Survival Analysis Final Project

Group 10

```
library(readr)
library(tidyverse)
library(janitor)
library(ggcorrplot)
library(dplyr)
library(gtsummary)
library(tidyr)
library(ggplot2)
```

EDA

Load the dataset and clean column names

```
file_path <- "Breast Cancer METABRIC.csv"

data <- read.csv(file_path, na.strings = "") %>%  # Treat blank strings as NA
  clean_names() %>%
  filter(cancer_type != "Breast Sarcoma") %>%  # only 3 patients are not Breast Cancer, exclude them
  rename(
    vital_status = patient_s_vital_status,
    three_gene_classifier_subtype = x3_gene_classifier_subtype
  ) %>%
  # Exclude patients with both overall_survival_months and overall_survival_status missing
  filter(!(is.na(overall_survival_months) & is.na(overall_survival_status)))

# View the cleaned data
head(data)
```

```
##   patient_id age_at_diagnosis type_of_breast_surgery   cancer_type
## 1    MB-0000            75.65             Mastectomy Breast Cancer
## 2    MB-0002            43.19      Breast Conserving Breast Cancer
## 3    MB-0005            48.87             Mastectomy Breast Cancer
## 4    MB-0006            47.68             Mastectomy Breast Cancer
## 5    MB-0008            76.97             Mastectomy Breast Cancer
## 6    MB-0010            78.77             Mastectomy Breast Cancer
##                        cancer_type_detailed cellularity chemotherapy
## 1          Breast Invasive Ductal Carcinoma        <NA>           No
## 2          Breast Invasive Ductal Carcinoma        High           No
## 3          Breast Invasive Ductal Carcinoma        High          Yes
## 4 Breast Mixed Ductal and Lobular Carcinoma    Moderate          Yes
## 5 Breast Mixed Ductal and Lobular Carcinoma        High          Yes
## 6          Breast Invasive Ductal Carcinoma    Moderate           No
```

```
##   pam50_claudin_low_subtype cohort er_status_measured_by_ihc er_status
## 1               claudin-low      1                   Positve  Positive
## 2                      LumA      1                   Positve  Positive
## 3                      LumB      1                   Positve  Positive
## 4                      LumB      1                   Positve  Positive
## 5                      LumB      1                   Positve  Positive
## 6                      LumB      1                   Positve  Positive
##   neoplasm_histologic_grade her2_status_measured_by_snp6 her2_status
## 1                         3                      Neutral    Negative
## 2                         3                      Neutral    Negative
## 3                         2                      Neutral    Negative
## 4                         2                      Neutral    Negative
## 5                         3                      Neutral    Negative
## 6                         3                      Neutral    Negative
##   tumor_other_histologic_subtype hormone_therapy inferred_menopausal_state
## 1                     Ductal/NST             Yes                       Post
## 2                     Ductal/NST             Yes                        Pre
## 3                     Ductal/NST             Yes                        Pre
## 4                          Mixed             Yes                        Pre
## 5                          Mixed             Yes                       Post
## 6                     Ductal/NST             Yes                       Post
##   integrative_cluster primary_tumor_laterality lymph_nodes_examined_positive
## 1                4ER+                    Right                             10
## 2                4ER+                    Right                              0
## 3                   3                    Right                              1
## 4                   9                    Right                              3
## 5                   9                    Right                              8
## 6                   7                     Left                              0
##   mutation_count nottingham_prognostic_index oncotree_code
## 1             NA                       6.044           IDC
## 2              2                       4.020           IDC
## 3              2                       4.030           IDC
## 4              1                       4.050          MDLC
## 5              2                       6.080          MDLC
## 6              4                       4.062           IDC
##   overall_survival_months overall_survival_status pr_status radio_therapy
## 1               140.50000                  Living  Negative           Yes
## 2                84.63333                  Living  Positive           Yes
## 3               163.70000                Deceased  Positive            No
## 4               164.93333                  Living  Positive           Yes
## 5                41.36667                Deceased  Positive           Yes
## 6                 7.80000                Deceased  Positive           Yes
##   relapse_free_status_months relapse_free_status    sex
## 1                     138.65        Not Recurred Female
## 2                      83.52        Not Recurred Female
## 3                     151.28            Recurred Female
## 4                     162.76        Not Recurred Female
## 5                      18.55            Recurred Female
## 6                       2.89            Recurred Female
##   three_gene_classifier_subtype tumor_size tumor_stage    vital_status
## 1                     ER-/HER2-         22           2          Living
## 2         ER+/HER2- High Prolif         10           1          Living
## 3                         <NA>         15           2 Died of Disease
## 4                         <NA>         25           2          Living
```

```
## 5         ER+/HER2- High Prolif         40           2 Died of Disease
## 6         ER+/HER2- High Prolif         31           4 Died of Disease
```

Our primary objective in this project is to investigate factors associated with overall survival (OS) in the METABRIC breast cancer cohort. Specifically, we define overall survival as the time from diagnosis to death from any cause, with overall_survival_months providing the follow-up time and overall_survival_status indicating whether the death event occurred.

For the survival analysis, both a valid survival time and an event indicator are required for each patient. In this dataset, some patients have overall_survival_months and overall_survival_status missing simultaneously, meaning that no follow-up or outcome information is available for these individuals. These cases are not censored observations but instead represent completely missing survival data. Therefore, we excluded patients with both overall_survival_months and overall_survival_status missing, so that the analysis dataset contains only patients with interpretable OS information for time-to-event modelling.

```
dim(data)             # number of rows and columns
```

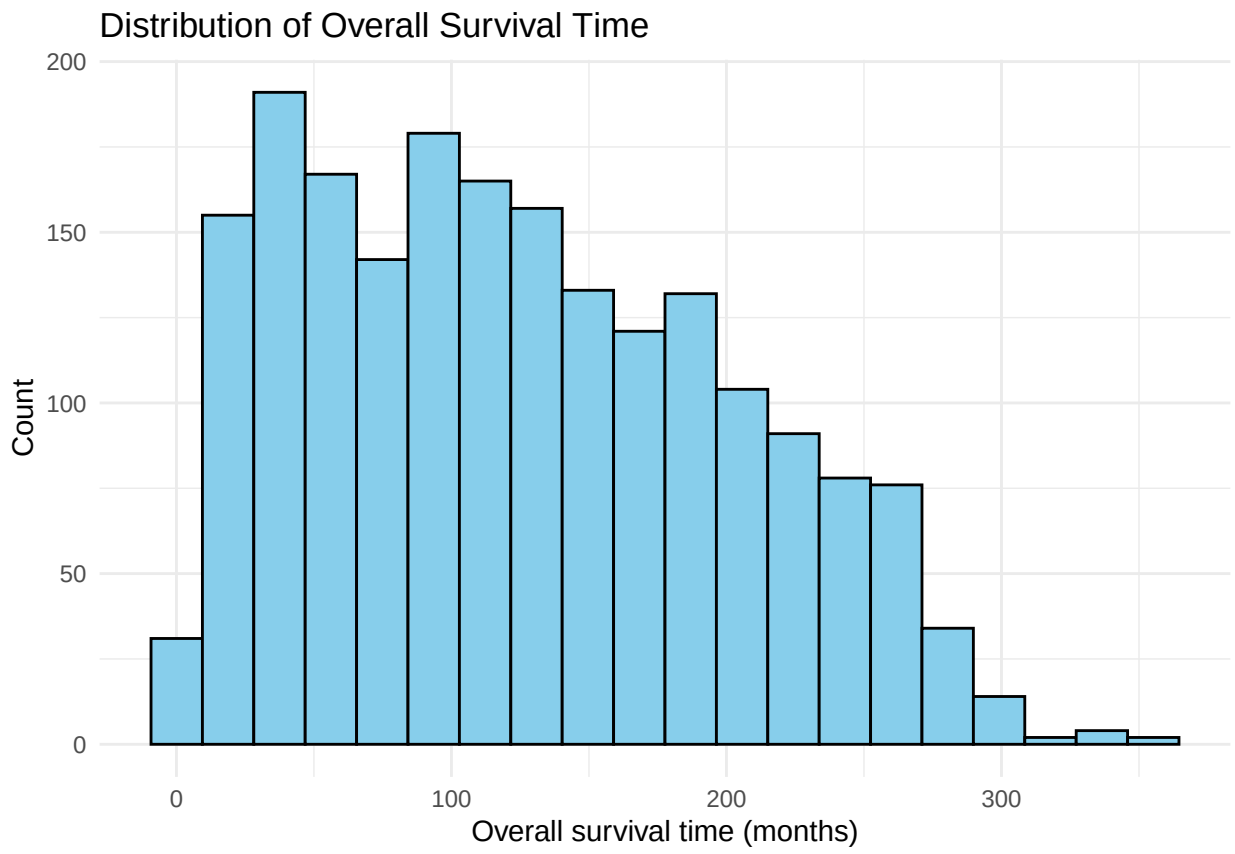
```
## [1] 1978   34
```

```
colnames(data)        # check all variable names
```

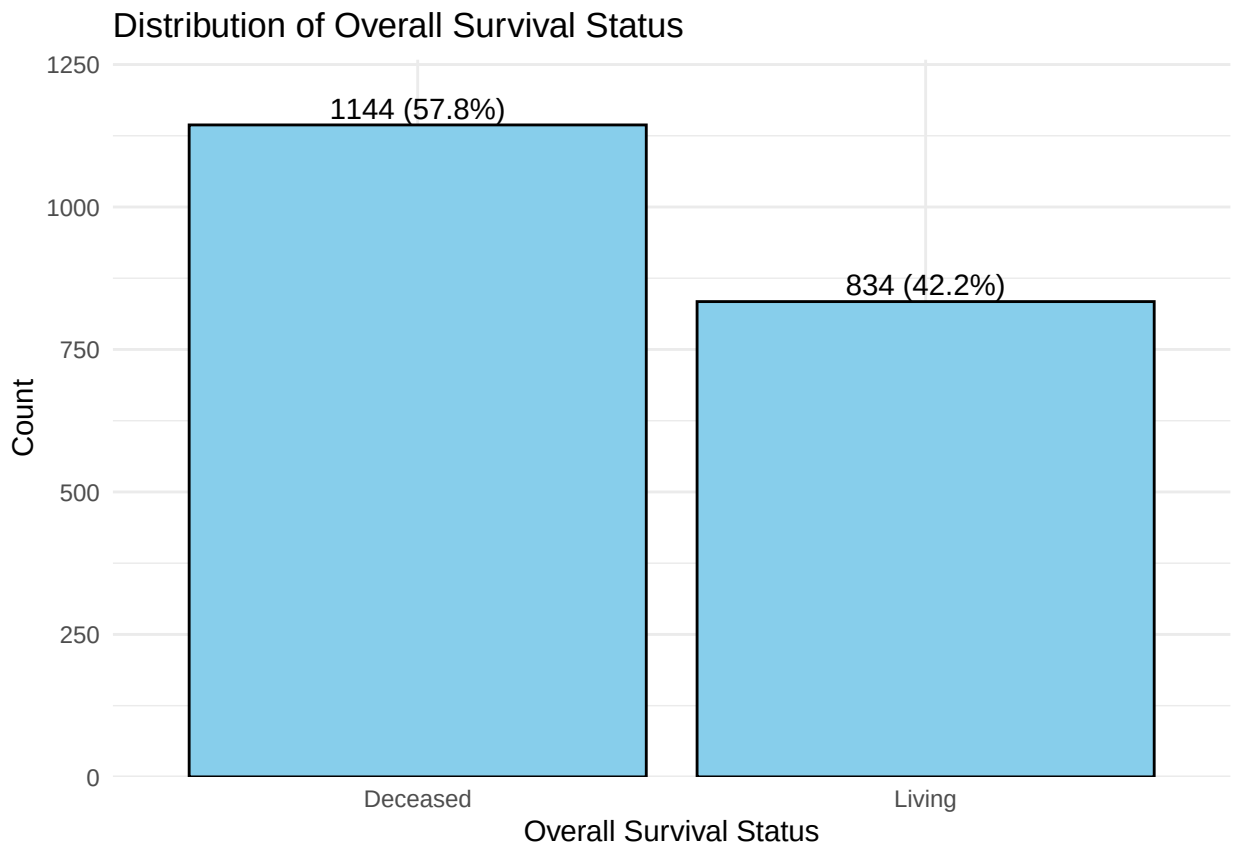
```
##  [1] "patient_id"                      "age_at_diagnosis"
##  [3] "type_of_breast_surgery"          "cancer_type"
##  [5] "cancer_type_detailed"            "cellularity"
##  [7] "chemotherapy"                    "pam50_claudin_low_subtype"
##  [9] "cohort"                          "er_status_measured_by_ihc"
## [11] "er_status"                       "neoplasm_histologic_grade"
## [13] "her2_status_measured_by_snp6"    "her2_status"
## [15] "tumor_other_histologic_subtype"  "hormone_therapy"
## [17] "inferred_menopausal_state"       "integrative_cluster"
## [19] "primary_tumor_laterality"        "lymph_nodes_examined_positive"
## [21] "mutation_count"                  "nottingham_prognostic_index"
## [23] "oncotree_code"                   "overall_survival_months"
## [25] "overall_survival_status"         "pr_status"
## [27] "radio_therapy"                   "relapse_free_status_months"
## [29] "relapse_free_status"             "sex"
## [31] "three_gene_classifier_subtype"   "tumor_size"
## [33] "tumor_stage"                     "vital_status"
```

Visualization of Overall Survival (OS)

```
ggplot(data, aes(x = overall_survival_months)) +
geom_histogram(bins = 20, color = "black", fill = "skyblue") +
labs(
title = "Distribution of Overall Survival Time",
x = "Overall survival time (months)",
y = "Count"
) +
theme_minimal()
```




```r
ggplot(data, aes(x = factor(overall_survival_status))) +
  geom_bar(aes(y = ..count..), fill = "skyblue", color = "black") +  # Count bars
  geom_text(
    stat = "count",
    aes(label = paste0(..count.., " (", round(..count.. / sum(..count..) * 100, 1), "%)")),
    vjust = -0.3,      # move labels slightly above the bar
    color = "black",
    size = 4
  ) +
  scale_y_continuous(
    expand = expansion(mult = c(0, 0.1))  # add 10% headroom on top so labels are fully visible
  ) +
  labs(
    title = "Distribution of Overall Survival Status",
    x = "Overall Survival Status",
    y = "Count"
  ) +
  theme_minimal()
```



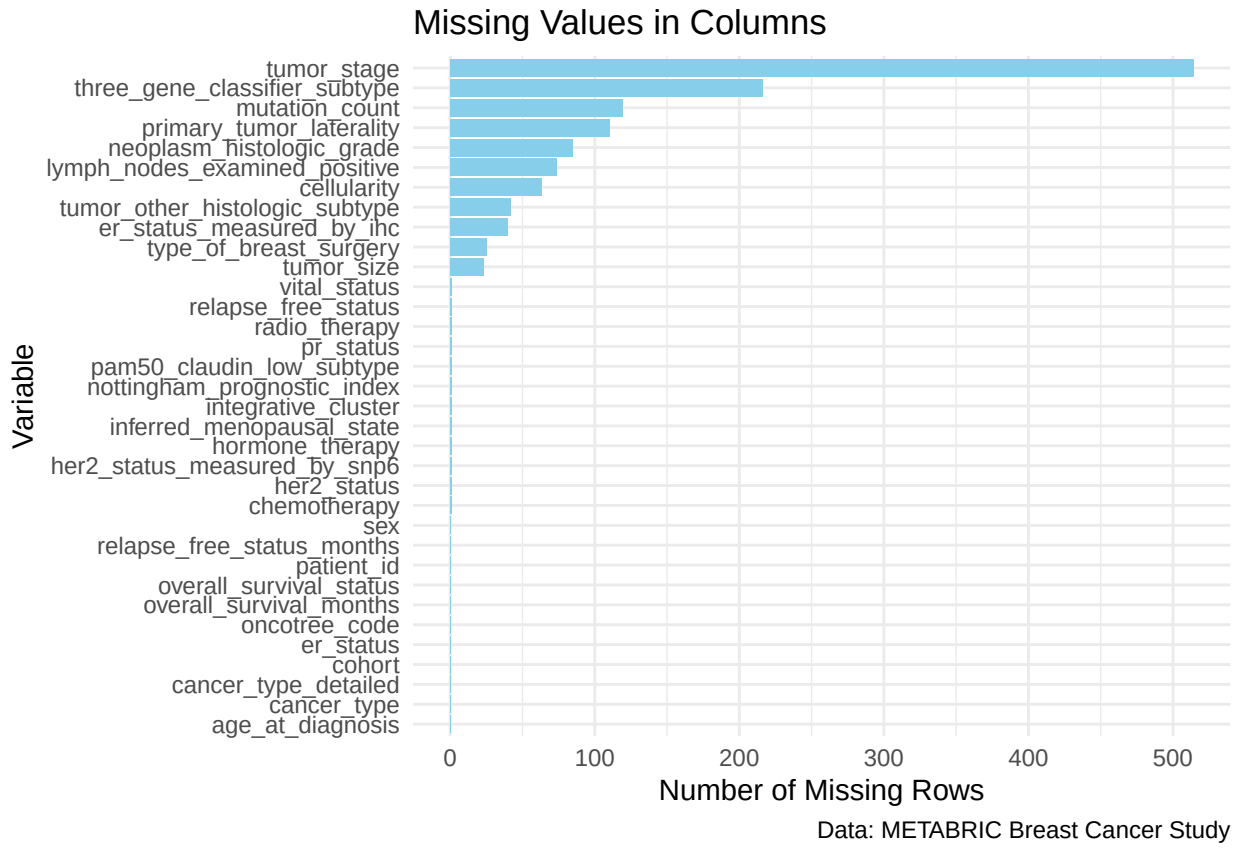
Check for missing values:

```
# Proportion and count of missing values per variable (only variables with missing values)
missing_summary <- data %>%
  summarise(across(everything(), ~ sum(is.na(.)))) %>%  # count missing values
  pivot_longer(
    cols = everything(),
    names_to = "variable",
    values_to = "missing_count"
  ) %>%
  mutate(
    prop_missing = missing_count / nrow(data)  # calculate proportion of missing values
  ) %>%     # keep only variables with any missing values
  arrange(desc(missing_count))       # sort by missing count (descending)

missing_summary
```

```
## # A tibble: 34 x 3
##    variable                       missing_count prop_missing
##    <chr>                                  <int>        <dbl>
##  1 tumor_stage                              514       0.260
##  2 three_gene_classifier_subtype            216       0.109
##  3 mutation_count                           119       0.0602
##  4 primary_tumor_laterality                 110       0.0556
```

```
##  5 neoplasm_histologic_grade                85       0.0430
##  6 lymph_nodes_examined_positive            74       0.0374
##  7 cellularity                              63       0.0319
##  8 tumor_other_histologic_subtype           42       0.0212
##  9 er_status_measured_by_ihc                40       0.0202
## 10 type_of_breast_surgery                   25       0.0126
## # i 24 more rows
```

```r
# Plot missing values per variable (count)
ggplot(missing_summary, aes(x = reorder(variable, missing_count), y = missing_count)) +
  geom_bar(stat = "identity", fill = "skyblue") +
  labs(
    title = "Missing Values in Columns",
    x = "Variable",
    y = "Number of Missing Rows",
    caption = "Data: METABRIC Breast Cancer Study"
  ) +
  theme_minimal() +
  coord_flip()  # Flip the chart for better readability
```



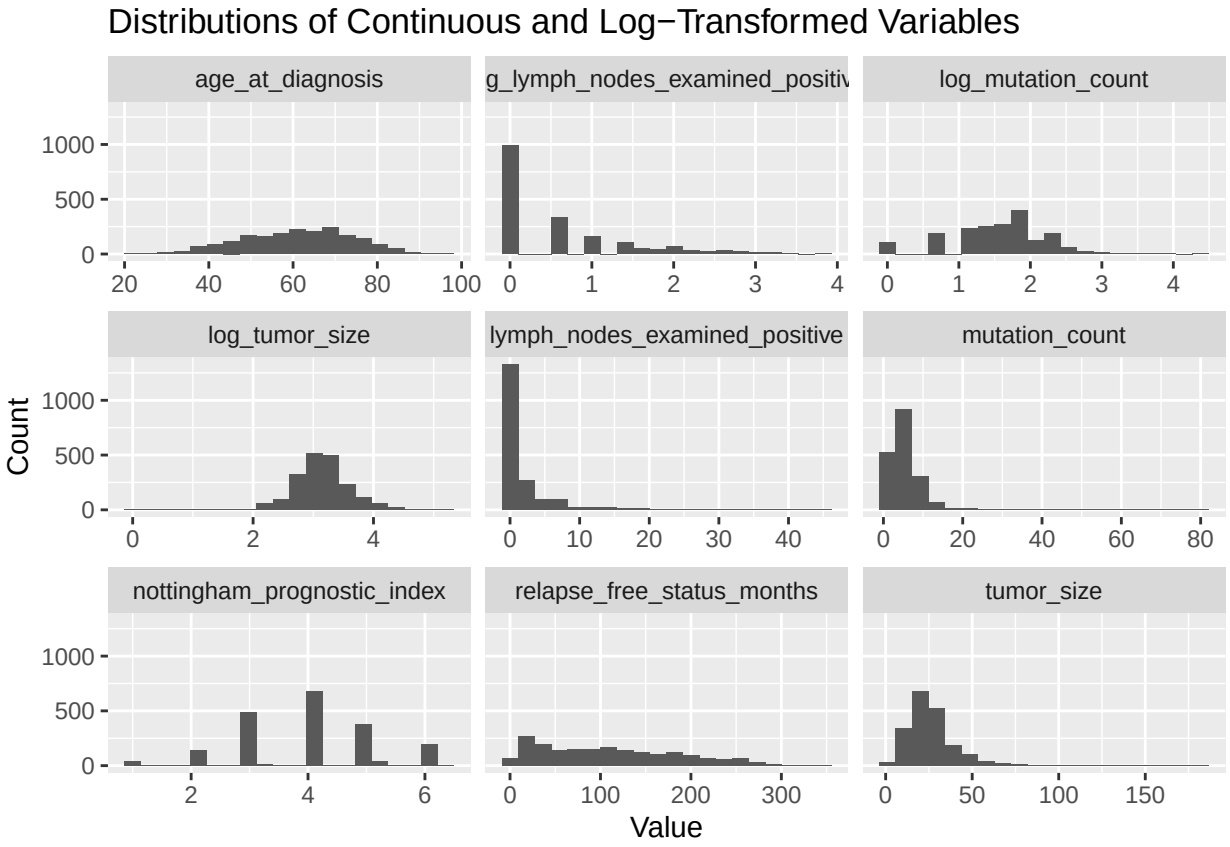
Define continuous and categorical variables manually:

```r
continuous_vars <- c(
  "age_at_diagnosis",
  "tumor_size",
  "lymph_nodes_examined_positive",
  "mutation_count",
  "nottingham_prognostic_index",
  "overall_survival_months",
  "relapse_free_status_months"
)

continuous_vars
```

Continuous variables:

```
## [1] "age_at_diagnosis"               "tumor_size"
## [3] "lymph_nodes_examined_positive" "mutation_count"
## [5] "nottingham_prognostic_index"   "overall_survival_months"
## [7] "relapse_free_status_months"
```

```r
data_plot <- data %>%
  mutate(
    log_tumor_size = log(tumor_size),
    log_mutation_count = log(mutation_count),
    log_lymph_nodes_examined_positive = log(lymph_nodes_examined_positive+1)
  )

# variables you want to plot (original + new logs)
vars_to_plot <- c(
  setdiff(continuous_vars, "overall_survival_months"),    # original ones
  "log_tumor_size",
  "log_mutation_count",
  "log_lymph_nodes_examined_positive"
)

# ---- PLOT ---------------------------------------------------------------

data_plot %>%
  select(all_of(vars_to_plot)) %>%
  pivot_longer(
    cols = everything(),
    names_to = "variable",
    values_to = "value"
  ) %>%
  ggplot(aes(x = value)) +
  geom_histogram(bins = 20) +
  facet_wrap(~ variable, scales = "free_x") +
  labs(
    title = "Distributions of Continuous and Log-Transformed Variables",
    x = "Value",
    y = "Count"
  )
```




```
# Treat other variables as categorical for EDA, but exclude patient_id
categorical_vars <- setdiff(names(data), c(continuous_vars, "patient_id"))
```

```
# Frequency and proportion for each categorical variable (excluding overall_survival_status)
for (var in setdiff(categorical_vars, "overall_survival_status")) {
  cat("\n\n==============================\n")
  cat("Variable:", var, "\n")

  tmp <- data %>%
    count(.data[[var]]) %>%                 # count each level
    mutate(prop = n / sum(n)) %>%           # proportion within the variable
    arrange(desc(n))                        # sort by frequency

  print(tmp)                 # print all rows for this variable
}
```

Categorical variables:

```
##
##
## ==============================
```

```
## Variable: type_of_breast_surgery
##   type_of_breast_surgery    n       prop
## 1             Mastectomy 1169 0.59100101
## 2      Breast Conserving  784 0.39635996
## 3                  <NA>   25 0.01263903
##
##
## ==============================
## Variable: cancer_type
##     cancer_type    n prop
## 1 Breast Cancer 1978    1
##
##
## ==============================
## Variable: cancer_type_detailed
##                         cancer_type_detailed    n        prop
## 1          Breast Invasive Ductal Carcinoma 1537 0.777047523
## 2 Breast Mixed Ductal and Lobular Carcinoma  211 0.106673407
## 3         Breast Invasive Lobular Carcinoma  146 0.073811931
## 4                 Invasive Breast Carcinoma   42 0.021233569
## 5  Breast Invasive Mixed Mucinous Carcinoma   23 0.011627907
## 6                                    Breast   17 0.008594540
## 7                 Metaplastic Breast Cancer    2 0.001011122
##
##
## ==============================
## Variable: cellularity
##   cellularity   n       prop
## 1        High 964 0.48736097
## 2    Moderate 736 0.37209302
## 3         Low 215 0.10869565
## 4        <NA>  63 0.03185035
##
##
## ==============================
## Variable: chemotherapy
##   chemotherapy    n         prop
## 1           No 1565 0.7912032356
## 2          Yes  412 0.2082912032
## 3         <NA>    1 0.0005055612
##
##
## ==============================
## Variable: pam50_claudin_low_subtype
##   pam50_claudin_low_subtype   n         prop
## 1                      LumA 700 0.3538928210
## 2                      LumB 475 0.2401415571
## 3                      Her2 224 0.1132457027
## 4               claudin-low 215 0.1086956522
## 5                     Basal 209 0.1056622851
## 6                    Normal 148 0.0748230536
## 7                        NC   6 0.0030333670
## 8                      <NA>   1 0.0005055612
##
```

```
##
## ==============================
## Variable: cohort
##   cohort   n      prop
## 1      3 763 0.3857432
## 2      1 519 0.2623862
## 3      2 288 0.1456016
## 4      4 238 0.1203236
## 5      5 170 0.0859454
##
##
## ==============================
## Variable: er_status_measured_by_ihc
##   er_status_measured_by_ihc    n       prop
## 1                   Positve 1499 0.75783620
## 2                  Negative  439 0.22194135
## 3                      <NA>   40 0.02022245
##
##
## ==============================
## Variable: er_status
##   er_status    n      prop
## 1  Positive 1506 0.7613751
## 2  Negative  472 0.2386249
##
##
## ==============================
## Variable: neoplasm_histologic_grade
##   neoplasm_histologic_grade   n       prop
## 1                         3 953 0.48179980
## 2                         2 771 0.38978766
## 3                         1 169 0.08543984
## 4                        NA  85 0.04297270
##
##
## ==============================
## Variable: her2_status_measured_by_snp6
##   her2_status_measured_by_snp6    n         prop
## 1                      Neutral 1433 0.7244691608
## 2                         Gain  438 0.2214357937
## 3                         Loss  101 0.0510616785
## 4                        Undef    5 0.0025278059
## 5                         <NA>    1 0.0005055612
##
##
## ==============================
## Variable: her2_status
##   her2_status    n         prop
## 1    Negative 1730 0.8746208291
## 2    Positive  247 0.1248736097
## 3        <NA>    1 0.0005055612
##
##
## ==============================
```

```
## Variable: tumor_other_histologic_subtype
##   tumor_other_histologic_subtype    n        prop
## 1                     Ductal/NST 1491 0.753791709
## 2                          Mixed  211 0.106673407
## 3                        Lobular  146 0.073811931
## 4                           <NA>   42 0.021233569
## 5                       Medullary   25 0.012639029
## 6                        Mucinous   23 0.011627907
## 7            Tubular/ cribriform   21 0.010616785
## 8                           Other   17 0.008594540
## 9                     Metaplastic    2 0.001011122
##
##
## ==============================
## Variable: hormone_therapy
##   hormone_therapy    n         prop
## 1             Yes 1216 0.6147623862
## 2              No  761 0.3847320526
## 3            <NA>    1 0.0005055612
##
##
## ==============================
## Variable: inferred_menopausal_state
##   inferred_menopausal_state    n         prop
## 1                      Post 1553 0.7851365015
## 2                       Pre  424 0.2143579373
## 3                      <NA>    1 0.0005055612
##
##
## ==============================
## Variable: integrative_cluster
##    integrative_cluster   n         prop
## 1                    8 299 0.1511627907
## 2                    3 290 0.1466127401
## 3                 4ER+ 259 0.1309403438
## 4                   10 225 0.1137512639
## 5                    5 190 0.0960566229
## 6                    7 190 0.0960566229
## 7                    9 146 0.0738119312
## 8                    1 139 0.0702730030
## 9                    6  85 0.0429726997
## 10                4ER-  82 0.0414560162
## 11                   2  72 0.0364004044
## 12                <NA>   1 0.0005055612
##
##
## ==============================
## Variable: primary_tumor_laterality
##   primary_tumor_laterality   n       prop
## 1                     Left 971 0.49089990
## 2                    Right 897 0.45348837
## 3                     <NA> 110 0.05561173
##
##
```

```
## ==============================
## Variable: oncotree_code
##   oncotree_code    n        prop
## 1           IDC 1537 0.777047523
## 2          MDLC  211 0.106673407
## 3           ILC  146 0.073811931
## 4          BRCA   42 0.021233569
## 5          IMMC   23 0.011627907
## 6        BREAST   17 0.008594540
## 7           MBC    2 0.001011122
##
##
## ==============================
## Variable: pr_status
##   pr_status    n         prop
## 1  Positive 1040 0.5257836198
## 2  Negative  937 0.4737108190
## 3      <NA>    1 0.0005055612
##
##
## ==============================
## Variable: radio_therapy
##   radio_therapy    n         prop
## 1           Yes 1173 0.5930232558
## 2            No  804 0.4064711830
## 3          <NA>    1 0.0005055612
##
##
## ==============================
## Variable: relapse_free_status
##   relapse_free_status    n         prop
## 1        Not Recurred 1174 0.5935288170
## 2            Recurred  803 0.4059656218
## 3                <NA>    1 0.0005055612
##
##
## ==============================
## Variable: sex
##      sex    n prop
## 1 Female 1978    1
##
##
## ==============================
## Variable: three_gene_classifier_subtype
##   three_gene_classifier_subtype   n      prop
## 1          ER+/HER2- Low Prolif 640 0.3235592
## 2         ER+/HER2- High Prolif 617 0.3119312
## 3                     ER-/HER2- 307 0.1552073
## 4                          <NA> 216 0.1092012
## 5                         HER2+ 198 0.1001011
##
##
## ==============================
## Variable: tumor_stage
```

```
##   tumor_stage   n        prop
## 1           2 825 0.417087968
## 2          NA 514 0.259858443
## 3           1 500 0.252780586
## 4           3 118 0.059656218
## 5           0  11 0.005561173
## 6           4  10 0.005055612
##
##
## ============================
## Variable: vital_status
##           vital_status   n         prop
## 1               Living 834 0.4216380182
## 2      Died of Disease 646 0.3265925177
## 3 Died of Other Causes 497 0.2512639029
## 4                 <NA>   1 0.0005055612
```

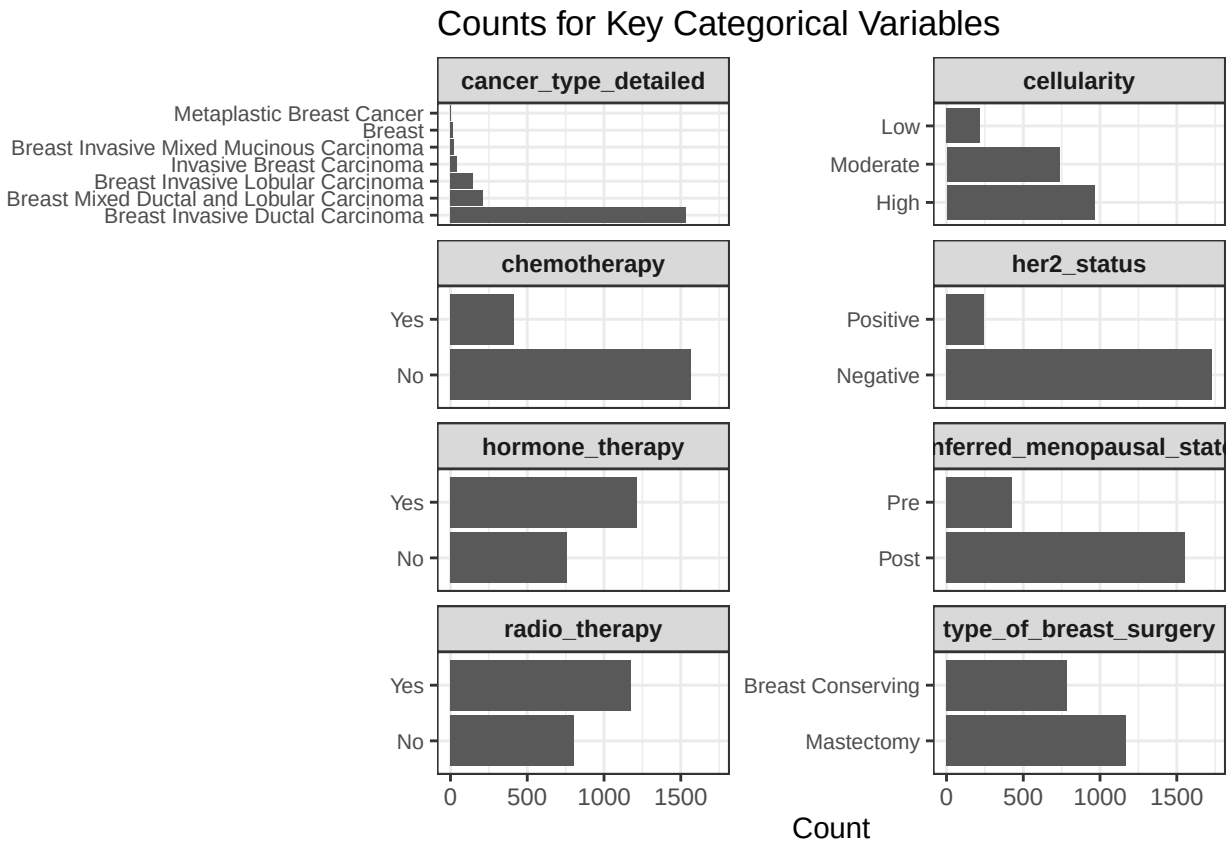
sex and cancer_type have only a single category (Female and Breast Cancer) in this dataset, making them uninformative for the survival analysis model, as they do not provide any variation in the data.

```
# Remove 'sex' and 'cancer_type' from categorical_vars
categorical_vars <- setdiff(categorical_vars, c("sex", "cancer_type"))

# Print updated categorical_vars
categorical_vars
```

```
##  [1] "type_of_breast_surgery"         "cancer_type_detailed"
##  [3] "cellularity"                    "chemotherapy"
##  [5] "pam50_claudin_low_subtype"      "cohort"
##  [7] "er_status_measured_by_ihc"      "er_status"
##  [9] "neoplasm_histologic_grade"      "her2_status_measured_by_snp6"
## [11] "her2_status"                    "tumor_other_histologic_subtype"
## [13] "hormone_therapy"                "inferred_menopausal_state"
## [15] "integrative_cluster"            "primary_tumor_laterality"
## [17] "oncotree_code"                  "overall_survival_status"
## [19] "pr_status"                      "radio_therapy"
## [21] "relapse_free_status"            "three_gene_classifier_subtype"
## [23] "tumor_stage"                    "vital_status"
```

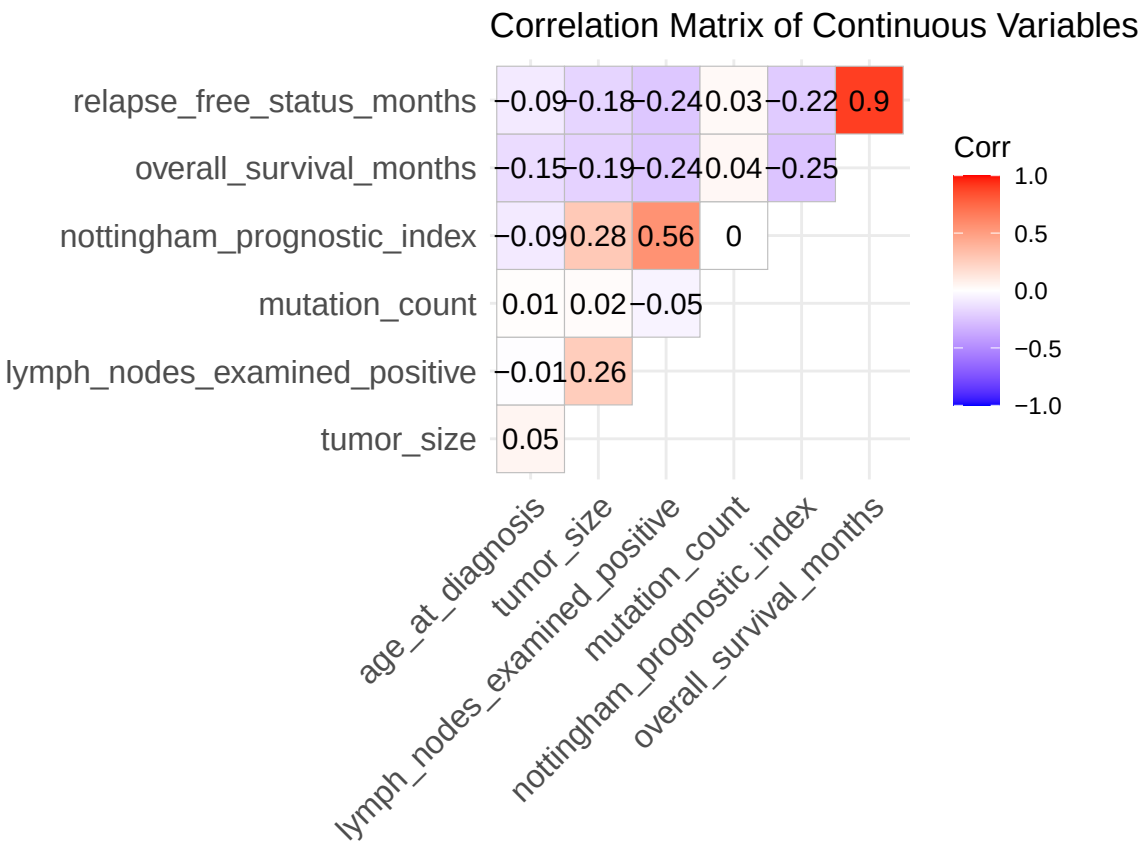
```
cats_for_plot <- c(
  "type_of_breast_surgery",
  "cancer_type_detailed",
  "cellularity",
  "chemotherapy",
  "her2_status",
  "hormone_therapy",
  "radio_therapy",
  "inferred_menopausal_state"
)

cat_long <- data %>%
  select(all_of(cats_for_plot)) %>%
  pivot_longer(
```

```
    cols = everything(),
    names_to  = "variable",
    values_to = "category"
  ) %>%
  drop_na(category) %>%
  # order levels within each variable by frequency
  group_by(variable) %>%
  mutate(category = fct_infreq(category)) %>%
  ungroup()

ggplot(cat_long, aes(x = category)) +
  geom_bar() +
  coord_flip() +  # make bars horizontal so labels are readable
  facet_wrap(~ variable, scales = "free_y", ncol = 2) +
  labs(
    title = "Counts for Key Categorical Variables",
    x = NULL,
    y = "Count"
  ) +
  theme_bw() +
  theme(
    axis.text.y = element_text(size = 8),
    strip.text  = element_text(face = "bold")
  )
```



Correlation analysis:

```
# Calculate correlation matrix for continuous variables
cor_matrix <- data %>%
  select(all_of(continuous_vars)) %>%
  cor(use = "pairwise.complete.obs")  # handle NA values by pairwise complete observation

ggcorrplot(cor_matrix,
           type = "upper",        # Show only the lower triangle of the matrix
           lab = TRUE,            # Display correlation values
           colors = c("blue", "white", "red"),  # Color gradient
           title = "Correlation Matrix of Continuous Variables")
```



Based on the correlation matrix shown, relapse_free_status_months and overall_survival_months exhibit a very strong positive correlation of 0.9, indicating that these two variables are highly related. However, other continuous variables, such as nottingham_prognostic_index, mutation_count, lymph_nodes_examined_positive, and tumor_size, do not show high correlations with each other.

If we are conducting survival analysis with overall_survival_status as the event indicator, we should exclude relapse_free_status_months as a predictor in the model, as it is strongly correlated with overall_survival_months. Including both would lead to multicollinearity, where these two variables would essentially provide redundant information, making it difficult to assess their independent effects on survival. Therefore, we should choose overall_survival_months as the time variable, as it directly represents the total survival time and includes all relevant information related to the occurrence of the event.

```r
# Remove 'relapse_free_status_months' from continuous_vars
continuous_vars <- setdiff(continuous_vars, "relapse_free_status_months")
```

```r
# Create an empty data frame to store results
chi_results <- data.frame(
  variable = character(),
  p_value = numeric(),
  stringsAsFactors = FALSE
)

# Perform Chi-Square Test for each categorical variable with overall_survival_status
for (var in categorical_vars) {

  # Create a contingency table for each variable and survival status
  contingency_table <- table(data[[var]], data$overall_survival_status)

  # Perform Chi-Square test
  chi_test <- chisq.test(contingency_table)

  # Store the results in chi_results dataframe
  chi_results <- rbind(chi_results, data.frame(variable = var, p_value = chi_test$p.value))

  # Print the contingency table and the p-value
  cat("\n\n==============================\n")
  cat("Variable:", var, "\n")
  print(contingency_table)
  cat("P-value for Chi-Square Test:", chi_test$p.value, "\n")
}
```

```
##
##
## ==============================
## Variable: type_of_breast_surgery
##
##                     Deceased Living
##   Breast Conserving      368    416
##   Mastectomy             759    410
## P-value for Chi-Square Test: 4.464438e-15
```

```
##
##
## ==============================
## Variable: cancer_type_detailed
##
##                                             Deceased Living
##   Breast                                           5     12
##   Breast Invasive Ductal Carcinoma               891    646
##   Breast Invasive Lobular Carcinoma               86     60
##   Breast Invasive Mixed Mucinous Carcinoma        10     13
##   Breast Mixed Ductal and Lobular Carcinoma      132     79
##   Invasive Breast Carcinoma                       18     24
##   Metaplastic Breast Cancer                        2      0
## P-value for Chi-Square Test: 0.02097761
```

```
##
##
## ==============================
## Variable: cellularity
##
##            Deceased Living
##   High          562    402
##   Low           116     99
##   Moderate      436    300
## P-value for Chi-Square Test: 0.3822673
##
##
## ==============================
## Variable: chemotherapy
##
##       Deceased Living
##   No       920    645
##   Yes      223    189
## P-value for Chi-Square Test: 0.09937019

##
##
## ==============================
## Variable: pam50_claudin_low_subtype
##
##               Deceased Living
##   Basal            115     94
##   claudin-low       94    121
##   Her2             157     67
##   LumA             378    322
##   LumB             315    160
##   NC                 5      1
##   Normal            79     69
## P-value for Chi-Square Test: 1.139447e-09
##
##
## ==============================
## Variable: cohort
##
##     Deceased Living
##   1      227    292
##   2      149    139
##   3      529    234
##   4      124    114
##   5      115     55
## P-value for Chi-Square Test: 2.669872e-20
##
##
## ==============================
## Variable: er_status_measured_by_ihc
##
##            Deceased Living
##   Negative      246    193
##   Positve       880    619
```

```
## P-value for Chi-Square Test: 0.3462201
##
##
## ==============================
## Variable: er_status
##
##            Deceased Living
##   Negative      262    210
##   Positive      882    624
## P-value for Chi-Square Test: 0.262618
##
##
## ==============================
## Variable: neoplasm_histologic_grade
##
##     Deceased Living
##   1       76     93
##   2      432    339
##   3      579    374
## P-value for Chi-Square Test: 0.0003979277

##
##
## ==============================
## Variable: her2_status_measured_by_snp6
##
##           Deceased Living
##   Gain         270    168
##   Loss          52     49
##   Neutral      818    615
##   Undef          3      2
## P-value for Chi-Square Test: 0.202126
##
##
## ==============================
## Variable: her2_status
##
##            Deceased Living
##   Negative      988    742
##   Positive      155     92
## P-value for Chi-Square Test: 0.1071625

##
##
## ==============================
## Variable: tumor_other_histologic_subtype
##
##                       Deceased Living
##   Ductal/NST               871    620
##   Lobular                   86     60
##   Medullary                 14     11
##   Metaplastic                2      0
##   Mixed                    132     79
##   Mucinous                  10     13
```

```
##   Other                      5     12
##   Tubular/ cribriform        6     15
## P-value for Chi-Square Test: 0.009518724
##
##
## ==============================
## Variable: hormone_therapy
##
##       Deceased Living
##   No       426    335
##   Yes      717    499
## P-value for Chi-Square Test: 0.2073769
##
##
## ==============================
## Variable: inferred_menopausal_state
##
##        Deceased Living
##   Post      966    587
##   Pre       177    247
## P-value for Chi-Square Test: 6.178334e-14
##
##
## ==============================
## Variable: integrative_cluster
##
##        Deceased Living
##   1          80     59
##   10        107    118
##   2          52     20
##   3         151    139
##   4ER-       44     38
##   4ER+      130    129
##   5         130     60
##   6          59     26
##   7         113     77
##   8         179    120
##   9          98     48
## P-value for Chi-Square Test: 1.504806e-06
##
##
## ==============================
## Variable: primary_tumor_laterality
##
##         Deceased Living
##   Left       571    400
##   Right      495    402
## P-value for Chi-Square Test: 0.1252675

##
##
## ==============================
## Variable: oncotree_code
##
```

```
##          Deceased Living
##   BRCA         18     24
##   BREAST        5     12
##   IDC         891    646
##   ILC          86     60
##   IMMC         10     13
##   MBC           2      0
##   MDLC        132     79
## P-value for Chi-Square Test: 0.02097761
##
##
## ==============================
## Variable: overall_survival_status
##
##            Deceased Living
##   Deceased     1144      0
##   Living          0    834
## P-value for Chi-Square Test: 0
##
##
## ==============================
## Variable: pr_status
##
##            Deceased Living
##   Negative      551    386
##   Positive      592    448
## P-value for Chi-Square Test: 0.4235425
##
##
## ==============================
## Variable: radio_therapy
##
##       Deceased Living
##   No       514    290
##   Yes      629    544
## P-value for Chi-Square Test: 6.420301e-06
##
##
## ==============================
## Variable: relapse_free_status
##
##                Deceased Living
##   Not Recurred      432    742
##   Recurred          711     92
## P-value for Chi-Square Test: 2.106947e-115
##
##
## ==============================
## Variable: three_gene_classifier_subtype
##
##                          Deceased Living
##   ER-/HER2-                   153    154
##   ER+/HER2- High Prolif       400    217
##   ER+/HER2- Low Prolif        329    311
```

```
##   HER2+                       121     77
## P-value for Chi-Square Test: 7.079376e-07

##
##
## ==============================
## Variable: tumor_stage
##
##     Deceased Living
##   0        2      9
##   1      228    272
##   2      497    328
##   3       87     31
##   4        9      1
## P-value for Chi-Square Test: 4.935459e-11
##
##
## ==============================
## Variable: vital_status
##
##                         Deceased Living
##   Died of Disease            646      0
##   Died of Other Causes       497      0
##   Living                       0    834
## P-value for Chi-Square Test: 0
```

```
# Print the final results with p-values for all variables except overall_survival_status
chi_results
```

```
##                           variable       p_value
## 1          type_of_breast_surgery  4.464438e-15
## 2            cancer_type_detailed  2.097761e-02
## 3                     cellularity  3.822673e-01
## 4                    chemotherapy  9.937019e-02
## 5       pam50_claudin_low_subtype  1.139447e-09
## 6                          cohort  2.669872e-20
## 7       er_status_measured_by_ihc  3.462201e-01
## 8                        er_status  2.626180e-01
## 9       neoplasm_histologic_grade  3.979277e-04
## 10   her2_status_measured_by_snp6  2.021260e-01
## 11                    her2_status  1.071625e-01
## 12 tumor_other_histologic_subtype  9.518724e-03
## 13                hormone_therapy  2.073769e-01
## 14      inferred_menopausal_state  6.178334e-14
## 15            integrative_cluster  1.504806e-06
## 16       primary_tumor_laterality  1.252675e-01
## 17                  oncotree_code  2.097761e-02
## 18        overall_survival_status  0.000000e+00
## 19                      pr_status  4.235425e-01
## 20                  radio_therapy  6.420301e-06
## 21            relapse_free_status 2.106947e-115
## 22  three_gene_classifier_subtype  7.079376e-07
## 23                    tumor_stage  4.935459e-11
## 24                   vital_status  0.000000e+00
```

Since "vital_status" variable is already directly related to the outcome of survival and is a proxy for the status of the patient, it is unnecessary to include it in the model. This variable is highly correlated with survival, and adding it could lead to perfect prediction of the outcome or multicollinearity.

Although the chi-square test showed a statistically significant association between "cohort" and overall survival status, we decided not to include "cohort" as a covariate in the survival model. In this dataset, "cohort" primarily reflects study batch or recruitment group rather than a meaningful clinical or biological characteristic of the patients. Therefore, it is better interpreted as a design-related or administrative label, rather than a true risk factor for overall survival.

Although "relapse_free_status" shows a highly significant association with overall survival status in the chi-square test, we chose not to include it as a covariate in the overall survival model. Clinically, relapse is an intermediate outcome that occurs after baseline and lies on the causal pathway between baseline risk factors and death. Treating relapse status as a predictor of overall survival would therefore introduce information leakage and could distort the estimated effects of true baseline covariates. In addition, "relapse_free_status" is closely related to "relapse_free_status_months", which we already excluded as an alternative time-to-event endpoint.

```
# Filter results to only show variables with p-value < 0.05 and exclude 'vital_status' and 'cohort'
significant_vars <- chi_results %>%
  filter(p_value < 0.05) %>%
  filter(!variable %in% c("vital_status","cohort","relapse_free_status"))

# Print the significant variables
significant_vars
```

```
##                          variable      p_value
## 1          type_of_breast_surgery 4.464438e-15
## 2            cancer_type_detailed 2.097761e-02
## 3       pam50_claudin_low_subtype 1.139447e-09
## 4       neoplasm_histologic_grade 3.979277e-04
## 5  tumor_other_histologic_subtype 9.518724e-03
## 6       inferred_menopausal_state 6.178334e-14
## 7             integrative_cluster 1.504806e-06
## 8                   oncotree_code 2.097761e-02
## 9         overall_survival_status 0.000000e+00
## 10                radio_therapy 6.420301e-06
## 11  three_gene_classifier_subtype 7.079376e-07
## 12                    tumor_stage 4.935459e-11
```

Final dataset after variable selection

```
# Extract significant variables' names from significant_vars (filter for p-value < 0.05)
significant_var_names <- significant_vars$variable

# Filter the data by including only the selected variables from both significant_vars and continuous_va
selected_vars <- c(significant_var_names, continuous_vars)

# Create a new dataset with only the selected variables
filtered_data <- data %>%
  select(all_of(selected_vars))
```

```r
# View the filtered dataset
head(filtered_data)
```

```
##   type_of_breast_surgery                     cancer_type_detailed
## 1             Mastectomy          Breast Invasive Ductal Carcinoma
## 2      Breast Conserving          Breast Invasive Ductal Carcinoma
## 3             Mastectomy          Breast Invasive Ductal Carcinoma
## 4             Mastectomy Breast Mixed Ductal and Lobular Carcinoma
## 5             Mastectomy Breast Mixed Ductal and Lobular Carcinoma
## 6             Mastectomy          Breast Invasive Ductal Carcinoma
##   pam50_claudin_low_subtype neoplasm_histologic_grade
## 1               claudin-low                         3
## 2                      LumA                         3
## 3                      LumB                         2
## 4                      LumB                         2
## 5                      LumB                         3
## 6                      LumB                         3
##   tumor_other_histologic_subtype inferred_menopausal_state integrative_cluster
## 1                     Ductal/NST                      Post                4ER+
## 2                     Ductal/NST                       Pre                4ER+
## 3                     Ductal/NST                       Pre                   3
## 4                          Mixed                       Pre                   9
## 5                          Mixed                      Post                   9
## 6                     Ductal/NST                      Post                   7
##   oncotree_code overall_survival_status radio_therapy
## 1           IDC                  Living           Yes
## 2           IDC                  Living           Yes
## 3           IDC                Deceased            No
## 4          MDLC                  Living           Yes
## 5          MDLC                Deceased           Yes
## 6           IDC                Deceased           Yes
##   three_gene_classifier_subtype tumor_stage age_at_diagnosis tumor_size
## 1                     ER-/HER2-           2            75.65         22
## 2         ER+/HER2- High Prolif           1            43.19         10
## 3                         <NA>           2            48.87         15
## 4                         <NA>           2            47.68         25
## 5         ER+/HER2- High Prolif           2            76.97         40
## 6         ER+/HER2- High Prolif           4            78.77         31
##   lymph_nodes_examined_positive mutation_count nottingham_prognostic_index
## 1                            10             NA                       6.044
## 2                             0              2                       4.020
## 3                             1              2                       4.030
## 4                             3              1                       4.050
## 5                             8              2                       6.080
## 6                             0              4                       4.062
##   overall_survival_months
## 1               140.50000
## 2                84.63333
## 3               163.70000
## 4               164.93333
## 5                41.36667
## 6                 7.80000
```

Overview of demographic and baseline variables (Table 1)

```
filtered_data <- filtered_data |>
  mutate(overall_survival_status = factor(overall_survival_status))

vars_for_table1 <- c(
  "age_at_diagnosis",
  "her2_status",
  "tumor_size",
  "lymph_nodes_examined_positive",
  "mutation_count",
  "nottingham_prognostic_index",
  "type_of_breast_surgery",
  "cancer_type_detailed",
  "pam50_claudin_low_subtype",
  "neoplasm_histologic_grade",
  "tumor_other_histologic_subtype",
  "inferred_menopausal_state",
  "integrative_cluster",
  "radio_therapy",
  "three_gene_classifier_subtype",
  "tumor_stage"
)

continuous_vars <- c(
  "age_at_diagnosis",
  "tumor_size",
  "lymph_nodes_examined_positive",
  "mutation_count",
  "nottingham_prognostic_index"
)
categorical_vars <- setdiff(vars_for_table1, continuous_vars)

pvalue_fmt <- function(x) {
  ifelse(x < 0.001, "<0.001", formatC(x, format = "f", digits = 3))
}

table1 <-
  data |>
  select(all_of(c("overall_survival_status", vars_for_table1))) |>
  tbl_summary(
    by = overall_survival_status,
    type = list(
      all_of(continuous_vars)  ~ "continuous2",
      all_of(categorical_vars) ~ "categorical"
    ),
    statistic = list(
      all_of(continuous_vars) ~ "{mean} ({sd})",
      all_categorical()       ~ "{n} ({p}%)"
    ),
    missing = "ifany"
  ) |>
  add_n() |>
```

```
  add_p(
    test = list(
      all_of(continuous_vars)  ~ "t.test",
      all_categorical()        ~ "chisq.test"
    ),
    pvalue_fun = pvalue_fmt
  ) |>
  modify_caption("**Table 1. Baseline characteristics by overall survival status**") |>
  bold_labels()
```

```
## The following warnings were returned during `modify_caption()`:
## ! For variable `cancer_type_detailed` (`overall_survival_status`) and
##   "statistic", "p.value", and "parameter" statistics: Chi-squared approximation
##   may be incorrect
## ! For variable `pam50_claudin_low_subtype` (`overall_survival_status`) and
##   "statistic", "p.value", and "parameter" statistics: Chi-squared approximation
##   may be incorrect
## ! For variable `tumor_other_histologic_subtype` (`overall_survival_status`) and
##   "statistic", "p.value", and "parameter" statistics: Chi-squared approximation
##   may be incorrect
## ! For variable `tumor_stage` (`overall_survival_status`) and "statistic",
##   "p.value", and "parameter" statistics: Chi-squared approximation may be
##   incorrect
```

```
table1
```

Multivariable Cox Model

```
library(survival)
library(broom)

final_inter_mod <- coxph(
  Surv(
    overall_survival_months,
    overall_survival_status == "Deceased"   # event indicator
  ) ~
    age_at_diagnosis +
    tumor_size +
    lymph_nodes_examined_positive +
    nottingham_prognostic_index +
    radio_therapy +
    inferred_menopausal_state +
    tumor_stage +
    three_gene_classifier_subtype +
    type_of_breast_surgery +
    cancer_type_detailed +
    pam50_claudin_low_subtype +
    tumor_other_histologic_subtype +
    integrative_cluster +
    mutation_count +
```

```
    radio_therapy:tumor_size, # treatment × tumor size interaction
  data = filtered_data
)
```

```
## Warning in coxph.fit(X, Y, istrat, offset, init, control, weights = weights, :
## Loglik converged before variable 12,13,14,15 ; coefficient may be infinite.
```

```
summary(final_inter_mod)
```

```
## Call:
## coxph(formula = Surv(overall_survival_months, overall_survival_status ==
##     "Deceased") ~ age_at_diagnosis + tumor_size + lymph_nodes_examined_positive +
##     nottingham_prognostic_index + radio_therapy + inferred_menopausal_state +
##     tumor_stage + three_gene_classifier_subtype + type_of_breast_surgery +
##     cancer_type_detailed + pam50_claudin_low_subtype + tumor_other_histologic_subtype +
##     integrative_cluster + mutation_count + radio_therapy:tumor_size,
##     data = filtered_data)
##
##   n= 1186, number of events= 665
##    (792 observations deleted due to missingness)
##
##                                                                 coef
## age_at_diagnosis                                          4.915e-02
## tumor_size                                                1.362e-02
## lymph_nodes_examined_positive                             5.022e-02
## nottingham_prognostic_index                               1.176e-01
## radio_therapyYes                                         -2.313e-02
## inferred_menopausal_statePre                              5.351e-01
## tumor_stage                                               8.522e-02
## three_gene_classifier_subtypeER+/HER2- High Prolif       -1.273e-01
## three_gene_classifier_subtypeER+/HER2- Low Prolif        -2.845e-01
## three_gene_classifier_subtypeHER2+                       -4.093e-01
## type_of_breast_surgeryMastectomy                          1.047e-01
## cancer_type_detailedBreast Invasive Ductal Carcinoma      1.518e+01
## cancer_type_detailedBreast Invasive Lobular Carcinoma     1.495e+01
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma  1.454e+01
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma 1.521e+01
## pam50_claudin_low_subtypeclaudin-low                     -2.838e-01
## pam50_claudin_low_subtypeHer2                             8.155e-02
## pam50_claudin_low_subtypeLumA                            -2.305e-01
## pam50_claudin_low_subtypeLumB                            -2.020e-01
## pam50_claudin_low_subtypeNC                              -9.304e-01
## pam50_claudin_low_subtypeNormal                           1.491e-01
## tumor_other_histologic_subtypeLobular                            NA
## tumor_other_histologic_subtypeMedullary                   3.351e-01
## tumor_other_histologic_subtypeMixed                              NA
## tumor_other_histologic_subtypeMucinous                           NA
## tumor_other_histologic_subtypeOther                              NA
## tumor_other_histologic_subtypeTubular/ cribriform        -5.608e-01
## integrative_cluster10                                    -3.848e-01
## integrative_cluster2                                      3.289e-02
## integrative_cluster3                                      1.285e-02
## integrative_cluster4ER-                                  -1.381e-01
```

```
## integrative_cluster4ER+                                          -1.361e-01
## integrative_cluster5                                              5.965e-01
## integrative_cluster6                                             -7.270e-02
## integrative_cluster7                                             -7.710e-02
## integrative_cluster8                                             -4.029e-02
## integrative_cluster9                                             -6.470e-02
## mutation_count                                                    4.164e-03
## tumor_size:radio_therapyYes                                      -6.761e-03
##                                                                   exp(coef)
## age_at_diagnosis                                                  1.050e+00
## tumor_size                                                        1.014e+00
## lymph_nodes_examined_positive                                     1.052e+00
## nottingham_prognostic_index                                       1.125e+00
## radio_therapyYes                                                  9.771e-01
## inferred_menopausal_statePre                                      1.708e+00
## tumor_stage                                                       1.089e+00
## three_gene_classifier_subtypeER+/HER2- High Prolif                8.804e-01
## three_gene_classifier_subtypeER+/HER2- Low Prolif                 7.524e-01
## three_gene_classifier_subtypeHER2+                                6.641e-01
## type_of_breast_surgeryMastectomy                                  1.110e+00
## cancer_type_detailedBreast Invasive Ductal Carcinoma              3.911e+06
## cancer_type_detailedBreast Invasive Lobular Carcinoma             3.111e+06
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma      2.067e+06
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma     4.013e+06
## pam50_claudin_low_subtypeclaudin-low                              7.529e-01
## pam50_claudin_low_subtypeHer2                                     1.085e+00
## pam50_claudin_low_subtypeLumA                                     7.941e-01
## pam50_claudin_low_subtypeLumB                                     8.171e-01
## pam50_claudin_low_subtypeNC                                       3.944e-01
## pam50_claudin_low_subtypeNormal                                   1.161e+00
## tumor_other_histologic_subtypeLobular                                    NA
## tumor_other_histologic_subtypeMedullary                           1.398e+00
## tumor_other_histologic_subtypeMixed                                      NA
## tumor_other_histologic_subtypeMucinous                                   NA
## tumor_other_histologic_subtypeOther                                      NA
## tumor_other_histologic_subtypeTubular/ cribriform                 5.708e-01
## integrative_cluster10                                             6.806e-01
## integrative_cluster2                                              1.033e+00
## integrative_cluster3                                              1.013e+00
## integrative_cluster4ER-                                           8.710e-01
## integrative_cluster4ER+                                           8.727e-01
## integrative_cluster5                                              1.816e+00
## integrative_cluster6                                              9.299e-01
## integrative_cluster7                                              9.258e-01
## integrative_cluster8                                              9.605e-01
## integrative_cluster9                                              9.373e-01
## mutation_count                                                    1.004e+00
## tumor_size:radio_therapyYes                                       9.933e-01
##                                                                   se(coef)      z
## age_at_diagnosis                                                  4.881e-03 10.069
## tumor_size                                                        5.780e-03  2.355
## lymph_nodes_examined_positive                                     1.188e-02  4.229
## nottingham_prognostic_index                                       5.235e-02  2.247
## radio_therapyYes                                                  1.990e-01 -0.116
```

```
## inferred_menopausal_statePre                                      1.569e-01  3.411
## tumor_stage                                                       8.412e-02  1.013
## three_gene_classifier_subtypeER+/HER2- High Prolif                2.136e-01 -0.596
## three_gene_classifier_subtypeER+/HER2- Low Prolif                 2.191e-01 -1.299
## three_gene_classifier_subtypeHER2+                                2.918e-01 -1.403
## type_of_breast_surgeryMastectomy                                  1.052e-01  0.995
## cancer_type_detailedBreast Invasive Ductal Carcinoma              8.744e+02  0.017
## cancer_type_detailedBreast Invasive Lobular Carcinoma             8.744e+02  0.017
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma      8.744e+02  0.017
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma     8.744e+02  0.017
## pam50_claudin_low_subtypeclaudin-low                              2.110e-01 -1.345
## pam50_claudin_low_subtypeHer2                                     2.221e-01  0.367
## pam50_claudin_low_subtypeLumA                                     2.330e-01 -0.989
## pam50_claudin_low_subtypeLumB                                     2.347e-01 -0.861
## pam50_claudin_low_subtypeNC                                       1.035e+00 -0.899
## pam50_claudin_low_subtypeNormal                                   2.608e-01  0.572
## tumor_other_histologic_subtypeLobular                             0.000e+00     NA
## tumor_other_histologic_subtypeMedullary                           3.487e-01  0.961
## tumor_other_histologic_subtypeMixed                               0.000e+00     NA
## tumor_other_histologic_subtypeMucinous                            0.000e+00     NA
## tumor_other_histologic_subtypeOther                               0.000e+00     NA
## tumor_other_histologic_subtypeTubular/ cribriform                 4.581e-01 -1.224
## integrative_cluster10                                             2.459e-01 -1.565
## integrative_cluster2                                              2.401e-01  0.137
## integrative_cluster3                                              2.048e-01  0.063
## integrative_cluster4ER-                                           2.905e-01 -0.476
## integrative_cluster4ER+                                           2.089e-01 -0.652
## integrative_cluster5                                              2.901e-01  2.056
## integrative_cluster6                                              2.331e-01 -0.312
## integrative_cluster7                                              2.110e-01 -0.365
## integrative_cluster8                                              1.991e-01 -0.202
## integrative_cluster9                                              2.139e-01 -0.303
## mutation_count                                                    8.942e-03  0.466
## tumor_size:radio_therapyYes                                       5.965e-03 -1.133
##                                                                  Pr(>|z|)
## age_at_diagnosis                                                  < 2e-16 ***
## tumor_size                                                       0.018504 *
## lymph_nodes_examined_positive                                    2.35e-05 ***
## nottingham_prognostic_index                                      0.024663 *
## radio_therapyYes                                                 0.907472
## inferred_menopausal_statePre                                     0.000647 ***
## tumor_stage                                                      0.311063
## three_gene_classifier_subtypeER+/HER2- High Prolif               0.551151
## three_gene_classifier_subtypeER+/HER2- Low Prolif                0.194077
## three_gene_classifier_subtypeHER2+                               0.160643
## type_of_breast_surgeryMastectomy                                 0.319882
## cancer_type_detailedBreast Invasive Ductal Carcinoma             0.986149
## cancer_type_detailedBreast Invasive Lobular Carcinoma            0.986358
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma     0.986731
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma    0.986126
## pam50_claudin_low_subtypeclaudin-low                             0.178585
## pam50_claudin_low_subtypeHer2                                    0.713564
## pam50_claudin_low_subtypeLumA                                    0.322483
## pam50_claudin_low_subtypeLumB                                    0.389483
```

```
## pam50_claudin_low_subtypeNC                                      0.368475
## pam50_claudin_low_subtypeNormal                                  0.567480
## tumor_other_histologic_subtypeLobular                                 NA
## tumor_other_histologic_subtypeMedullary                          0.336487
## tumor_other_histologic_subtypeMixed                                   NA
## tumor_other_histologic_subtypeMucinous                                NA
## tumor_other_histologic_subtypeOther                                   NA
## tumor_other_histologic_subtypeTubular/ cribriform                0.220930
## integrative_cluster10                                            0.117660
## integrative_cluster2                                             0.891047
## integrative_cluster3                                             0.949964
## integrative_cluster4ER-                                          0.634429
## integrative_cluster4ER+                                          0.514676
## integrative_cluster5                                             0.039742 *
## integrative_cluster6                                             0.755177
## integrative_cluster7                                             0.714836
## integrative_cluster8                                             0.839616
## integrative_cluster9                                             0.762239
## mutation_count                                                   0.641432
## tumor_size:radio_therapyYes                                      0.257030
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                                                                  exp(coef)
## age_at_diagnosis                                                 1.050e+00
## tumor_size                                                       1.014e+00
## lymph_nodes_examined_positive                                    1.052e+00
## nottingham_prognostic_index                                      1.125e+00
## radio_therapyYes                                                 9.771e-01
## inferred_menopausal_statePre                                     1.708e+00
## tumor_stage                                                      1.089e+00
## three_gene_classifier_subtypeER+/HER2- High Prolif               8.804e-01
## three_gene_classifier_subtypeER+/HER2- Low Prolif                7.524e-01
## three_gene_classifier_subtypeHER2+                               6.641e-01
## type_of_breast_surgeryMastectomy                                 1.110e+00
## cancer_type_detailedBreast Invasive Ductal Carcinoma             3.911e+06
## cancer_type_detailedBreast Invasive Lobular Carcinoma            3.111e+06
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma     2.067e+06
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma    4.013e+06
## pam50_claudin_low_subtypeclaudin-low                             7.529e-01
## pam50_claudin_low_subtypeHer2                                    1.085e+00
## pam50_claudin_low_subtypeLumA                                    7.941e-01
## pam50_claudin_low_subtypeLumB                                    8.171e-01
## pam50_claudin_low_subtypeNC                                      3.944e-01
## pam50_claudin_low_subtypeNormal                                  1.161e+00
## tumor_other_histologic_subtypeLobular                                 NA
## tumor_other_histologic_subtypeMedullary                          1.398e+00
## tumor_other_histologic_subtypeMixed                                   NA
## tumor_other_histologic_subtypeMucinous                                NA
## tumor_other_histologic_subtypeOther                                   NA
## tumor_other_histologic_subtypeTubular/ cribriform                5.708e-01
## integrative_cluster10                                            6.806e-01
## integrative_cluster2                                             1.033e+00
## integrative_cluster3                                             1.013e+00
```

```
## integrative_cluster4ER-                                          8.710e-01
## integrative_cluster4ER+                                          8.727e-01
## integrative_cluster5                                             1.816e+00
## integrative_cluster6                                             9.299e-01
## integrative_cluster7                                             9.258e-01
## integrative_cluster8                                             9.605e-01
## integrative_cluster9                                             9.373e-01
## mutation_count                                                   1.004e+00
## tumor_size:radio_therapyYes                                      9.933e-01
##                                                                 exp(-coef)
## age_at_diagnosis                                                 9.520e-01
## tumor_size                                                       9.865e-01
## lymph_nodes_examined_positive                                    9.510e-01
## nottingham_prognostic_index                                      8.890e-01
## radio_therapyYes                                                 1.023e+00
## inferred_menopausal_statePre                                     5.856e-01
## tumor_stage                                                      9.183e-01
## three_gene_classifier_subtypeER+/HER2- High Prolif               1.136e+00
## three_gene_classifier_subtypeER+/HER2- Low Prolif                1.329e+00
## three_gene_classifier_subtypeHER2+                               1.506e+00
## type_of_breast_surgeryMastectomy                                 9.006e-01
## cancer_type_detailedBreast Invasive Ductal Carcinoma             2.557e-07
## cancer_type_detailedBreast Invasive Lobular Carcinoma            3.214e-07
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma     4.839e-07
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma    2.492e-07
## pam50_claudin_low_subtypeclaudin-low                             1.328e+00
## pam50_claudin_low_subtypeHer2                                    9.217e-01
## pam50_claudin_low_subtypeLumA                                    1.259e+00
## pam50_claudin_low_subtypeLumB                                    1.224e+00
## pam50_claudin_low_subtypeNC                                      2.535e+00
## pam50_claudin_low_subtypeNormal                                  8.615e-01
## tumor_other_histologic_subtypeLobular                                   NA
## tumor_other_histologic_subtypeMedullary                          7.153e-01
## tumor_other_histologic_subtypeMixed                                     NA
## tumor_other_histologic_subtypeMucinous                                  NA
## tumor_other_histologic_subtypeOther                                     NA
## tumor_other_histologic_subtypeTubular/ cribriform                1.752e+00
## integrative_cluster10                                            1.469e+00
## integrative_cluster2                                             9.676e-01
## integrative_cluster3                                             9.872e-01
## integrative_cluster4ER-                                          1.148e+00
## integrative_cluster4ER+                                          1.146e+00
## integrative_cluster5                                             5.507e-01
## integrative_cluster6                                             1.075e+00
## integrative_cluster7                                             1.080e+00
## integrative_cluster8                                             1.041e+00
## integrative_cluster9                                             1.067e+00
## mutation_count                                                   9.958e-01
## tumor_size:radio_therapyYes                                      1.007e+00
##                                                                 lower .95
## age_at_diagnosis                                                  1.04038
## tumor_size                                                        1.00229
## lymph_nodes_examined_positive                                     1.02731
## nottingham_prognostic_index                                       1.01512
```

```
## radio_therapyYes                                                0.66153
## inferred_menopausal_statePre                                    1.25565
## tumor_stage                                                     0.92343
## three_gene_classifier_subtypeER+/HER2- High Prolif              0.57922
## three_gene_classifier_subtypeER+/HER2- Low Prolif               0.48976
## three_gene_classifier_subtypeHER2+                              0.37486
## type_of_breast_surgeryMastectomy                                0.90340
## cancer_type_detailedBreast Invasive Ductal Carcinoma            0.00000
## cancer_type_detailedBreast Invasive Lobular Carcinoma           0.00000
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma    0.00000
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma   0.00000
## pam50_claudin_low_subtypeclaudin-low                            0.49791
## pam50_claudin_low_subtypeHer2                                   0.70197
## pam50_claudin_low_subtypeLumA                                   0.50303
## pam50_claudin_low_subtypeLumB                                   0.51579
## pam50_claudin_low_subtypeNC                                     0.05192
## pam50_claudin_low_subtypeNormal                                 0.69625
## tumor_other_histologic_subtypeLobular                               NA
## tumor_other_histologic_subtypeMedullary                         0.70592
## tumor_other_histologic_subtypeMixed                                 NA
## tumor_other_histologic_subtypeMucinous                              NA
## tumor_other_histologic_subtypeOther                                 NA
## tumor_other_histologic_subtypeTubular/ cribriform               0.23253
## integrative_cluster10                                           0.42027
## integrative_cluster2                                            0.64553
## integrative_cluster3                                            0.67807
## integrative_cluster4ER-                                         0.49285
## integrative_cluster4ER+                                         0.57954
## integrative_cluster5                                            1.02838
## integrative_cluster6                                            0.58881
## integrative_cluster7                                            0.61221
## integrative_cluster8                                            0.65018
## integrative_cluster9                                            0.61639
## mutation_count                                                  0.98673
## tumor_size:radio_therapyYes                                     0.98172
##                                                               upper .95
## age_at_diagnosis                                                  1.060
## tumor_size                                                        1.025
## lymph_nodes_examined_positive                                     1.076
## nottingham_prognostic_index                                       1.246
## radio_therapyYes                                                  1.443
## inferred_menopausal_statePre                                      2.322
## tumor_stage                                                       1.284
## three_gene_classifier_subtypeER+/HER2- High Prolif                1.338
## three_gene_classifier_subtypeER+/HER2- Low Prolif                 1.156
## three_gene_classifier_subtypeHER2+                                1.176
## type_of_breast_surgeryMastectomy                                  1.365
## cancer_type_detailedBreast Invasive Ductal Carcinoma                Inf
## cancer_type_detailedBreast Invasive Lobular Carcinoma               Inf
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma        Inf
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma       Inf
## pam50_claudin_low_subtypeclaudin-low                              1.139
## pam50_claudin_low_subtypeHer2                                     1.677
## pam50_claudin_low_subtypeLumA                                     1.254
```

```
## pam50_claudin_low_subtypeLumB                                    1.294
## pam50_claudin_low_subtypeNC                                      2.996
## pam50_claudin_low_subtypeNormal                                  1.935
## tumor_other_histologic_subtypeLobular                               NA
## tumor_other_histologic_subtypeMedullary                          2.769
## tumor_other_histologic_subtypeMixed                                 NA
## tumor_other_histologic_subtypeMucinous                              NA
## tumor_other_histologic_subtypeOther                                 NA
## tumor_other_histologic_subtypeTubular/ cribriform                1.401
## integrative_cluster10                                            1.102
## integrative_cluster2                                             1.654
## integrative_cluster3                                             1.513
## integrative_cluster4ER-                                          1.539
## integrative_cluster4ER+                                          1.314
## integrative_cluster5                                             3.206
## integrative_cluster6                                             1.469
## integrative_cluster7                                             1.400
## integrative_cluster8                                             1.419
## integrative_cluster9                                             1.425
## mutation_count                                                   1.022
## tumor_size:radio_therapyYes                                      1.005
##
## Concordance= 0.693  (se = 0.011 )
## Likelihood ratio test= 330  on 35 df,   p=<2e-16
## Wald test            = 339.5  on 35 df,   p=<2e-16
## Score (logrank) test = 379  on 35 df,   p=<2e-16
```

```
cox_tidy <- broom::tidy(
  final_inter_mod,
  exponentiate = TRUE,
  conf.int     = TRUE
)

cox_tidy
```

```
## # A tibble: 39 x 7
##    term                 estimate std.error statistic  p.value conf.low conf.high
##    <chr>                   <dbl>     <dbl>     <dbl>    <dbl>    <dbl>     <dbl>
##  1 age_at_diagnosis         1.05    0.00488    10.1   7.56e-24    1.04       1.06
##  2 tumor_size               1.01    0.00578     2.36  1.85e- 2    1.00       1.03
##  3 lymph_nodes_examine~     1.05    0.0119      4.23  2.35e- 5    1.03       1.08
##  4 nottingham_prognost~     1.12    0.0523      2.25  2.47e- 2    1.02       1.25
##  5 radio_therapyYes         0.977   0.199      -0.116 9.07e- 1    0.662      1.44
##  6 inferred_menopausal~     1.71    0.157       3.41  6.47e- 4    1.26       2.32
##  7 tumor_stage              1.09    0.0841      1.01  3.11e- 1    0.923      1.28
##  8 three_gene_classifi~     0.880   0.214      -0.596 5.51e- 1    0.579      1.34
##  9 three_gene_classifi~     0.752   0.219      -1.30  1.94e- 1    0.490      1.16
## 10 three_gene_classifi~     0.664   0.292      -1.40  1.61e- 1    0.375      1.18
## # i 29 more rows
```

The multivariable Cox proportional hazards model evaluates how demographic, tumor, and treatment characteristics jointly affect overall survival among METABRIC breast cancer patients. After adjustment for all covariates, traditional prognostic factors such as older age at diagnosis, larger tumor size, a higher number

of positive lymph nodes, and a higher Nottingham prognostic index generally show associations compatible with increased hazard of death, indicating worse survival as these measures of disease burden increase.

Tumor-related categorical variables, including tumor stage, three_gene_classifier_subtype (ER/HER2 profile), pam50_claudin_low_subtype, tumor_other_histologic_subtype, cancer_type_detailed, and integrative_cluster, capture biologic and histologic differences between tumors and contribute additional information on risk. Treatment variables such as radio_therapy, along with menopausal status and type_of_breast_surgery, help describe differences in management patterns and their impact on survival. The inclusion of a radio_therapy × tumor_size interaction allows the association between tumor size and mortality risk to differ between patients who did and did not receive radiotherapy.

Hazard ratios from this model represent the multiplicative change in the instantaneous risk of death associated with each covariate, holding all others constant. The directions of effect are broadly consistent with clinical expectations; however, these interpretations rely on the proportional hazards assumption, which is examined in the next section.

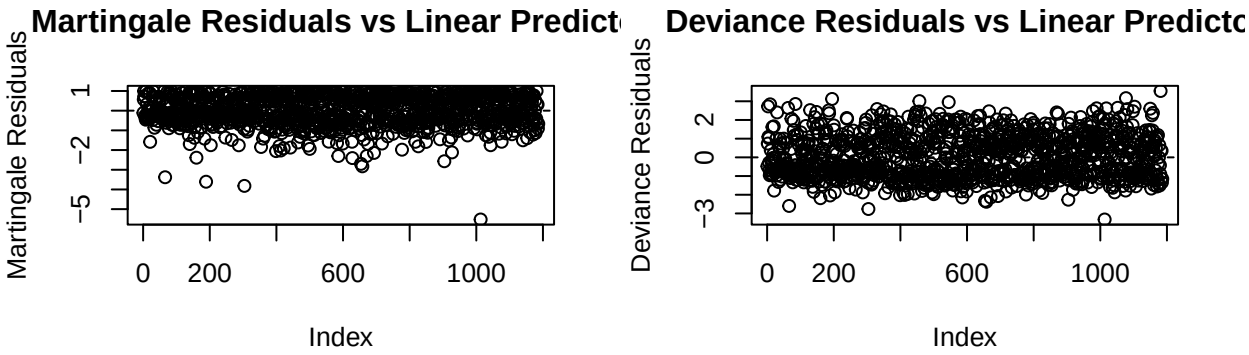
Proportional hazards (PH) diagnostics

```
# Residual diagnostics
par(mfrow = c(2, 2))

plot(
  resid(final_inter_mod, type = "martingale"),
  main = "Martingale Residuals vs Linear Predictor",
  ylab = "Martingale Residuals"
)
abline(h = 0, lty = 2)

plot(
  resid(final_inter_mod, type = "deviance"),
  main = "Deviance Residuals vs Linear Predictor",
  ylab = "Deviance Residuals"
)
abline(h = 0, lty = 2)

# Schoenfeld residual PH test
ph_test <- cox.zph(final_inter_mod)
ph_test
```

```
##                                  chisq df       p
## age_at_diagnosis                56.2469  1 6.4e-14
## tumor_size                       2.6581  1 0.10303
## lymph_nodes_examined_positive    4.1983  1 0.04046
## nottingham_prognostic_index     36.1266  1 1.8e-09
## radio_therapy                    0.8096  1 0.36825
## inferred_menopausal_state       26.2766  1 3.0e-07
## tumor_stage                     10.9739  1 0.00092
## three_gene_classifier_subtype   48.0542  3 2.1e-10
## type_of_breast_surgery           0.0169  1 0.89668
## cancer_type_detailed             8.7272  4 0.06829
## pam50_claudin_low_subtype       54.7164  6 5.3e-10
## tumor_other_histologic_subtype   1.0153  2 0.60190
## integrative_cluster             73.8193 10 8.1e-12
```

```
## mutation_count                  0.1202  1 0.72884
## tumor_size:radio_therapy        1.2559  1 0.26242
## GLOBAL                        139.5229 35 2.0e-14
```

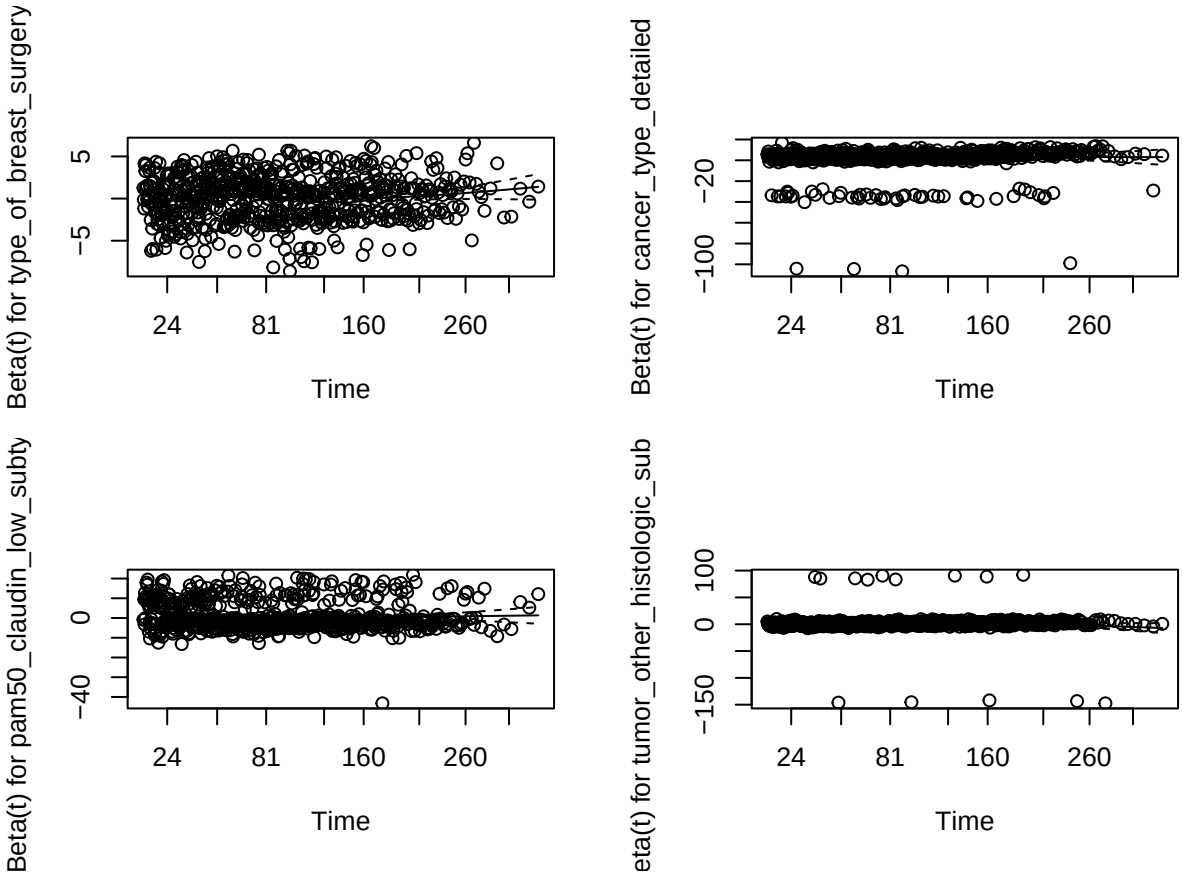
```r
# Schoenfeld residual plots
par(mfrow = c(2, 2))
```



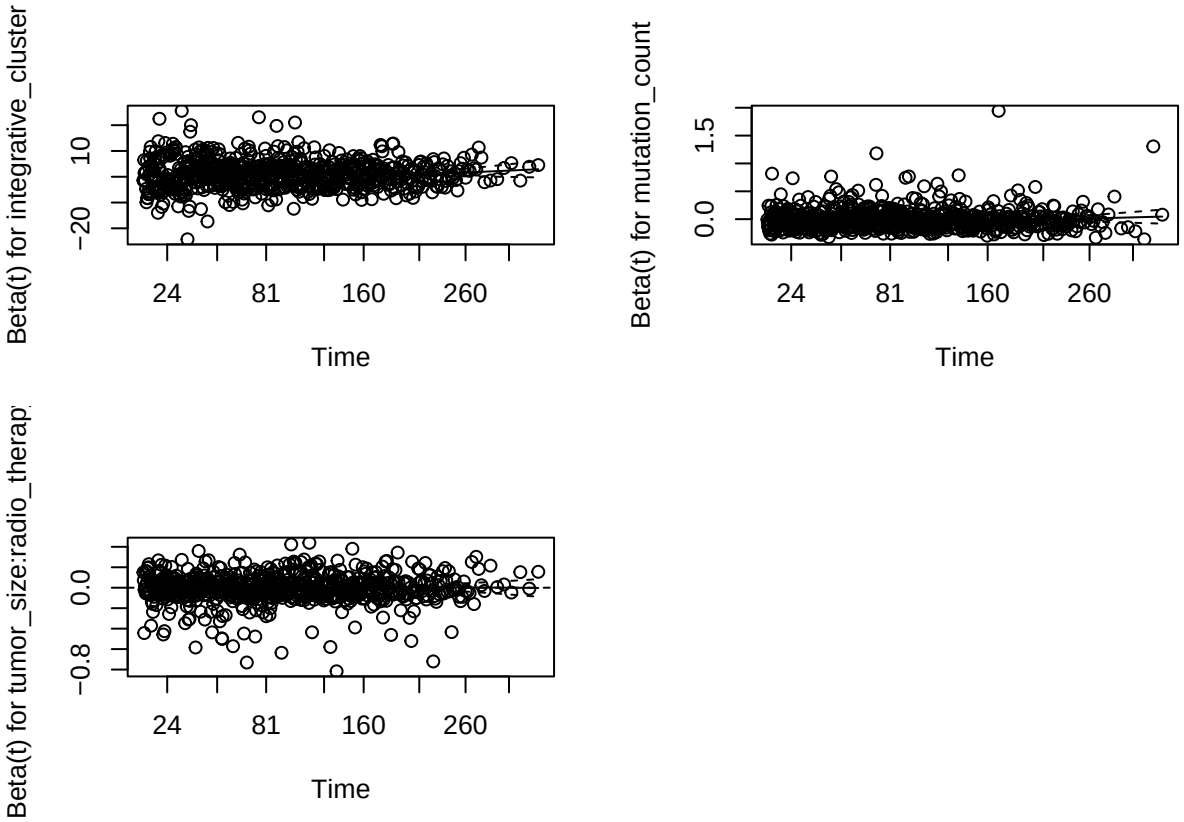

```r
plot(ph_test)
```

Beta(t) for age_at_diagnosis
−0.2
0.4
24
81
160
260
Time
Beta(t) for tumor_size
−0.4
0.4
24
81
160
260
Time
eta(t) for lymph_nodes_examined_po
0
2
24
81
160
260
Time
Beta(t) for nottingham_prognostic_inc
−4
0
24
81
160
260
Time

Beta(t) for radio_therapy
−15
0
15
24
81
160
260
Time
Beta(t) for tumor_stage
−10
0
10
24
81
160
260
Time
Beta(t) for three_gene_classifier_subt
Beta(t) for inferred_menopausal_sta
−5
5
24
81
160
260
Time
−40
0
40
24
81
160
260
Time




```
abline(h = 0, lty = 2)
par(mfrow = c(1, 1))
```



Martingale and deviance residual plots do not reveal severe global model misfit, although a small number of influential observations and mild departures from perfect linearity are apparent. These diagnostics mainly suggest that the overall functional form of the model is reasonable but not flawless.

The Schoenfeld residual test provides a more direct assessment of the proportional hazards assumption. The global test, along with several covariate-specific tests, indicates statistically significant time-varying effects for some predictors. In particular, variables such as age_at_diagnosis, radiotherapy, tumor characteristics, and their interaction (radio_therapy × tumor_size) show patterns in their Schoenfeld residual plots that deviate from a flat horizontal line, suggesting that their effects on the hazard of death change over time rather than remaining constant.

Because the proportional hazards assumption is a key requirement of the Cox model, these findings imply that hazard ratios should be interpreted with some caution. To investigate robustness under an alternative modeling framework that does not require proportional hazards, we fit accelerated failure time (AFT) models as a sensitivity analysis.

AFT sensitivity analysis

```
aft_weibull <- survreg(
  Surv(
    overall_survival_months,
    overall_survival_status == "Deceased"
  ) ~
    age_at_diagnosis +
    tumor_size +
    lymph_nodes_examined_positive +
```

```
    nottingham_prognostic_index +
    radio_therapy +
    inferred_menopausal_state +
    tumor_stage +
    three_gene_classifier_subtype +
    type_of_breast_surgery +
    cancer_type_detailed +
    pam50_claudin_low_subtype +
    tumor_other_histologic_subtype +
    integrative_cluster +
    mutation_count +
    log(tumor_size):radio_therapy +
    age_at_diagnosis:radio_therapy,
  data = filtered_data,
  dist = "weibull"
)

# Compare alternative distributions
aft_lognormal   <- update(aft_weibull, dist = "lognormal")
aft_loglogistic <- update(aft_weibull, dist = "loglogistic")

AIC(aft_lognormal)
```

```
## [1] 8307.446
```

```
AIC(aft_weibull)
```

```
## [1] 8260.395
```

```
AIC(aft_loglogistic)
```

```
## [1] 8266.172
```

```
# Extract time ratios with confidence intervals for Weibull model
aft_ci <- exp(confint(aft_weibull))
aft_tr <- exp(coef(aft_weibull))

aft_table <- data.frame(
  Variable   = names(aft_tr),
  Time_Ratio = aft_tr,
  CI_Lower   = aft_ci[, 1],
  CI_Upper   = aft_ci[, 2]
)

aft_table
```

```
##
## (Intercept)
## age_at_diagnosis
## tumor_size
## lymph_nodes_examined_positive                                                    lymph_
```

```
## nottingham_prognostic_index                                                                  nott
## radio_therapyYes
## inferred_menopausal_statePre                                                                 infer
## tumor_stage
## three_gene_classifier_subtypeER+/HER2- High Prolif                          three_gene_classifier_subtyp
## three_gene_classifier_subtypeER+/HER2- Low Prolif                           three_gene_classifier_subty
## three_gene_classifier_subtypeHER2+                                                  three_gene_
## type_of_breast_surgeryMastectomy                                                      type_of_br
## cancer_type_detailedBreast Invasive Ductal Carcinoma                    cancer_type_detailedBreast Inv
## cancer_type_detailedBreast Invasive Lobular Carcinoma                  cancer_type_detailedBreast Inva
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma   cancer_type_detailedBreast Invasive Mi
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma cancer_type_detailedBreast Mixed Ductal
## pam50_claudin_low_subtypeclaudin-low                                                pam50_claudin_
## pam50_claudin_low_subtypeHer2                                                              pam50_c
## pam50_claudin_low_subtypeLumA                                                              pam50_c
## pam50_claudin_low_subtypeLumB                                                              pam50_c
## pam50_claudin_low_subtypeNC                                                                  pam5
## pam50_claudin_low_subtypeNormal                                                          pam50_cla
## tumor_other_histologic_subtypeLobular                                                 tumor_other_his
## tumor_other_histologic_subtypeMedullary                                              tumor_other_histo
## tumor_other_histologic_subtypeMixed                                                     tumor_other_h
## tumor_other_histologic_subtypeMucinous                                                tumor_other_hist
## tumor_other_histologic_subtypeOther                                                     tumor_other_h
## tumor_other_histologic_subtypeTubular/ cribriform                          tumor_other_histologic_subt
## integrative_cluster10
## integrative_cluster2
## integrative_cluster3
## integrative_cluster4ER-                                                                              1
## integrative_cluster4ER+                                                                              1
## integrative_cluster5
## integrative_cluster6
## integrative_cluster7
## integrative_cluster8
## integrative_cluster9
## mutation_count
## radio_therapyNo:log(tumor_size)                                                            radio_the
## radio_therapyYes:log(tumor_size)                                                           radio_ther
## age_at_diagnosis:radio_therapyYes                                                         age_at_diag
##                                                                 Time_Ratio
## (Intercept)                                                   3.981209e+08
## age_at_diagnosis                                              9.660603e-01
## tumor_size                                                    1.001310e+00
## lymph_nodes_examined_positive                                 9.621810e-01
## nottingham_prognostic_index                                   9.162981e-01
## radio_therapyYes                                              1.180931e+00
## inferred_menopausal_statePre                                  6.926896e-01
## tumor_stage                                                   9.730263e-01
## three_gene_classifier_subtypeER+/HER2- High Prolif            1.100052e+00
## three_gene_classifier_subtypeER+/HER2- Low Prolif             1.240856e+00
## three_gene_classifier_subtypeHER2+                            1.356524e+00
## type_of_breast_surgeryMastectomy                              9.562415e-01
## cancer_type_detailedBreast Invasive Ductal Carcinoma          1.336101e-05
## cancer_type_detailedBreast Invasive Lobular Carcinoma         1.551825e-05
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma  2.017107e-05
```

```
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma 1.300091e-05
## pam50_claudin_low_subtypeclaudin-low                          1.227576e+00
## pam50_claudin_low_subtypeHer2                                 9.263517e-01
## pam50_claudin_low_subtypeLumA                                 1.155411e+00
## pam50_claudin_low_subtypeLumB                                 1.142379e+00
## pam50_claudin_low_subtypeNC                                   1.957232e+00
## pam50_claudin_low_subtypeNormal                               8.807838e-01
## tumor_other_histologic_subtypeLobular                                   NA
## tumor_other_histologic_subtypeMedullary                       7.454257e-01
## tumor_other_histologic_subtypeMixed                                     NA
## tumor_other_histologic_subtypeMucinous                                  NA
## tumor_other_histologic_subtypeOther                                     NA
## tumor_other_histologic_subtypeTubular/ cribriform             1.382164e+00
## integrative_cluster10                                         1.293235e+00
## integrative_cluster2                                          8.970724e-01
## integrative_cluster3                                          9.756006e-01
## integrative_cluster4ER-                                       1.080654e+00
## integrative_cluster4ER+                                       1.068352e+00
## integrative_cluster5                                          6.520211e-01
## integrative_cluster6                                          1.027033e+00
## integrative_cluster7                                          1.032745e+00
## integrative_cluster8                                          1.005275e+00
## integrative_cluster9                                          1.013440e+00
## mutation_count                                                9.955238e-01
## radio_therapyNo:log(tumor_size)                               7.446536e-01
## radio_therapyYes:log(tumor_size)                              7.266791e-01
## age_at_diagnosis:radio_therapyYes                             1.001072e+00
##                                                                CI_Lower
## (Intercept)                                                   0.0000000
## age_at_diagnosis                                              0.9577066
## tumor_size                                                    0.9942822
## lymph_nodes_examined_positive                                 0.9468032
## nottingham_prognostic_index                                   0.8527211
## radio_therapyYes                                              0.4282061
## inferred_menopausal_statePre                                  0.5583204
## tumor_stage                                                   0.8627505
## three_gene_classifier_subtypeER+/HER2- High Prolif            0.8189749
## three_gene_classifier_subtypeER+/HER2- Low Prolif             0.9170685
## three_gene_classifier_subtypeHER2+                            0.9048474
## type_of_breast_surgeryMastectomy                              0.8252283
## cancer_type_detailedBreast Invasive Ductal Carcinoma          0.0000000
## cancer_type_detailedBreast Invasive Lobular Carcinoma         0.0000000
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma  0.0000000
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma 0.0000000
## pam50_claudin_low_subtypeclaudin-low                          0.9180968
## pam50_claudin_low_subtypeHer2                                 0.6831930
## pam50_claudin_low_subtypeLumA                                 0.8383571
## pam50_claudin_low_subtypeLumB                                 0.8265686
## pam50_claudin_low_subtypeNC                                   0.4693102
## pam50_claudin_low_subtypeNormal                               0.6147883
## tumor_other_histologic_subtypeLobular                                NA
## tumor_other_histologic_subtypeMedullary                       0.4603267
## tumor_other_histologic_subtypeMixed                                  NA
## tumor_other_histologic_subtypeMucinous                               NA
```

```
## tumor_other_histologic_subtypeOther                                    NA
## tumor_other_histologic_subtypeTubular/ cribriform             0.7337697
## integrative_cluster10                                         0.9230238
## integrative_cluster2                                          0.6442743
## integrative_cluster3                                          0.7351044
## integrative_cluster4ER-                                       0.7249431
## integrative_cluster4ER+                                       0.8004487
## integrative_cluster5                                          0.4358867
## integrative_cluster6                                          0.7446676
## integrative_cluster7                                          0.7719673
## integrative_cluster8                                          0.7638130
## integrative_cluster9                                          0.7540969
## mutation_count                                                0.9833782
## radio_therapyNo:log(tumor_size)                               0.5702929
## radio_therapyYes:log(tumor_size)                              0.5350255
## age_at_diagnosis:radio_therapyYes                             0.9917696
##                                                                CI_Upper
## (Intercept)                                                         Inf
## age_at_diagnosis                                              0.9744869
## tumor_size                                                    1.0083881
## lymph_nodes_examined_positive                                 0.9778086
## nottingham_prognostic_index                                   0.9846152
## radio_therapyYes                                              3.2568400
## inferred_menopausal_statePre                                  0.8593971
## tumor_stage                                                   1.0973974
## three_gene_classifier_subtypeER+/HER2- High Prolif            1.4775971
## three_gene_classifier_subtypeER+/HER2- Low Prolif             1.6789631
## three_gene_classifier_subtypeHER2+                            2.0336673
## type_of_breast_surgeryMastectomy                              1.1080543
## cancer_type_detailedBreast Invasive Ductal Carcinoma                Inf
## cancer_type_detailedBreast Invasive Lobular Carcinoma               Inf
## cancer_type_detailedBreast Invasive Mixed Mucinous Carcinoma        Inf
## cancer_type_detailedBreast Mixed Ductal and Lobular Carcinoma       Inf
## pam50_claudin_low_subtypeclaudin-low                          1.6413768
## pam50_claudin_low_subtypeHer2                                 1.2560543
## pam50_claudin_low_subtypeLumA                                 1.5923699
## pam50_claudin_low_subtypeLumB                                 1.5788519
## pam50_claudin_low_subtypeNC                                   8.1625280
## pam50_claudin_low_subtypeNormal                               1.2618655
## tumor_other_histologic_subtypeLobular                               NA
## tumor_other_histologic_subtypeMedullary                       1.2070981
## tumor_other_histologic_subtypeMixed                                 NA
## tumor_other_histologic_subtypeMucinous                              NA
## tumor_other_histologic_subtypeOther                                 NA
## tumor_other_histologic_subtypeTubular/ cribriform             2.6035126
## integrative_cluster10                                         1.8119335
## integrative_cluster2                                          1.2490627
## integrative_cluster3                                          1.2947774
## integrative_cluster4ER-                                       1.6109025
## integrative_cluster4ER+                                       1.4259206
## integrative_cluster5                                          0.9753258
## integrative_cluster6                                          1.4164671
## integrative_cluster7                                          1.3816161
## integrative_cluster8                                          1.3230698
```

```
## integrative_cluster9                                  1.3619740
## mutation_count                                        1.0078194
## radio_therapyNo:log(tumor_size)                       0.9723231
## radio_therapyYes:log(tumor_size)                      0.9869858
## age_at_diagnosis:radio_therapyYes                     1.0104622
```

Given the evidence of proportional hazards violations in the Cox model, we fitted accelerated failure time (AFT) models as a robustness check. AFT models describe how covariates multiply survival time directly, rather than affecting the hazard, and therefore do not require proportional hazards.

Using the same core predictors as in the Cox model, along with interactions involving log-transformed tumor_size and radiotherapy and age_at_diagnosis with radiotherapy, we fitted Weibull, lognormal, and log-logistic AFT models. Comparison of AIC values identified the Weibull distribution as the best-fitting parametric form among the three candidate models.

In the AFT framework, exponentiated coefficients are interpreted as time ratios: a time_ratio greater than 1 indicates longer expected survival, whereas a time_ratio less than 1 indicates shorter expected survival, holding other factors constant. Consistent with the Cox model, factors reflecting greater tumor burden or worse prognosis (e.g., larger tumor_size, more lymph_nodes_examined_positive, higher nottingham_prognostic_index, and more advanced tumor_stage) are associated with shorter survival times. The general agreement between the Cox and Weibull AFT results suggests that the main substantive conclusions about key prognostic factors are robust, even when relaxing the proportional hazards assumption.

Table 1: **Table 1. Baseline characteristics by overall survival status**

Characteristic	N	Deceased N = 1,144[1]	Living N = 834[1]	p-
age_at_diagnosis	1,978			<
Mean (SD)		64 (13)	57 (11)	
her2_status	1,977			
Negative		988 (86%)	742 (89%)	
Positive		155 (14%)	92 (11%)	
Unknown		1	0	
tumor_size	1,955			<
Mean (SD)		28 (16)	23 (13)	
Unknown		16	7	
lymph_nodes_examined_positive	1,904			<
Mean (SD)		2.6 (4.8)	1.2 (2.7)	
Unknown		40	34	
mutation_count	1,859			<
Mean (SD)		6.0 (4.5)	5.3 (3.3)	
Unknown		55	64	
nottingham_prognostic_index	1,977			<
Mean (SD)		4.15 (1.20)	3.83 (1.08)	
Unknown		1	0	
type_of_breast_surgery	1,953			<
Breast Conserving		368 (33%)	416 (50%)	
Mastectomy		759 (67%)	410 (50%)	
Unknown		17	8	
cancer_type_detailed	1,978			
Breast		5 (0.4%)	12 (1.4%)	
Breast Invasive Ductal Carcinoma		891 (78%)	646 (77%)	
Breast Invasive Lobular Carcinoma		86 (7.5%)	60 (7.2%)	
Breast Invasive Mixed Mucinous Carcinoma		10 (0.9%)	13 (1.6%)	
Breast Mixed Ductal and Lobular Carcinoma		132 (12%)	79 (9.5%)	
Invasive Breast Carcinoma		18 (1.6%)	24 (2.9%)	
Metaplastic Breast Cancer		2 (0.2%)	0 (0%)	
pam50_claudin_low_subtype	1,977			<
Basal		115 (10%)	94 (11%)	
claudin-low		94 (8.2%)	121 (15%)	
Her2		157 (14%)	67 (8.0%)	
LumA		378 (33%)	322 (39%)	
LumB		315 (28%)	160 (19%)	
NC		5 (0.4%)	1 (0.1%)	
Normal		79 (6.9%)	69 (8.3%)	
Unknown		1	0	
neoplasm_histologic_grade	1,893			<
1		76 (7.0%)	93 (12%)	
2		432 (40%)	339 (42%)	
3		579 (53%)	374 (46%)	
Unknown		57	28	
tumor_other_histologic_subtype	1,936			
Ductal/NST		871 (77%)	620 (77%)	
Lobular		86 (7.6%)	60 (7.4%)	
Medullary		14 (1.2%)	11 (1.4%)	
Metaplastic		2 (0.2%)	0 (0%)	