Department of Biostatistics
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Internal data analysis Report

Title	PRIAS
Version	1
Date	10 February 2017
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1 Introduction

In this report we present a preliminary analysis of the prostate cancer data set from the PRIAS study. The original data set as of December 7 2016 contains contains information about 6039 patients who received kidney transplants. PSA, DRE and Gleason scores were obtained from these patients based on a fixed schedule. The age of the patients at baseline was also available. The goal of the analysis we present in this report was to know how do the 3 aforementioned biological measurements affect time to progression of cancer. We however have not performed a full analysis and hence we have not answered how the 3 types of measurements are related to each other. However a complete analysis will be performed later to answer the latter question. In the analysis presented here, we considered only 5164 patients out of the 6039 available. The rest of the patients were not considered because of the following reasons.

- Patients having no other information other than the ID.
- Patients having age less than 5.
- Patients not having any information on follow ups.
- Patients who discontinued but do not have any date of discontinuation.
- Patients not having reasons of discontinuation.
- Patients with incomprehensible reasons of discontinuation.

Further we also removed all those observations where:

- PSA/DRE/Gleason scores were available but the date of measurement was not.
- Date of measurement is available but neither of the 3 scores are available.
- Measurements were dummy.
- Gleason scores were 0 or 1.

The patients who did not have an event till the last follow up date were considered to be lost to follow up (i.e. censored) and their last follow up date was considered as their date of censoring. Further we combined the categories anxiety, watchful waiting, death from other reasons and lost to follow up into a single "censored" category. The subjects who had the treatment were considered to in the "event" category. The event of interest here is disease progression, at the advent of which the treatment is given. Lastly, we dichotomized DRE and Gleason scores because some of the categories of Gleason and DRE scores had too less patients and besides our software doesn't support categorical outcomes with more than 2 levels at this moment. We considered Gleason scores which were less than or equal to 6 as low and the greater than 6 as high. For DRE, all DRE scores higher than T1c were considered high and the rest as low.

1.1 Various transformations of available data

In this analysis we did transformations of available data in multiple scenarios. For e.g. in the longitudinal analysis of PSA measurements we used log(PSA + 1) measurements instead of the raw data. The log transformation was done after considering that certain patients had very large PSA scores and thus suggested that the underlying distribution is right skewed. Secondly a lot of patients had PSA score 0, and thus we added a constant 1 to all PSA scores before log transformation. We found the same transformation in literature as well [McGreevy et al., 2006, Sène et al., 2016].

For the variable Age in the Cox model, we wanted to also consider the quadratic effect however doing so led many numerical instabilities while doing the joint model analysis. To avoid these pitfalls we had to mean center the Age variable.

Lastly, we used piecewise regression techniques for modeling the evolution of log (odds) for Gleason and DRE and we used splines for log(PSA+1) score. We tried models with linear evolutions over time as well, however they lead to a very sharp evolution of the responses, which did not match the observed evolutions. If in reality the evolutions were indeed linear, then a piecewise approach

would've given us the same result as the model with linear evolution. Since the results with the two approaches were very different and the observed trends also showed non linear evolutions, we decided not to use linear evolutions. For ease of interpretation of results we compensate the model complexity with graphs of fitted evolutions.

2 Descriptive Statistics

Table 1 shows the number of subjects in the study by event category. As we can see not everyone who was given a treatment based on protocol had an increase in DRE or had a gleason score reclassification. We can also see that many of the subjects who had gleason reclassification or had an increase in DRE are still on AS. For the latter scenario, we lack the clinical knowledge to give a reason for continuation on AS.

	Died	Treatment	WW	LFU	Anxiety, On-Req., Other	Active	Total
Gleason >6 at least once	2	488	28	1	45	137	701
Increase in DRE at least once	15	279	29	16	63	482	884
Total	63	1133	180	74	375	3339	5164

Table 1: Number of subjects by event category.
WW: Watchful waiting, LFU: Lost to follow up, On-Req: On request.

3 Time to event analysis of disease progression

We began with a non parametric analysis for time to progression. Figure 1 shows the Kaplan Meier survival curves for 3 age groups, Age $\leq$ 67 years, Age $>$ 73 years and Age between 67 and 73 years. We can see that for the lowest Age group the survival probability is higher in the first few years. However the effect is quite weak.

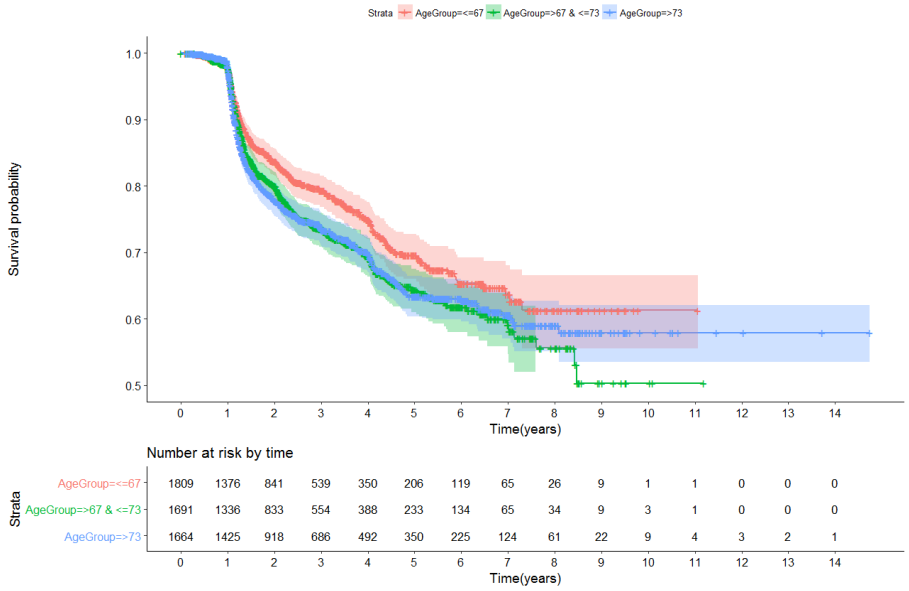
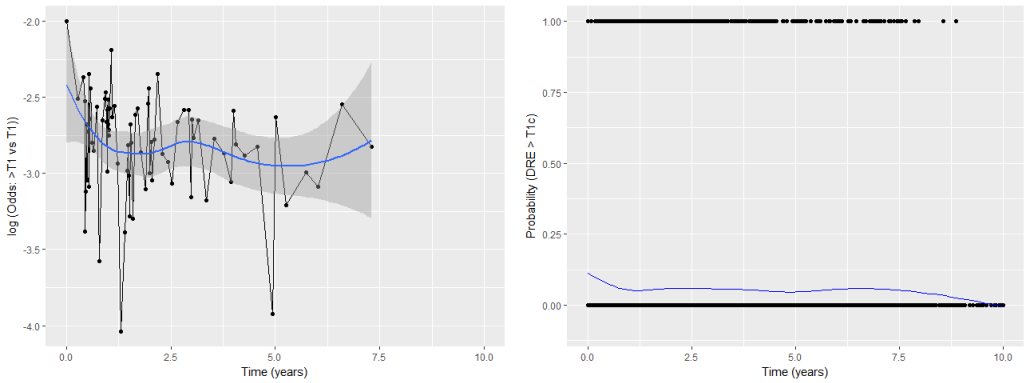


Figure 1: Survival probability for 3 age groups. Age $\leq$ 67 years, Age $>$ 73 years and Age between 67 and 73 years.

To confirm the effect of Age, we fitted a Cox model for time to event analysis of disease progression, with both Age and its quadratic effect as covariates. We found both covariates to be small and significant at 95% level of significance.

4 Longitudinal analysis of PSA/DRE and Gleason

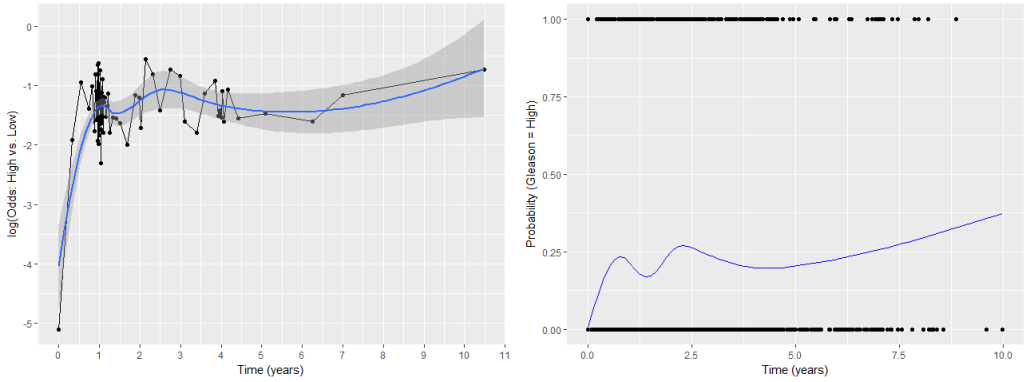
For the univariate longitudinal analysis of DRE and Gleason scores, we first plotted the observed evolutions of the log odds based on a categorized time scale. This was done because we modeled the log odds for both of these responses using Generalized linear mixed models (GLMM). The observed evolutions for log(odds) are shown in Figure 2a and Figure 3a. Correspondingly, the observed evolution of probabilities of high DRE and high Gleason scores are shown in Figure 2b and Figure 3b. Based on these plots we decided to use segmented evolutions with 2 segments in total to model the evolution for each of these responses. The choice of knot between the segments was only based on plots of log(odds) and a formal model selection was not performed in this preliminary analysis. The knot for evolution of log odds of DRE score was selected at 1.5 years and for Gleason scores at 0.5 years. For the random effects we only considered the random intercept for both of the responses.



(a) Observed evolution of log(odds: >T1c against T1c).

(b) Observed evolution of Probability(DRE > T1c).

Figure 2: Observed evolutions of log(odds: >T1c against T1c) and Prob(DRE > T1c) for DRE scores. The time scale in the log(odds) plot is categorized. Thus log(odds) at time point t are calculated by taking all observations between time t and $t-1$.



(a) Observed evolution of log(odds: High against Low).

(b) Observed evolution of Probability(Gleason = High).

Figure 3: Observed evolutions of log(odds: High against Low) and Prob(Gleason = High) for Gleason scores. The time scale in the log(odds) plot is categorized. Thus log(odds) at time point t are calculated by taking all observations between time t and $t-1$.

To understand the evolution of log(PSA+1) scores, we plotted the observed evolutions of log(PSA+1) scores after adjusting for Age (Figure 4). However after checking various subsamples of patients (individual as well as marginal over the entire subsample) we could not see a clear trend visually. So instead we then fitted various models to come up with a good fit. After comparing various models and considering the computational restrictions we chose a longitudinal model

with a spline with 3 internal knots to model fixed effect and with 1 internal knot to model random effect of time.

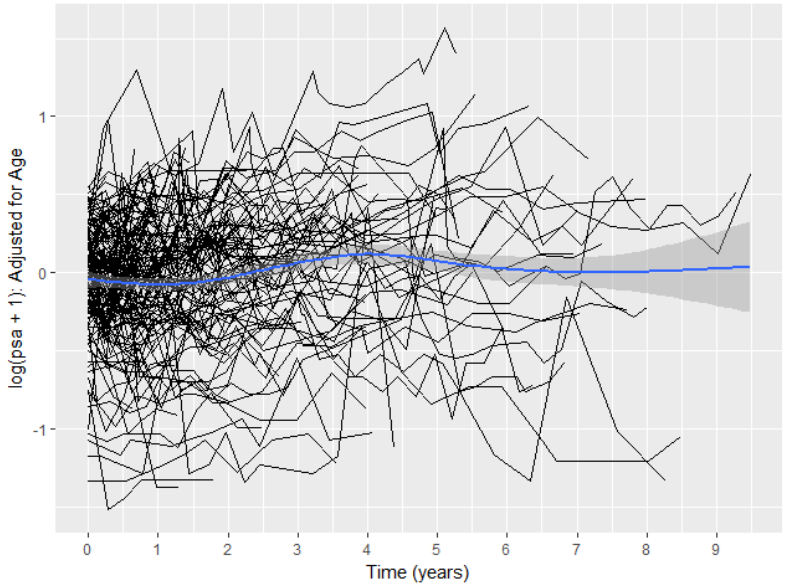


Figure 4: Observed evolutions for log(PSA + 1) measurements after adjusting for Age of the patients. A random sample of 150 patients is used.

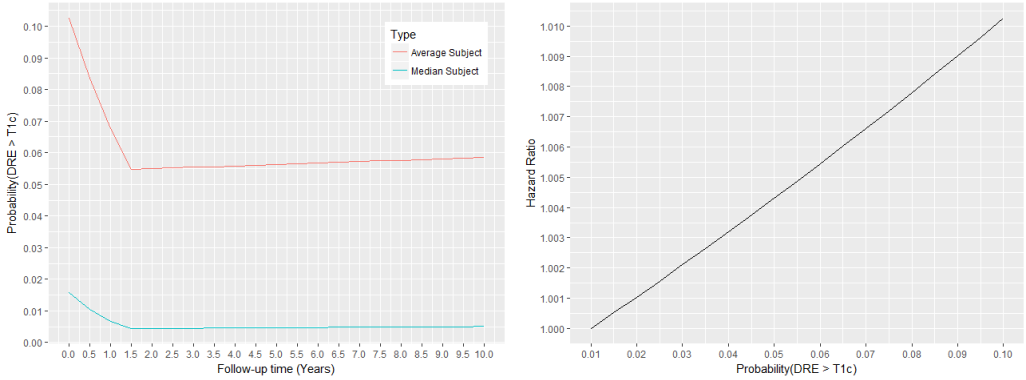
5 Joint model for PSA, DRE and Gleason scores

In this preliminary analysis, we present 3 separate joint models consisting of longitudinal submodels for PSA, DRE and Gleason measurements. The univariate models were fitted with mvJointModelBayes API instead of jointModelBayes because the jointModelBayes API did not lead to models with convergence for MCMC outcomes. Convergence was evaluated graphically using traceplots.

5.1 DRE score

In the joint model for DRE score we used the Odds of DRE score > T1c against DRE score T1 as the association parameter. For the resulting model the MCMC outcomes did not show any sign of non convergence for any of the parameter estimates. The resulting parameter estimates are shown in Table 2 and Table 3. The fitted evolution of Probability(DRE > T1c) is shown in Figure 5a. The average evolution a patient of Age 70 years is shown in red. The evolution for a median subject is shown in blue and it corresponds to a subject of Age 70 with 98.4% chance of having a DRE = T1c at the time of induction in the study. These fitted evolutions are comparable to the observed evolution in Figure 2b. The effect of Age is also significant, and for a particular patient, if Age of induction was 8.5 years year more than what they had, then their odds of having a DRE score > T1c would've been twice. The odds would've been 4 times if the Age of induction was 17 years more than what they had. We further verified that this particular odds ratio increases more or less linearly with increase in Age.

The association of Odds of DRE score on survival outcome is significant. However the size of this association is very small. This is also evident in the hazard ratio plot shown in Figure 5b. This plot shows the hazard ratio for the same patient, had it been having a different probability of DRE score > T1c. As we can see, the hazard of having a progression increases trivially with change in probability. It is important to note that these comparisons are made for the same patient and at the same time. The effect of Age and its quadratic effect is so small that they can be safely ignored for all practical purposes.



(a) Fitted evolution of probability of having a DRE score > T1c over a period of 12 months, for a patient of Age 70 years.

(b) Hazard ratio for various Prob(DRE > T1c) against Prob (DRE > T1c) = 0.01. Only valid for the same subject at the same time point.

Figure 5: Fitted evolution of probability of having a DRE score > T1c over time and Hazard ratio for various Prob(DRE > T1c) against Prob (DRE > T1c) = 0.01.

Variable	Mean	Std. Dev	2.5%	97.5%	P
Intercept	-9.729	0.671	-11.075	-8.416	0.000
Age	0.080	0.009	0.062	0.098	0.000
visitTimeYears	-0.863	0.064	-0.985	-0.733	0.000
(visitTimeYears - 1.5) × I(visitTimeYears >1.5)	0.879	0.085	0.717	1.051	0.000

Table 2: Longitudinal submodel estimates for joint model with DRE score outcome. Outcome modeled is log odds of DRE score >T1c against T1c.

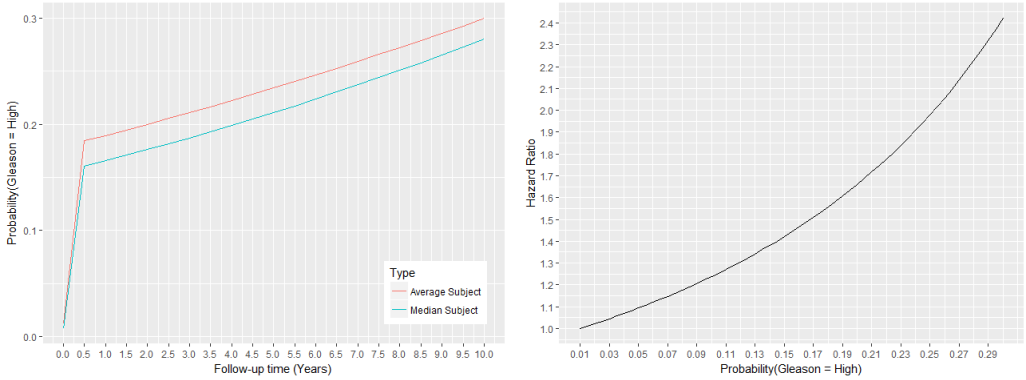
Variable	Mean	Std. Dev	2.5%	97.5%	P
Age - 70	0.006	0.005	-0.004	0.017	0.258
(Age - 70) × (Age - 70)	-0.001	0.001	-0.003	-2.905 $\times 10^{-4}$	0.010
Odds(>T1c against T1c)	0.101	0.018	0.064	0.134	0.000

Table 3: Survival submodel estimates for joint model with DRE score outcome.

5.2 Gleason score

In the joint model for Gleason score we used the Odds of Gleason = High against Gleason = Low as the association parameter. For the resulting model the MCMC outcomes had convergence issues. More specifically, the random intercept variance, association parameter and fixed effect estimates corresponding to time had signs of non convergence. Interestingly, the difference in the two coefficients related to time was equal to the difference in the two coefficients obtained from frequentist results, even though the coefficients themselves were not equal. This meant that the estimated evolution of log(odds) after 18 days (i.e. in second segment in the model) was estimated well despite the convergence issues. The resulting parameter estimates are shown in Table 4 and Table 5. The fitted evolution of Probability(Gleason = High) is shown in Figure 6a. The average evolution a patient of Age 70 years is shown in red. The evolution for a median subject is shown in blue and it corresponds to a subject of Age 70 with 99.2% chance of having a Gleason = Low at the time of induction in the study. These fitted evolutions are comparable to the observed evolution in Figure 3b. The effect of Age on odds is so small that if a person would've been inducted 15.5 years later than the time at which he is inducted, only then his odds of having a High baseline Gleason score would've become twice. The odds would've been 4 times if the Age of induction was 31 years more than what they had at the time of induction. So for all practical purposes the odds ratio increases more or less linearly with increase in Age.

The association of Odds of Gleason score on survival outcome is significant. To understand it



(a) Fitted evolution of probability of having a Gleason score = High over a period of 12 months, for a patient of Age 70 years.

(b) Hazard ratio for various Prob(Gleason = High) vs. Prob(Gleason = High) = 0.01. Only valid for the same subject at the same time.

Figure 6: Fitted evolution of probability of having a Gleason score = High over time and hazard ratio for various Prob(Gleason = High) against Prob (Gleason = High) = 0.01.

Variable	PostMean	Std. Dev	2.5%	97.5%	P
Intercept	-7.981	0.584	-9.144	-6.851	0.000
Age	0.045	0.007	0.031	0.058	0.000
visitTimeYears	6.409	0.297	5.797	6.913	0.000
(visitTimeYears - 0.5) × I(visitTimeYears >0.5)	-6.334	0.298	-6.850	-5.732	0.000

Table 4: Longitudinal submodel estimates for joint model with Gleason score outcome. Outcome modeled is log odds of High Gleason score against Low Gleason score.

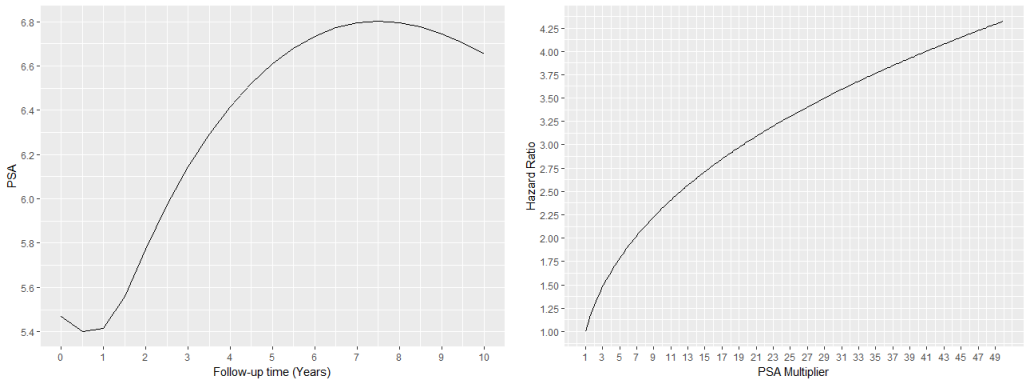
better we show a hazard ratio plot in Figure 6b. Similar to the plot for DRE score in section 5.1, this plot shows the hazard ratio for the same patient, had it been having a different probability of Gleason score = High at any given point in time. The effect of Age on hazard of progression is small and linear for all practical purposes. Secondly, if a patient was inducted in the study at an older age then his hazard of progression is lesser if we compare the two situations at some particular time point. More specifically if the patient was inducted 9.5 years later then his hazard of failure is 50% of what it would've been otherwise. It is important to note that all these comparisons are made for the same patient and at the same point in time.

Variable	Mean	Std. Dev	2.5%	97.5%	P
Age - 70	-0.073	0.022	-0.123	-0.038	0.000
(Age - 70) × (Age - 70)	-0.002	0.001	-0.003	1.436×10^{-5}	0.052
Odds (High against Low)	2.113	0.446	1.429	3.152	0.000

Table 5: Survival submodel estimates for joint model with Gleason score outcome.

5.3 PSA score

In the joint model for PSA score, the MCMC outcomes did not show any sign of non convergence for any of the parameter estimates including the components of variance covariance matrix. The resulting parameter estimates are shown in Table 6 and Table 7. Since the longitudinal evolution of log(PSA + 1) is fitted with non-linear terms, the interpretation of the coefficients corresponding to time is not straightforward. However in Figure 7a we present the fitted evolution of PSA over a period of 10 years for a patient who is 70 years old. Since the model has only additive terms, this evolution remains same for all patients and the effect of Age only affects the baseline PSA score. Furthermore the effect of Age on PSA scores is so small that it can be ignored for all practical purposes.



(a) Fitted evolution of PSA over a period of 10 years, for a patient who was inducted in AS at the Age of 70 years.

(b) Hazard ratio for PSA scores which are multiple of PSA score 5.7. Time and rate of change of log(PSA+1) remain same.

Figure 7: Fitted evolution of PSA over time and Hazard ratio if PSA becomes multiple of itself at the same time, with the same rate of change of log(PSA+1).

Variable	Mean	Std. Dev	2.5%	97.5%	P
Intercept	1.867	0.006	1.855	1.880	0.000
Age - 70	0.002	0.001	0.001	0.004	0.000
(Age - 70) × (Age - 70)	-3.506×10^{-4}	$7.413e\times10^{-5}$	-4.881×10^{-4}	-2.040×10^{-4}	0.000
Spline: visitTimeYears[0.0, 0.1]	0.074	0.007	0.061	0.087	0.000
Spline: visitTimeYears[0.1, 0.2]	0.278	0.021	0.237	0.319	0.000
Spline: visitTimeYears[0.2, 0.4]	0.127	0.071	-0.009	0.259	0.080
Spline: visitTimeYears[0.4, 1.5]	0.060	0.134	-0.203	0.304	0.660

Table 6: Longitudinal submodel estimates for joint model with log(PSA + 1) score outcome.

For the survival submodel it can be seen that both log(PSA + 1) and its slope are associated with time to event. The impact oflog(PSA + 1) on survival outcome can be seen in Figure 7b. In this graph we show the ratio of hazards of having disease progression for two patients, one with a PSA score of 5.7 (median PSA score at baseline) and another with a multiple of this score. The multiple is shown on X-axis and the corresponding hazard ratio is shown on Y-axis. It must be noted that we assume that the two people are measured at the same time point in progression history and the rate of change of log(PSA + 1) score for both patients remains the same. Lastly, for the effect of Age on hazard we can say that it can be safely ignored for all practical purposes.

Variable	Mean	Std. Dev	2.5%	97.5%	P
Age - 70	0.010	0.005	-0.001	0.020	0.084
(Age - 70) × (Age - 70)	-0.001	0.001	-0.002	0.000	0.038
log(PSA + 1)	0.390	0.105	0.176	0.595	0.000
Slope: log(PSA + 1)	0.750	0.070	0.622	0.884	0.000

Table 7: Survival submodel estimates for joint model with log(PSA + 1) score outcome.

References

[McGreevy et al., 2006] McGreevy, K., Rodgers, K., Lipsitz, S., Bissada, N., and Hoel, D. (2006). Impact of race and baseline psa on longitudinal psa. *International journal of cancer*, 118(7):1773–1776.

[Sène et al., 2016] Sène, M., Taylor, J. M., Dignam, J. J., Jacqmin-Gadda, H., and Proust-Lima, C. (2016). Individualized dynamic prediction of prostate cancer recurrence with and without the initiation of a second treatment: Development and validation. *Statistical methods in medical research*, 25(6):2972–2991.