A failure time approach to mediation analysis to investigate the role of time to treatment in explaining disparities in cancer survival

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I. Objectives

The interest of the study is to investigate the variability in treatment waiting time in patient population and quantify its contribution to the survival disparities in a racially diverse US based cohort study, while adjusting for age, gender and income. Towards this goal we:

- Evaluated the disparities in time to treatment receipt adjusted by cancer stage at diagnosis.
- Evaluated the effect of time to treatment receipt on cancer survival adjusted by cancer stage at diagnosis.
- Estimated the residual survival disparities had the distribution of time to treatment had been equalized across groups.

II. Background

Significant differences in cancer survival among racial/ethnic groups are widening over time. Interest lies in identifying which factors might be driving such racial disparities. Our recent work has provided compelling evidence that the colorectal cancer (CRC) patient population of the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) might benefit from the elimination of racial disparities in stage at diagnosis (Valeri et al., 2016). However, stage at diagnosis does not account for all the racial survival disparity. We wish therefore to investigate the role of treatment in explaining this survival disparity. This investigation is challenged by the complexity of the health care dimensions that affect its uptake. In particular, choice of treatment strategy, quality of the provider, and timing are simultaneously interdependent concerns. We focused on timing of treatment receipt from time at diagnosis as potential determinant in this study.

III. Methods

(a) Data Source

We obtained data from the CanCORS (Cancer Care Outcomes Research and Surveillance) cohort study. For the purpose of our analysis, we employed the imputed versions of CanCORS data. The study population consisted of non-Hispanic White and non-Hispanic Black cancer patients diagnosed above the age of 18, with CRC as first histologically confirmed diagnosis and followed up for seven years since the date of diagnosis. We included patients enrolled in the first wave of CanCORS(CanCORS1) within 14 months from CRC diagnosis. Information on survival time from diagnosis, time from diagnosis to first line surgery receipt, stage at diagnosis according to the American Joint Committee on Cancer (AJCC) staging criteria, age, gender, race/ethnicity, origin was obtained from the CORE dataset. Information on education, smoking behavior, physical activity, weight, alcohol use, health insurance, household income, comorbidities (heart disease, lung disease, diabetes, renal disease) was obtained from CanCORS1 datasets derived from the instruments administered.

(b) Analytic Methods

The primary baseline exposure for this specific analysis is race. Gender, income and age at diagnosis are other exposures of interest (X). The primary outcome of the study is the indicator of five year survival (S) – we assumed no censoring in survival time. The hypothesized mediator is time to treatment from diagnosis in months (T). We log-transformed this variable to reduce the skewness that might lead to influential points in outcome regression (See **Appendix**). Cancer stage at diagnosis is a confounder of the mediator-outcome relationship. Their conceptual relationship is shown in **Figure 1.**

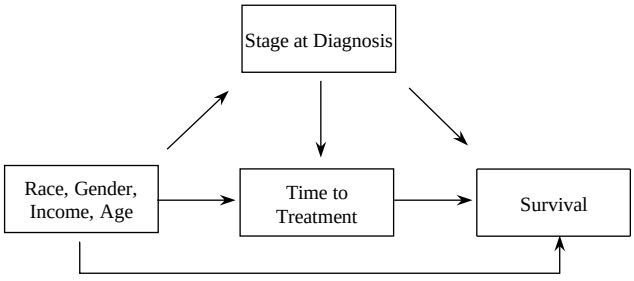


Figure 1. Conceptual Relation Diagram

i. Machine Learning Analysis

To have a sense for which characteristics might be related to survival outcome among patients, we applied random forest probability machine, a non-parametric method to predict conditional probability of survival for each observation. Consider S as the binary outcome, we also need to convert all the categorical predictors into dummy variables. Therefore, each dummy variable, which takes on values 0 and 1, would represent one level of a categorical variable. Our main interest is to determine the ideal set of predictors which indicates better survival.

For further investigation of potential interactions between covariates, the intuitive interaction detection method proposed by Dasgupta et al. was applied. Using a single random forest probability machine, it features computing probability estimates for both multiplicative and additive interaction effect. Our main interest is to determine if there exists significant interaction between any possible combinations of predictors, given the prevalence of predictor pairs exceeding a prespecified level (e.g. 10%) .

ii. Regression modeling Analysis

To investigate the mediating effect of time to treatment in explaining survival disparities, we developed our model-based mediation analysis in three main steps:

i. Mediator Model

First, we examined the disparities in time to treatment using nonparametric methods and then fit an *Accelerated Failure Time* (AFT) model for the mediator to parametrize the conditional distribution of time to treatment given baseline covariates. We allowed for possible interactions between exposure and confounder:

$$\log(T_i) = \boldsymbol{\beta_0} + \boldsymbol{\beta_1} race_i + \boldsymbol{\beta_2} stage_i + \boldsymbol{\beta_3 X_i} + (\boldsymbol{\beta_4} race_i * stage_i) + \sigma_M W \quad (3\text{-}1)$$

The reason why we chose AFT method is that we found not all included patients received surgery treatment during each follow-up period in CanCORS study. For these patients, time to treatment is calculated by follow-up end date minus cancer diagnosis date, but their actual treatment dates were not captured. So we think their time to treatment is censored and should be indicated by surgery status.

Outcome Model

Next, we examined the survival disparity among different patient groups and fit a logistic model for the outcome to parametrize the conditional distribution of five-year survival given the mediator as well as the baseline covariates. We employed polynomial regression to model the non-linear relationship between mediator and outcome and allowed for possible interactions between exposure and mediator or confounder to correctly specify the outcome model.:

$$\text{logit}[\text{P}(\text{S}_i = 1)] = \boldsymbol{\theta_0} + \boldsymbol{\theta_1} race_i + \boldsymbol{\theta_2} stage_i + \boldsymbol{\theta_3 X_i} + \boldsymbol{\theta_4} T_i + \boldsymbol{\theta_5} race_i * T_i + (\boldsymbol{\theta_6} race_i * stage_i) \quad (3\text{-}2)$$

The best mediator model and outcome model were selected based on the likelihood ratio test and AIC criteria. We also fit a baseline model for the outcome that excludes the effect of time to treatment to learn the relative changes in coefficient estimates:

$$\text{logit}[\text{P}(\text{S}_i = 1)] = \boldsymbol{\theta_0} + \boldsymbol{\theta_1} race_i + \boldsymbol{\theta_2} stage_i + \boldsymbol{\theta_3 X_i} + (\boldsymbol{\theta_4} race_i * stage_i) \quad (3\text{-}3)$$

ii. Mediation Analysis

Last, we took the selected mediator model and outcome model from previous steps as the main inputs to the mediate function under the R package mediation (Tingley et al., 2014). The mediate function takes various standard model objects (such as obtained with *survreg* and *glm*), which correspond to mediator and outcome models, and returns the estimates of the *average causal mediation effects* (ACME), *average direct effects* (ADE) along with other causal quantities of interest. The primary goal of inference is the direct effect which we interpret as the residual 5 year survival disparity had we intervened shifting the time to surgery distribution in the blacks to match the distribution observed in the white population. This weaker interpretation of the direct effect is warranted provided 1) the models are correctly specified 2) we adjust for confounders of the time to surgery-survival time relationship 3) no semi competing risks (that is no patient dies before receiving treatment).

IV. Results

(a) Data Description

The population is not well balanced in terms of patients' ethnic identity (shown in **Table 1)**. The number of white patients is about four times that of non-white patients. Their distributions also differ significantly across gender, age and income. More non-white patients are younger, less than

64 years old, and lower paid. And their average five-year survival outcome is significantly below white patients.

Characteristic	White(n=1331)	Black(n=351)	p
Gender			
Male	776 (58.3%)	181 (51.6%)	0.027
Female	555 (41.7%)	170 (48.4%)	
Age			
≤52	268 (20.1%)	97 (27.6%)	<0.001
>52	432 (32.5%)	138 (39.3%)	
>64	631 (47.4%)	116 (33.1%)	
Income			
1	644 (48.4%)	254 (72.4%)	<0.001
2	406 (30.5%)	69 (19.7%)	
3	281 (21.1%)	28 (8.0%)	
Stage			
I	292 (23.4%)	67 (20.6%)	
II	293 (23.5%)	69 (21.2%)	0.424
III	408 (32.7%)	114 (35.1%)	
IV	254 (20.4%)	75 (23.1%)	
Missing	84 (6.31%)	26 (7.41%)	
Survival	929 (69.8%)	215 (61.7%)	0.003
Surgery	1234(92.7%)	326(92.6%)	1

Note: Survival - binary outcome of five-year survival; Surgery - binary outcome of surgery status.

Table 1. Baseline Descriptive Statistics

(b) Statistical Analysis

i. Mediator Model

We firstly examined the distribution of time to treatment using density plots and Kaplan-Meier curves (shown in **Figure 2**). It seems that the mediator has a similar two-peak distribution across different cancer stages and the trough values falling between 2.7 and 2.9. We also noticed that white patients (in yellow) are more likely to receive early treatment than non-white patients (in blue) when diagnosed at Stage I and II. But this difference in waiting time is not significant among patients diagnosed at stage III and IV.

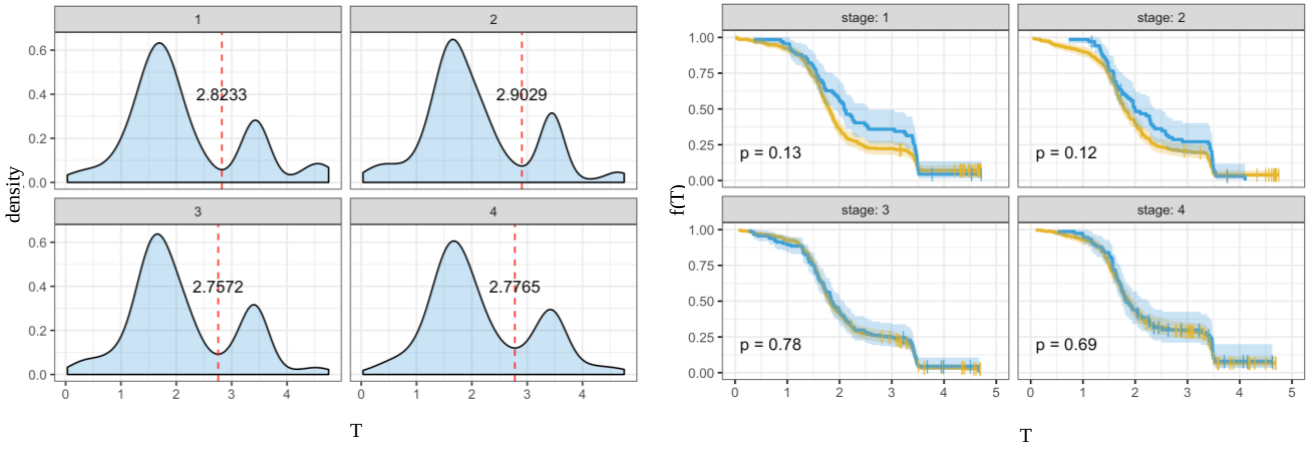


Figure 2. Left: Density Plot of Time to Treatment Stratified by Cancer Stage.
Right: KM Estimates of Time to Treatment Stratified by Race and Cancer Stage.

We built different models with or without race/stage interaction to further quantify the relationship between time to treatment and exposures. We also tried to reduce the parameters by transforming *stage* into a continuous variable. Estimates of model coefficients in both condition were shown in **Appendix.** Overall, the model considering *race*/*stage* interaction did not prove to be a more superior choice to the model ignoring this effect. But we still decided to include the interaction term in our model considering its predictive power might be limited by insufficient black patients in our population. The model comparison of employing a numeric *stage* variable against a categorical one did not show significant difference based on likelihood test result (p=0.21). So we finally chose the model with *race*/*stage* interaction and fitted by numeric *stage* variable. The average treatment waiting time for black patients diagnosed at stage I is 8.2% longer than that of the white patients diagnosed at the same stage, when controlling for other factors. But this disparity in treatment waiting time between black patients and white patients narrows with the progression of cancer stages - there is no statistically significant difference among patients diagnosed at stage III and IV. A significant effect for gender and a marginal effect for age were also observed from our results.

To account for the bimodal characteristic of time to treatment, we applied latent class analysis, based on Bayesian method, to further identify the mixture distribution of time to treatment. Class membership for each observation was determined by maximizing the posterior probabilities.

Outcome

We applied smoothing methods to visualize the distribution pattern of 5-year survival as a function of time to treatment (shown in **Figure 3**). The top and bottom black band are the observed binary survival outcomes in our data. We noticed the relationship between time to treatment and survival outcome is not linear. There is a slope changing point around 2.9, approximately 18 months since cancer diagnosis**.** Within this period, patients' survival probability would decline with the prolongation of time to treatment. In other words, the longer the treatment waiting time, the lower the survival odds for patients. But time to treatment starts to exert a positive effect on survival after this changing point. Also, race stratified survival curves indicate a relatively higher odds of survival for white patients than black patients, controlling for other factors. This supports our hypothesis that the effect of time to treatment is potentially modified by race.

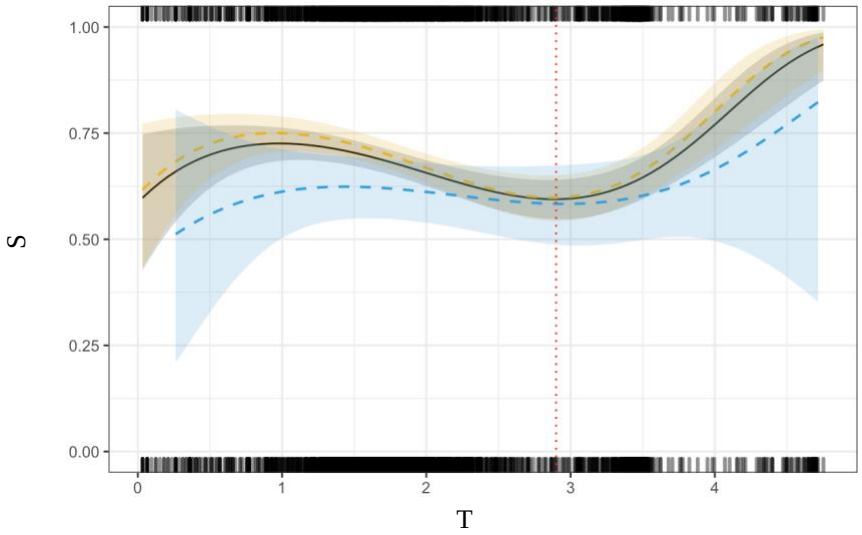


Figure 3. Five-year Survival as a function of Time to Treatment

To account for the nonlinear effect of time to treatment, we employed polynomial regression with three degree and fit a logistic model for the outcome. Coefficient estimates of outcome model and baseline model were shown in **Appendix.** In baseline model, the odds ratio of 5-year survival for black patients with versus white patients ranges from 70.3%-73.3%, controlling for gender, income,

age and cancer stage at diagnosis. This odds ratio additionally changes with T in the outcome model, when adjusting for other factors (shown in **Table 2**). It shows that the odds ratio of 5-year survival for black patients with versus white patients is much lower at T=3, which is 65.29%-74.44%, compared to that at T=1 and from baseline model. Therefore, late treatment would probably enlarge the survival disparity between white patients and black patients and make it exceed the average level between T=2 to T=3. We also observed significant survival disparities in gender, income and age, i.e., the odds ratio of 5-year survival is 0.73 (p=0.013) for male patients versus female patients, controlling for other factors.

The best outcome model includes the grouping variable as a predictor and its interaction with T. We fit the logistic regression weighted by posterior probability for each observation belonging to the hypothesized group.

	Baseline Model	**Outcome Model**		
		T=1	**T=2**	**T=3**
stage I	73.27%	82.67%	78.45%	74.44%
stage II	72.27%	79.14%	75.09%	71.26%
stage III	71.28%	75.76%	71.88%	68.21%
stage IV	70.30%	72.52%	68.81%	65.29%

Table 2. Odds Ratio of five-year Survival for Black Patients vs.White Patients

Exposure	**Effect**	**Estimate**	**CI_{lower}**	**CI_{upper}**	**p-value**
race	ACME	0.0014	-0.0029	0.01	0.52
	ADE	-0.0567	-0.1090	-0.01	0.04 *
	Total Effect	-0.0553	-0.1079	0.00	0.04
gender	ACME	0.0058	0.0004	0.01	0.02 *
	ADE	-0.0524	-0.0855	-0.01	0.02 ***
	Total Effect	-0.0467	-0.0804	-0.01	0.02 *
income	ACME	-0.0014	-0.0059	0.00	0.46
	ADE	0.0784	0.0343	0.12	<2e-16 ***
	Total Effect	0.0771	0.0327	0.12	<2e-16 ***
age	ACME	-0.0006	-0.0065	0.00	0.72
	ADE	0.0098	-0.0406	0.05	0.86
	Total Effect	0.0093	-0.0415	0.05	0.9

*Nonparametric bootstrap simulation was performed for variance estimation

Table 3. Mediation Analysis with Estimation of ACMEs and ADEs

ii. Mediation Analysis

We used the selected mediator model and outcome model as the input for mediation function. Separate Mediation Analysis was performed to test the mediation effect of time to surgery with different exposures, namely race, gender, income and age at diagnosis(shown in **Table 3**). The

results show that estimated ACMEs are only significant in gender, indicating the mediation effect of time to surgery is only significant between male and female patients (p=0.04). Similarly, the estimates of ADE demonstrate that race, gender and income are also directly associated with the survival outcome.

V. Conclusions

In this study, we observed disparities in cancer survival but only modest evidence of the role of time to treatment in explaining such disparities. We think the predictive power of mediation analysis is probably limited by the lack of included black patients in our data. Our fitted models considered the *race*/*time to treatment* interaction as well as the *race*/*stage* interaction, but do not account for the time-varying nature of the effects, which might again limit our ability to detect mediated effects.

The mediator displays complex non-linear effects on the survival probability. We observed a positive effect of time to treatment on cancer survival when T is greater than 2.9, after 18 months of diagnosis, which did not align with our expectation. We think there might be other unmeasured confounders, like patients' health status, also affecting the relationship between time to treatment and survival time, thus bias our analysis. But we only have the baseline information in our data which is cancer stage at diagnosis. Generally, patients health status would deteriorate with the progression of colorectal cancer. Our basis is that for patients potentially undergoing rapid progression, early treatment would benefit their survival outcome. As they are probably represented by the first peak in the distribution plot of time to treatment (shown in **Figure 2** left), this could explain the decreasing trend of survival probability with the prolongation of time to treatment when T is less than 2.9. However, for patients in relatively stable disease status, time to treatment is not a decisive factor to impact their survival. As they are probably represented by the second peak in the same plot, only a small percentage of the population, increasing survival rate in this group might be masked by insufficient observations. Another possible reason is that we had to ignore the censoring in time to treatment when fitting the outcome model in order to match the observations in mediator model. But for patients who did not receive the surgery treatment, actually, their waiting time(3.744 ± 0.854) was much longer than those who had the surgery(1.985 ± 0.844). In this way, their longer waiting time was interpreted as longer survival time, which directly

resulted in higher five-year survival probability for them. Therefore, we might overestimate the survival probability for T greater than 2.9 by simply taking waiting time as time to treatment. Finally, the mediation analysis conducted using the R package mediation does not account for the semi-competing risk structure of our data. As a next step, we will perform latent class analysis trying to cluster the patients in terms of their disease and treatment characteristics. Then, we will allow for time-dependent effects of survival probability and time to treatment and model these failure times jointly to improve upon the causal interpretation of the analysis. We might also consider multiple mediators in our analysis to better explain the racial disparities in cancer survival.

VI. References

[1] Valeri, L., Chen, J. T., Garcia-Albeniz, X., Krieger, N., Vanderweele, T. J., Coull, B. A. (2015). The Role of Stage at Diagnosis in Colorectal Cancer Black-White Survival Disparities: A Counterfactual Causal Inference Approach. Cancer Epidemiology Biomarkers & Prevention,25(1), 83-89.

[2] Catalano PJ, Ayanian JZ, Weeks JC, et al. Representativeness of participants in the cancer care outcomes research and surveillance consortium relative to the surveillance, epidemiology, and end results program. Med Care. 2013;51(2):e9–e15.

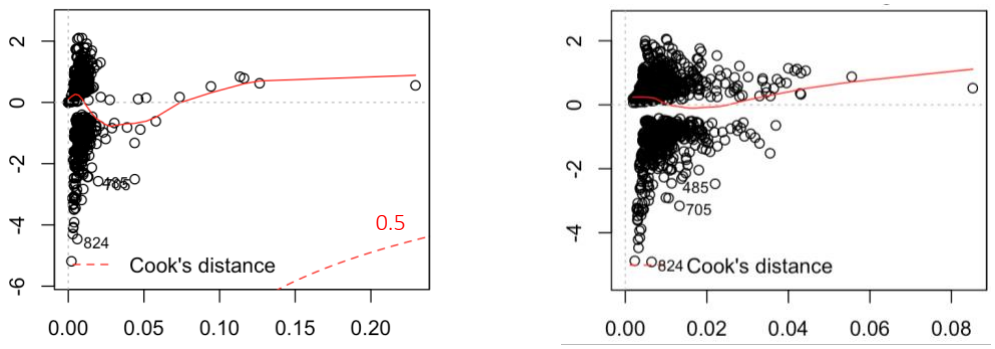
[3] Valeri, L., Vanderweele, T. J. (2013). Mediation analysis allowing for exposure–mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. *Psychological Methods,18*(2), 137-150.

[4] Tingley, D., Yamamoto, T., Hirose, K., Keele, L., Imai, K. (2014). mediation: R Package for Causal Mediation Analysis. Journal of Statistical Software, 59(5), 1 - 38.

[5] Valeri, L., Lin, X., and VanderWeele, T. J. (2014), Mediation analysis when a continuous mediator is measured with error and the outcome follows a generalized linear model, Statistics in Medicine, 33, 4875–4890.

VII. Appendix

(a) Pearson Residual vs. Leverage Plot. Left: time to treatment in original scale. Right: time to treatment in log scale. Residuals are more concentrated around reference line when log-transformed time to treatment was used in model fitting.



(b) Coefficient Estimates Table. Left: exclude *race*/*stage* interaction; Right: allow for *race*/*stage* interaction. Including *race*/*stage* interaction in fitting mediator model and outcome model does not improve prediction based on AIC criteria.

Coefficient Estimates of Mediator Model

	Estimate	Std.Error	z	Pr(>|z|)
(Intercept)	0.86153	0.03973	21.69	<2e-16
race1	0.03829	0.031	1.24	0.21678
stage	0.00284	0.01131	0.25	0.80209
gender1	0.08466	0.02479	3.42	0.00064
age_dx>52	-0.00989	0.03409	-0.29	0.77171
age_dx>64	-0.05789	0.03339	-1.73	0.08292
income2	-0.02091	0.02903	-0.72	0.4714
income3	-0.00409	0.03461	-0.12	0.90594
Log(scale)	-0.77124	0.02048	-37.65	<2e-16

AIC=4351.884

Coefficient Estimates of Mediator Model

	Estimate	Std.Error	z	Pr(>|z|)
(Intercept)	0.85268	0.04071	20.94	<2e-16
race1	0.07869	0.05296	1.49	0.13736
stage	0.00836	0.01271	0.66	0.51051
gender1	-0.08471	0.02478	-3.42	0.00063
age_dx>52	-0.00808	0.03413	-0.24	0.8129
age_dx>64	-0.05716	0.03338	-1.71	0.08684
income2	-0.02161	0.02904	-0.74	0.45692
income3	-0.00464	0.03461	-0.13	0.89324
race1:stage	-0.02651	0.02781	-0.95	0.34059
Log(scale)	-0.77142	0.02048	-37.67	<2e-16

AIC=4352.974

Coefficient Estimates of Outcome Model

a. Not adjusting for Time to Treatment

	Estimate	Std.Error	z	Pr(>|z|)
(Intercept)	2.76919	0.2245	12.335	<2e-16
race1	-0.34105	0.15174	-2.248	0.0246
stage	-1.02912	0.06799	-15.137	<2e-16
income2	0.46549	0.14775	3.15	0.00163
income3	0.50946	0.17606	2.894	0.00381
gender1	-0.31933	0.12534	-2.548	0.01084
age_dx>52	0.06312	0.17139	0.368	0.71265
age_dx>64	-0.50109	0.16748	-2.992	0.00277

AIC=1652.069

Coefficient Estimates of Outcom Model

a. Not adjusting for Time to Treatment

	Estimate	Std.Error	z	Pr(>|z|)
(Intercept)	2.76563	0.23459	11.789	<2e-16
race1	-0.31096	0.33558	-0.927	0.35412
stage	-1.02774	0.07682	-13.378	<2e-16
income2	0.47226	0.14783	3.195	0.0014
income3	0.51531	0.17641	2.921	0.00349
gender2	0.32671	0.12541	2.605	0.00918
age_dx>52	0.06505	0.17151	0.379	0.70447
age_dx>64	-0.50681	0.16759	-3.024	0.00249
race1:stage	-0.01383	0.1612	-0.086	0.93162

AIC=1654.06

b. Adjusting for Time to Treatment (T)

	Estimate	Std.Error	z	Pr(>|z|)
(Intercept)	2.0873	0.46197	4.518	6.24E-06
T	1.76828	0.64489	2.742	0.006107
I(T^2)	-1.102	0.32697	-3.37	0.000751
I(T^3)	0.18454	0.05053	3.652	0.00026
race1	-0.23794	0.38293	-0.621	0.534355
stage	-1.03426	0.06896	-14.997	<2e-16
income2	0.45039	0.14916	3.02	0.002532
income3	0.50636	0.17707	2.86	0.00424
gender1	-0.30641	0.12654	-2.422	0.015455
age_dx>52	0.05908	0.1728	0.342	0.732439
age_dx>64	-0.49249	0.16858	-2.921	0.003485
T:race1	-0.0456	0.16318	-0.279	0.779911

AIC=1639.784

b. Adjusting for Time to Treatment (T)

	Estimate	Std.Error	z	Pr(>|z|)
(Intercept)	2.07982	0.46642	4.459	8.23E-06
T	1.74619	0.64413	2.711	0.00671
I(T^2)	-1.09024	0.32653	-3.339	0.00084
I(T^3)	0.18292	0.05045	3.625	0.00029
race1	-0.13779	0.50598	-0.272	0.78537
stage	-1.02617	0.07783	-13.184	< 2e-16
income2	0.45673	0.14918	3.062	0.00220
income3	0.5102	0.17732	2.877	0.00401
gender2	-0.3139	0.12663	-2.479	0.01318
age_dx>52	0.06158	0.17294	0.356	0.72178
age_dx>64	-0.49728	0.1687	-2.948	0.00320
race1:T	-0.05247	0.16423	-0.319	0.74937
race1:stage	-0.0437	0.16349	-0.267	0.78923

AIC=1641.706