the patients was 54.5 with little difference between patients who achieved complete remission and who did not. Most of the patients had relapsed relapse AML (86.6%), and only 9 patients were considered to have primary refractory AML (13.4%) who failed to achieve CR after the initial induction. For patients who achieved CR, 11 (64.7%) had an ECOG PS of 0-1 and 6 (35.3%) had an ECOG PS of 2-3. For patients who did not achieve CR, 12 (24%) had an ECOG PS of 0-1 and

38 (76%) had an ECOG PS of 2-3. There is a trend of strong association between ECOG PS and whether achieving a CR which was proved in the following analysis.

3.2 Univariate and multivariable logistic regression

The crude odds ratio and confidence interval for each variable on its own fitted in the model were shown in table 2. For binary risk factors, the reference cell coding was used and 2 was coded as reference group. For categorical risk factors with more 2 levels, the last level was coded as reference group. From the result of crude odds ratio, the odds of achieving CR for 0-1 ECOG PS group was approximately 6 times the odds for 2-3 ECOG PS group; the odds of achieving CR for patients that were alive at 1 year was 50 times the odds for patients that were dead at 1 year. ECOG PS at relapse, OS from date of relapse (categorical) and OS from date of relapse (continuous) were significantly associated with CR with p-value equaling to 0.0037, 0.0021 and <0.0001 separately.

After the step 1 of general forward variable selection procedure, whether patients were alive at 1 year (OS from date of relapse categorical) was selected (AIC=47.484). Since OS from date of relapse (continuous) represented the same variable, this continuous variable was not counted as a potential risk factor. After adding the other variables to the model selected from step 1, all AIC increased. So the final model only had one risk factor which was OS from date of relapse (categorical).

3.3 Survival Analysis

The results of univariate analysis were shown in table 3. Again, for binary variables, 2 was coded as reference group. The relative risk of unfavorable cytogenetics vs favorable cytogenetics was approximately 2 with p-value equaling to 0.027, indicating that there was a different overall survival between different cytogenetics. The chance of dying for patients in 2-3 ECOG PS was nearly 4 times the chance of dying for patients in 0-1 ECOG PS. Another two risk factors considered associated with OS diagnosed from the univariate analysis were BMT in CR2 (p-value=0.0002) and type of treatment received (p-value=0.0007).

Estimated Kaplan-Meier survival curves (Figure 1 to 4) were plotted for these four risk factors that were diagnosed to have potential association with OS. The Kaplan-Meier curves visualized the difference of overall survival between different levels in these four risk factors. The survival curves stratified by risk factors in Kaplan-Meier plots did not cross except for types of treatment received, which indicated that the proportional hazard assumption that ratio of hazard is constant and does not depend on time held except for types of treatment receive.

Following the general procedure of forward model selection, the minimum AIC model (AIC=386.8) was selected and the variables fitted in this model were bmt in CR2, Cytogenetics, ECOG PS and type of treatment received. Adjusted hazard ratios and p-values were calculated. The final model took the following form:

$$h(t|Z)=h_0(t)\exp(\beta_1 Z_1+\beta_2 Z_2+\beta_3 Z_3+\beta_4 Z_4+\beta_5 Z_5+\beta_6 Z_6)$$

Where $h_0(t)$ was the baseline hazard function; β_1 was coefficient for bmt in CR2 which had the answer of Yes, and Z_1 was covariate for bmt in CR2; was β_2 coefficient for favorable cytogenetics, and Z_2 was covariate for cytogenetics; β_3 was coefficient for ECOG PS in 0-1, and Z_3 was covariate for ECOG PS; β_4 - β_6 were coefficient for different types of treatment

(reinduction to non/other), and Z_4 - Z_6 were covariate for treatment. The estimated adjusted hazard ratios and p-values were shown in table 4.

The proportional hazard assumption was checked both by Supremum test for proportional hazards assumption and graphically by standardized score process plots. Tests results were shown in table 5 and none of the risk factors in the final model violated the PH assumption. Figure 5 to Figure 10 were the standardized score process plots for each risk factor, which did not show significant violation of the PH assumption.

4. Conclusion and Discussion

In logistic regression analysis, It is not surprising to identify overall survival as the most significant risk factor for complete remission. Patients that survived for at least one year had a much larger chance to achieve CR1 than patients who failed to survive for one year. Another important prognostic risk factor for achieving CR1 was ECOG PS, so ECOG PS can be counted as an important assessment for AML patients, although some other approaches such as ADL and IADL were proven to better improve the sensitivity of the functional assessment of the elderly patients than ECOG PS [13]. None of the primary refractory AML patients in this study achieved a CR1, no matter what types of treatments they received. This finding suggests that if patients were enrolled in the clinical trial just after the diagnosis of primary refractory AML they may be better served.

In the Cox PH model, cytogenetics was shown to be a prognostic factor for patients' OS. Patients with favorable cytogenetics tended to have better overall survival outcomes. Following up

treatments seemed to exert good influence on patients' OS. Re-induction and combo of re-induction and hypomethylating agents increased significantly the patients' chance of survival, however, the decision of following up treatments was based on based on the diagnosis of PRRA from initial induction chemotherapy and the patients' physical condition, so the patients who did not receive subsequent treatments were meant to have a relatively adverse overall survival. Despite the fact that patients were screened, re-induction and combo of re-induction and hypomethylating agents were still better than hypomethylating agents alone. It suggests that there may be btaenefit in using re-induction or combined treatment as standard therapy after initial induction.

The limitation of this study is obvious: a sample size of 67 was small (although sample sizes of clinical trials are typically small); interactions were not considered when the logistic regression and Cox proportional hazards models were constructed. In spite of these limitations, this study has some strengths. The patient population was diverse and representative. Other than a diverse patient population, this study had an extended follow-up.

Generally, the overall survival for PRRA patients was dismal. In order to improve PRRA patients' overall survival, new and less toxic treatments as well as improving patients' general well-being and daily activities were crucial, as ECOG PS accounted for a large amount of patients' CR1 and OS. Further studies would be needed to find both new treatment strategies and ways to provide better patients care.

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6. Tables and Figures

Table 1 Baseline Characteristics of 67 PRRA Patients

Variable		Overall (n=67)	Achieved CR (n=17)	Not achieved CR (n=50)	P-value
Age at diagnosis of PRRA		54.5 (16.8)	54.3 (18.9)	54.6 (16.2)	0.949
Age < or >= 60	<60	35 (52.2%)	10 (58.8%)	25 (50.0%)	0.529
	>=60	32 (47.8%)	7 (41.2%)	25 (50.0%)	
Gender	Male	34 (50.7%)	6 (35.3%)	28 (56.0%)	0.140
	Female	33 (49.3%)	11 (64.7%)	22 (44.0%)	
Secondary AML	Yes	13 (19.4%)	3 (17.7%)	10 (20.0%)	0.832
	No	54 (80.6%)	14 (82.4%)	40 (80.0%)	
Relapse type	Relapse	58 (86.6%)	17 (100%)	41 (82.0%)	0.060
	Primary Refractory	9 (13.4%)	0 (0%)	9 (18.0%)	
Cytogenetics	Favorable+interm	47 (70.0%)	15 (88.2%)	32 (64.0%)	0.059
	Unfavorable	20 (30.0%)	2 (11.8%)	18 (36.0%)	
ECOG PS at relapse	0-1	23 (34.3%)	11 (64.7%)	12 (24.0%)	0.002
	2-3	44 (65.7%)	6 (35.3%)	38 (76.0%)	
Time from CR1 to relapse (continuous)*		14.6 (16.8)	20.4 (19.1)	11.5 (14.7)	0.078
Time from CR1 to relapse (categorical)*	1-6 months	17 (35.4%)	2 (11.8%)	15 (48.4%)	0.026
	7-18 months	19 (39.6%)	8 (47.0%)	11 (35.5%)	
	>18 months	12 (25.0%)	7 (41.2%)	5 (16.1%)	
OS from date of relapse (continuous)		12.5 (19.4)	37.1 (24.9)	4.1 (4.9)	<0.001
OS from date of relapse (categorical)	<=12 months	51 (76.1%)	4 (23.5%)	47 (94.0%)	<.0001
	>12 months	16 (23.9%)	13 (76.5%)	3 (6.0%)	

Type of treatment received	Re-induction	26 (38.8%)	8 (47.0%)	18 (36.0%)	0.1368
	Hypometh	10 (14.9%)	1 (5.9%)	9 (18.0%)	
	Combo	18 (26.9%)	7 (41.2%)	11 (22.0%)	
	Non/other	13 (19.4%)	1 (5.9%)	12 (24.0%)	
Extramedullary disease	Yes	7 (10.4%)	3 (17.7%)	4 (8.0%)	0.2613
	No	60 (89.6%)	14 (82.4%)	46 (92.0%)	
BMT in CR2	Yes	13 (19.4%)	11 (64.7%)	2 (4.0%)	<.0001
	No	54 (80.6%)	6 (35.3%)	48 (96.0%)	

* There are 19 missing value in the variable: time from CR1 to relapse

All the percentages in the table are column percentages

Mean and standard deviation are calculated for continuous variables

Table 2 Crude Odds Ratio And 95% Confidence Interval for Univariate Model Effect

Variable		Model Effect	
		Crude Odds Ratio (95% CI)	p-value
Age < or >= 60	<60	1.429 (0.469, 4.351)	0.5302
	>=60	Reference	
Gender	Male	0.429 (0.137, 1.341)	0.1454
	Female	Reference	
Secondary AML	Yes	0.857 (0.206, 3.569)	0.8323
	No	Reference	
Cytogenetics	Favorable+interm	4.217 (0.865, 20.558)	0.0750
	Unfavorable	Reference	
ECOG PS at relapse	0-1	5.805 (1.770, 19.039)	0.0037
	2-3	Reference	
Time from complete response	1-6 months	0.095 (0.015, 0.617)	0.0450
	7-18 months	0.519 (0.120, 2.248)	

to relapse (categorical)	>18 months	Reference	
OS from date of relapse (categorical)	<=12 months	0.020 (0.004, 0.099)	<0.0001
	>12 months	Reference	
Type of treatment received	Re-induction	5.333 (0.589, 48.299)	0.1925
	Hypometh	1.333 (0.073, 24.315)	
	Combo	7.636 (0.805, 72.405)	
	Non/other	Reference	
Extramedullary disease	Yes	2.464 (0.492, 12.354)	0.2728
	No	Reference	

Table 3 The Univariate Analysis for Overall Survival

Variable		OS	
		Hazard Ratio (95% CI)	p-value
BMT in CR2	Yes	0.211 (0.093, 0.478)	0.0002
	No	Reference	
Relapse type	Relapse	0.789 (0.387, 1.610)	0.5154
	Primary Refractory	Reference	
Age < or >= 60	<60	0.737 (0.442, 1.231)	0.2439
	>=60	Reference	
Gender	Male	1.467 (0.873, 2.464)	0.1481
	Female	Reference	
Secondary AML	Yes	1.646 (0.885, 3.060)	0.1152
	No	Reference	
Cytogenetics	Favorable+interm	0.525 (0.297, 0.928)	0.0267
	Unfavorable	Reference	
ECOG PS at relapse	0-1	0.251 (0.132, 0.478)	<.0001

	2-3	Reference	
Time from CR1 to relapse (categorical)	1-6 months	1.356 (0.599, 3.073)	0.4679
	7-18 months	0.866 (0.387, 1.937)	
	>18 months	Reference	
Type of treatment received	Re-induction	0.293 (0.141, 0.608)	0.0007
	Hypometh	0.881 (0.383, 2.030)	
	Combo	0.294 (0.138, 0.625)	
	Non/other	Reference	
Extramedullary disease	Yes	0.946 (0.406, 2.203)	0.8967
	No	Reference	

The last category of a variable is the reference

Table 4 Multivariable Analysis With A Best Predictive Model of OS Using Variables Found to be Significant in the Univariate Analysis

Variable		OS	
		Hazard Ratio (95% CI)	p-value
BMT in CR2	Yes	0.341 (0.138, 0.843)	0.0198
	No	Reference	
Cytogenetics	Favorable+interm	0.629 (0.340, 1.163)	0.1395
	Unfavorable	Reference	
ECOG PS at relapse	0-1	0.272 (0.130, 0.569)	0.0005
	2-3	Reference	
Type of treatment received	Re-induction	0.440 (0.206, 0.938)	0.0113
	Hypometh	0.466 (0.192, 1.134)	
	Combo	0.247 (0.108, 0.564)	
	Non/other	Reference	

Figure 1 Kaplan-Meier Survival Curves Stratified by Bmt in CR2

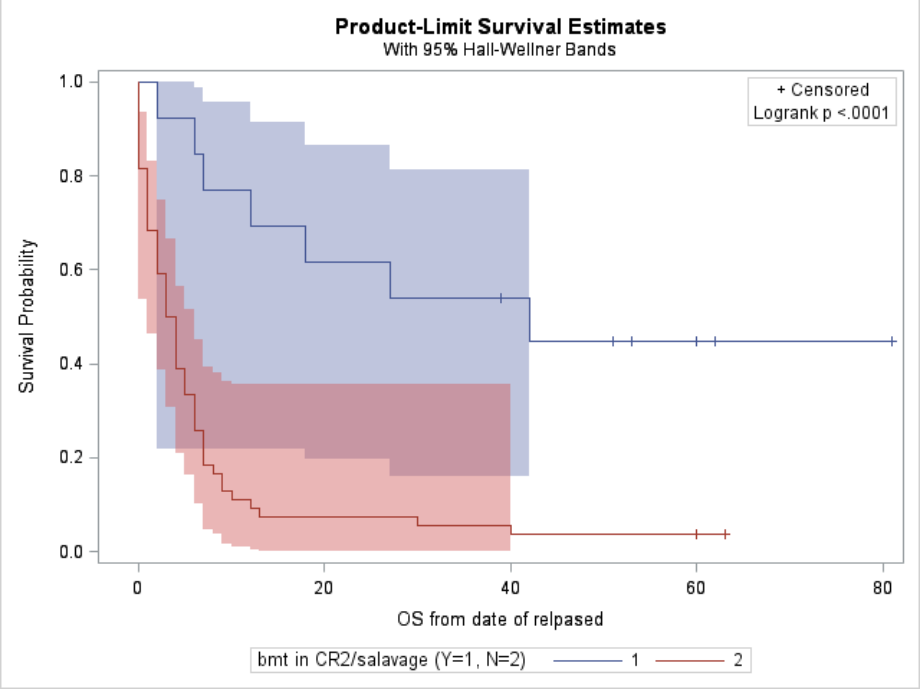


Figure 2 Kaplan-Meier Survival Curves Stratified by Cytogenetics

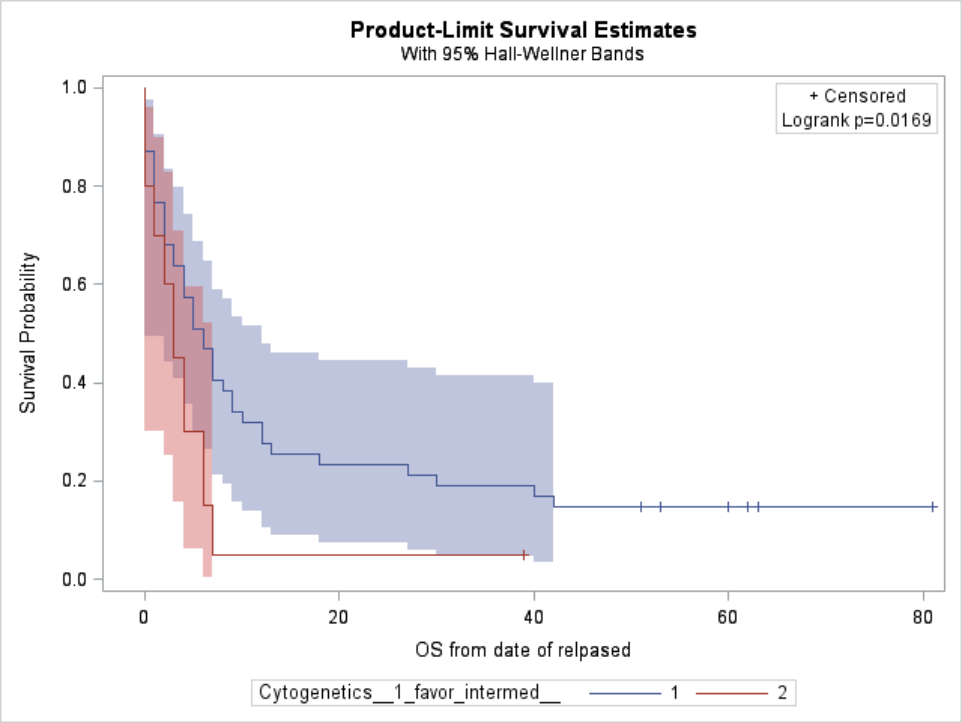


Figure 3 Kaplan-Meier Survival Curves Stratified by ECOG PS

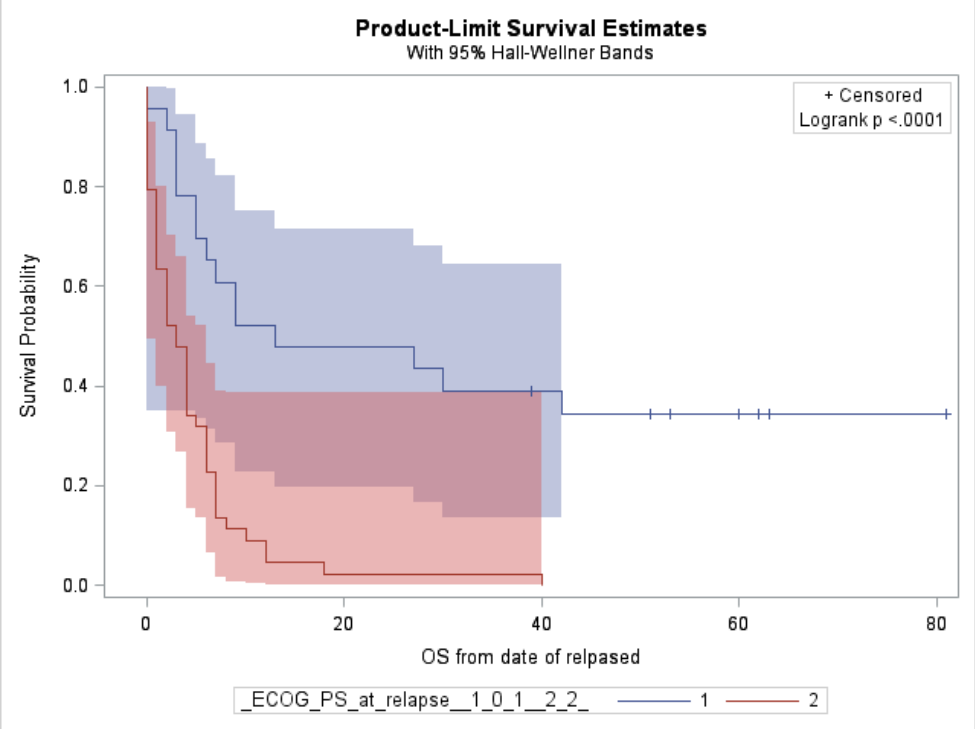
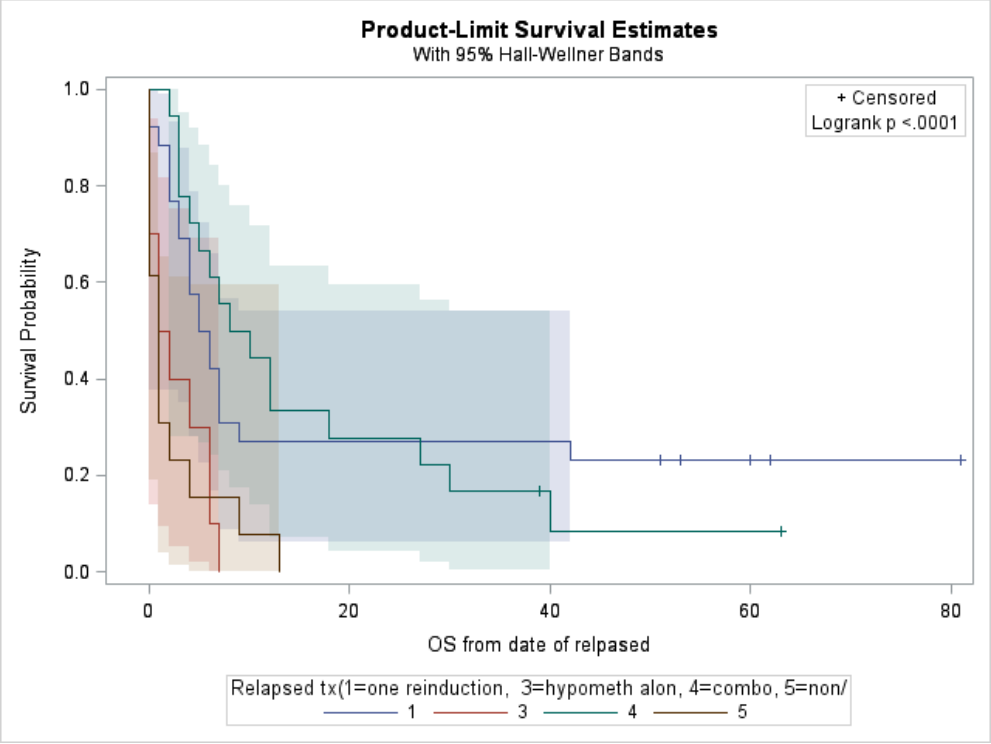


Figure 4 Kaplan-Meier Survival Curves Stratified by Treatments



7.Appendix

TABEL 5. SUPREMUM TEST FOR PROPORTIONALS HAZARDS ASSUMPTION

VARIABLE	Maximum Absolute Value	Replications	Seed	Pr > MaxAbsVal
BMT_IN_CR2	0.4315	1000	19	0.8390
CYTOGENETICS	0.5749	1000	19	0.6150
_ECOG_PS	0.8422	1000	19	0.3770
RELAPSED_TX_REINDUCTION	1.0504	1000	19	0.2990
RELAPSED_TX_HYPOMETH	0.7561	1000	19	0.5100
RELAPSED_TX_COMBO	1.0921	1000	19	0.2090

Figure 5 Standardized Score Process Plot for Bmt in CR2

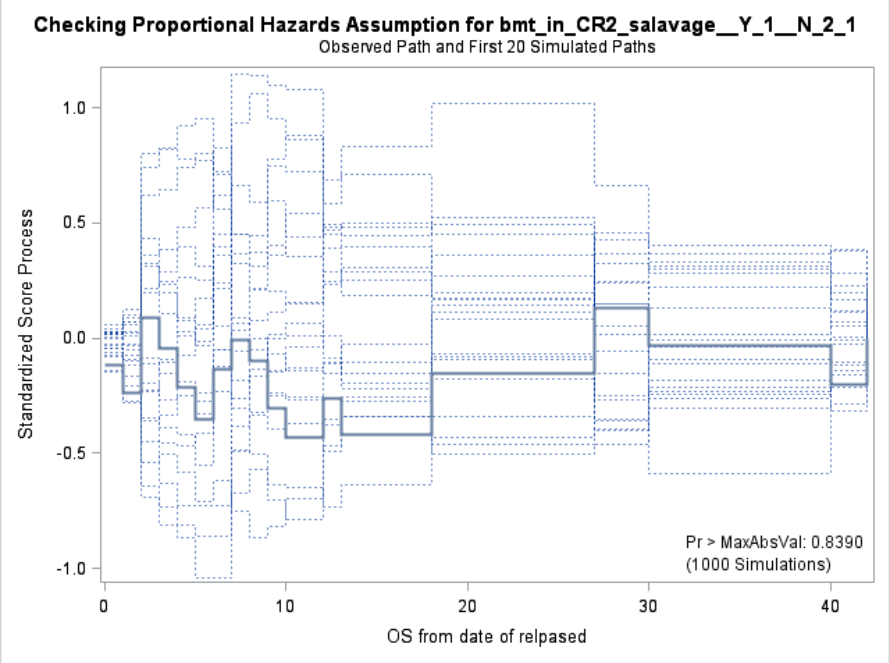


Figure 6 Standardized Score Process Plot for Cytogenetics

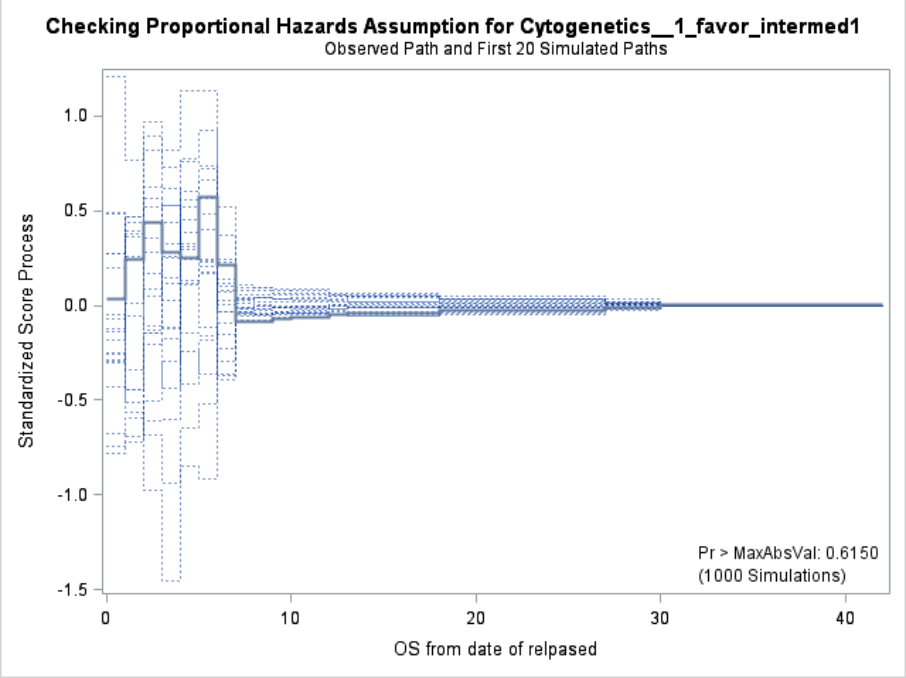


Figure 7 Standardized Score Process Plot for ECOG PS

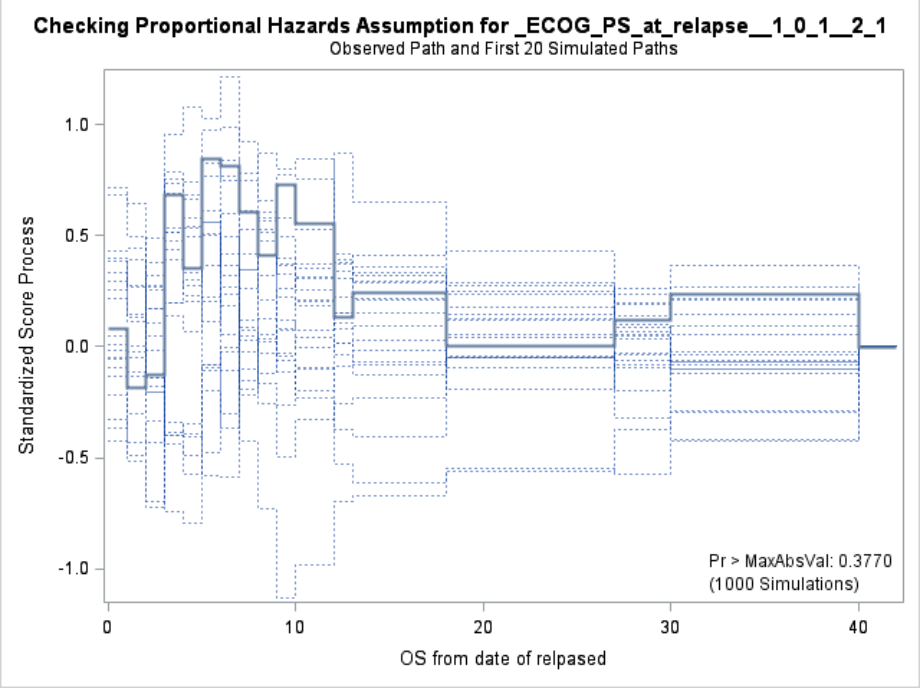


Figure 8 Standardized Score Process Plot for One Reinduction Treatment

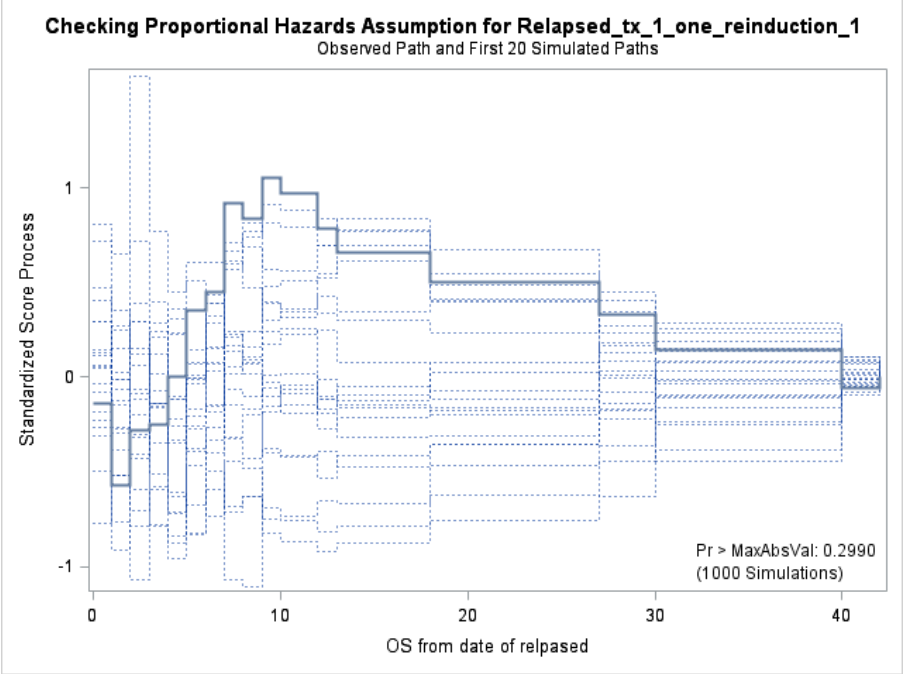


Figure 9 Standardized Score Process Plot for Hypomethylating Agents Treatment

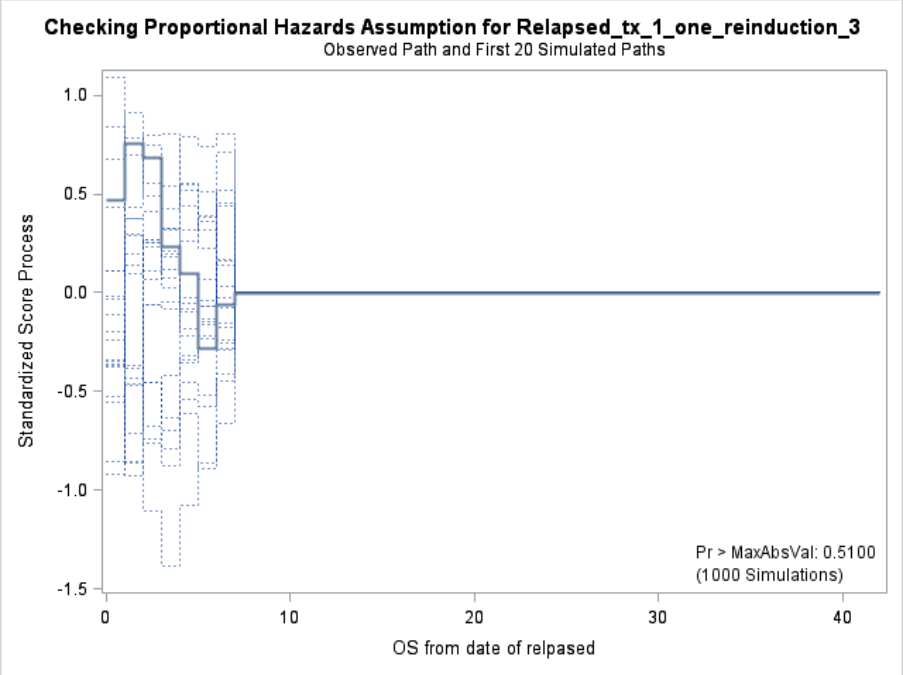


Figure 10 Standardized Score Process Plot for Combo Treatment