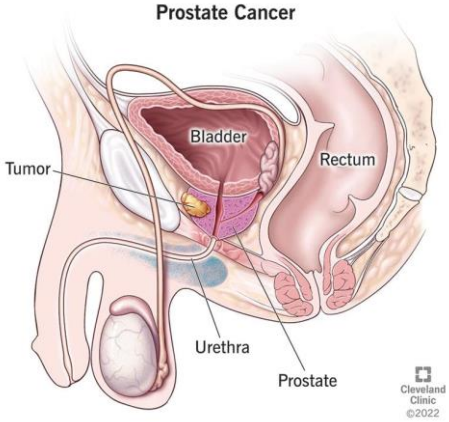
Analyzing the Impact of Three Treatments on Health Utility (EQ-5D) in Prostate Cancer Patients

Leen Madani | Data Science in Health I | October 23, 2023

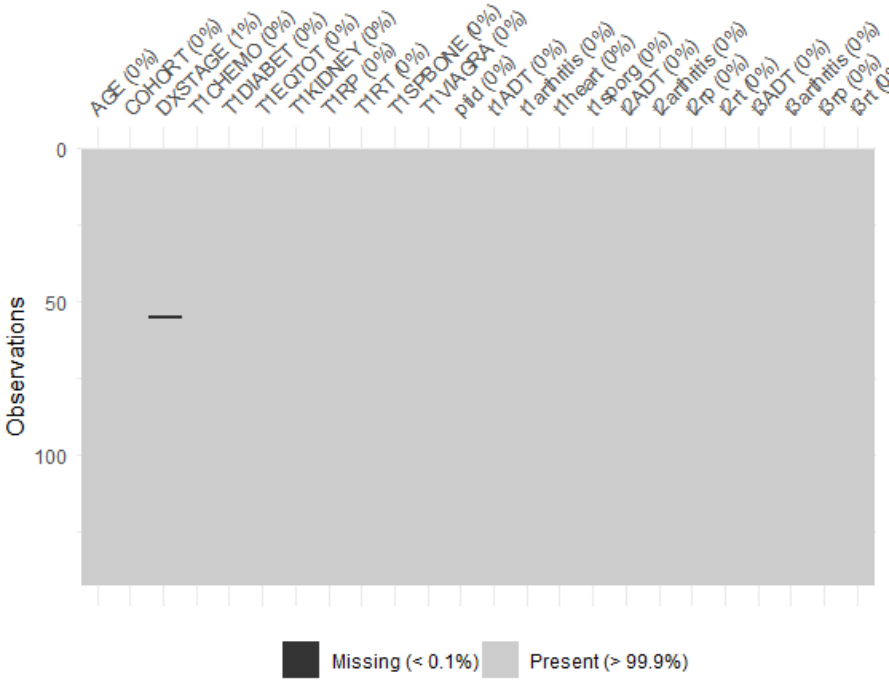
Introduction & Objective

- **Prostate Cancer:** Uncontrolled growth of cells in the prostate
  - Physicians utilize TNM staging system
    - ✓ "T": Tumor → size and extent
      - Classified from 1 to 4 (4 being most advanced)
- **Treatment Modalities:**
  - Radical Prostatectomy (RP)
  - Radiation Therapy (RT)
  - Hormone Therapy (ADT): Often used as secondary treatment following RP or RT
- **Health Utility (EQ-5D):** Measure of quality of life, capturing five dimensions
  - Ranges from 0 – 1 (1 being the best health state)
- **Objective:** Assess the impact of these treatments on EQ-5D health utility in prostate cancer patients over time



Data Overview and Cleaning

- Final dataset consisted **of 141 patients** from cohort A (mean: age 64.4y, ~0.8 EQ-5D) and 26 patient-related variables.
- Patient information was collected at three time points (T1, T2, T3).
- Missing data:
  - Clinically-supported imputation was done for diagnosis staging based on information in other variables



Analysis Approach

1. EQ-5D score is a continuous response variable; treatments (RP, RT, ADT) and patient history are categorical predictors

2. Categorical variables can be included as predictors in linear regression using dummy variables

3. Luckily, treatments are binary and take values 0 or 1 (0=no treatment; 1= received treatment)

4. Assumption of normality should hold true for response variable, EQ-5D.

5. Use Kruskal-Wallis test (a non-parametric test) to assess the significance of treatments on health utility

6. Realized test of normality that you will need to perform, after fitting your regression model, is that of the residuals

7. Use linear regression (adhering to assumptions) to check the direction & magnitude of effect of treatment

Results & Insights

1. Both tests indicate that treatments have no statistically significant impact on health utility at T1., which is expected since T1 represents the baseline (prior to treatment)
2. At T1 (baseline), arthritis was significant as pre-existing arthritis may affect patients' baseline health utility, potentially due to the burden of arthritis-related symptoms
3. Both tests showed that hormone therapy (ADT) secondary treatment has significant impact at T3, and this is because it may have long-term effects on health utility, potentially due to side effects
4. Kruskal Wallis showed that radical proctectomy (RP) has significant impact at T2, which may be expected as patients recover from the surgical procedure.
5. Radiation therapy (RT) does not show a significant impact in the analysis, but clinical evidence might provide further insights into its effects on health utility.

Supplementary

#1 Data Preparation & Cleaning

Data Overview and Cleaning

- Final dataset consisted of **141 patient observations from cohort A** (mean: age 64.4y, ~0.8 EQ-5D) and 26 patient-related variables.
- Patient information was collected at three time points (T1, T2, T3).
- Missing data was imputed based on clinical literature review.
- Imputation Criteria:

Bone Metastasis (T1SPBONE == 1):

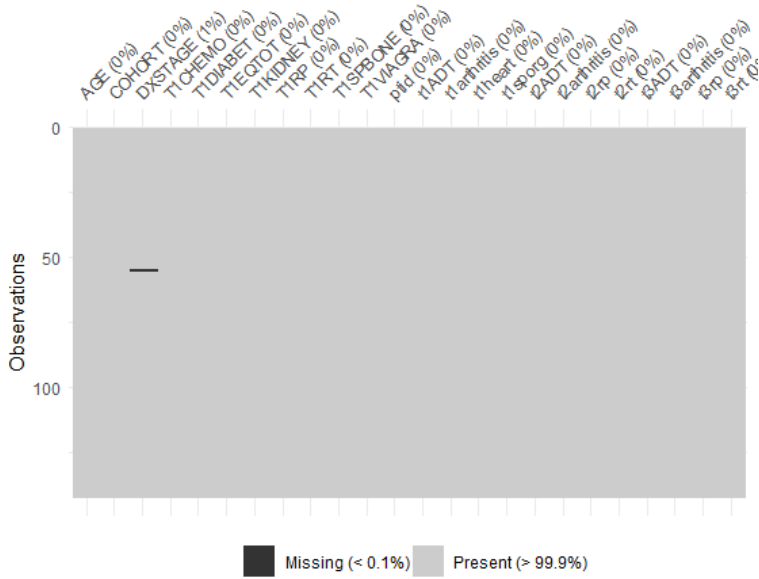
- Cases with bone metastasis were imputed as "T4".

Tumor Spread (T1SPORG == 1):

- Cases with tumor spreading to other organs were also imputed as "T4."

No Tumor Spread (T1SPORG == 0):

- No tumor spread cases but received treatment interventions (T1RP or T1RT) were imputed as "T2."
- If both T1RP and T1RT were not administered (encoded as 0), "T1" was imputed.



Data Preparation

0% missingness was shown when looking for Na's value using > is.na

Three Na's were encoded as character strings and not as the natural encoding of Na's in R

Emptiness was checked and 18 observations had empty entries

Replaced both character strings "na" and empty entries with NA encoded by R → 21 observations missing or empty

Replace "MO" with "M0" in the DXSTAGE column

→ Two observations (instead of 1) have T3BNXM0 because previously the MO was 0.

What to do with missing values?

Three approaches for dealing with missing stage data based on the literature:

Method	Pros & cons

1. Ad-hoc
• Complete case: omitting all cases with missing information and analysing them as a separate group
• Mean imputation: Replacing missing values with values imputed from the observed data (only continuous so will not work for dxstage)
• LOCF: Using a missing category indicator and replacing missing values with the last measured value (no observable pattern to perform LOCF)
	• Simple and quicky
	• Widely known to produce biased results
	  • However, if missing data occurs only in an outcome variable that is measured **once** in each individual → analyses not biased, provided that all variables associated with the outcome being missing can be included as covariates (under a MAR assumption).
	  • missing data in predictor variables do not cause bias in analyses of complete **cases if the reasons for the missing data are unrelated to the outcome**

2. Distributing all cases with unknown stage proportionally to the known stages	• Yields accurate population-based analyses when there is an equal distribution of tumor stages among cases with unknown T-stage and known T-stage. • In the absence of this balance, the results will exhibit bias. • Analyzing individual-level data is not feasible using this approach. • Should address missing tumor stage values using an appropriate statistical method (like approach 3) before calculating stage-specific incidence rates to avoid bias.
3. Multiple imputation	Simulation analysis to address missing tumor stage data. 1. Start with cancer registry data, one with few missing values and another with a high proportion of missing data. 2. Generate datasets with simulated missing stage information, drawing from cases with complete stage data. The analysis considers individual stage estimations, the distribution of cases across stages, and stage-specific survival curves after treatment.

Diagnosis Staging: Clinical

Stage	T	N	M
I	T1a, T1b, or T1c	N0	M0
	T2a	N0	M0
	Any T1 or T2a	N0	M0
IIA	T1a, T1b, or T1c	N0	M0
	T1a, T1b, or T1c	N0	M0
	T2a	N0	M0
	T2b	N0	M0
	T2b	N0	M0
IIB	T2c	N0	M0
	Any T1 or T2	N0	M0
	Any T1 or T2	N0	M0
III	T3a or T3b	N0	M0
IV	T4	N0	M0
	Any T (lymph nodes +)	N1	M0
	Any T	Any N	M1

- Based on the results of the urologist's physical examination of the patient's prostate: including a digital rectal exam (DRE)) and any other tests done prior to definitive treatment (i.e., surgery or radiation).
- **T1:** The tumor is not detectable during a digital rectal exam (DRE) or imaging. It may be found incidentally during surgery for another medical condition.
  - T1a: Discovered accidentally during surgery for benign prostatic hyperplasia (BPH), with cancer in less than 5% of removed tissue
  - T1b: Also found during BPH surgery, with cancer in more than 5% of removed tissue.
  - T1c: Detected through a needle biopsy due to elevated PSA levels.
- **T2:** The tumor is confined to the prostate, palpable during a DRE, and visible on imaging.
  - T2a: Limited to one side of the prostate.
  - T2b: Spread to more than one-half of one side of the prostate, but not both.
  - T2c: Invaded both sides of the prostate.
- **T3:** The tumor has grown outside the prostate and may have reached the seminal vesicles.
  - T3a: Outside the prostate but not in the seminal vesicles.
  - T3b: Spread to the seminal vesicles.
- **T4:** The tumor has spread to nearby tissues, such as the rectum, bladder, urethral sphincter, or pelvic wall.

Diagnosis Staging: Pathological

Stage	T	N	M
I	T1a, T1b, or T1c	N0	M0
	T2a	N0	M0
	Any T1 or T2a	N0	M0
IIA	T1a, T1b, or T1c	N0	M0
	T1a, T1b, or T1c	N0	M0
	T2a	N0	M0
	T2b	N0	M0
	T2b	N0	M0
IIB	T2c	N0	M0
	Any T1 or T2	N0	M0
	Any T1 or T2	N0	M0
III	T3a or T3b	N0	M0
IV	T4	N0	M0
	Any T (lymph nodes +)	N1	M0
	Any T	Any N	M1

- Pathological staging can be determined when a patient has surgery to remove a tumor. It combines the results of both the clinical staging with the surgical results.
- The pathologist uses the TNM Staging System to describe how far the prostate cancer has spread after reviewing the clinical information.
- This system describes the tumor (T), lymph node (N) and metastasis (M) to lymph nodes and/or bones or other organs.
- NX or MX: The regional lymph nodes and metastasis cannot be evaluated, respectively.
- N0 = No positive regional nodes.
- M0 = No distant metastasis.
- N1 = Metastases in regional node(s).
- M1 = Distant metastasis.
- –M1a = Nonregional lymph node(s).
- –M1b = Bone(s).
- –M1c = Other site(s) with or without bone disease.

What does the literature has to say about missing data in diagnosis staging? (1)

- Concerning melanoma and breast cancer, the federal cancer registries in Germany report 10-20% [5, 6] of missing staging data based on TNM staging system [4].
- What are the reasons for missing staging data?
  1. Tumour stage is often not known at the time of diagnosis; if the case is reported to the registry without additional notification, e.g. from the physician or pathologists, stage information is lost.
  2. Some cancer cases are only reported by a pathologist (after surgery). These notifications - in general - do not provide any information on lymph node status or metastasis (hence MX and NX)
  3. Missing data record are more prevalent among patients from racial and ethnic minority groups.[24,25,26]
  4. The records of patients with fewer comorbid conditions were also more frequently missing data, which may reflect less available documentation because of fewer medical visits.
  5. Patients with advanced-stage cancer → associated with the increased complexity of care → increased difficulty in documenting and abstracting all data elements.[27]

Based on literature, staging data can be missing at random, but not completely in random! In this case, analyses based on complete case may be biased (Sterne, J. et al.). Let's investigate!

Classification of the DXSTAGE missing data: Missing Not At Random (MNAR) or Missing At Random (MAR)?

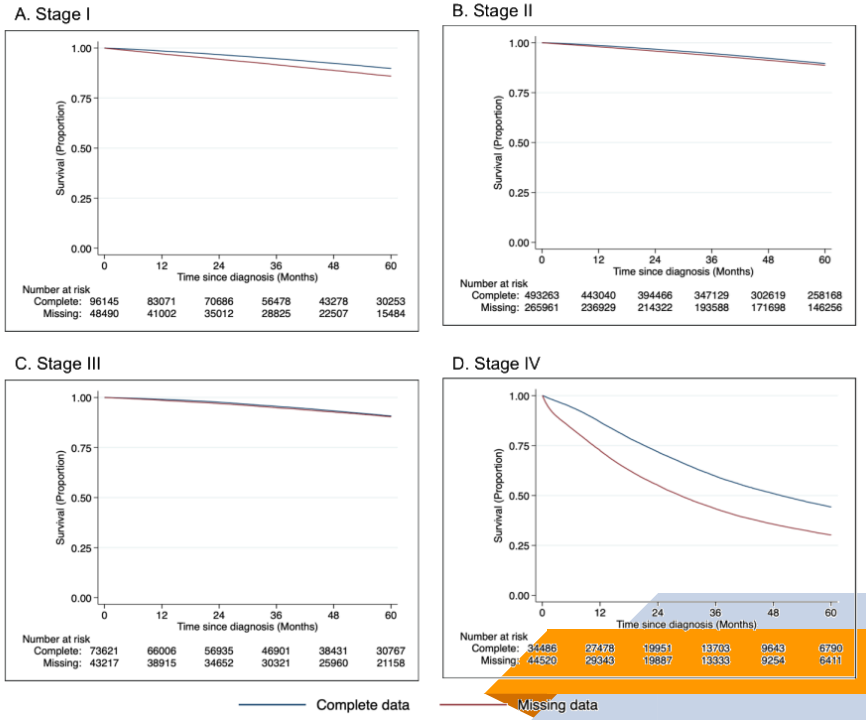
✓ Alternative hypothesis #1: The missing tumor stage information is *most likely* not at random.

- Based on literature, it is likely that there is a systematic difference between the missing values and the observed values in staging data attributed to:
    1. Source of reporting
    2. Clinical data collection practices
- For example, a study by Robinson, A. *et al.* (2023) on an Ontario cohort of 51,152 patients with NSCLC found that 11.2% (n=5,707) were unstaged, and there was evidence that stage data was not missing completely at random. Those without assigned stage were more likely than staged patients to be:
    1. Older
    2. Have a higher comorbidity index
    3. Have a lower socioeconomic class

Study 1: Missingness in prostate cancer study & its impact on survival by Yang, D. *et al.* 2021

- ✓ Participants: 1,158,635 patients with prostate cancer (mean [SD] age, 65.2 [9.0] years; 100% men) taken from abstracted medical records from the National Cancer Database who received cancer diagnoses from January 1, 2006, to December 31, 2015.
- ✓ Objective: To assess the prevalence of missing data and its association with overall survival among patients with cancer.
- ✓ Findings: The study's findings suggest substantial gaps in documentation and data capture via the medical record for patients with cancer.
- ✓ ***Among those with prostate cancer, 700 523 patients (60.5%) had missing data, and 458 112 patients (39.5%) had complete data; 2-year overall survival was 91.7% for patients with missing data and 97.0% for patients without missing data (P < .001). Patients with missing data had worse overall survival than those with complete data.***

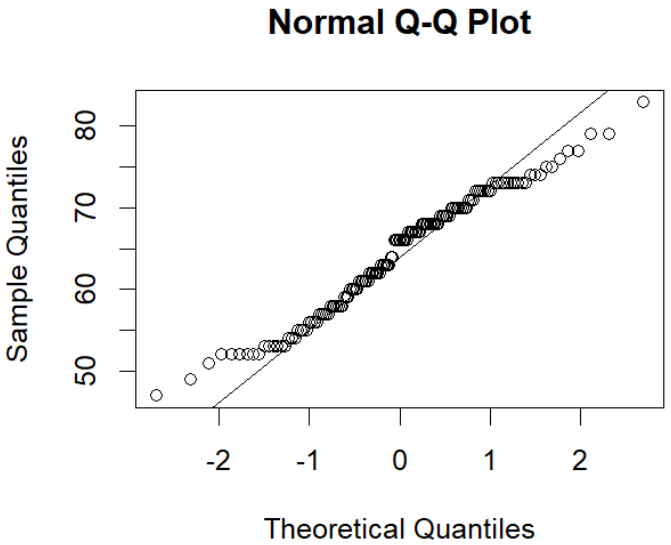
eFigure 3. Prostate Cancer Overall Survival by Whether Data Are Missing in Variables of Interest and by Cancer Stage



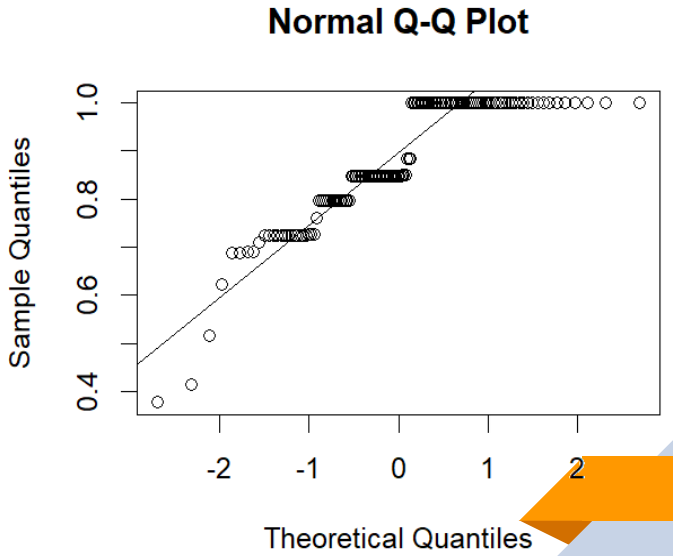
Investigate potential differences between patients with missing DXSTAGE data and complete data (Part 1)

- ✓ Conduct normality tests (Q-Q Plot & Saphiro-Wilk) for continuous variables to choose the proper statistical tests
- ✓ Q-q plot shows that age could be considered normal
- ✓ Saphiro-Wilk results shows both age and T1EQTOT are not normally distributed as p-value is lower than 0.05

Age



T1EQTOT (health utility)



Investigate potential differences between patients with missing DXSTAGE data and complete data (Part 2)

- ✓ Based on the assumption that age and T1EQTOT do not follow normality, Wilcoxon rank-sum test is more appropriate.
- ✓ Expectation Those who are older have more missingness based on the literature.
- ✓ Null hypothesis (H0): There is no significant difference between the missing DXSTAGE and complete group.
- ✓ Alternative hypothesis (Ha): There is a significant difference between the two groups, which could suggest that missing data is MNAR.

Age

Based on the p-value (0.2045) which is greater than the assumed significance level of 0.05, there is no strong evidence to suggest a significant difference in the *distribution of ages* between patients with missing DXSTAGE data and those with complete data

T1EQTOT (health utility)

Based on the p-value (0.337), there is no strong evidence to suggest a significant difference in the distribution of "T1EQTOT" values between patients with missing DXSTAGE data and those with complete data

Investigate potential differences between patients with missing DXSTAGE data and complete data (Part 3)

- ✓ Compare the presence of comorbid conditions (e.g., diabetes, kidney problems, arthritis, heart problems) between two groups to see if those with more comorbid conditions are more likely to have missing staging data.
- ✓ Method: Comorbid conditions (such as diabetes, kidney problems, arthritis, heart problems) are recoded to create new binary variables where values of 1 and 2 are combined to represent "presence" (coded as 1), while other values (0=no, 3 = not sure) indicate "absence" (coded as 0).
- ✓ The proportions of individuals with each comorbid condition are calculated for both groups.
- ✓ Cons: Doesn't assess the statistical significance of these differences

Comorbid Condition	Proportion Missing	Proportion Complete
T1DIABET	0.047619	0.049587
T1KIDNEY	0.095238	0.041322
t1arthritis	0	0.033058
t1heart	0.190476	0.198347
t2arthritis	0	0.016529
t3arthritis	0	0.057851

- *It is hard to distinguish between MAR and MNAR based on given observed data.*
- *Let’s investigate the approaches generally used in this case*

Study 2: Imputation of missing prostate cancer stage based on clinical assumptions by Parry, M. *et al.*

- ✓ Participants: 139,807 male participants diagnosed with prostate cancer in the English cancer registry between 2010 and 2013.
- ✓ Objective: Perform imputation based on clinical rather than statistical assumptions. Test these clinical assumptions by comparing 4-year survival in men with the same recorded and imputed cancer stage. Multi-variable Cox regression was used to test the validity of the clinical assumptions.

1. Men with recorded N-stage but missing M-stage have no distant metastases (M0)
2. Low/intermediate-risk men with missing N- and/or M-stage have no nodal disease (N0) or metastases
3. High-risk men with missing M-stage have no metastases.

- ✓ Findings: Overall survival of patients with available N- or M-stage were similar to those with imputed results based on three of the four clinical assumptions, thus providing evidence for their validity.

Selected approach: Clinical-Based and Data Driven Imputation

- Single imputation based on clinical data.
  - Analyze other variables & check if you can deduce DXSTAGE from them
  - Gleason score would have been very useful
    - ✓ Describes the spread and growth of the tumor accurately based on a score.
  - After applying the imputation criteria discussed above, all missing values were filled except one observation, which I proceeded to omit.

Table. Omitted observation

AGE	COHORT	DXSTAGE	T1CHEMO	T1DIABET	T1EQTOT	T1KIDNEY	T1RP	T1RT	T1SPBONE	T1VIAGRA	ptid	t1ADT	t1arthritis	t1heart	t1sporg	t2ADT	t2arthritis	t2rp	t2rt	t3ADT	t3arthritis	t3rp	t3rt
61	A	NA	0	0	1	0	0	0	2	0	2399095	1	0	1	2	1	0	1	0	1	0	1	0

Selected approach: Clinical-Based and Data Driven Imputation

- Before imputing DXSTAGE (only extracting the first two values “T#”, which correspond to tumor diagnosis):

T1	T2	T3	T4
40	64	16	1

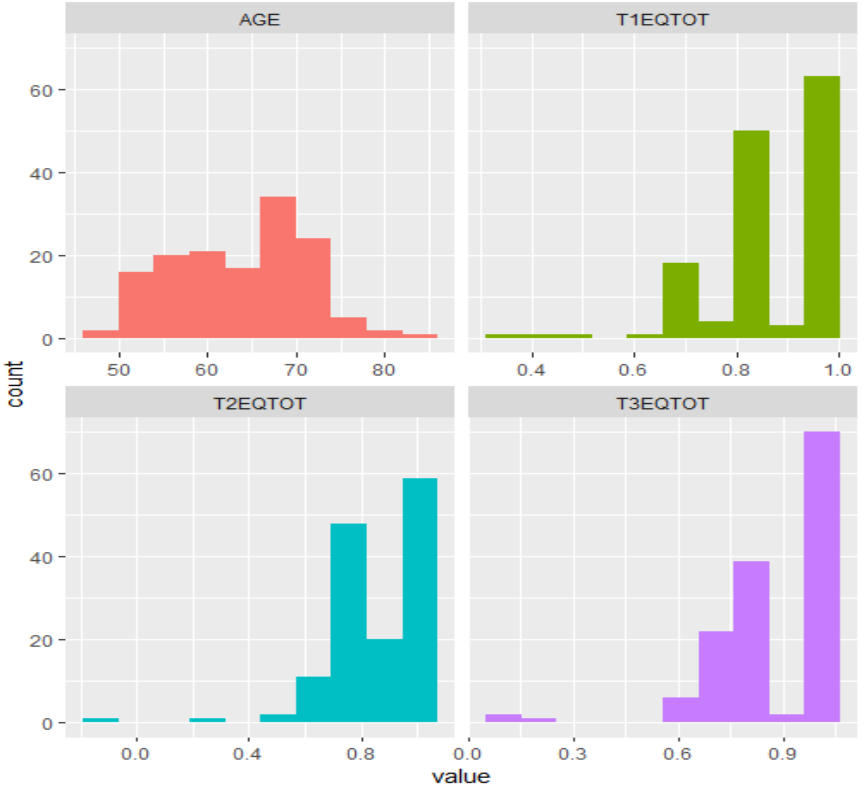
- After imputation:

T1	T2	T3	T4
59	65	16	1

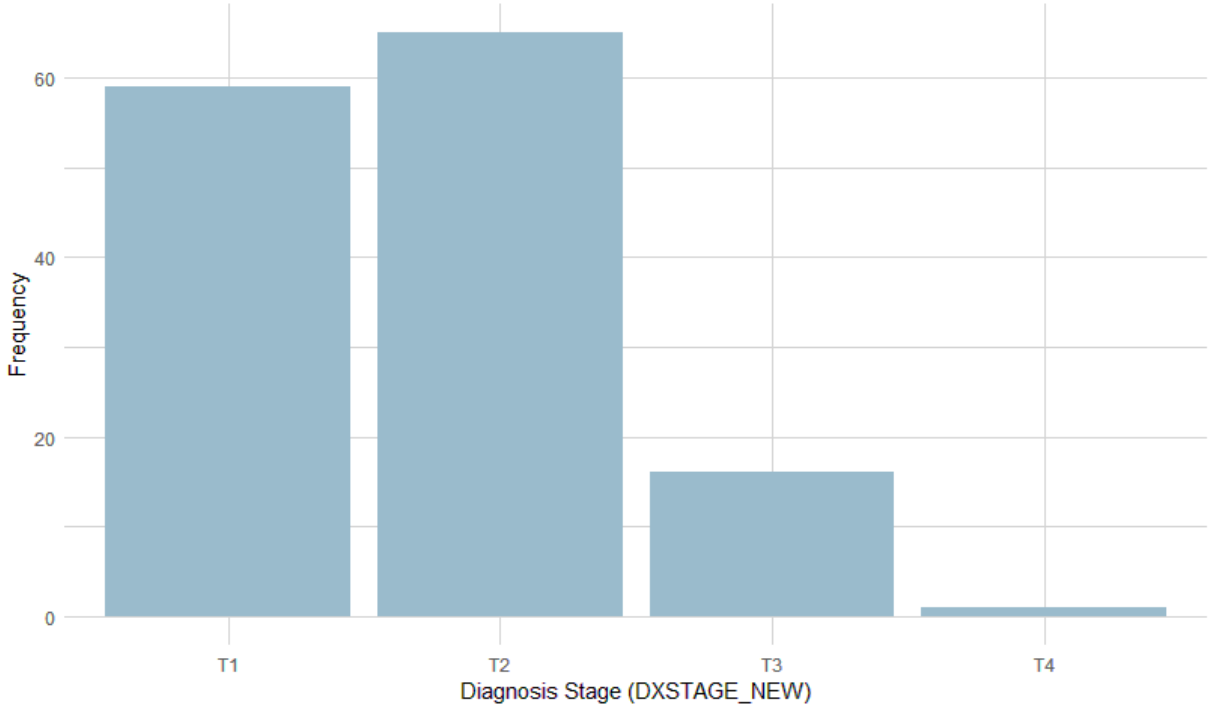
#2 Descriptive Stats

Visualization of the Patient Variables: Continuous

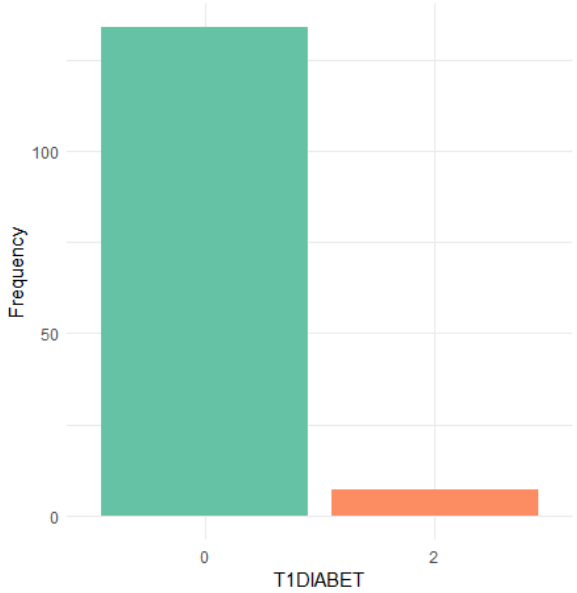
Variable	Mean	Sd	Q1	Median	Q3
Age	64.4	7.53	58	66	70
T1EQTOT	0.879	0.127	0.796	0.848	1
T2EQTOT	0.855	0.159	0.359	0.850	1
T3EQTOT	0.868	0.155	0.130	0.883	1

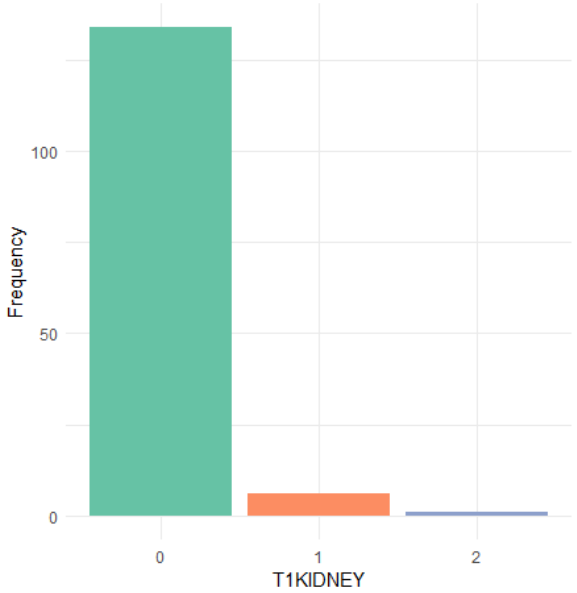


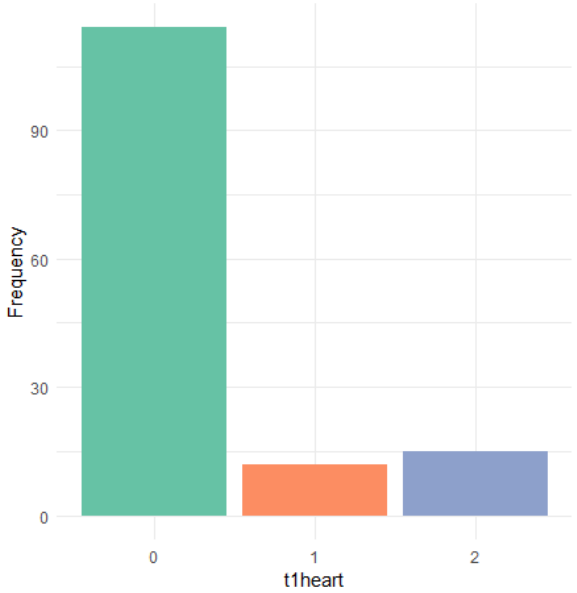
Visualization of the Diagnosis Staging Based on Tumor Only from TNM



Visualization of the Patient Medical History at T1

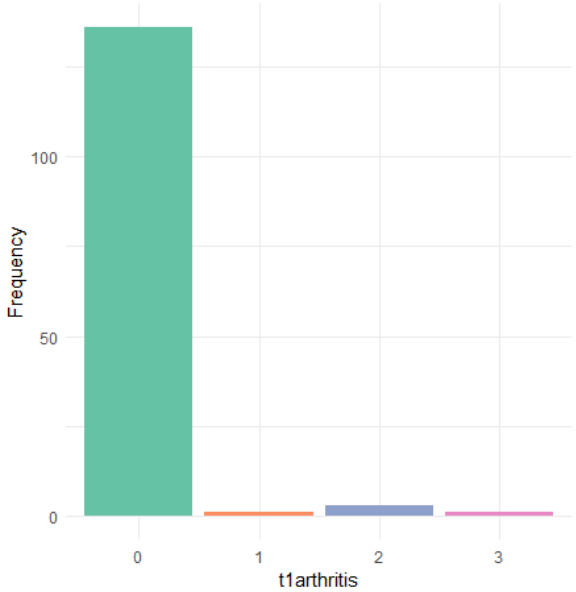


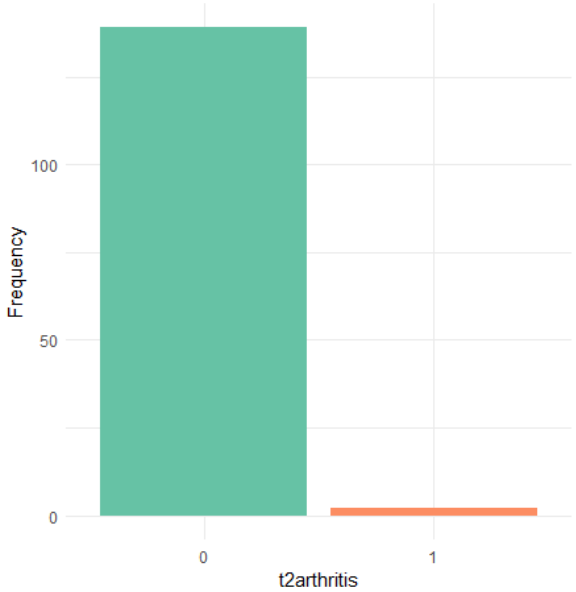


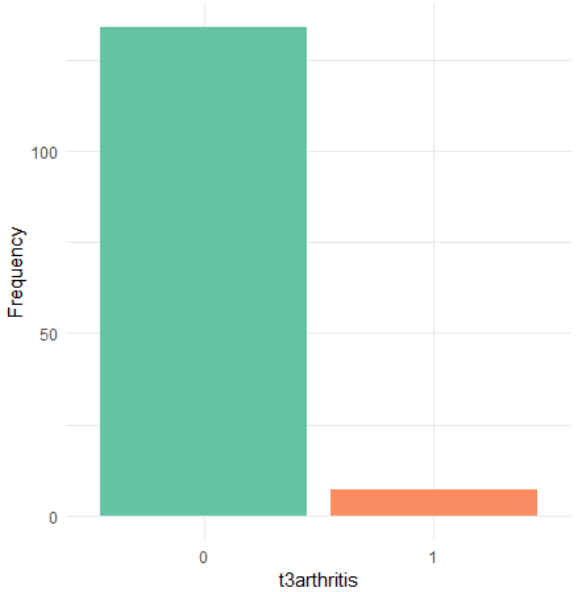


Legend: 0=no; 1=yes (past, not now); 2=Yes (now); 3=not sure

Visualization of the Disabling Arthritis at T, T2, T3







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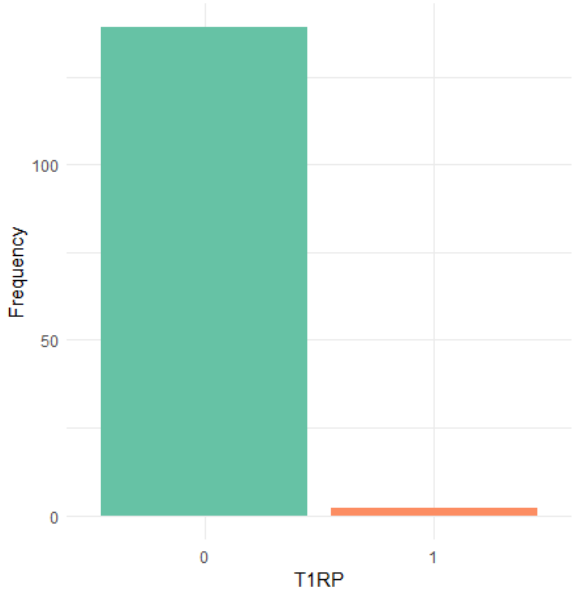
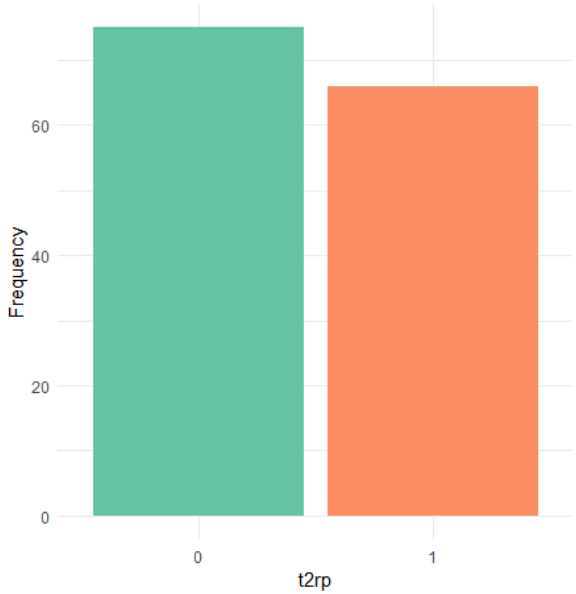
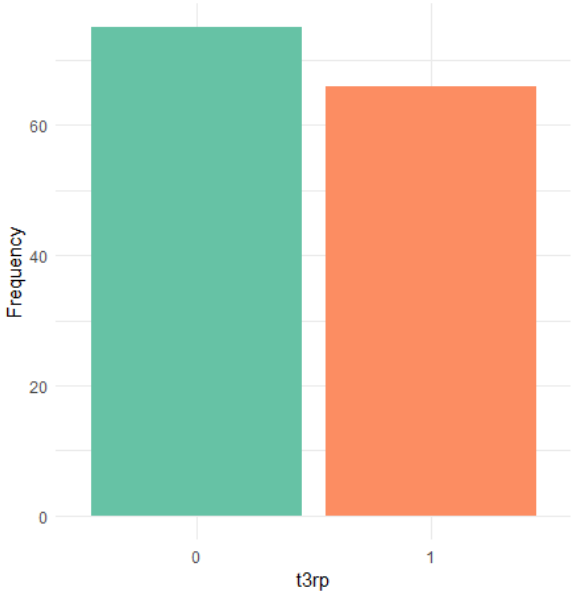
Visualization of the Radical Proctectomy Treatment at T1, T2, T3







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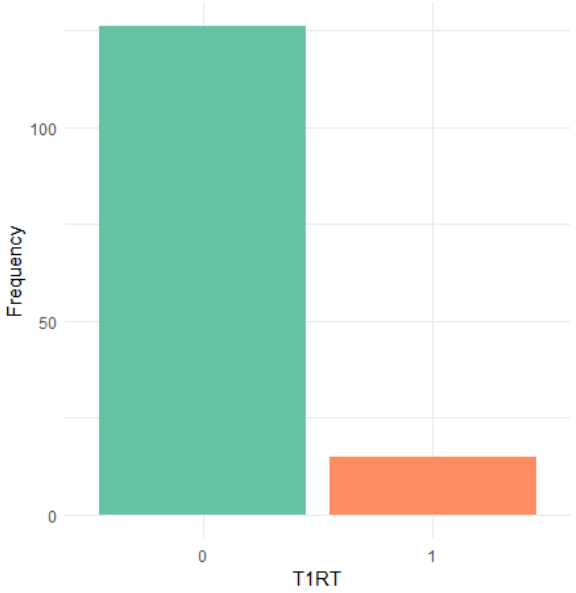
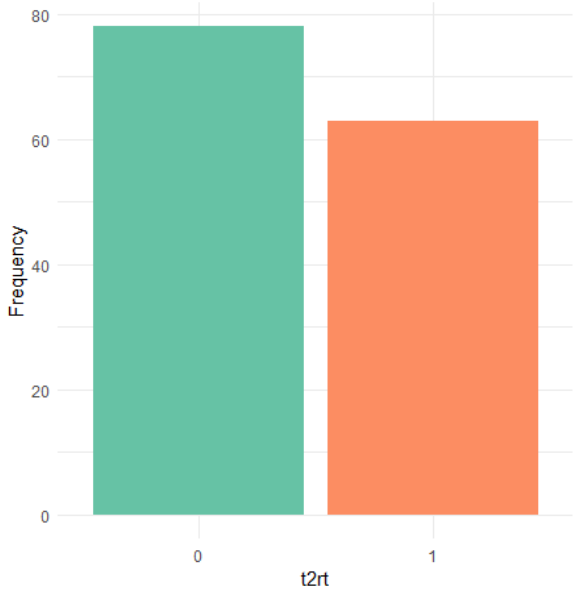
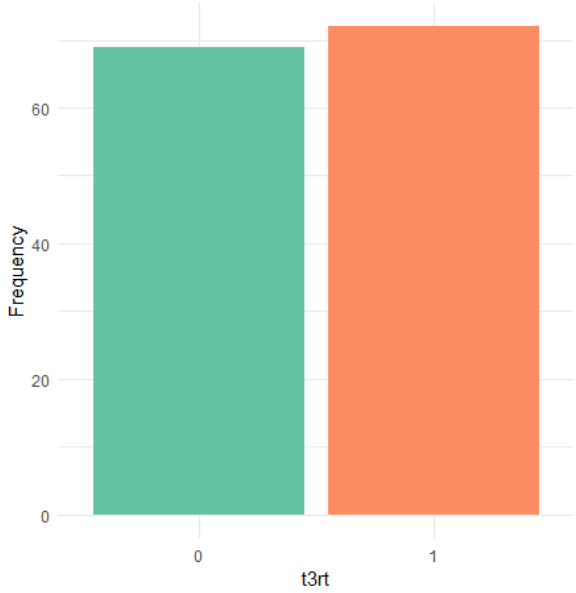
Visualization of the Radiation Therapy Treatment at T1, T2, T3







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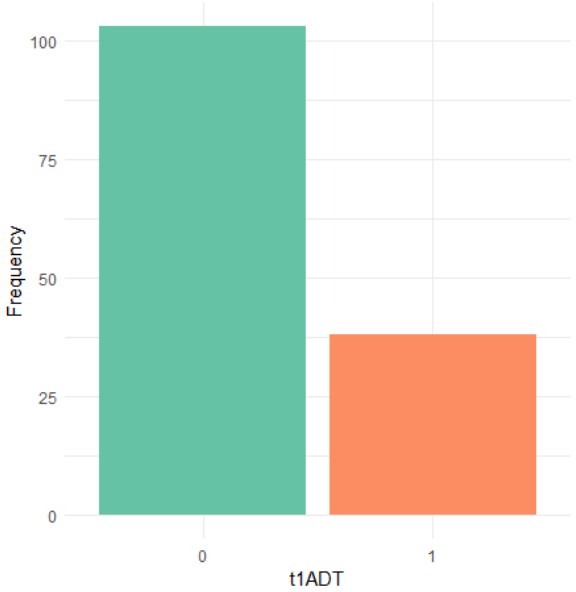
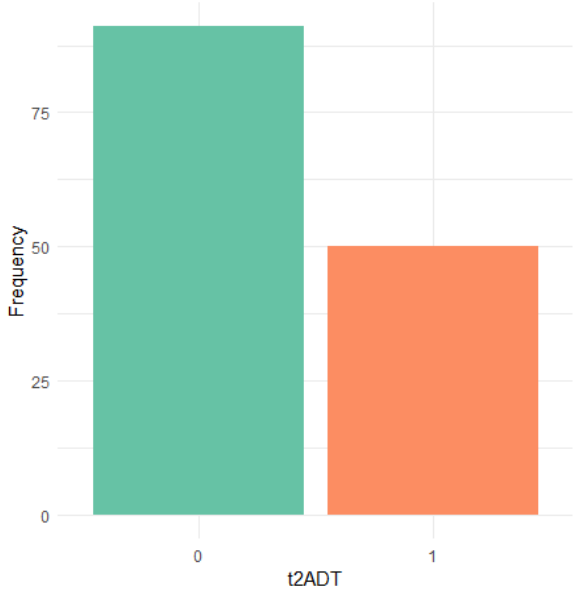
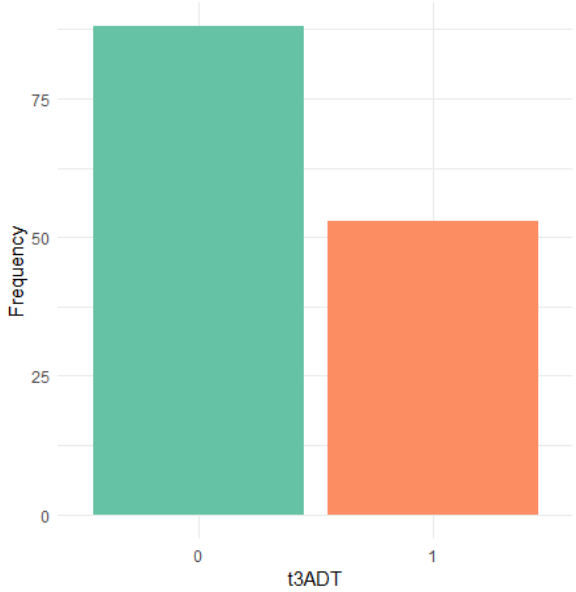
Visualization of the Hormone Treatment at T1, T2, T3







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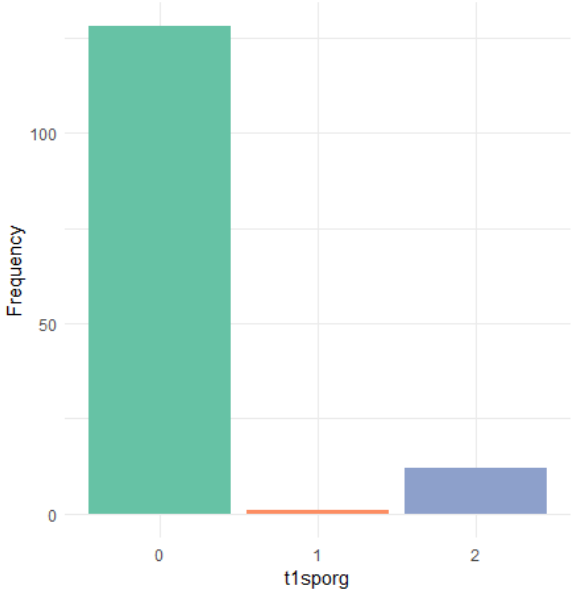
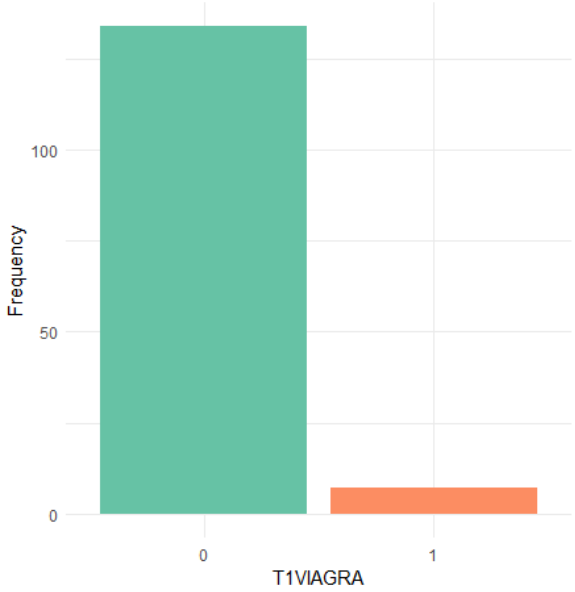
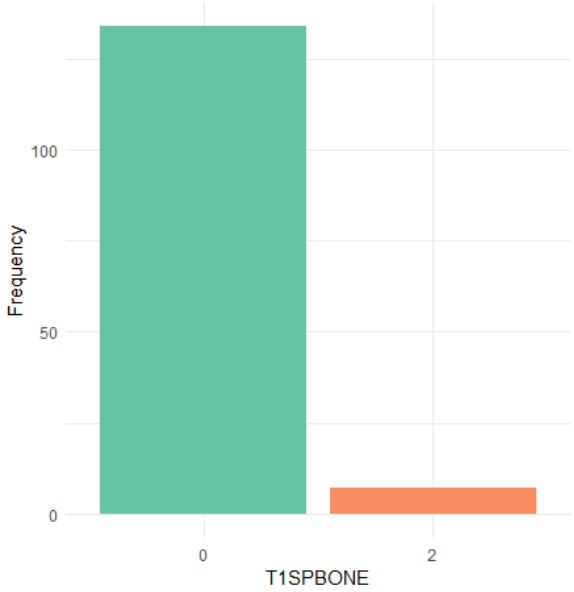
Visualization Remaining Categorical Variables







#3 Analysis

Limitations of approaches used

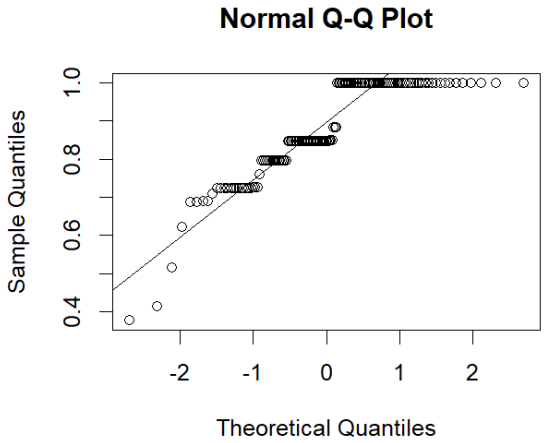
- **Kruskal Wallis**
  - Operates on a **pairwise basis,** comparing one group to all others (e.g. received treatment vs not)
    - ✓ Tedious if you have multiple predictors as you need to perform it for each predictor separately
  - **Can only know if there is a significant different between groups & response variable,** *but we don't know which pairings of groups are* ***different****.*
  - Nonparametric tests require large sample sizes (our sample size is 141, small)
- **Linear regression**
  - Results show that homoscedasticity may be at risk
    - ✓ Violating this assumption will not alter the regression line (i.e. relationship if negative or positive between the predictors and EQ-5d is still accurately represented).
    - ✓ Standard errors, however, will be upwardly biased, while hypothesis tests and the standardized slope coefficients will be downwardly biased

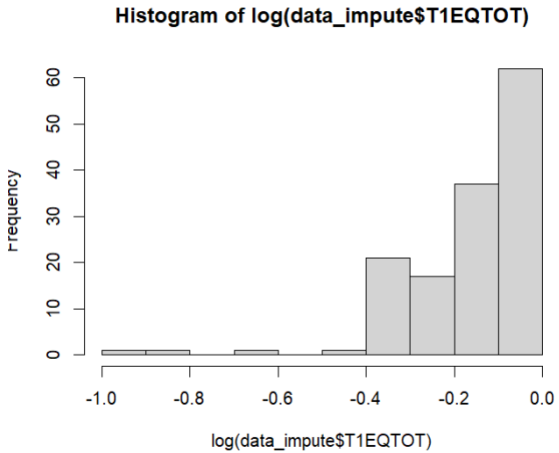
Data considerations for Kruskal-Wallis Test

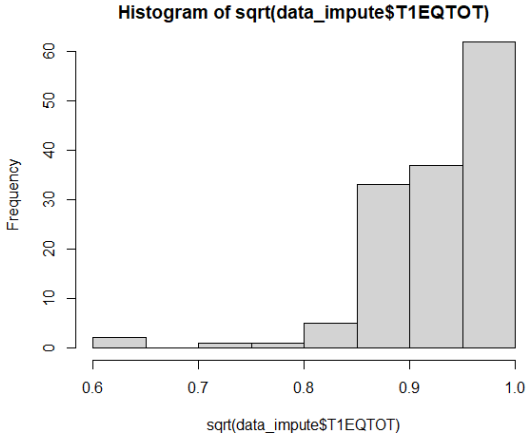
- **The independent variable should consist of two or more categorical groups. Typically, a Kruskal-Wallis H test is used for three or more categorical, independent groups, but it can be used for just two groups (i.e., a Mann-Whitney U test is more commonly used for two groups).**
  - In our case, treatment groups (0: not treated; 1: received treatment)
- **The response variable should be continuous (health utility in our case)**
- **The sample data do not need to be normally distributed**
  - *If the distributions of the groups are normally distributed, consider using One-Way ANOVA because it has more power.*
- **The sample size should be less than 15 or 20 observations or your process should be better represented by the median**
  - *Nonparametric tests tend to have less power than parametric tests. Also, parametric tests can perform well with nonnormal data given a sufficiently large sample size. Consider using a parametric test even with nonnormal data unless your sample size is very small or if the median is more meaningful for your study.*
- **The sample size for each group should be at least five** *(or else p-value is inaccurate)*
- **Each observation should be independent from all other observations**

To use linear regression, we should check if EQTOT (health utility) is normally distributed.

- Unfortunately, based on the Q-Q plot and Saphiro-wilk results (p-value less than 0.05), T1EQTOT is not normally distributed
- Solution? Transformation
- Transformation did not solve the issue.



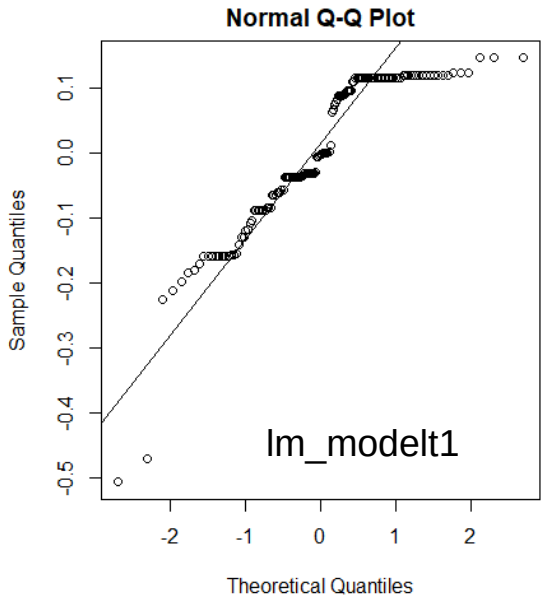


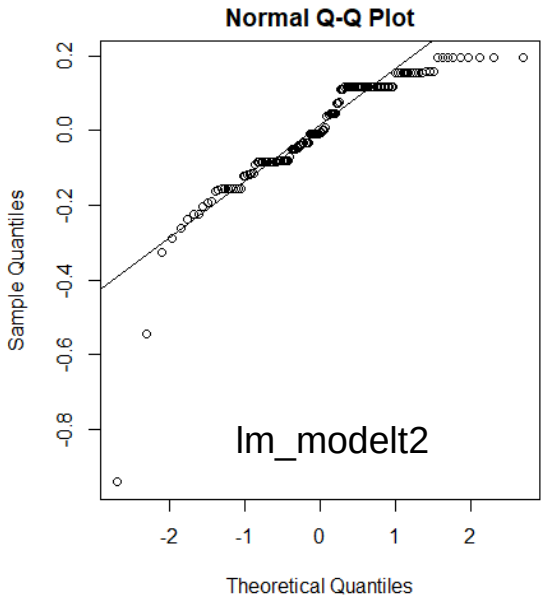


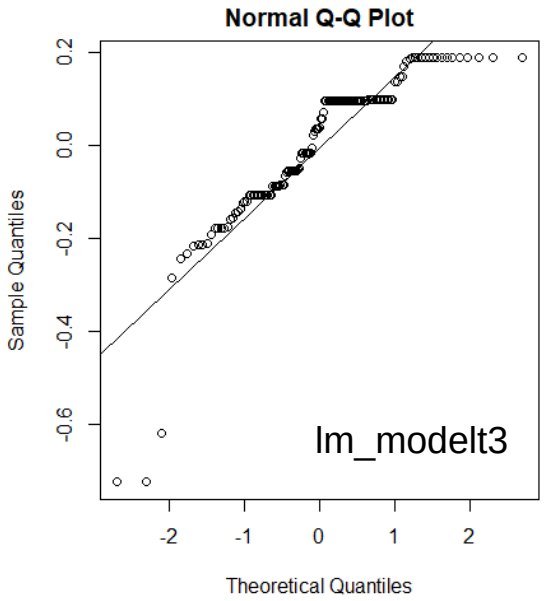
Assumptions for linear regression: Linearity of variables or residuals?

- Checking the normality of residuals is a standard practice in linear regression
  - We are indirectly assessing the normality assumption for the response variable (in this case, health utility) because residuals are the differences between the observed values (the response variable) and the predicted values (the values predicted by the linear regression model)
- However, you should take a look at the distribution of your “Y” and of all your “X”:
  - The presence of highly skewed variables can, more likely, influence the distribution of residuals making them, in turn, non-normal;
  - the presence of variables with very large tails of outliers could require a complex analysis of leverage (i.e. how much these outliers impact on the estimate of the regression coefficients).

Assumptions for linear regression: Normality of residuals

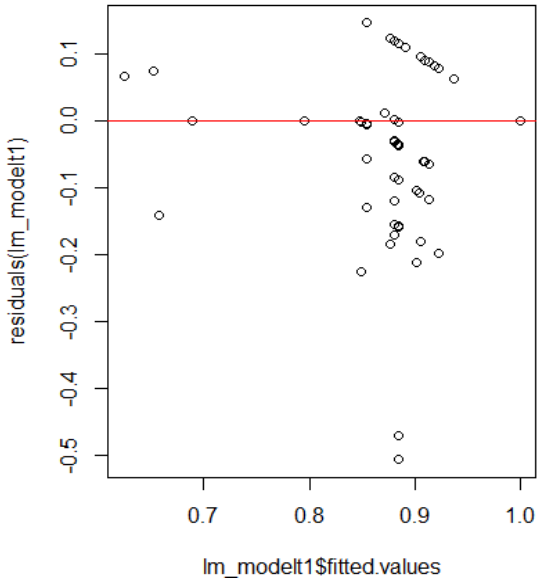


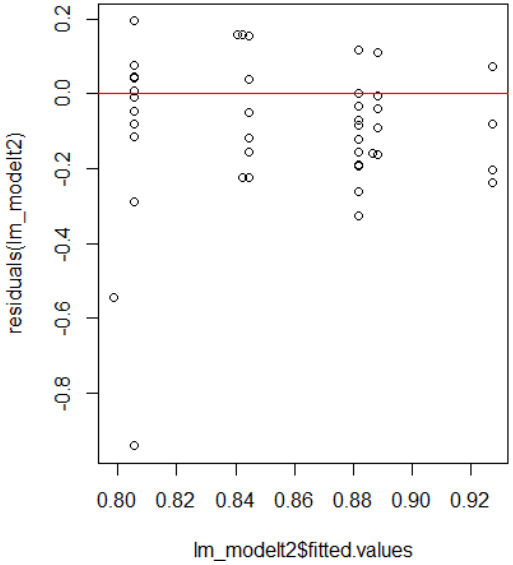


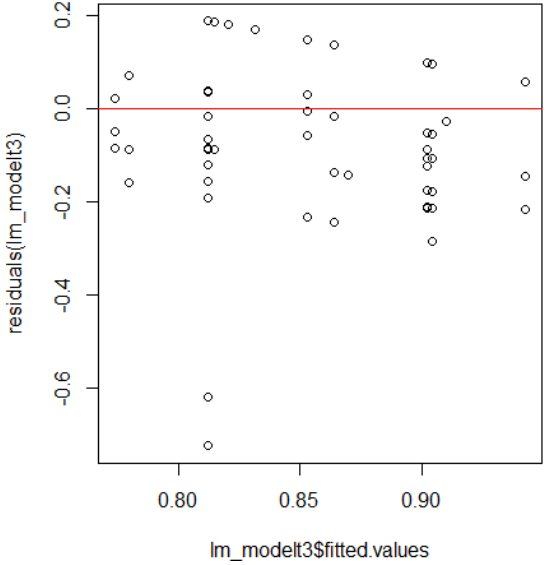


- ✓ if the points closely follow a straight line or appear bell-shaped, normality is assumed.

Assumptions for linear regression: Linearity & homoscedasticity using residual plots

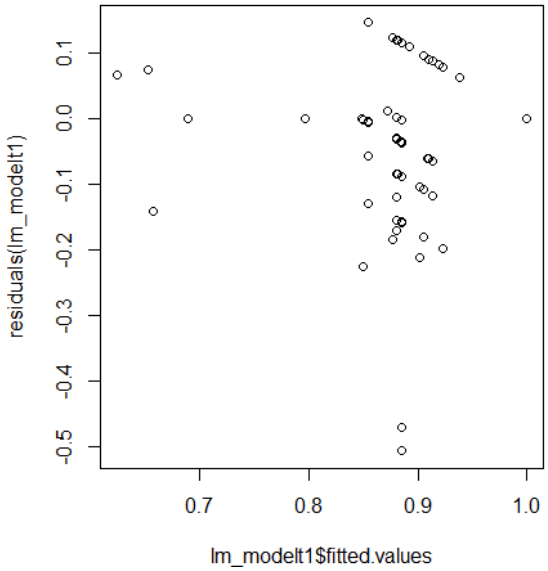


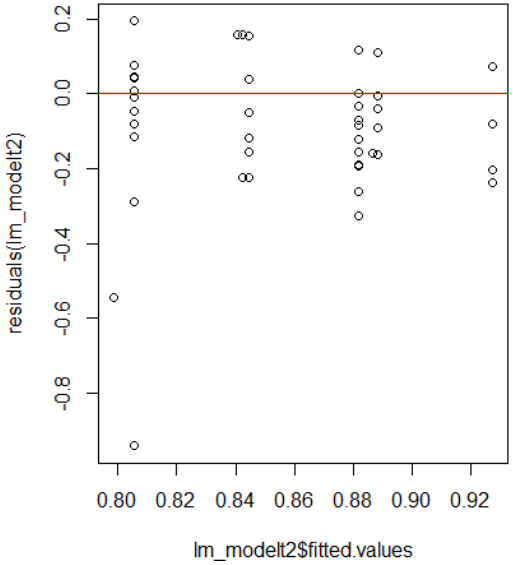


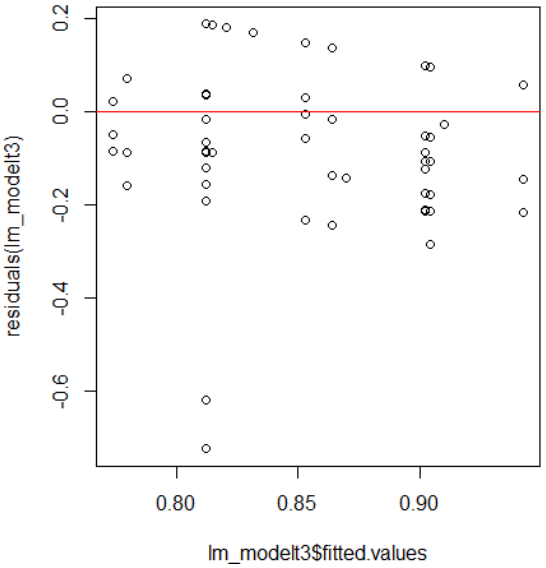


- ✓ The plot should show a random pattern, indicating a good fit for a linear model.
- ✓ If the spread of residuals is roughly constant as fitted values increase, homoscedasticity is assumed.

Assumptions for linear regression: Homoscedasticity using plot of residuals against fitted values







If the spread of residuals is roughly constant as fitted values increase, homoscedasticity is assumed.

Results & Insights

Test (sig. level 0.05)	T1 (Baseline)	T2 (3 months)	T3 (1 year)
Kurskal Wallis	Treatments do not have a statistically significant impact on health utility.	RP has a statistically significant impact on health utility, but RT and ADT do not.	ADT has a statistically significant impact on health utility, but RP and RT do not.
Linear Regression	Only disabling arthritis is statistically significant & associated with lower EQ-5D scores.	No result was statistically significant.	Only hormone therapy (ADT) is statistically significant & associated with lower EQ-5D scores.

1. Both tests indicate that treatments have no statistically significant impact on health utility at T1., which is expected since T1 represents the baseline (prior to treatment)
2. At T1, arthritis was significant as pre-existing arthritis may affect patients' baseline health utility, potentially due to the burden of arthritis-related symptoms
3. Hormone therapy (ADT) secondary treatment may have long-term effects on health utility, as seen at T3, potentially due to side effects
4. Radical prostatectomy (RP) has a shorter-term impact, as seen at T2, which may be expected as patients recover from the surgical procedure.
5. Radiation therapy (RT) does not show a significant impact in the analysis, but clinical evidence might provide further insights into its effects on health utility.

R output

Kruskal-Wallis: Treatments & Health Utility at T1

1. Kruskal-Wallis test for T1EQTOT by T1RP:
    1. Kruskal-Wallis chi-squared = 0.22779
    2. df (degrees of freedom) = 1
    3. p-value = 0.6332
    4. Interpretation: The p-value of 0.6332 is greater than the typical significance level of 0.05. This suggests that there is no statistically significant difference in EQ-5D utility scores among the different levels of T1RP at the baseline (T1). In other words, T1RP does not seem to have a significant impact on health utility at this time point.
2. Kruskal-Wallis test for T1EQTOT by T1RT:
    1. Kruskal-Wallis chi-squared = 0.0010037
    2. df = 1
    3. p-value = 0.9747
    4. Interpretation: The p-value of 0.9747 is much greater than 0.05. This indicates that there is no statistically significant difference in EQ-5D utility scores among the different levels of T1RT at the baseline (T1). T1RT also does not appear to have a significant impact on health utility at this time point.
3. Kruskal-Wallis test for T1EQTOT by t1ADT:
    1. Kruskal-Wallis chi-squared = 0.0015318
    2. df = 1
    3. p-value = 0.9688
    4. Interpretation: Similar to the previous tests, the p-value of 0.9688 is greater than 0.05. This indicates that there is no statistically significant difference in EQ-5D utility scores among the different levels of t1ADT at the baseline (T1). t1ADT also does not seem to have a significant impact on health utility at this time point.

Kruskal-Wallis: Treatments & Arthrites at T1

- Kruskal-Wallis rank sum test
- data: T1EQTOT by t1arthritis
- Kruskal-Wallis chi-squared = 8.3179, df = 3,
- p-value = 0.03988

Kruskal-Wallis: Treatments & Health Utility at T2

1. Kruskal-Wallis test for T2EQTOT by t2rp (Radiation Therapy):
    1. Chi-squared = 3.0032
    2. Degrees of freedom (df) = 1
    3. P-value = 0.0831 Interpretation: There is no statistically significant difference in health utility scores based on the type of radiation therapy at T2.
2. Kruskal-Wallis test for T2EQTOT by t2rt (Radical Prostatectomy):
    1. Chi-squared = 4.2649
    2. Degrees of freedom (df) = 1
    3. P-value = 0.03891 Interpretation: There is a statistically significant difference in health utility scores based on the type of radical prostatectomy at T2. The p-value suggests that the difference is significant.
3. Kruskal-Wallis test for T2EQTOT by t2ADT (Hormone Therapy):
    1. Chi-squared = 2.5711
    2. Degrees of freedom (df) = 1
    3. P-value = 0.1088 Interpretation: There is no statistically significant difference in health utility scores based on hormone therapy at T2.

Kruskal-Wallis: Treatments & Health Utility at T3

1. Kruskal-Wallis test for T3EQTOT by t3rp:
    1. Kruskal-Wallis chi-squared = 0.86958
    2. df (degrees of freedom) = 1
    3. p-value = 0.3511
    4. Interpretation: The p-value of 0.3511 is greater than the typical significance level of 0.05. This suggests that there is no statistically significant difference in EQ-5D utility scores at time point T3 among the different levels of t3rp. In other words, t3rp does not seem to have a significant impact on health utility at this time point.
2. Kruskal-Wallis test for T3EQTOT by t3rt:
    1. Kruskal-Wallis chi-squared = 2.5172
    2. df = 1
    3. p-value = 0.1126
    4. Interpretation: The p-value of 0.1126 is slightly above the typical significance level of 0.05. This indicates that there is no strong evidence of a statistically significant difference in EQ-5D utility scores at time point T3 among the different levels of t3rt. However, the p-value is relatively close to 0.05, suggesting a borderline result.
3. Kruskal-Wallis test for T3EQTOT by t3ADT:
    1. Kruskal-Wallis chi-squared = 6.4701
    2. df = 1
    3. p-value = 0.01097
    4. Interpretation: The p-value of 0.01097 is less than the typical significance level of 0.05, indicating a statistically significant difference in EQ-5D utility scores at time point T3 among the different levels of t3ADT. This suggests that t3ADT has a significant impact on health utility at this time point.

Linear regression: Treatments & Health Utility at T1 (1)

- **Intercept (Intercept)**: The estimated EQ5D utility score at T1 when all other variables are 0. It's 0.885107.
- **T1RP1**: The coefficient for radical prostatectomy (T1RP1) is -0.196107, indicating that, on average, patients who had a radical prostatectomy have a lower EQ5D score compared to those who didn't. However, this difference is not statistically significant ($p = 0.12314 > 0.05$).
- **T1RT1**: The coefficient for radiation therapy (T1RT1) is -0.003992, suggesting that patients who had radiation therapy have a slightly lower EQ5D score at T1. However, this difference is not statistically significant ($p = 0.91215 > 0.05$).
- **t1ADT1**: The coefficient for hormone therapy (t1ADT1) is -0.004323, indicating that hormone therapy is associated with a slightly lower EQ5D score at T1, but this difference is not statistically significant ($p = 0.86541 > 0.05$).
- **T1DIABET2**: The coefficient for having diabetes (T1DIABET2) is 0.037717, showing that patients with diabetes have a slightly higher EQ5D score at T1. However, this difference is not statistically significant ($p = 0.47137 > 0.05$).
- **t1arthritis1, t1arthritis2, t1arthritis3**: These variables represent different levels of arthritis. Only t1arthritis2 has a significant negative impact on EQ5D scores ($p = 0.00083$), indicating that patients with current arthritis have lower EQ5D scores at T1.

Linear regression: Treatments & Health Utility at T2

- **t1heart2**: Having heart problems (t1heart2) has a negative, though not statistically significant, impact on EQ5D scores at T1 (p = 0.39107).
- **t1sporg2**: The coefficient for tumor spread to other organs (t1sporg2) is 0.028231, suggesting that patients with tumor spread to other organs have a slightly higher EQ5D score at T1, but this difference is not statistically significant (p = 0.46851 > 0.05).
- T1VIAGRA1: the coefficient estimate is -0.002060, with a standard error of 0.054980. The t-value is -0.037, and the p-value is 0.970178. This suggests that the variable T1VIAGRA1 is not statistically significant in explaining the variation in health utility (T1EQTOT) at T1.
- T1SPBONE2: the coefficient estimate is 0.032469, with a standard error of 0.055632. The t-value is 0.584, and the p-value is 0.560510. Similarly, this indicates that the variable T1SPBONE2 is not statistically significant in explaining the variation in health utility at T1.
- Diagnosis stages (DXSTAGE_NEWT2, DXSTAGE_NEWT3, DXSTAGE_NEWT4) do not seem to have a significant impact either, except for DXSTAGE_NEWT3, which is borderline.
  - DXSTAGE_NEWT3 has a p-value of 0.0659
  - Beta coeff: -0.074408

Linear regression: Treatments & Health Utility at T2

- **Intercept (Intercept)**: The estimated EQ5D utility score at T2 when all other variables are 0 is 0.92751.
- **t2rp1**: Having had a radical prostatectomy (t2rp1) does not have a significant effect on EQ5D scores at T2 (p = 0.3437).
- **t2rt1**: Receiving radiation therapy (t2rt1) shows a borderline effect on EQ5D scores at T2 (p = 0.0635).
- **t2ADT1**: Taking any type of hormone therapy (t2ADT1) does not significantly affect EQ5D scores at T2 (p = 0.2676).
- **t2arthritis1**: Having arthritis (t2arthritis1) does not have a significant impact on EQ5D scores at T2 (p = 0.7182).

```
Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)   0.92751    0.04577  20.263   <2e-16 ***
t2rp1        -0.04585    0.04825  -0.950   0.3437
t2rt1        -0.08302    0.04437  -1.871   0.0635 .
t2ADT1       -0.03910    0.03512  -1.113   0.2676
t2arthritis1  0.04194    0.11598   0.362   0.7182
```

Linear regression: Treatments & Health Utility at T3

- **Intercept (Intercept)**: The estimated EQ5D utility score at T3 when all other variables are 0 is 0.94248.
- **t3rp1**: Having had a radical prostatectomy (t3rp1) does not have a significant effect on EQ5D scores at T3 (p = 0.3613).
- **t3rt1**: Receiving radiation therapy (t3rt1) does not significantly affect EQ5D scores at T3 (p = 0.2978).
- **t3ADT1**: Taking any type of hormone therapy (t3ADT1) has a significant negative effect on EQ5D scores at T3 (p = 0.0117). Patients who received hormone therapy tend to have lower EQ5D scores at T3.
- **t3arthritis1**: Having arthritis (t3arthritis1) does not have a significant impact on EQ5D scores at T3 (p = 0.6119).

```
Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)   0.94248    0.04155  22.683   <2e-16 ***
t3rp1        -0.03825    0.04175  -0.916   0.3613
t3rt1        -0.04060    0.03884  -1.045   0.2978
t3ADT1       -0.08967    0.03507  -2.557   0.0117 *
t3arthritis1 -0.03235    0.06361  -0.509   0.6119
```

Classification of the DXSTAGE missing data: Missing Not At Random (MNAR) or Missing At Random (MAR)?

- ✓ Alternative hypothesis #2: The missing data in diagnosis staging could at random. If there is a significant association between DXSTAGE and other variables, then the missingness could be MAR.
- `anova_t1eqtot <- aov(T1EQTOT ~ DXSTAGE, data = data_categ)`
- `summary(anova_t1eqtot)`

	Df	Sum Sq	Sum Sq	F value	Pr(>F)
DXSTAGE	33	0.5088	0.01542	0.852	0.692
Residuals	87	1.5749	0.01810		

*21 observations deleted due to missingness

- Results suggest that the missingness in the DXSTAGE variable could be at random
  - No significant association between the DXSTAGE and T1EQTOT: p-value > 0.05
- If survival outcomes are given, Kaplan-Meier estimates can help assess the overall survival differences between patients with and without missing staging data and cox regression analysis could have been used in the context of sensitivity analysis to explore the impact of missing staging data on for survival outcomes.

CREDITS

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