Final report

Graded

Group

Kevin Liu
Ivy Cheung
Kaichi Nakajima
...and 1 more
View or edit group

Total Points

41 / 102 pts

Question 1

Reader 1

19 / 34 pts

Motivation

- ✔ **+ 1 pt** Background or context provided for data
- ✔ **+ 1 pt** Reasonable motivation for analyzing data provided

Data

- ✔ **+ 1 pt** Source of data specified
- ✔ **+ 1 pt** Variables fully described
- ✔ **+ 1 pt** Performed data cleaning procedure clearly explained

Explanatory analysis

- ✔ **+ 2 pts** Relevant summary statistics presented and discussed
- ✔ **+ 1 pt** figures/results are not well explained. -1
- ✔ **+ 0 pts** The chosen analysis doesn't align well with the objective of this study

Statistical analysis

- ✔ **+ 2 pts** Assumptions of chosen methodology addressed and reasonable
- ✔ **+ 1 pt** model/variable selection not very well justified. -1
- ✔ **+ 1 pt** the chosen model and analysis does not answer the proposed research question -1
- ✔ **+ 1 pt** For these type of survival analysis, linear regression might not be very suitable

Discussion

- ✔ **+ 1 pt** Interpretation of analysis findings correct and reasonable
- ✔ **+ 1 pt** Potential limitations of study addressed and solutions proposed
- ✔ **+ 0 pts** didn't discuss the limitation of removing data points.

Writing

- ✔ **+ 2 pts** Report follows proposed structure
- ✔ **+ 0 pts** Report presented only in bullet points, not well structured text for explanation.

  Figures/tables are not properly refered/explained in the text.

Data file and R script

✔ **+ 2 pts** R script runs and is neatly documented

1. what does "categorical variables" mean?
2. there seems to be very clear clustering patterns in the residual...how would you explain them?
3. breast cancer samples as patients? And when is the data collected?
4. what is light-tailed normal?
5. how many data points are disgarded?
   What will be the potential concern of disgarding these data points?
6. should not perform model diagnostic before explanatory analysis and model selection
7. the objective is to understand the influence of type of therapies given the rest of the covariates. However, the explanatory analysis is dedicated to understand interactions between age and all other categorical variables, which doesn't provide much insights of the research question.

Question 2

Reader 2

0 / 34 pts

✔ **+ 0 pts** Not read

Question 3

Reader 3

22 / 34 pts

Motivation

- ✔ **+ 1 pt** Background or context provided for data
- ✔ **+ 1 pt** Reasonable motivation for analyzing data provided

Data

- ✔ **+ 1 pt** Source of data specified
- ✔ **+ 0 pts** Data collection methodology of source unclear and not addressed: -1
- ✔ **+ 1 pt** Variables fully described
- ✔ **+ 1 pt** Performed data cleaning procedure clearly explained

Explanatory analysis

- ✔ **+ 1 pt** Inappropriate exploratory plots: -1
- ✔ **+ 2 pts** Relevant summary statistics presented and discussed
- ✔ **+ 1 pt** Observations from exploratory plots made but not discussed: -1
- ✔ **+ 1 pt** Much information thrown at reader without guiding reader through it and explaining what the key insights are: -1

Statistical analysis

- ✔ **+ 1 pt** Not convinced linear regression is appropriate for this survival data (is there *censoring* here? i.e., a bound on survival months?): -1
- ✔ **+ 2 pts** Assumptions of chosen methodology addressed and reasonable
- ✔ **+ 2 pts** Model is appropriately chosen
- ✔ **+ 1 pt** Hard to interpret outputs when referred to by variable names: -1

Discussion

- ✔ **+ 1 pt** Interpretation of analysis findings correct and reasonable
- ✔ **+ 1 pt** Study objective addressed
- ✔ **+ 1 pt** Potential limitations of study addressed and solutions proposed
- ✔ **+ 0 pts** Clusters in residual plot not discussed: -1

Writing

- ✔ **+ 2 pts** Report follows proposed structure

✔ **− 1 pt** Analysis written in point form and without guiding reader: -1

✔ **+ 1 pt** Important conclusions written in a way that are easily misinterpreted: -1

Data file and R script

✔ **+ 0 pts** Data file not submitted

✔ **+ 1 pt** Code not commented/documented: -1

8 Refer to variables by what they represent rather than by their name in code

9 Do you have a sense of why these values were missing? Removing these points could potentially introduce bias

10 It's not clear what this plot is saying. How were the patients included in the database? How is overall survival months calculated? If survival months is calculated from when patient was first added to database and not when they were first diagnosed, this might not be meaningful.

11 Hard to see plots. Rather than including them all, pick the few that are most interesting and just briefly describe the others in text

12 Description of your analysis should be written like a paper or essay, not point form

13 Cancer patients? Tissue samples? Unclear language

14 This is important to highlight, and the conclusions drawn about treatments decreasing survival should be phrased carefully accordingly

15 These are model diagnostic plots, not exploratory plots. What is the model considered here?

16 No need to mention minor details like this

17 Make it clear formal statistical analyses start here

18 What do these two clusters represent?

19 When/over what time period was this data collected? Relevant if doing a survival analysis or things that could improve over time

Question assigned to the following page: 1

STAT 306 Project (Group 10)

Nicholas Tam (45695970), Ivy Cheung (97777726), Kaichi Nakajima (74175712), Kevin Liu (94200474)

Introduction

Breast invasive ductal carcinoma (IDC) is the most common type of breast cancer, with about 80% of all forms of breast cancer being IDC, according to the American Cancer Society (DePolo, 2024). There are numerous nonsurgical treatments of IDC, such as radiotherapy, chemotherapy, and hormone therapy (Wright, 2023), and each of their effectiveness is partly determined by the patient's condition, such as age and tumor stage. For instance, due to interactions between other treatments or conditions as a consequence of aging (e.g. Diabetes, liver disease, metabolism), more optimal doses of chemotherapy are generally discouraged for older patients due to potentially toxic side effects, implying a smaller difference in survival between older patients with or without chemotherapy (Given, Given, 2008). However, it is unclear how combinations of treatments can interact in a model to predict a patient's survival until death.

For our research project, we have selected a dataset of approximately 1900 primary breast cancer samples, obtained from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) database through cBioPortal for Cancer Genomics.

Our project question is: **"How do radiotherapy, chemotherapy, and hormone therapy influence the length of time a patient with IDC will survive, given control variables age, surgery type, tumor stage, and their present survival status?"**

Our analysis will involve the inference of covariates within linear models, as we seek to determine the interaction of cancer therapies on allowing patients to survive longer from IDC.

- Variables from columns 32 to 693 consist of genetic attributes containing m-RNA levels z-score for 331 genes, and mutation for 175 genes; they have been omitted due to being difficult to interpret.
- Due to the distribution of "cancer_type_detailed" categories and for ease of computation, we will be filtering the dataset for IDC patients that are either alive or dead from disease, as IDC consists of the majority of the dataset, and the patients that have died from other causes are irrelevant to the project question and not specific enough (e.g. Accident, non-cancer diseases). As such, we have narrowed down the data to the following attributes:

Variable	Definition	Unit	Categories
age_at_diagnosis	Age of the patient at diagnosis time	Years	
type_of_breast_surgery	Breast cancer surgery type	N/A	“MASTECTOMY”, “BREAST CONSERVING”
cancer_type_detailed	Detailed breast cancer types	N/A	“Breast Invasive Ductal Carcinoma”, “Breast Mixed Ductal and Lobular Carcinoma”, “Breast Invasive Lobular Carcinoma”, “Breast Invasive Mixed Mucinous Carcinoma”, “Metaplastic Breast Cancer”
chemotherapy	Boolean on whether or not patient had chemotherapy as a treatment	Boolean	
hormone_therapy	Whether or not the patient had hormonal therapy as a treatment	Boolean	

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overall_survival_months	Duration from the time of the intervention to death	Months	
death_from_cancer	Whether the patient's death was due to cancer or not	N/A	“Living”, “Died of Disease”, “Died of Other Causes”
radio_therapy	Whether or not the patient had radiotherapy as a treatment	Boolean	
tumor_stage	Stage of cancer based on involvement of surrounding structures, lymph nodes and distant spread	N/A	0, 1, 2, 3, 4, N/A

Analysis

Uploading relevant table and cleaning data

- All rows with "N/A" or "" for any relevant columns have been removed to ensure no data is missing.
- ~~All categorical variables are transformed to be treated as categorical by the table.~~
- After initial analysis, "tumor_stage==0" and "tumor_stage==4" have been removed due to lack of sufficient amounts of data points (1 case of stage 0 tumors, 5 cases of stage 4 tumors).

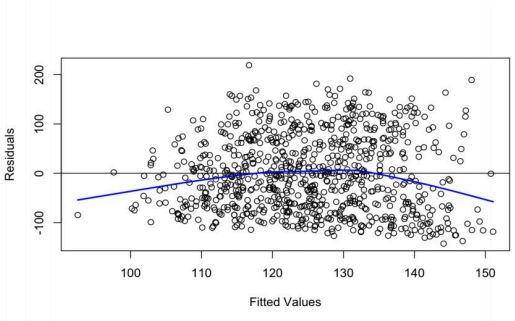
type_of_breast_surgery	tumor_stage	chemotherapy	hormone_therapy	radio_therapy	death_from_cancer
BREAST CONSERVING: 372 MASTECTOMY: 464	1: 277 2: 485 3: 74	0: 586 1: 250	0: 349 1: 487	0: 246 1: 590	Living: 468 Died of Disease: 368

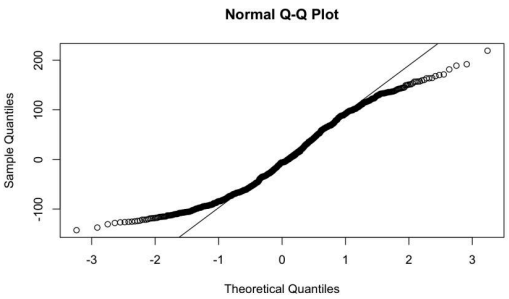
	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
age_at_diagnosis	26.36	48.24	57.33	57.31	67.05	96.29
overall_survival_months	0.10	57.67	115.10	125.18	186.71	337.03

Exploratory data analysis

Residual plot and QQ-plot (overall_survival_months against age_at_diagnosis)

- There does not appear to be any observable patterns in residual values beyond being centered around 0, though the slight variation in residual spread as fitted values increase may indicate heteroscedasticity.
- QQ-plot indicates distribution of residuals is light-tailed normal.





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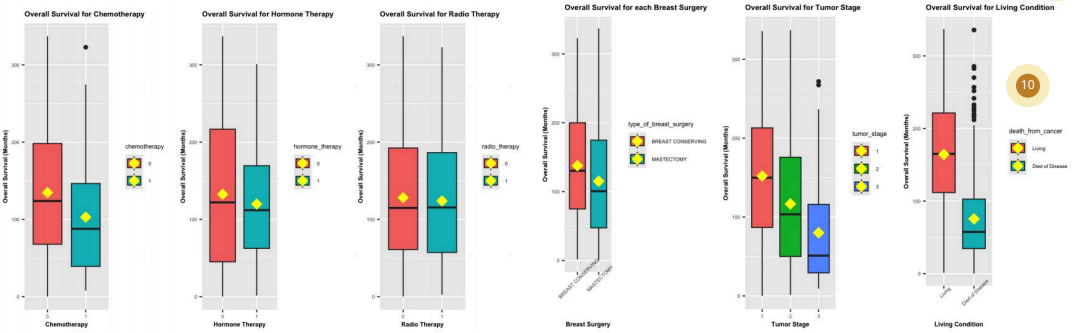
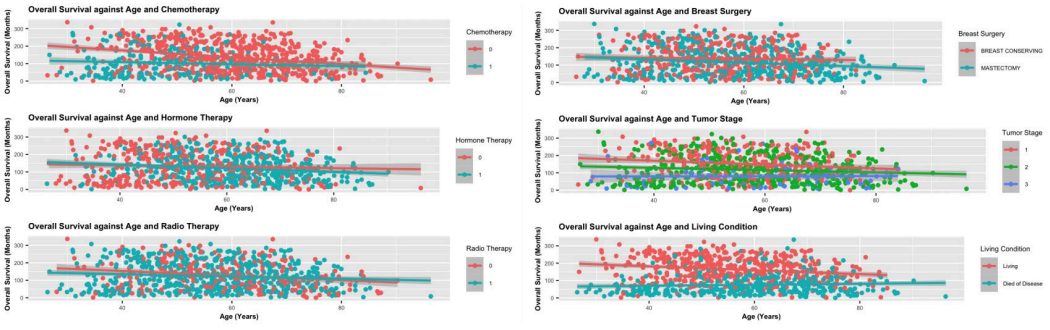
Boxplots of survival against interactions between age and categorical variables

- overall_survival_months for those that took chemotherapy is generally lower than for those without in terms of mean and median, and the range of overall_survival_months is smaller.
- Mean and median overall_survival_months for patients with hormone therapy are lower than those without, while the interquartile range for those with hormone therapy is smaller than for those without.
- Boxplots for overall_survival_months against each radio_therapy class are extremely similar, including the mean and median values.
- overall_survival_months for those with mastectomy is lower than for those with breast conserving surgery in terms of mean and median, and the values are more skewed toward lower values.
- Increasing levels of tumor stages provide decreasing mean, median and percentile values.
- Patients that died from disease have significantly lower overall_survival_months values than those who lived and the most extreme outliers.



Scatterplots of survival against interactions between age and categorical variables

- overall_survival_months varies significantly by chemotherapy, tumor_stage, and death_from_cancer, and the interaction terms for age with chemotherapy, type_of_breast_surgery, tumor_stage, and death_from_cancer appear to be statistically significant.
- Confidence intervals of linear models heavily overlap for hormone_therapy and radio_therapy.
- Confidence intervals of linear models for chemotherapy, type_of_breast_surgery and tumor_stage only overlap for more extreme age values.



Histograms of survival against interactions between age and categorical variables

- The histograms for those that took chemotherapy, mastectomy or had died from disease compared to those without chemotherapy, with breast preserving surgery or are alive respectively are significantly more skewed to the right.
- Histogram peaks for those that took hormone therapy are generally greater than for those without hormone therapy within the range of overall_survival_months between 45 and 195.

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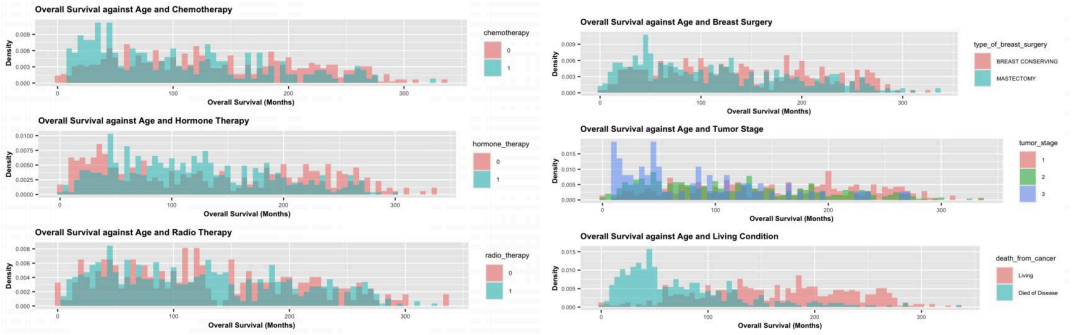
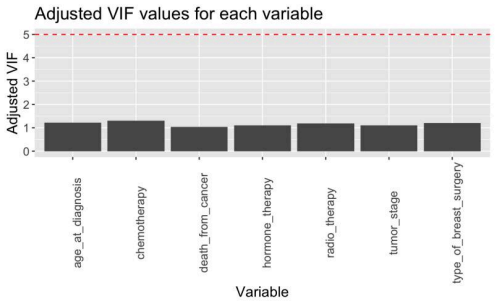
- The histogram distributions between radio therapy categories are relatively similar.
- The histogram for those with stage 3 tumors compared to that for the other tumor stages is significantly more skewed to the right.
- Given our exploratory analysis on overall_survival_months within boxplots and histograms, we will assume that the overall distribution of the variable is skewed to the right, and thus may have heteroscedasticity; as such, a log transformation would be beneficial for model fitting.



Variance Inflation Factor (VIF) on covariates



- VIF for each variable is calculated to test for multicollinearity, which could make it difficult to interpret coefficients, and it reduces the power of the model to identify statistically significant independent variables.
- GVIF..1..2.Df.. is used for comparison due to different degrees of freedom for some variables.
- Horizontal line of VIF = 5 to indicate severe correlation of a variable with other variables; any variables with VIF > 5 are to be removed to reduce multicollinearity in the model.
- GVIF..1..2.Df.. for all variables are significantly lower than 5; multicollinearity between all variables is relatively low, thus no variables need to be removed.

Model selection 1

- The baseline used are living, stage 1 cancer patients without any therapies as the baseline.
- As our goal is to determine how the various forms of therapy influence a patient's survival until death, interaction terms regarding all combinations of therapies are considered, since it is unclear if the effect of one therapy will influence the effect of another (e.g. Chemotherapy and hormone therapy in similar timeframe).
- Interaction terms for age and each type of therapy are included, as prior studies have indicated varying degrees of influence between age and treatment method (Given, Given 2008; Cleveland Clinic, 2024; U.S. National Library of Medicine; Steinfeld, Diamond, Hanks, Coia, Kramer, 1989).
- Interaction terms for tumor_stage and each type of therapy are also included since prior studies have indicated that the type of treatment a patient receives is influenced by the stage, size of tumor and the spread of cancer cells. (“Invasive Ductal Carcinoma”, 2024; “Treatment of breast cancer”, 2024)
- Due to not being significant parts of the question of interest and the indeterminate interaction between them and the therapies, interaction terms for type_of_breast_surgery and death_from_cancer are ignored for the full model.
- We had attempted to fit linear models without the log transformation, and the resulting residual plots had demonstrated heteroscedasticity.
- Full model: log(overall_survival_months) ~ age_at_diagnosis + chemotherapy * hormone_therapy * radio_therapy + age_at_diagnosis : chemotherapy + age_at_diagnosis : hormone_therapy +

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age_at_diagnosis : radio_therapy + tumor_stage + tumor_stage : chemotherapy + tumor_stage : hormone_therapy + tumor_stage : radio_therapy + type_of_breast_surgery + death_from_cancer

- Forward and backward AIC selection with the same full model was attempted, but only backward selection produced the same model, while forward selection produced a less optimal model.
- Model finalmod_both has age_at_diagnosis:chemotherapy1 and hormone_therapy1:tumor_stage2 to be not statistically significant on the 5% significance level.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	5.947000	0.214458	27.730	< 2e-16
age_at_diagnosis	-0.014682	0.003806	-3.857	0.000124
chemotherapy1	-0.701659	0.294312	-2.384	0.017348
hormone_therapy1	-0.622362	0.266825	-2.332	0.019915
tumor_stage2	-0.238917	0.093835	-2.546	0.011073
tumor_stage3	-0.815091	0.166351	-4.900	1.15e-06
death_from_cancerDied of Disease	-0.857453	0.054094	-15.851	< 2e-16
age_at_diagnosis:chemotherapy1	0.009678	0.005384	1.797	0.072624
age_at_diagnosis:hormone_therapy1	0.009458	0.004510	2.097	0.036273
hormone_therapy1:tumor_stage2	0.216084	0.117380	1.841	0.065997
hormone_therapy1:tumor_stage3	0.711055	0.203734	3.490	0.000508

Model selection 2

- finalmod_both was compared to a version of the final model without interaction term age_at_diagnosis:chemotherapy1 (finalmod_both_1), as indicated below.
- Model finalmod_both_1 has only age_at_diagnosis:hormone_therapy1 to be not statistically significant on the 5% significance level.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	5.773782	0.191845	30.096	< 2e-16
age_at_diagnosis	-0.011469	0.003365	-3.408	0.000685
chemotherapy1	-0.189144	0.073044	-2.589	0.009782
hormone_therapy1	-0.570923	0.265644	-2.149	0.031908
tumor_stage2	-0.271223	0.092222	-2.941	0.003363
tumor_stage3	-0.830862	0.166344	-4.995	7.19e-07
death_from_cancerDied of Disease	-0.857409	0.054167	-15.829	< 2e-16

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age_at_diagnosis:hormone_therapy1	0.008276	0.004467	1.852	0.064316
hormone_therapy1:tumor_stage2	0.240445	0.116753	2.059	0.039766
hormone_therapy1:tumor_stage3	0.726981	0.203816	3.567	0.000382

Model comparisons

- regsubsets() applied to the original full model for selection of best subsets (see Appendix section 1)
- For the best subsets with 11 and 12 parameters from regsubsets(), both contain the parameters age_at_diagnosis, chemotherapy1, hormone_therapy1, tumor_stage2, death_from_cancerDied of Disease, age_at_diagnosis:chemotherapy1, age_at_diagnosis:hormone_therapy1, hormone_therapy1:tumor_stage3 and radio_therapy1:tumor_stage3; the interaction term radio_therapy1:tumor_stage3 was not present in finalmod_both or finalmod_both_1.
- The parameters tumor_stage3 and hormone_therapy1:tumor_stage2 are included for the selected best subset with 11 parameters but not the selected best subset with 12 parameters, though both were present in finalmod_both and finalmod_both_1.
- The parameters chemotherapy1:hormone_therapy1, hormone_therapy1:radio_therapy1 and age_at_diagnosis:radio_therapy1 are included for the selected best subset with 12 parameters but not the selected best subset with 11 parameters, but the interaction terms involving radiotherapy are not present in finalmod_both or finalmod_both_1.

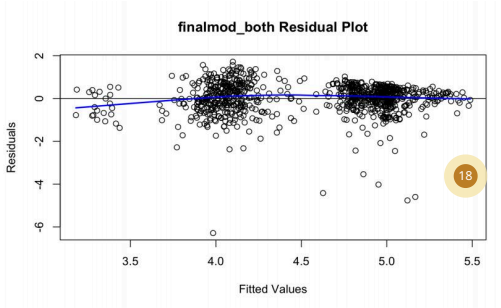
Model statistics

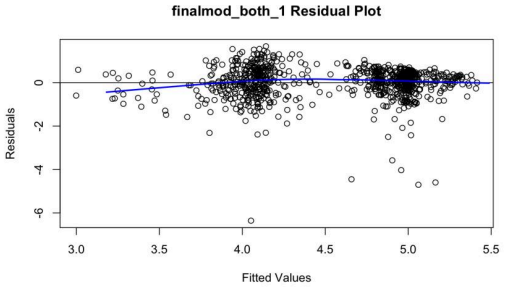
- Compared to finalmod_both, the model finalmod_both_1 has an AIC value increased by 1.21, and adjusted R^2 decreased by 0.0018577 (7 d.p.).

Statistics	finalmod_both	finalmod_both_1
Number of estimated parameters	12	11
Residual standard error	0.7441687	0.7451730
Multiple R-squared	0.3204380	0.3177766
Adjusted R-squared	0.3122009	0.3103432
AIC	1891.72	1892.93

Residual plot and QQ-plot

- For both models, there does not appear to be any observable patterns in residual values beyond being centered around 0, though there are outliers present for larger fitted values.





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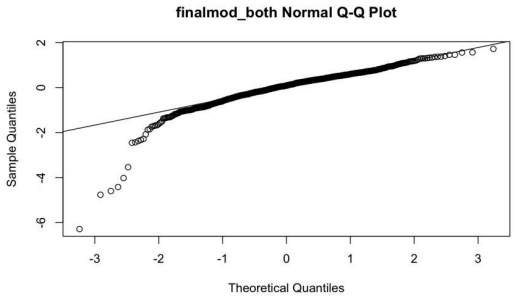
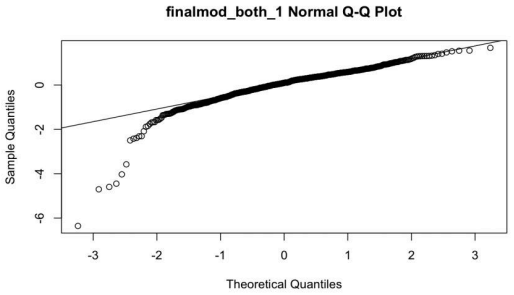
- The QQ-plots indicate the distribution of residuals are normal distributions that are slightly left-skewed for both models; given the outliers in the residual plot, the left-skew may be due to outliers as well.





- By the parsimony principle, and due to our project question's focus on inference, the model finalmod_both_1 was selected due to having fewer variables, and thus being easier to interpret, while producing similar results and a marginally worse fit to the data.

Discussion

Analysis

The final regression model includes the following key variables: age, chemotherapy, hormone therapy, and tumor stage (specifically stages 2 and 3). It also accounts for the outcome of death from cancer (death from cancer and death from other causes) and incorporates interaction terms between age and hormone therapy, as well as hormone therapy and tumor stage (for stages 2 and 3).

The results from bidirectional selection and backward selection consistently provided the same set of covariates, but the results from forward selection did not, possibly due to it missing covariates that are only significant in combination with other covariates. The covariates of the final regression model are all statistically significant on the 5% significance level, with the exception of the interaction term between age and hormone therapy. This consistency between bidirectional and backward selection enhances the credibility of the findings, indicating that the observed relationships are relatively robust and not due to random chance.

In the model selection, we discarded radiotherapy, indicating that it doesn't provide a significant influence on the log survival period of patients. For chemotherapy, regardless of tumor stage, the log survival period is decreased by 0.189144. This indicates that chemotherapy consistently reduces survival periods, and its negative effects on survival do not change significantly at higher tumor stages.

For hormone therapy, it initially reduces the log survival period by 0.570923 at tumor stage 1, but its effect decreases to a reduction of 0.330478 in log survival at stage 2, and it even leads to an increase in log survival by 0.156058 in stage 3. From tumor stage 1 to stage 3, the impact of hormone therapy changes from harmful to beneficial, ultimately improving survival chances. This highlights the importance of carefully considering the use of hormone therapy based on tumor stage.

The model shows a negative correlation between age_at_diagnosis and overall_survival_months, indicating that for each year of age (at the time of diagnosis), the patient's log months of survival is decreased by 0.011469. This indicates that younger cancer patients will have a higher chance of recovering from IDC (higher overall survival months). The presence of hormone therapy increases change in survival to 0.003193, implying that the impact of age on survival months becomes less severe with hormone therapy.

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The final model shows that the intercept for patients who have died from disease is lower by 0.857409 compared to living patients. This is consistent with the scatterplot between age/living condition from the exploratory analysis, where the overall survival was significantly lower for deceased patients compared to living ones. The scatterplot does not show the two slopes to be parallel, which would have been accounted for by the interaction term between death_from_cancer and age_at_diagnosis; however, this term was removed during model selection due to low significance.

To further validate the reliability of the model, the plot of fitted values versus residuals shows a good fit with residuals centered around zero, demonstrating homoscedasticity. Additionally, the residuals are randomly scattered without any discernible pattern beyond being centered around 0, suggesting that the errors are independent and that the relationship between the independent variables and the dependent variable is assumed to be linear. Furthermore, the points in the QQ plot align closely along the diagonal line, indicating that the residuals are approximately normally distributed. These observations confirm that the regression model does not violate the key assumptions of regression analysis, thereby minimizing the risk of drawing incorrect conclusions.

Conclusion

To address our initial research question, our model suggests that chemotherapy and hormone therapy have varying influences on survival time before death depending on the initial tumor stage while radiotherapy does not have a significant association with survival time before death. In general, our model suggests that chemotherapy has a negative association with survival time before death regardless of tumor stage level while hormone therapy has a negative association for patients with an initial tumor stage of 1 and 2 while it has a positive association when the patient's original tumor stage was 3. Our model does not align with prior research as prior research suggests that chemotherapy is generally effective and increases the survival time before death. Similarly prior research suggests that hormone therapy and radiotherapy are generally effective at treating patients with IDC. However, our model aligns with prior research suggesting chemotherapy is most effective for later stages of cancer (Penn Medicine, n.d.).

Our model likely differs from prior research due to several limitations in our model. One limitation is our variable selection method, a bidirectional stepwise selection starting with a full model. While bidirectional model selection allows for better flexibility and model fit onto the data, there is also the risk of the final model being overfitted to the existing data. Our response variable being the log of overall_survival_months in order to maintain homoscedasticity also makes our model estimates to be rather difficult to interpret. Moreover, our results may have been skewed from using tumor stage 1 as our baseline, since we did not have enough data points for tumor stage 0. Lastly, our model could not account for the context of the patients undergoing such treatments, such as the patients that took the treatment likely already being in poorer health than those that did not, or the side effects of such treatments impacting health, such as organ damage from chemotherapy ("Side effects of chemotherapy", Canadian Cancer Society, 2024), osteoporosis from hormone therapy ("Side effects of hormone therapy", Canadian Cancer Society, 2017) and low blood cell counts from radiation therapy ("Side effects of radiation therapy", Canadian Cancer Society, 2017). Overall, the limitations of our model are reflected by the relatively low adjusted R^2 of 0.3103432 (7 s.f.), which indicates our model only accounts for around 31.03% (2 d.p.) of the variability in survival time before death for IDC patients.

The R code script was submitted by Nicholas Tam.

Question assigned to the following page: 1

Sources

- *Breast cancer gene expression profiles (METABRIC)*. Kaggle. (2016, May 10). https://www.kaggle.com/datasets/raghadalharbi/breast-cancer-gene-expression-profiles-metabric
- CBioPortal for Cancer Genomics. (n.d.). https://www.cbioportal.org/study/summary?id=brca_metabric
- DePolo, J. (2024, October 2). *Invasive ductal carcinoma (IDC)*. Breastcancer.org - Breast Cancer Information and Support. https://www.breastcancer.org/types/invasive-ductal-carcinoma
- Wright , P. (2023, March 21). *Invasive ductal carcinoma (IDC)*. Johns Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/breast-cancer/invasive-ductal-carcinoma-idc#:~:text=Radiation%20therapy%20might%20be%20part,lymph%20nodes%2C%E2%80%9D%20Wright%20says.
- *Tumor size and staging*. Susan G. Komen®. (2024, May 2). https://www.komen.org/breast-cancer/diagnosis/stages-staging/tumor-size/#:~:text=Tumor%20size%20is%20related%20to,the%20size%20of%20the%20tumor.
- Given, B., & Given, C. W. (2008, December 15). *Older adults and cancer treatment*. Cancer. https://pmc.ncbi.nlm.nih.gov/articles/PMC2606910/#S10
- *Hormone therapy for cancer*. Cleveland Clinic. (2024, May 1). https://my.clevelandclinic.org/health/treatments/17108-hormone-therapy-to-treat-cancer
- U.S. National Library of Medicine. (n.d.). *Aging changes in hormone production: Medlineplus medical encyclopedia*. MedlinePlus. https://medlineplus.gov/ency/article/004000.htm#:~:text=In%20women%2C%20estrogen%20and%20prolactin,Cortisol
- Steinfeld, A. D., Diamond, J. J., Hanks, G. E., Coia, L. R., & Kramer, S. (1989). Patient age as a factor in radiotherapy. Data from the patterns of care study. *Journal of the American Geriatrics Society*, *37*(4), 335–338. https://doi.org/10.1111/j.1532-5415.1989.tb05501.x
- *Invasive Ductal Carcinoma*. Cleveland Clinic (June 27, 2024) https://my.clevelandclinic.org/health/diseases/22117-invasive-ductal-carcinoma-idc
- Penn Medicine. (n.d.). *Invasive Ductal Carcinoma (IDC)*. Pennmedicine.org. https://www.pennmedicine.org/cancer/types-of-cancer/breast-cancer/types-of-breast-cancer/invasive-ductal-carcinoma#:~:text=The%20IDC%20treatment%20your%20physician,focuses%20only%20on%20breast%20cancer
- "Treatment of breast cancer stages I-III". (2024, September 22). *Treatment of breast cancer stages I-III*. American Cancer Society. https://www.cancer.org/cancer/types/breast-cancer/treatment/treatment-of-breast-cancer-by-stage/treatment-of-breast-cancer-stages-i-iii.html#:~:text=The%20stage%20of%20your%20breast,gone%20through%20menopause%20or%20not
- *Side effects of chemotherapy*. Canadian Cancer Society. (2024, May). https://cancer.ca/en/treatments/treatment-types/chemotherapy/side-effects-of-chemotherapy
- *Side effects of hormone therapy*. Canadian Cancer Society. (2017). https://cancer.ca/en/treatments/treatment-types/hormone-therapy/side-effects-of-hormone-therapy
- *Side effects of radiation therapy*. Canadian Cancer Society. (2017b). https://cancer.ca/en/treatments/treatment-types/radiation-therapy/side-effects-of-radiation-therapy

Question assigned to the following page: 1

Appendix

Section 1

Table 1: Regsubsets() output

	age_at_diagnosis	chemotherapy1	hormone_therapy1	radio_therapy1	tumor_stage2	tumor_stage3
1 (1)	" "	" "	" "	" "	" "	" "
2 (1)	" "	"*"	" "	" "	" "	" "
3 (1)	"*"	"*"	" "	" "	" "	" "
4 (1)	"*"	"*"	" "	" "	" "	" "
5 (1)	"*"	"*"	" "	" "	" "	" "
6 (1)	"*"	"*"	" "	" "	" "	" "
7 (1)	"*"	"*"	" "	" "	"*"	" "
8 (1)	"*"	"*"	" "	" "	"*"	" "
9 (1)	"*"	"*"	"*"	" "	" "	" "
10 (1)	"*"	"*"	"*"	" "	"*"	"*"
11 (1)	"*"	"*"	"*"	" "	"*"	"*"
12 (1)	"*"	"*"	"*"	" "	"*"	" "
13 (1)	"*"	"*"	"*"	" "	"*"	"*"

	type_of_breast_surgeryMASTECTOMY	death_from_cancerDiedof Disease
1 (1)	" "	"*"
2 (1)	" "	"*"
3 (1)	" "	"*"
4 (1)	" "	"*"
5 (1)	" "	"*"
6 (1)	" "	"*"
7 (1)	" "	"*"
8 (1)	" "	"*"
9 (1)	" "	"*"
10 (1)	" "	"*"
11 (1)	" "	"*"

Question assigned to the following page: 1

12 (1)	" "	"*"
13 (1)	" "	"*"

	chemotherapy1: hormone_therapy1	chemotherapy1: radio_therapy1	hormone_therapy1:radio_therapy1
1 (1)	" "	" "	" "
2 (1)	" "	" "	" "
3 (1)	" "	" "	" "
4 (1)	" "	" "	" "
5 (1)	" "	" "	" "
6 (1)	" "	" "	" "
7 (1)	" "	" "	" "
8 (1)	" "	" "	" "
9 (1)	"*"	" "	" "
10 (1)	" "	" "	" "
11 (1)	" "	" "	" "
12 (1)	"*"	" "	"*"
13 (1)	" "	" "	" "

	age_at_diagnosis:chemotherapy1	age_at_diagnosis:hormone_therapy1	age_at_diagnosis:radio_therapy1
1 (1)	" "	" "	" "
2 (1)	" "	" "	" "
3 (1)	" "	" "	" "
4 (1)	" "	" "	" "
5 (1)	" "	" "	" "
6 (1)	"*"	" "	" "
7 (1)	"*"	" "	" "
8 (1)	"*"	" "	" "
9 (1)	"*"	"*"	" "
10 (1)	"*"	"*"	" "
11 (1)	"*"	"*"	" "

Question assigned to the following page: 1

12 (1)	"*"	"*"	"*"
13 (1)	"*"	"*"	" "

	chemotherapy1:tumor_stage2	chemotherapy1:tumor_stage3
1 (1)	" "	" "
2 (1)	" "	" "
3 (1)	" "	" "
4 (1)	" "	" "
5 (1)	" "	" "
6 (1)	" "	" "
7 (1)	" "	" "
8 (1)	" "	" "
9 (1)	" "	" "
10 (1)	" "	" "
11 (1)	" "	" "
12 (1)	" "	" "
13 (1)	"*"	"*"

	hormone_therapy1:tumor_stage2	hormone_therapy1:tumor_stage3
1 (1)	" "	" "
2 (1)	" "	" "
3 (1)	" "	" "
4 (1)	" "	" "
5 (1)	" "	"*"
6 (1)	" "	"*"
7 (1)	" "	"*"
8 (1)	"*"	"*"
9 (1)	" "	"*"
10 (1)	"*"	"*"
11 (1)	"*"	"*"
12 (1)	" "	"*"

Question assigned to the following page: 1

13 (1)	"*"	"*"

	radio_therapy1:tumor_stage2	radio_therapy1:tumor_stage3	chemotherapy1: hormone_therapy1: radio_therapy1
1 (1)	" "	" "	" "
2 (1)	" "	" "	" "
3 (1)	" "	" "	" "
4 (1)	" "	"*"	" "
5 (1)	" "	"*"	" "
6 (1)	" "	"*"	" "
7 (1)	" "	"*"	" "
8 (1)	" "	"*"	" "
9 (1)	" "	"*"	" "
10 (1)	" "	" "	" "
11 (1)	" "	"*"	" "
12 (1)	" "	"*"	" "
13 (1)	" "	"*"	" "