

5231 pj V3

```
library(dplyr)
```

Attaching package: 'dplyr'

The following objects are masked from 'package:stats':

filter, lag

The following objects are masked from 'package:base':

intersect, setdiff, setequal, union

```
library(tidyr)  
library(survival)  
library(survminer)
```

Loading required package: ggplot2

Loading required package: ggpubr

Attaching package: 'survminer'

The following object is masked from 'package:survival':

myeloma

```
library(ggplot2)  
library(corrplot)
```

corrplot 0.95 loaded

```
library(glmnet)
```

Loading required package: Matrix

Attaching package: 'Matrix'

The following objects are masked from 'package:tidyr':

expand, pack, unpack

Loaded glmnet 4.1-8

```
library(flexsurv)
library(patchwork)
```

```
df <- read.csv('~Downloads/METABRIC_RNA_Mutation.csv')
```

```
#data selection: we choose clinical data and the gene we interested:tp53
#tp53: This gene is consider to have a tumor suppressor effect
df$tp53_mut_bin <- ifelse(df$tp53_mut=='0', 0, 1)
df_model<-df %>%
  select(overall_survival_months,
         overall_survival,
         age_at_diagnosis,
         tumor_size,
         tumor_stage,
         neoplasm_histologic_grade,
         chemotherapy,
         hormone_therapy,
         radio_therapy,
         er_status,
         pr_status,
         her2_status,
         tp53_mut_bin,
         type_of_breast_surgery,
         tp53)%>%
  mutate(tumor_stage = as.factor(tumor_stage),
         neoplasm_histologic_grade = as.factor(neoplasm_histologic_grade),
         chemotherapy = as.factor(chemotherapy),
         hormone_therapy = as.factor(hormone_therapy),
         radio_therapy = as.factor(radio_therapy),
         tp53_mut_bin = as.factor(tp53_mut_bin))%>%
  drop_na()
```

```
df_model <- df_model %>%
  mutate(tumor_stage_grp = case_when(
    tumor_stage %in% c(0, 1) ~ "Early",
    tumor_stage == 2 ~ "Intermediate",
    tumor_stage %in% c(3, 4) ~ "Late"
  )) %>%
  mutate(tumor_stage_grp = as.factor(tumor_stage_grp))
df_model$age_group <- ifelse(df_model$age_at_diagnosis <= 60, "<= 60", "> 60")
df_model$size_group <- ifelse(df_model$tumor_size <= 20, "<= 20mm", "> 20mm")
```

```
numeric_df <- df_model %>% select(where(is.numeric))
numeric_vars <- names(numeric_df)

par(mfrow = c(2, 3))

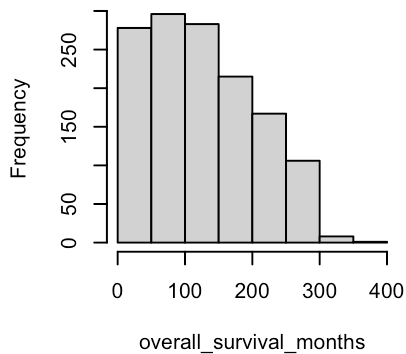
for (col in numeric_vars) {
```

```

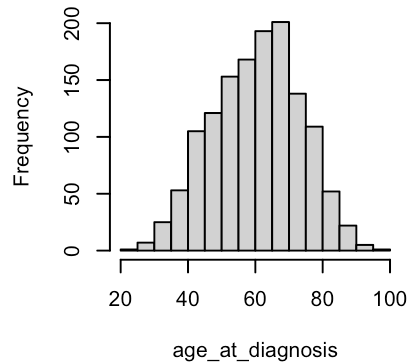
if (col == "overall_survival") next
hist(df_model[[col]],
     main = paste("Histogram of", col),
     xlab = col)
}

```

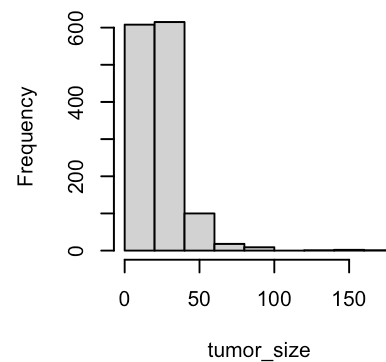
Histogram of overall_survival_mont



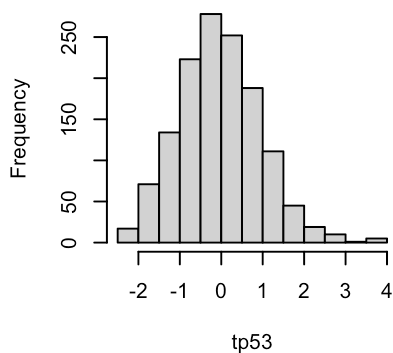
Histogram of age_at_diagnosis



Histogram of tumor_size



Histogram of tp53



```

make_pie <- function(data1, var, title_text) {
  df <- data1 %>%
    count(!!sym(var)) %>%
    mutate(percent = round(100 * n / sum(n), 1),
           label = paste0(!!sym(var), "\n", percent, "%"))
  ggplot(df, aes(x = "", y = n, fill = !!sym(var))) +
    geom_col(width = 1) +
    coord_polar(theta = "y") +
    geom_text(aes(label = label), position = position_stack(vjust = 0.5), size = 3) +
    labs(title = title_text, x = NULL, y = NULL) +
    theme_void() +
    theme(legend.position = "none")
}

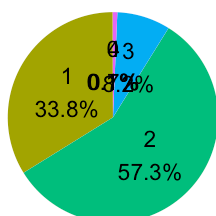
p1 <- make_pie(df_model, "tumor_stage", "Tumor Stage")
p2 <- make_pie(df_model, "neoplasm_histologic_grade", "Histologic Grade")
p3 <- make_pie(df_model, "chemotherapy", "Chemotherapy")
p4 <- make_pie(df_model, "hormone_therapy", "Hormone Therapy")

```

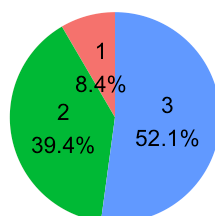
```
p5 <- make_pie(df_model, "radio_therapy", "Radiotherapy")
p6 <- make_pie(df_model, "tp53_mut_bin", "TP53 Mutation")
p7 <- make_pie(df_model, "er_status", "ER Status")
p8 <- make_pie(df_model, "pr_status", "PR Status")
p9 <- make_pie(df_model, "her2_status", "Her2 Status")
```

```
(p1 | p2 | p3) /
(p4 | p5 | p6) /
(p7 | p8 | p9)
```

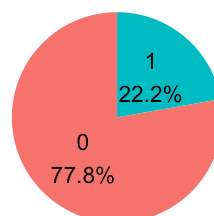
Tumor Stage



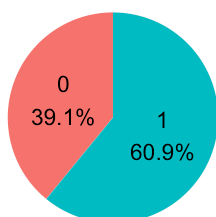
Histologic Grade



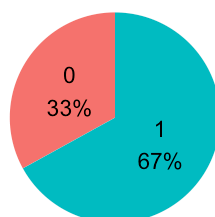
Chemotherapy



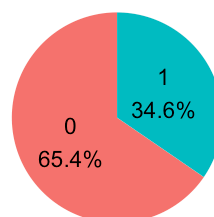
Hormone Therapy



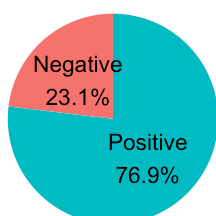
Radiotherapy



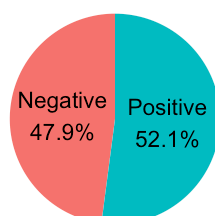
TP53 Mutation



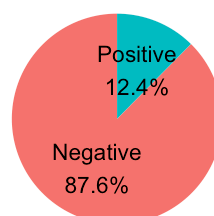
ER Status



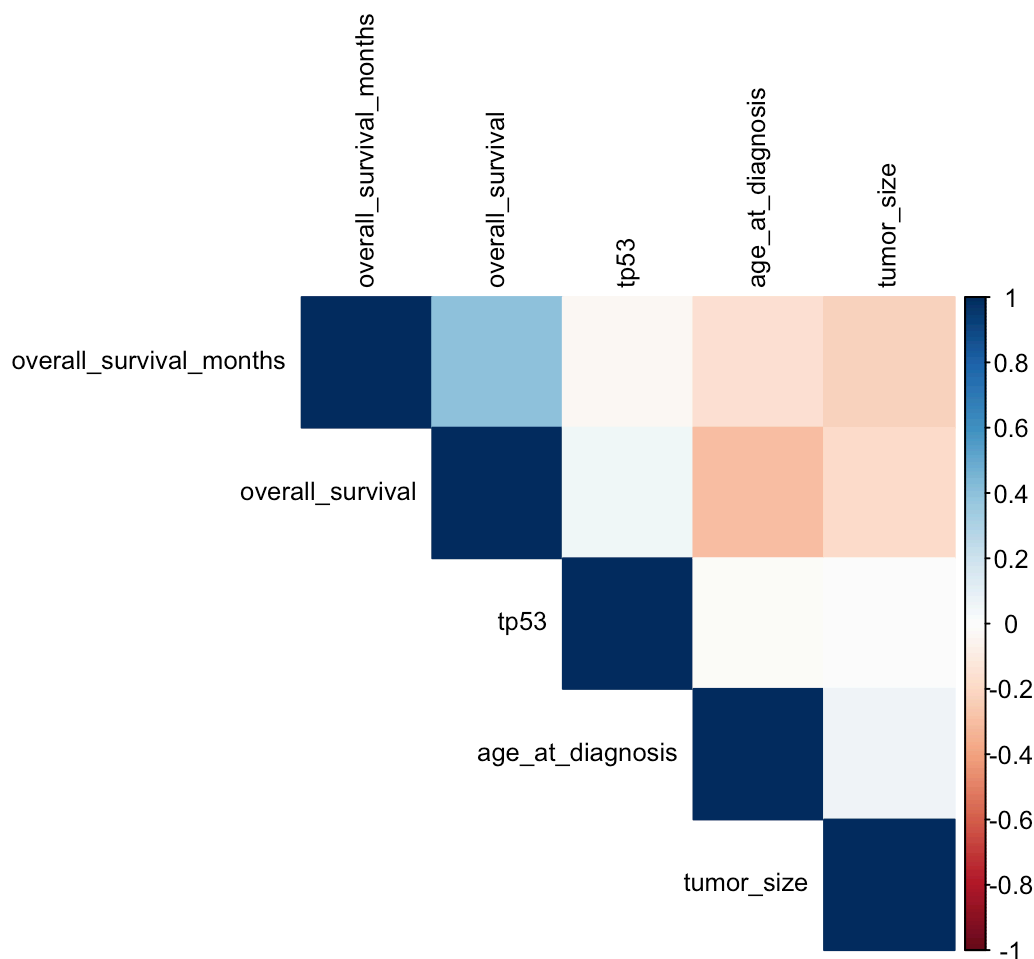
PR Status



Her2 Status



```
cor_mat <- cor(numeric_df, use = "complete.obs")
corrplot(cor_mat, method = "color", type = "upper",
          tl.cex = 0.8, tl.col = "black", order = "hclust")
```

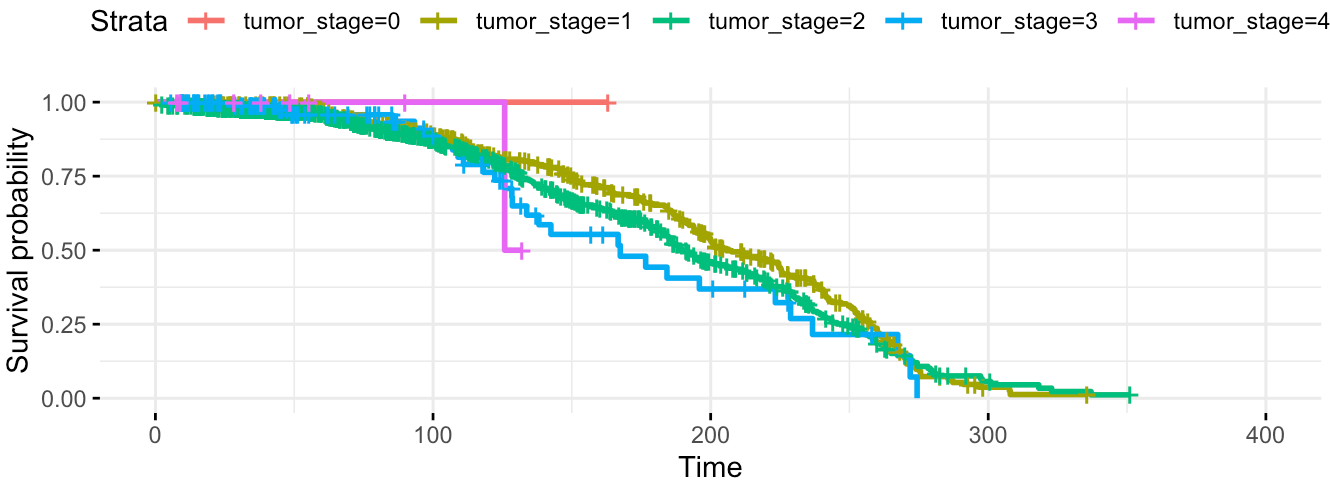


```
#KM plot
#looking for group feature,I assume the unique length less than 3 is also group not number
group_vars <- names(df_model)[sapply(df_model, function(x) {
  is.factor(x) || is.character(x) || (is.numeric(x) && length(unique(x)) <= 3)
})]
group_vars <- group_vars[group_vars != "overall_survival"]
for (var in group_vars) {
  formula <- as.formula(paste("Surv(overall_survival_months, overall_survival) ~", var))
  model <- survfit(formula, data = df_model)

  model$call <- list(formula = formula)

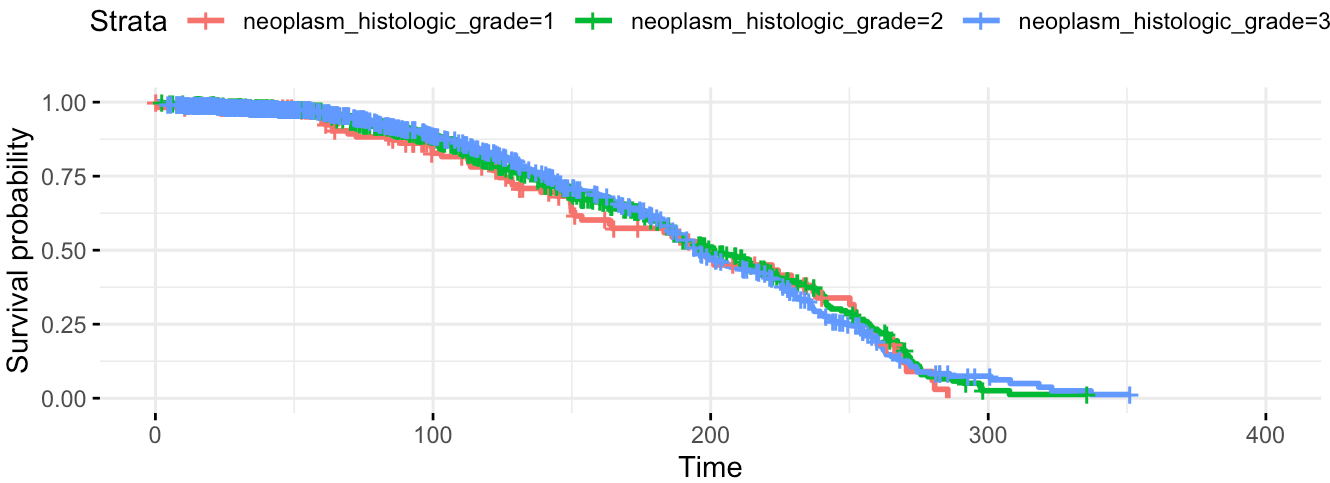
  print(ggsurvplot(model, data = df_model,
    risk.table = TRUE,
    risk.table.height = 0.4,
    title = paste("KM curve by", var),
    ggtheme = theme_minimal()))
}
```

KM curve by tumor_stage



Number at risk						
Strata	tumor_stage=0	1	1	0	0	0
	tumor_stage=1	457	326	142	3	0
	tumor_stage=2	776	414	130	6	0
	tumor_stage=3	111	37	10	0	0
	tumor_stage=4	9	2	0	0	0
		0	100	200	300	400
		Time				

KM curve by neoplasm_histologic_grade

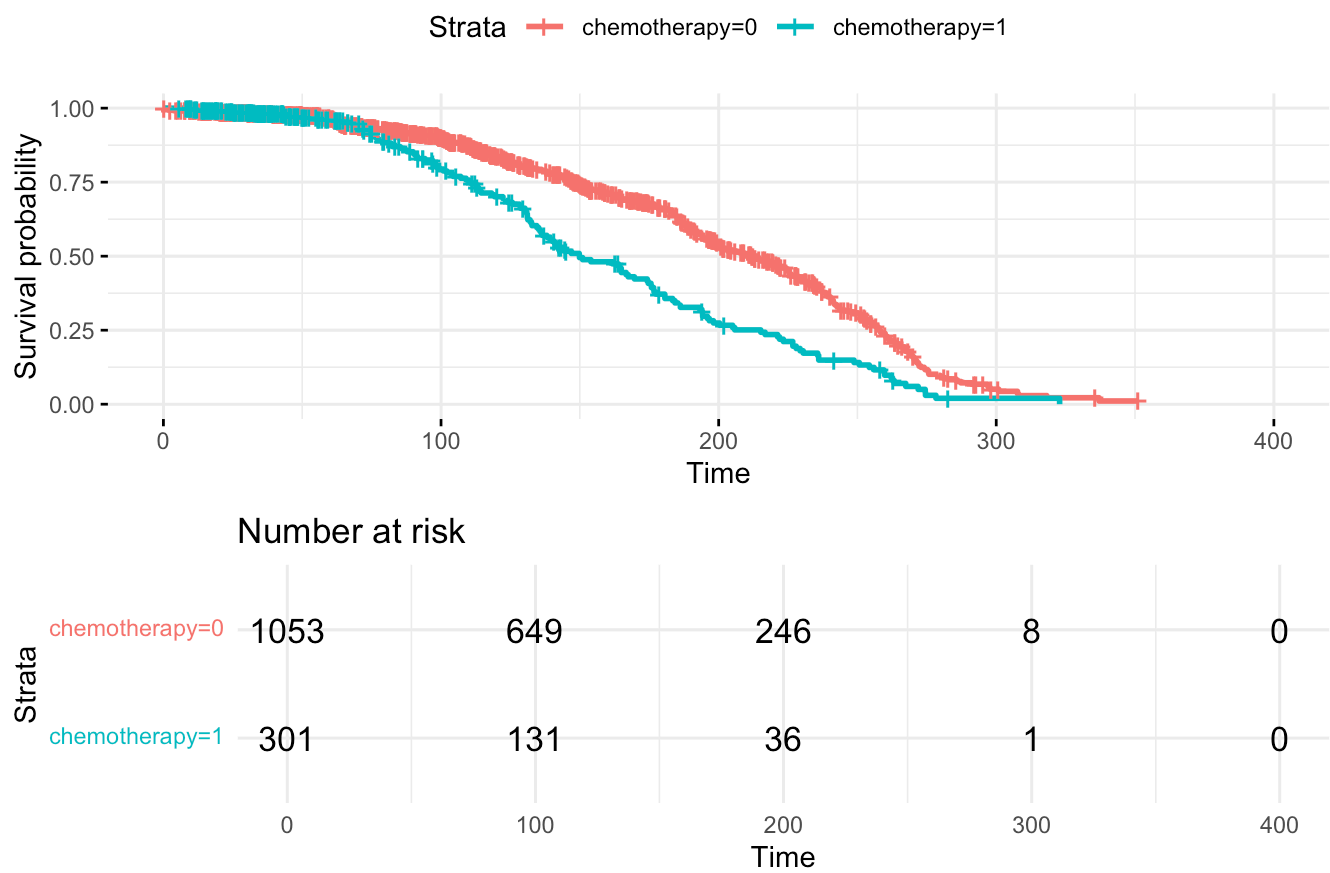


Number at risk

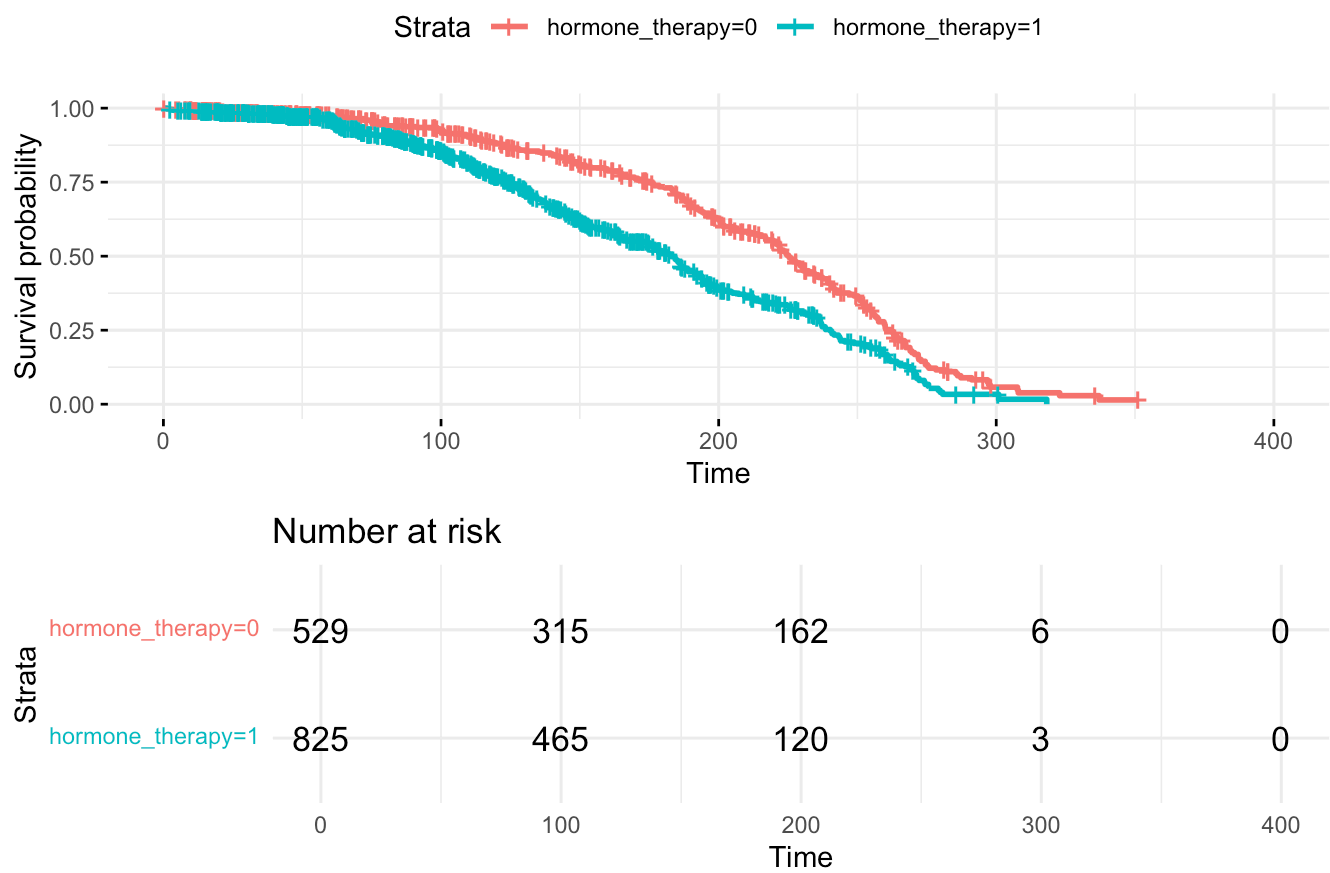
Strata	neoplasm_histologic_grade=1	114	72	30	0	0
	neoplasm_histologic_grade=2	534	342	118	2	0
	neoplasm_histologic_grade=3	706	366	134	7	0
		0	100	200	300	400

Time

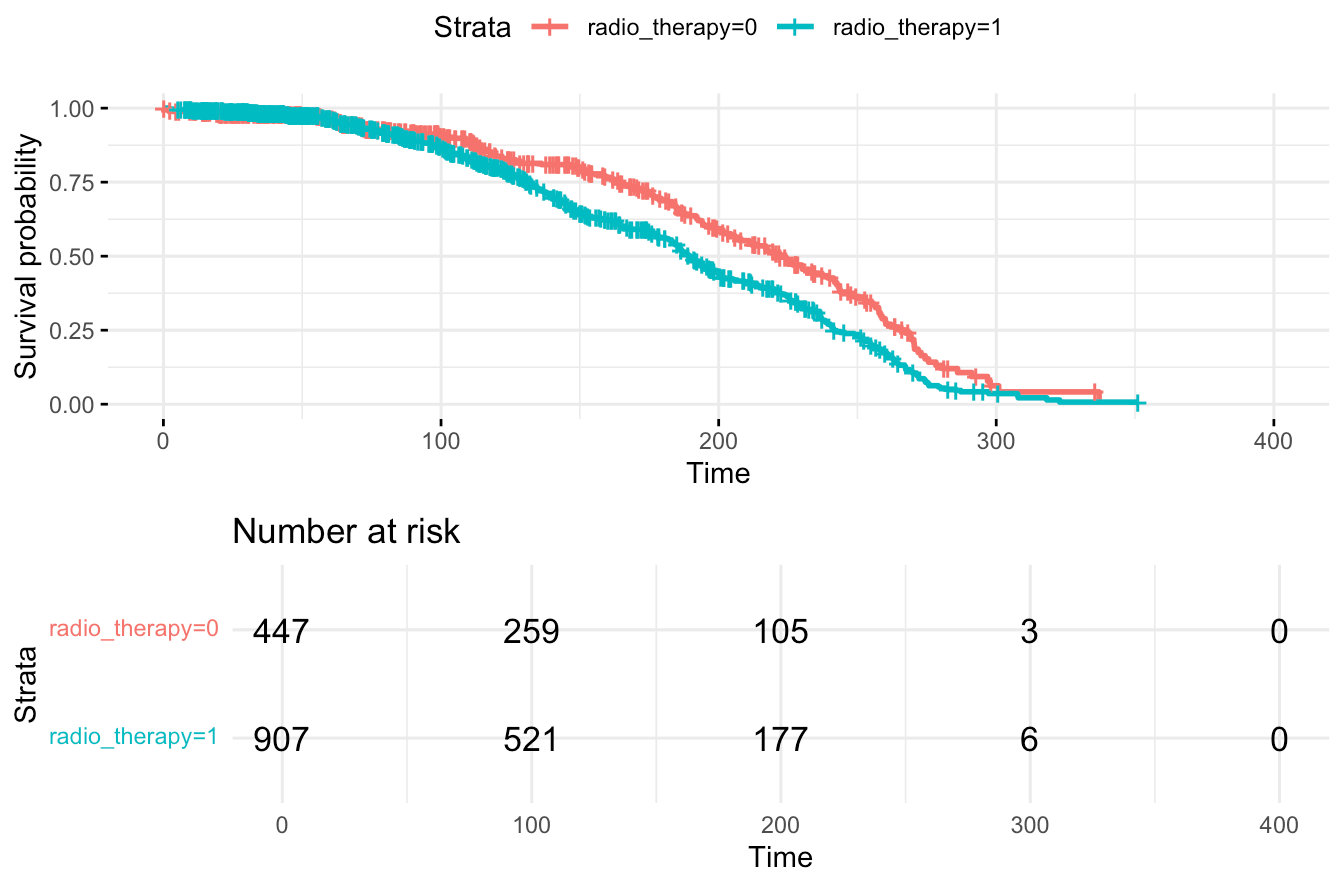
KM curve by chemotherapy



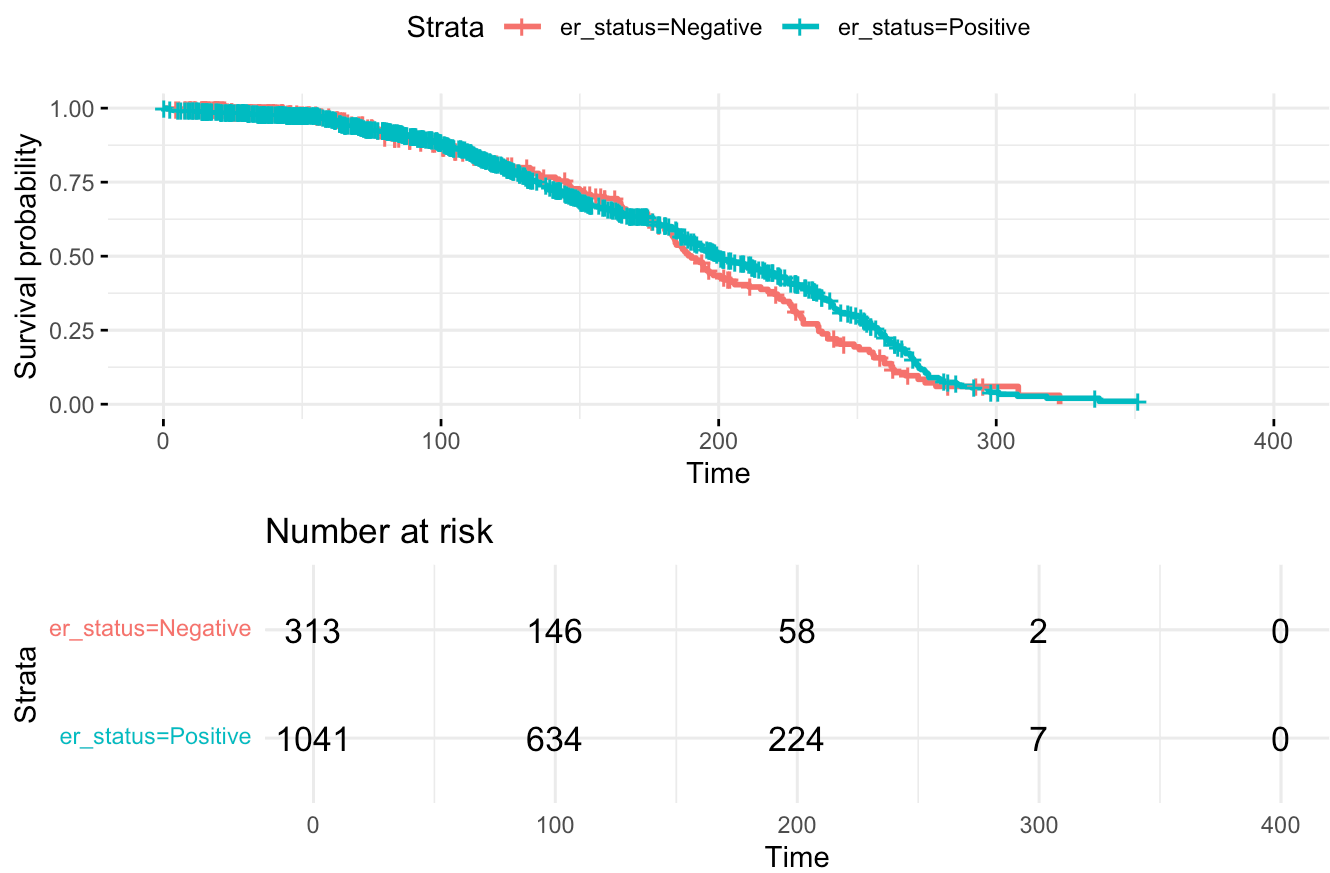
KM curve by hormone_therapy



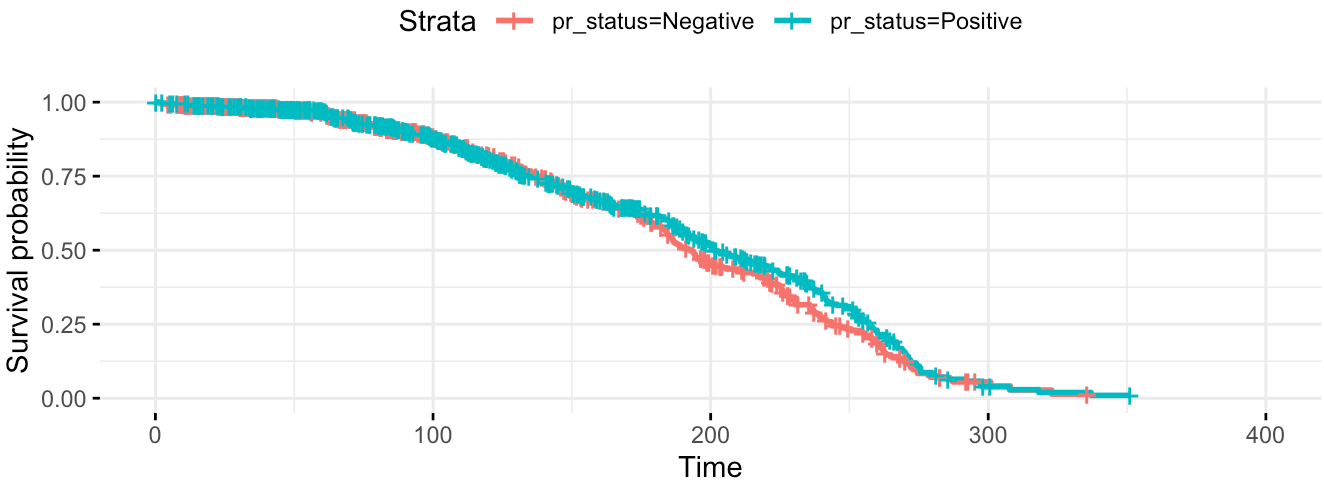
KM curve by radio_therapy



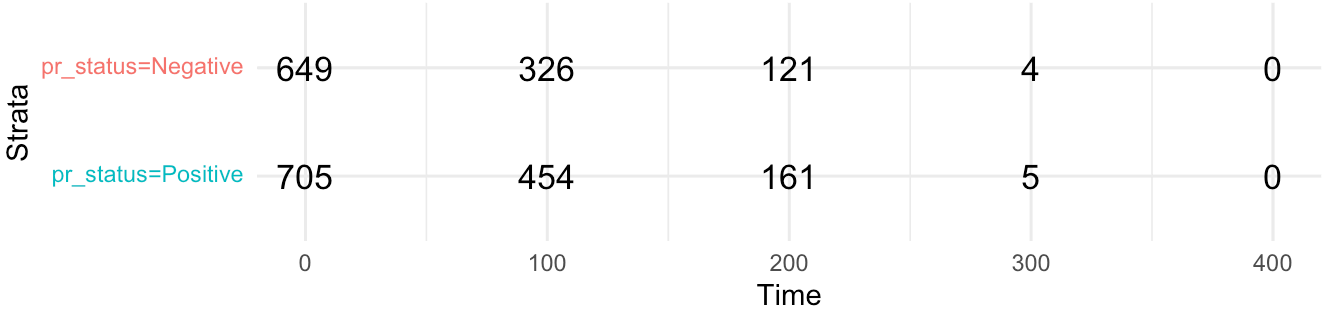
KM curve by er_status



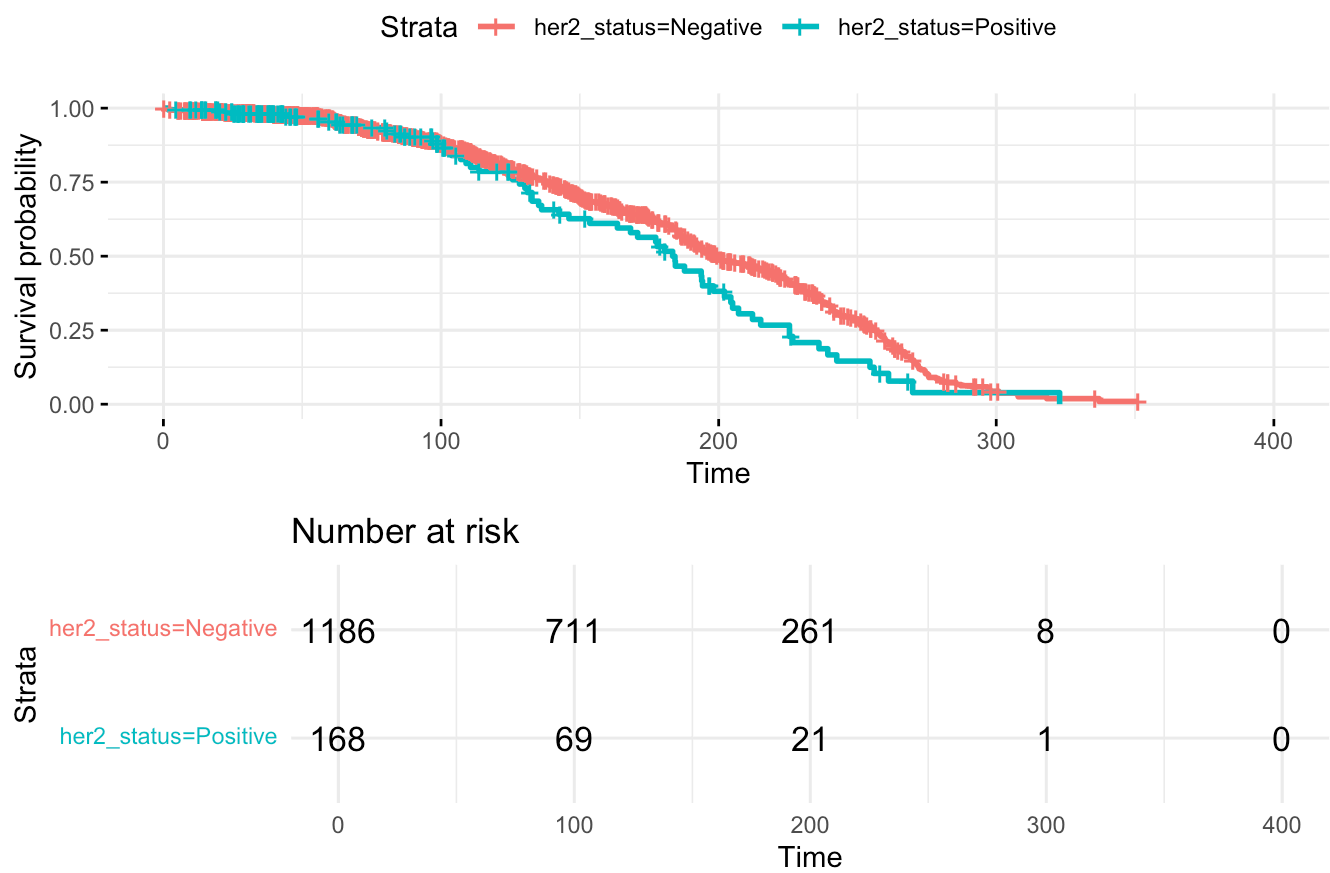
KM curve by pr_status



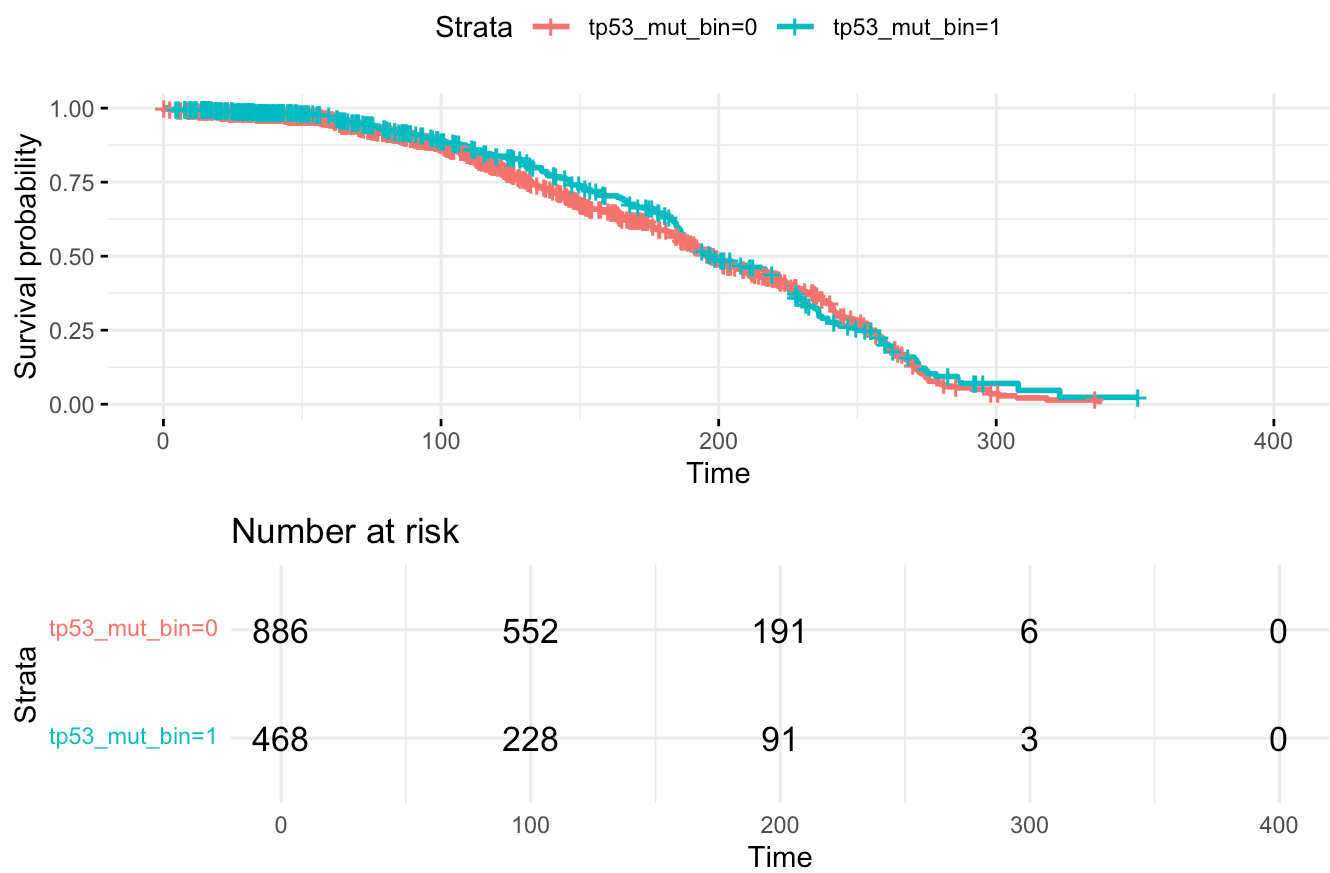
Number at risk



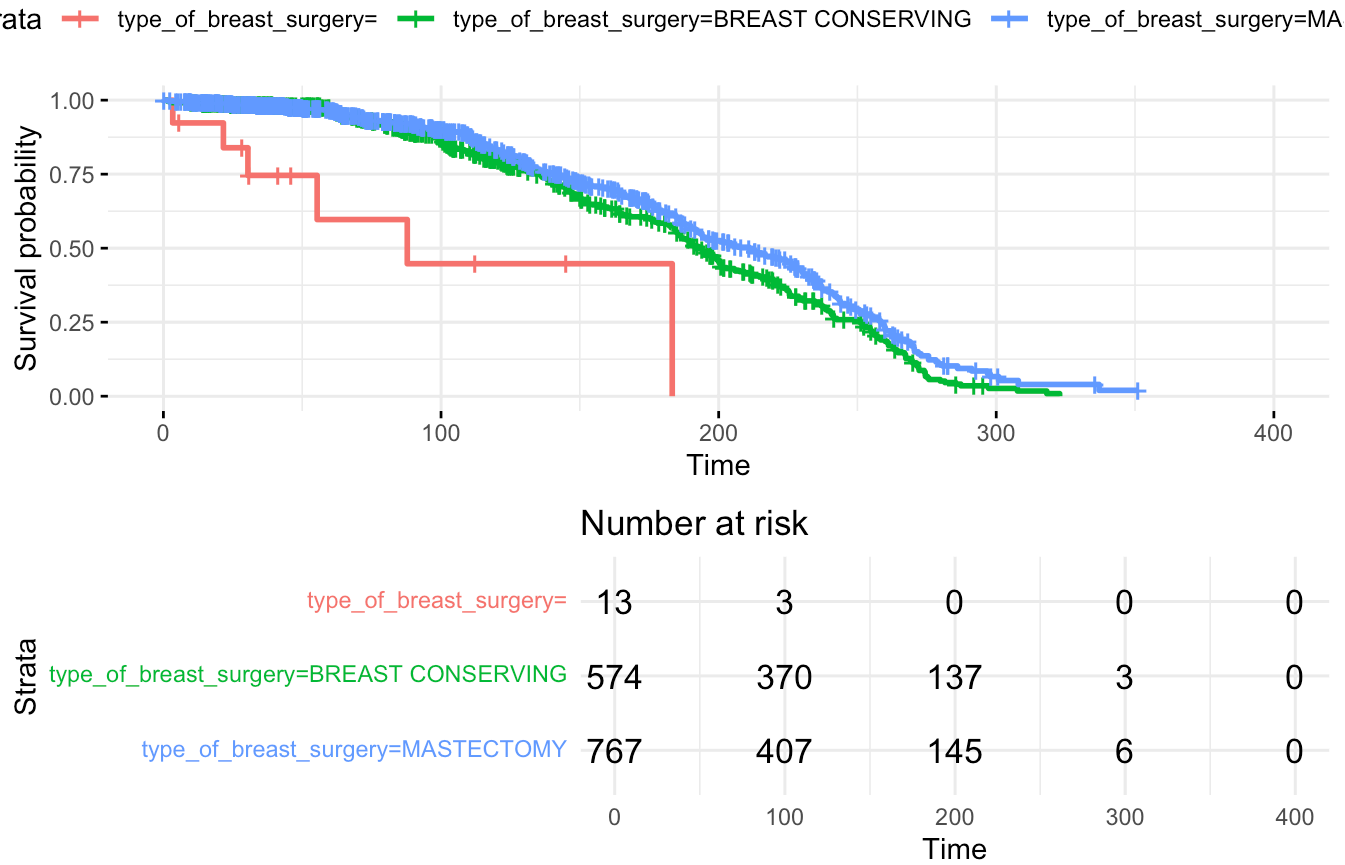
KM curve by her2_status



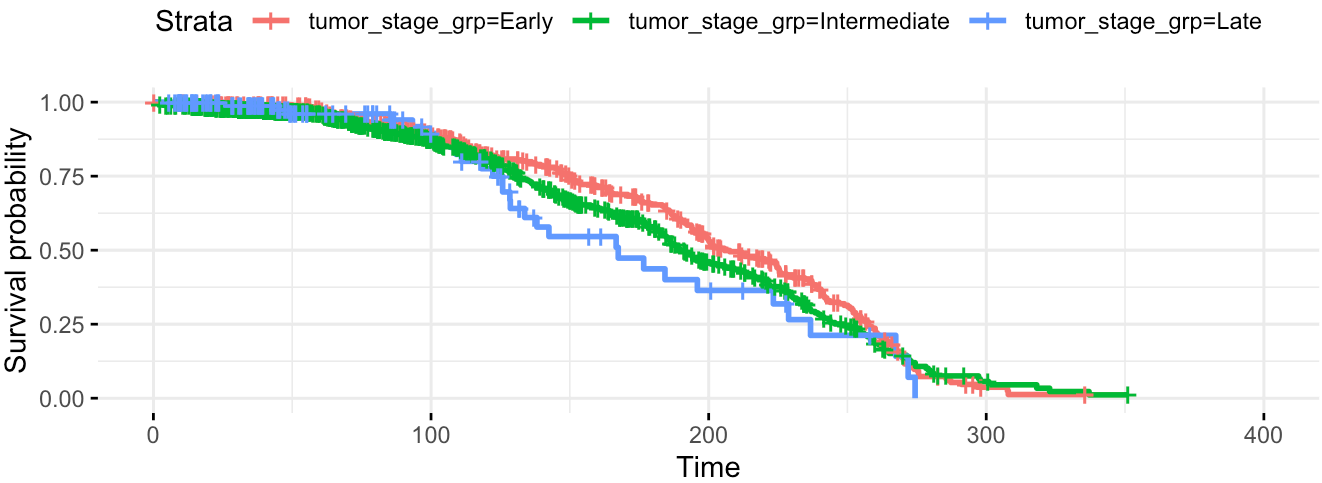
KM curve by tp53_mut_bin



KM curve by type_of_breast_surgery



KM curve by tumor_stage_grp

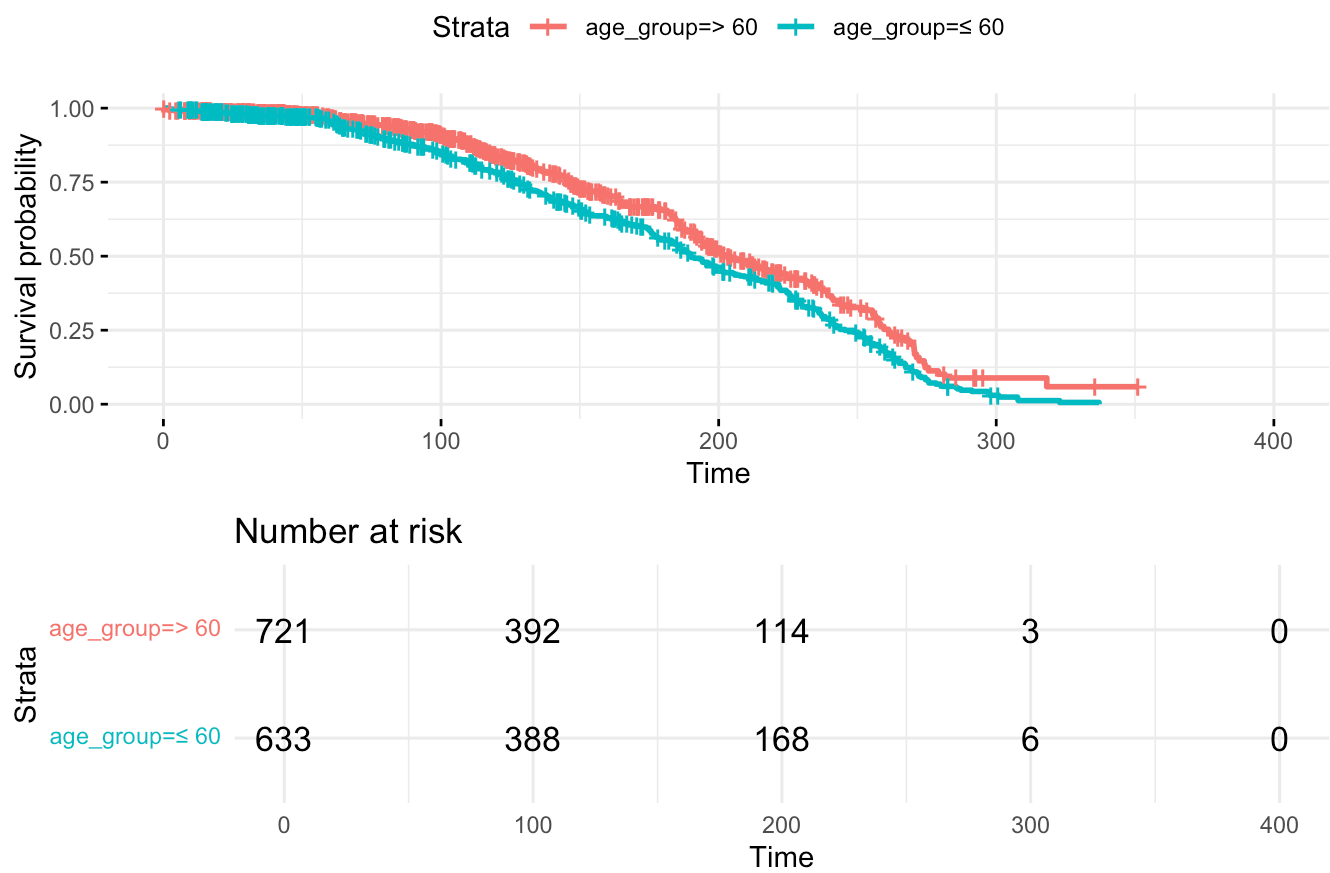


Number at risk

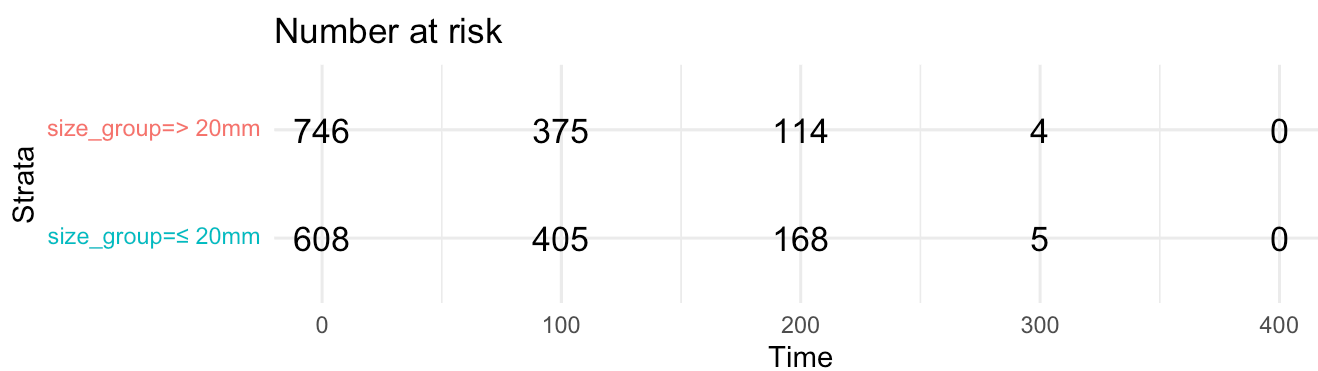
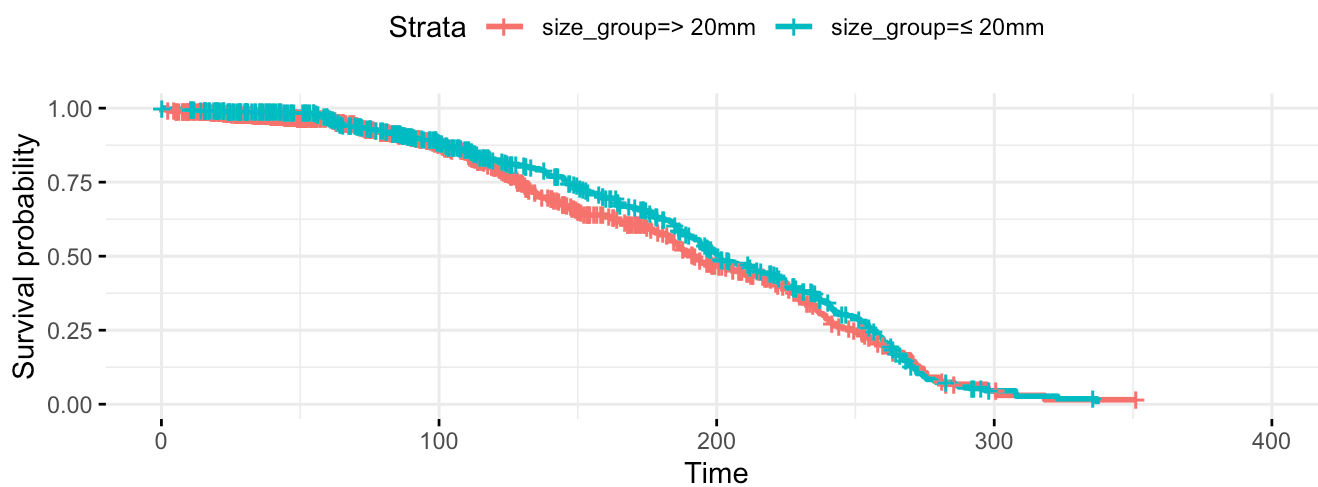
Strata	tumor_stage_grp=Early	458	327	142	3	0
	tumor_stage_grp=Intermediate	776	414	130	6	0
	tumor_stage_grp=Late	120	39	10	0	0
		0	100	200	300	400

Time

KM curve by age_group



KM curve by size_group

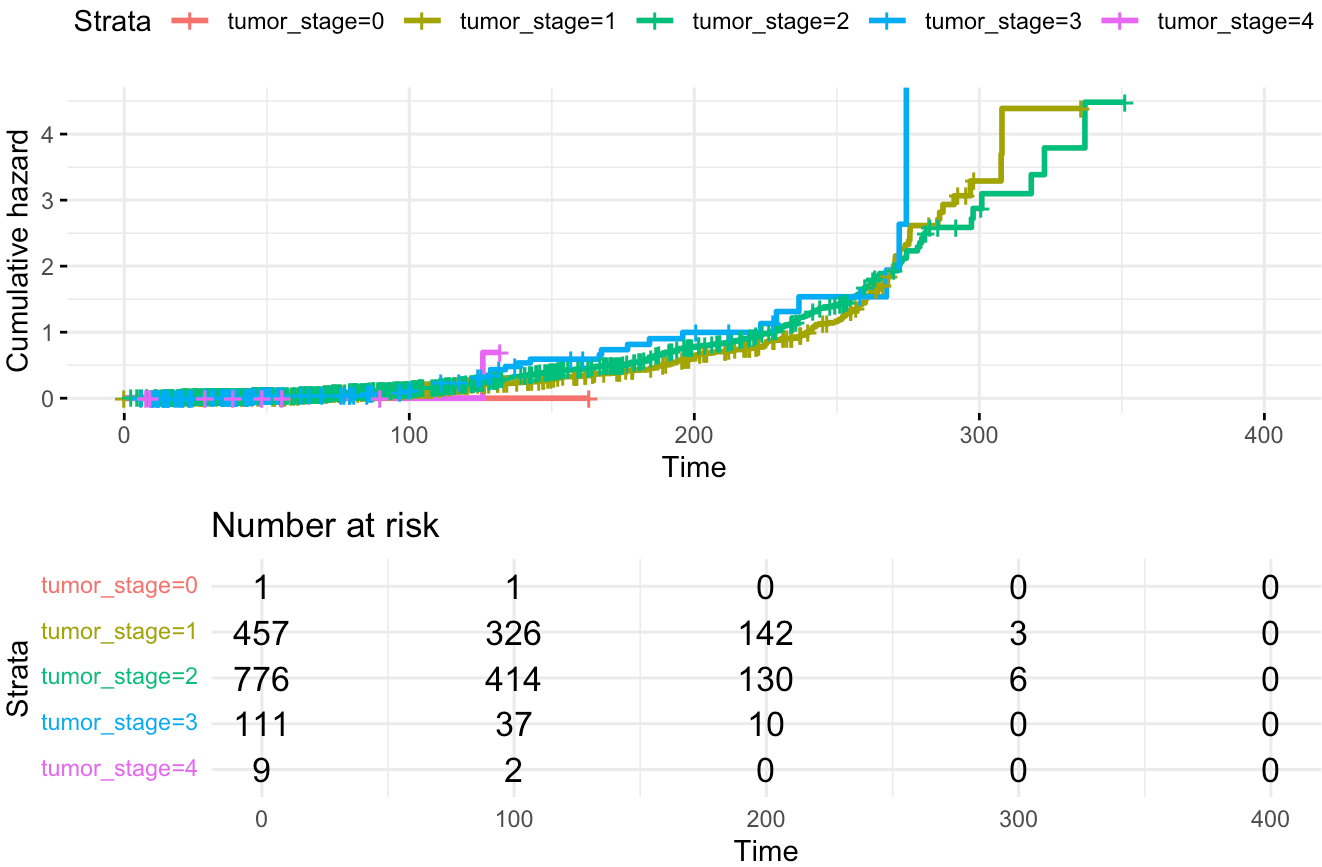


```
#Cumulative Hazard Plot
for (var in group_vars) {
  formula <- as.formula(paste("Surv(overall_survival_months, overall_survival) ~", var))
  model <- survfit(formula, data = df_model)

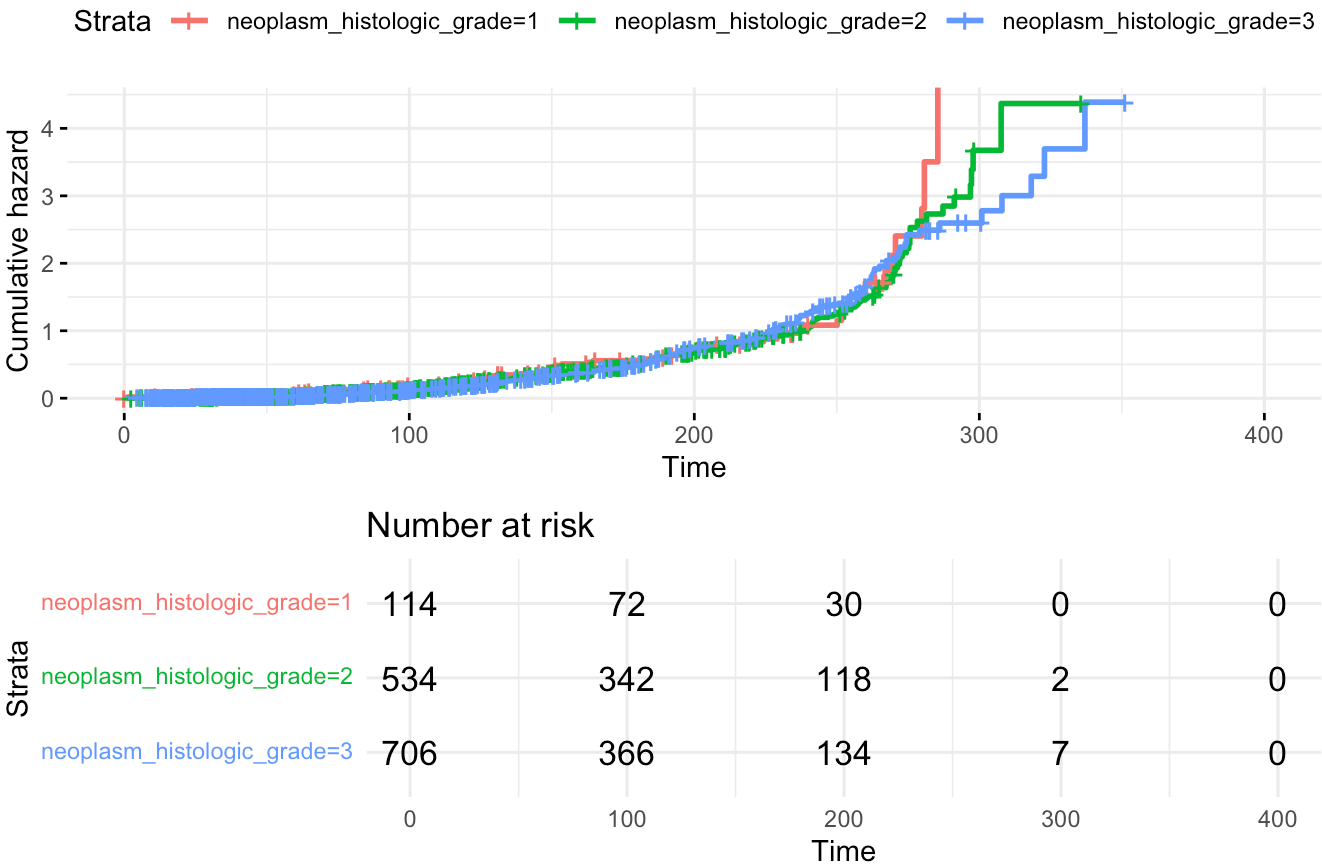
  model$call <- list(formula = formula)

  print(ggsurvplot(model, fun = "cumhaz", data = df_model,
    risk.table = TRUE,
    risk.table.height = 0.4,
    title = paste("KM curve by", var),
    ggtheme = theme_minimal()))
}
```

KM curve by tumor_stage

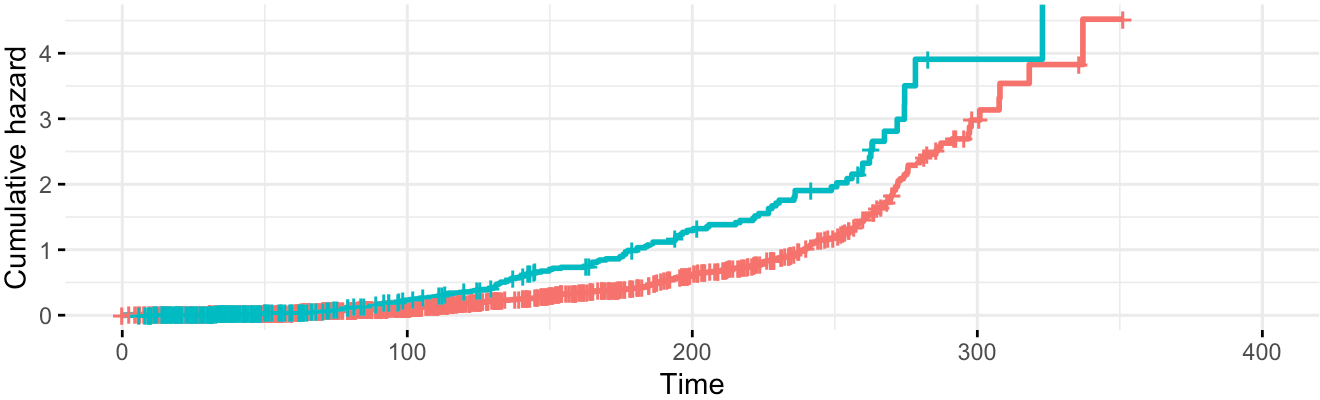


KM curve by neoplasm_histologic_grade

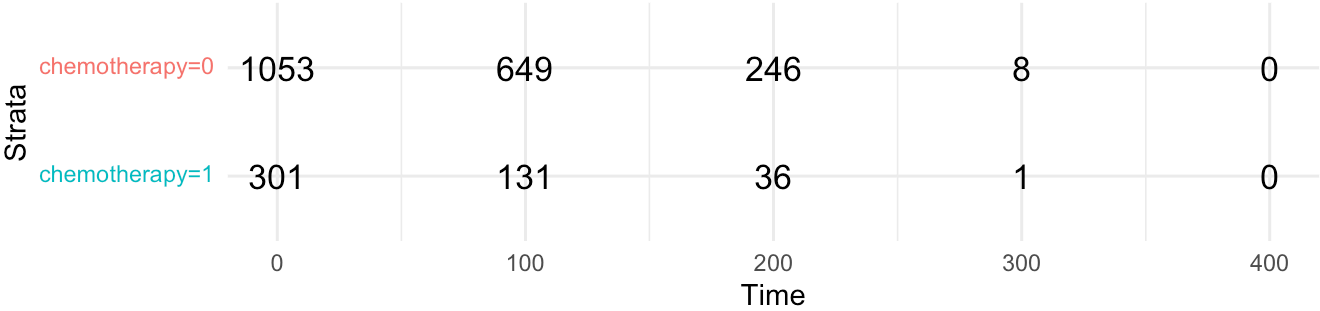


KM curve by chemotherapy

Strata chemotherapy=0 chemotherapy=1

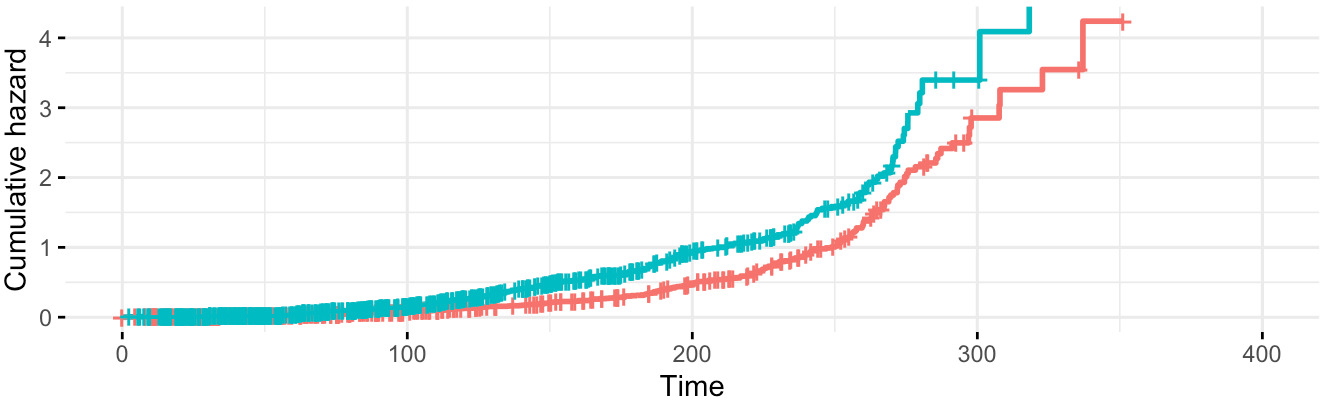


Number at risk

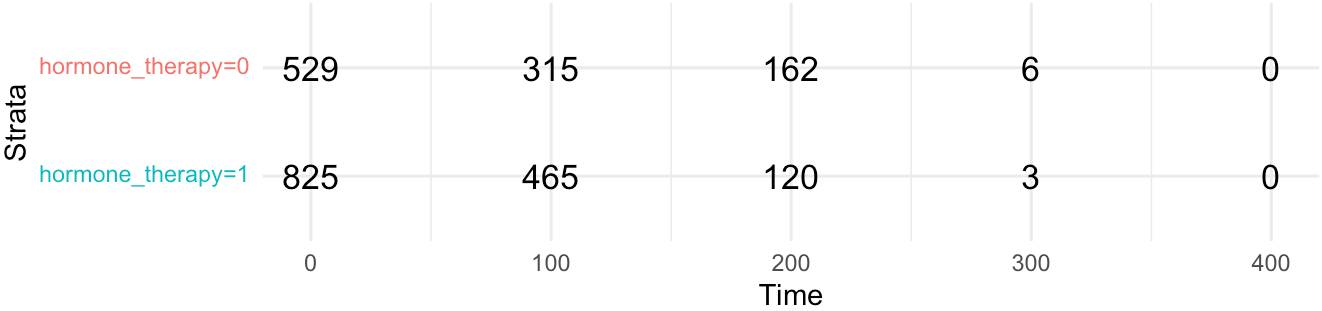


KM curve by hormone_therapy

Strata hormone_therapy=0 hormone_therapy=1

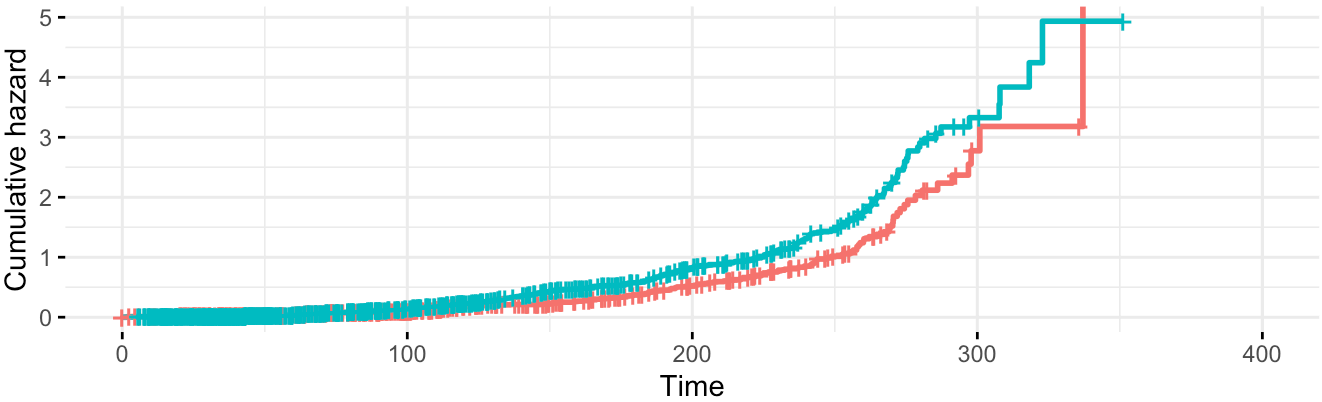


Number at risk

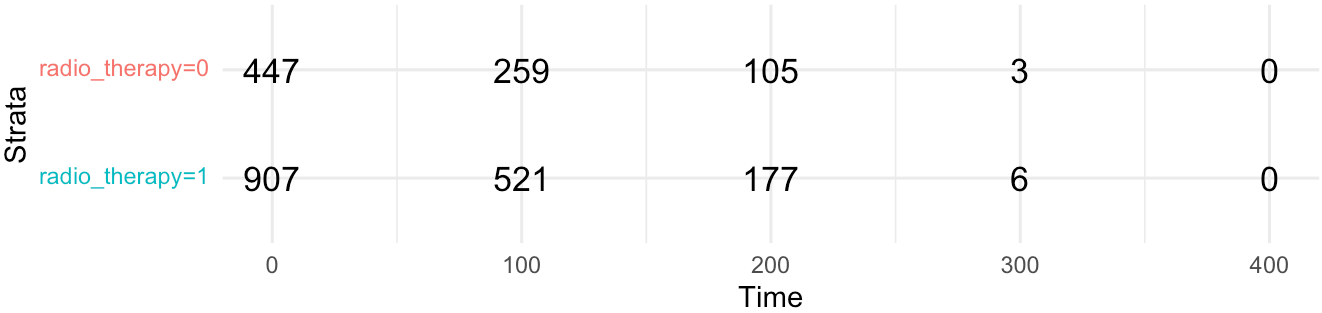


KM curve by radio_therapy

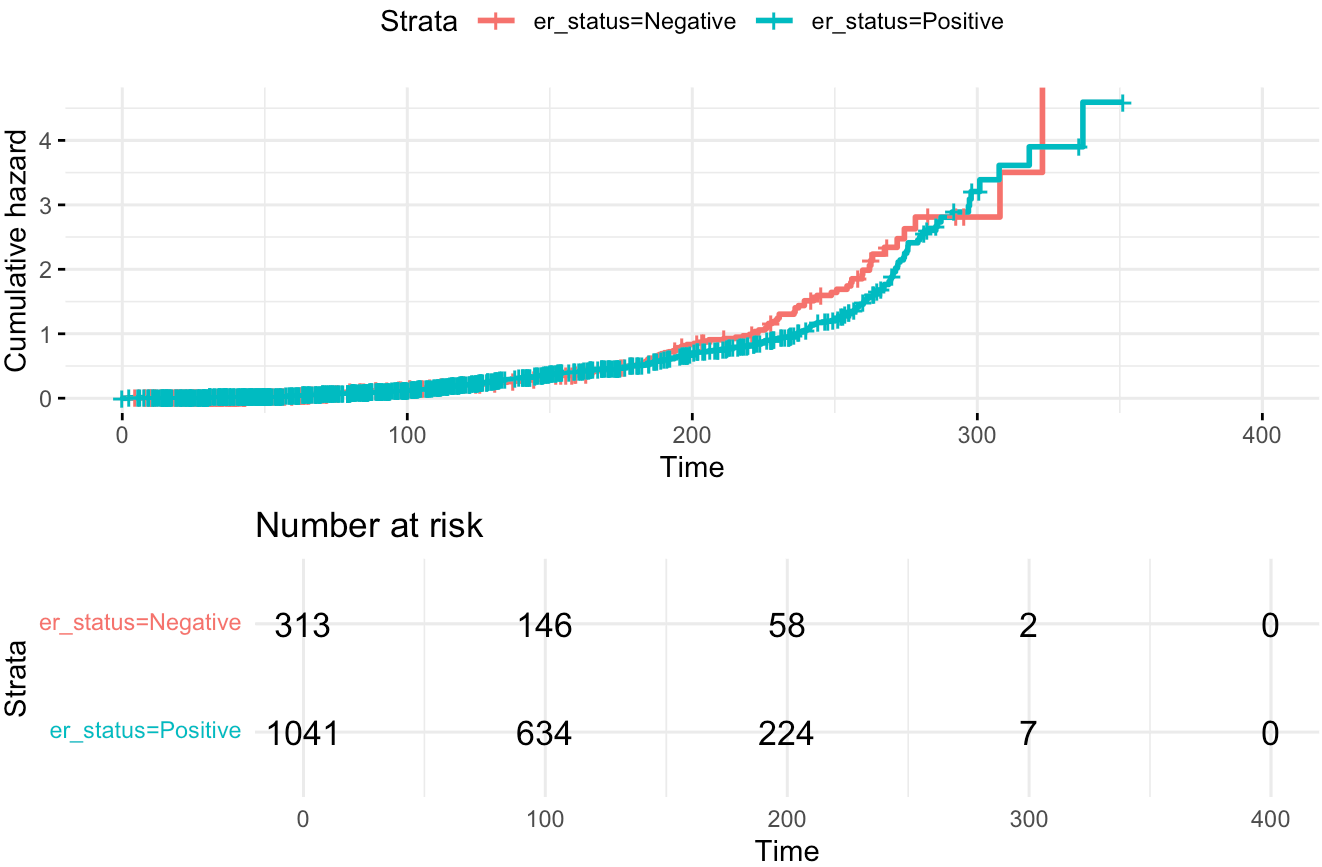
Strata radio_therapy=0 radio_therapy=1



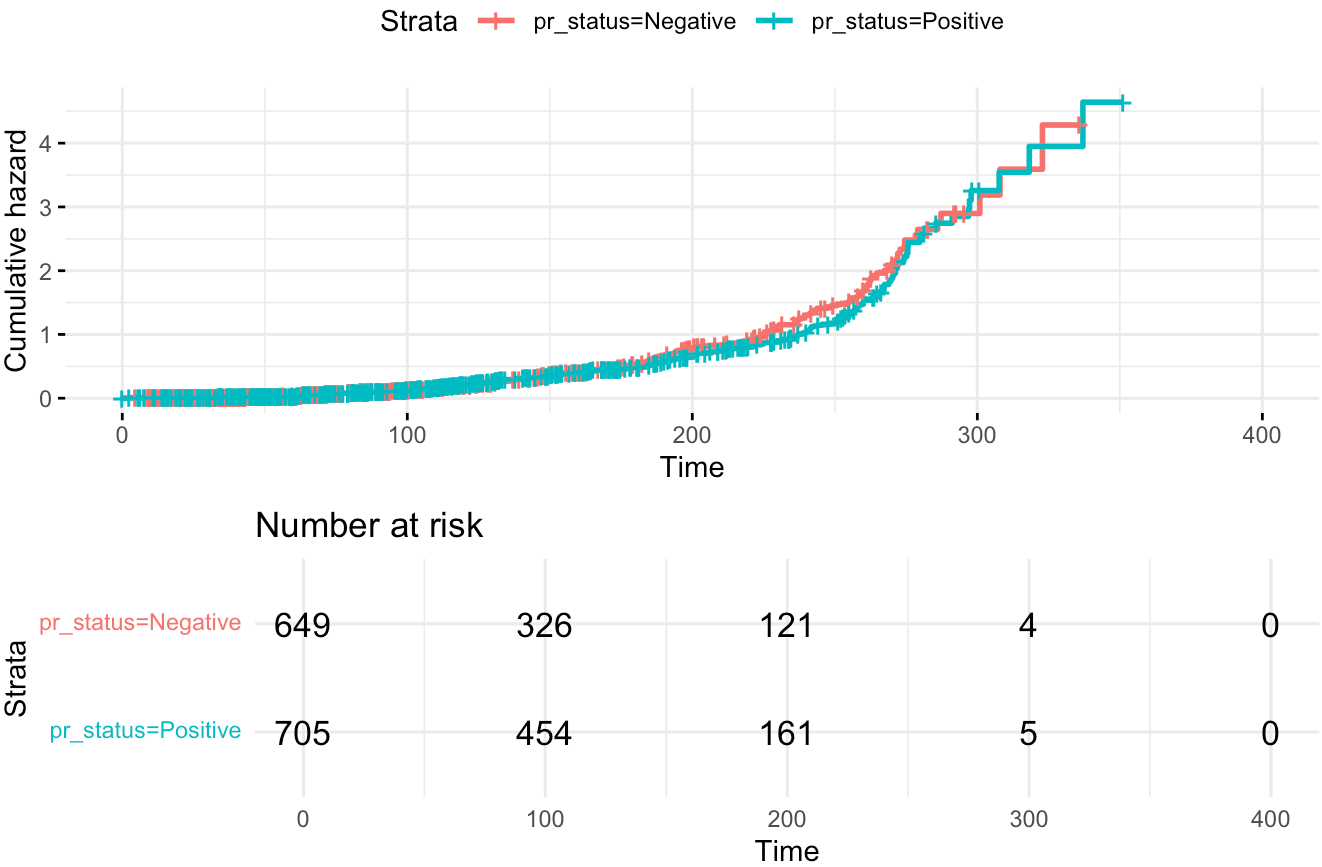
Number at risk



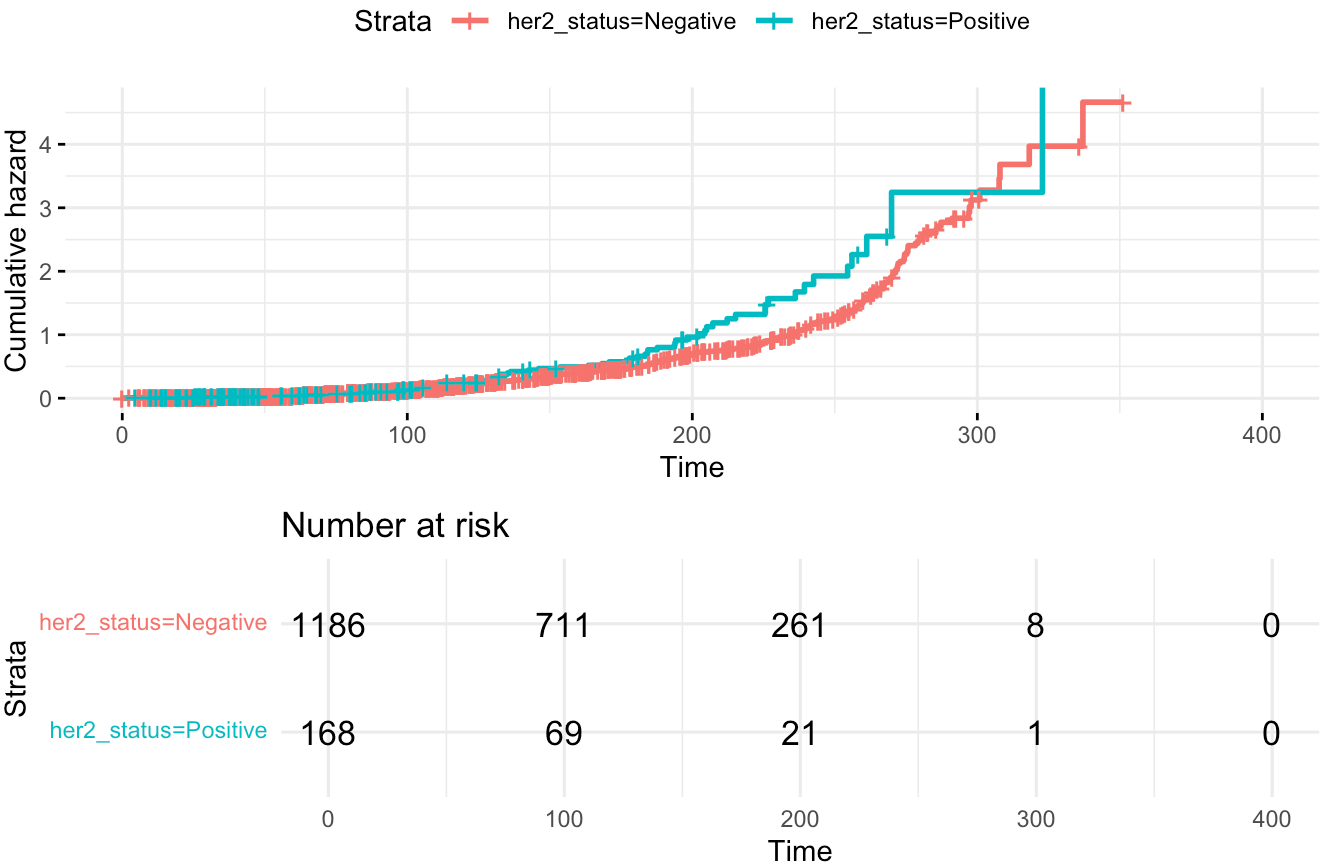
KM curve by er_status



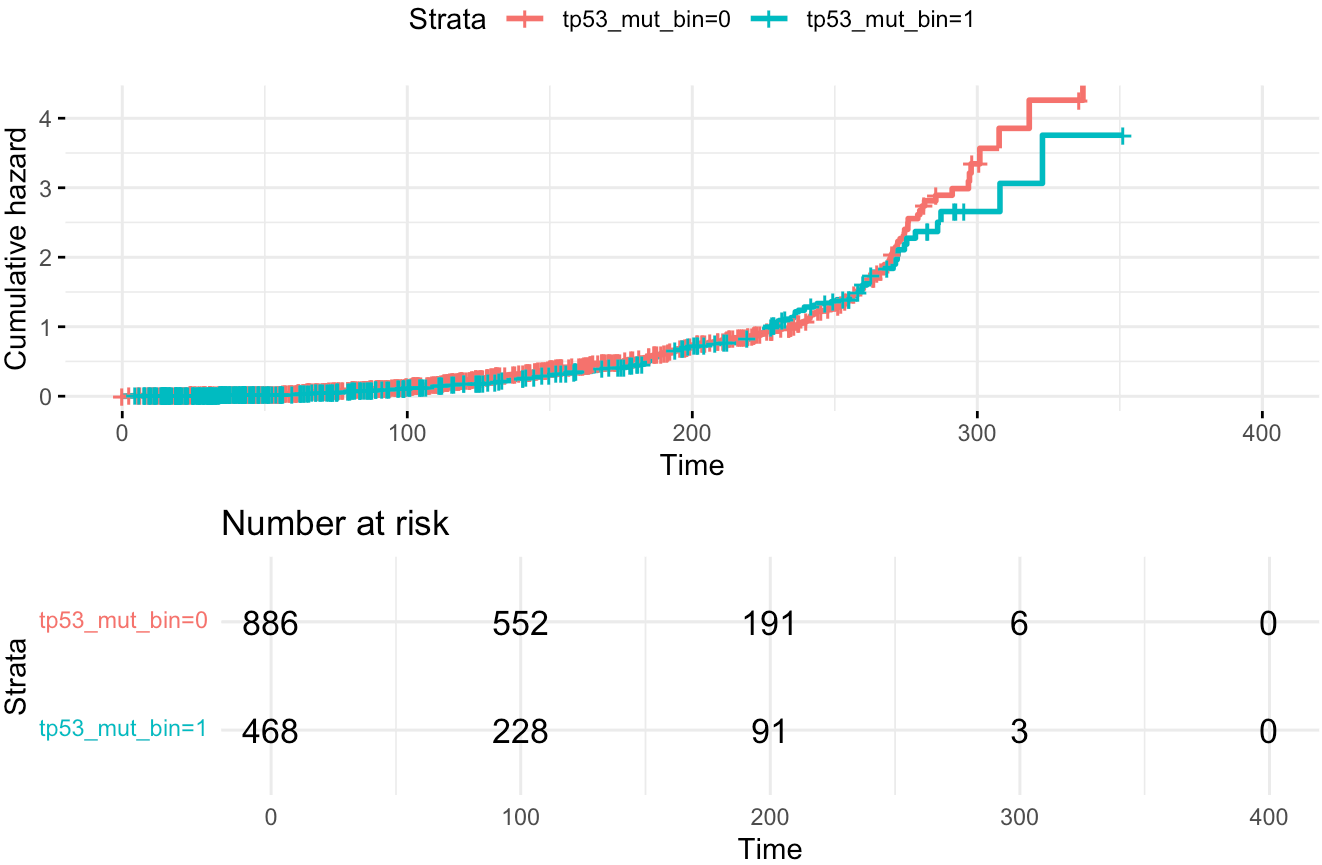
KM curve by pr_status



KM curve by her2_status

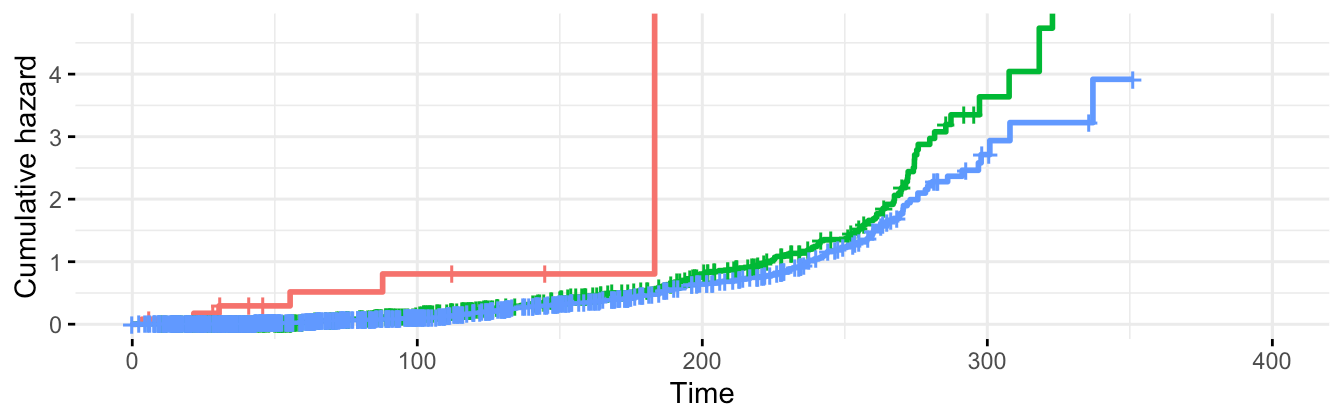


KM curve by tp53_mut_bin



KM curve by type_of_breast_surgery

ta + type_of_breast_surgery= + type_of_breast_surgery=BREAST CONSERVING + type_of_breast_surgery=MAS

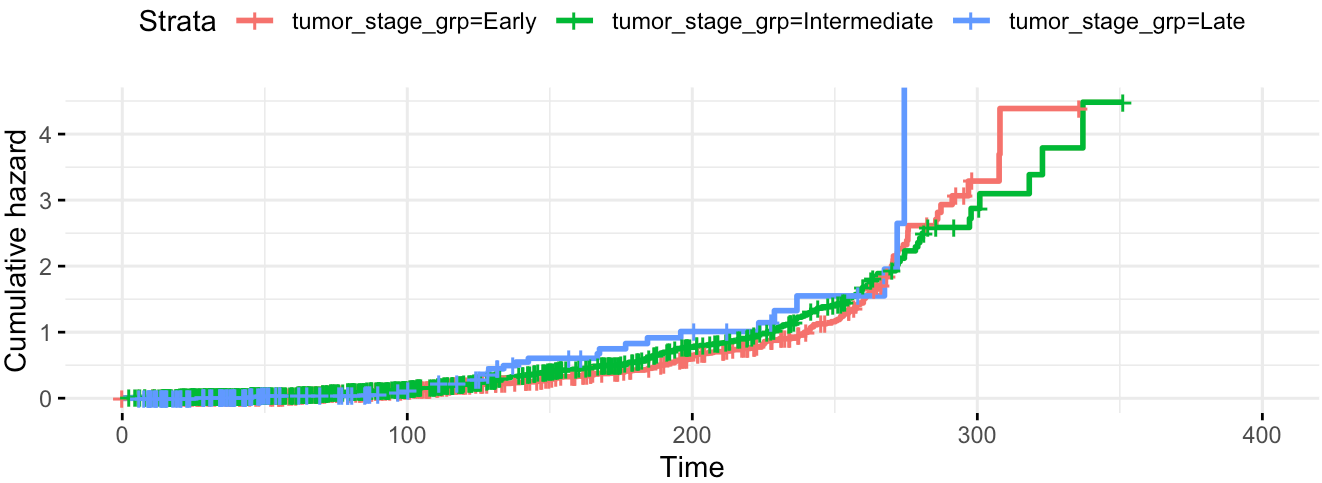


Number at risk

		0	100	200	300	400
type_of_breast_surgery=	13	3	0	0	0	
type_of_breast_surgery=BREAST CONSERVING	574	370	137	3	0	
type_of_breast_surgery=MASTECTOMY	767	407	145	6	0	

Time

KM curve by tumor_stage_grp



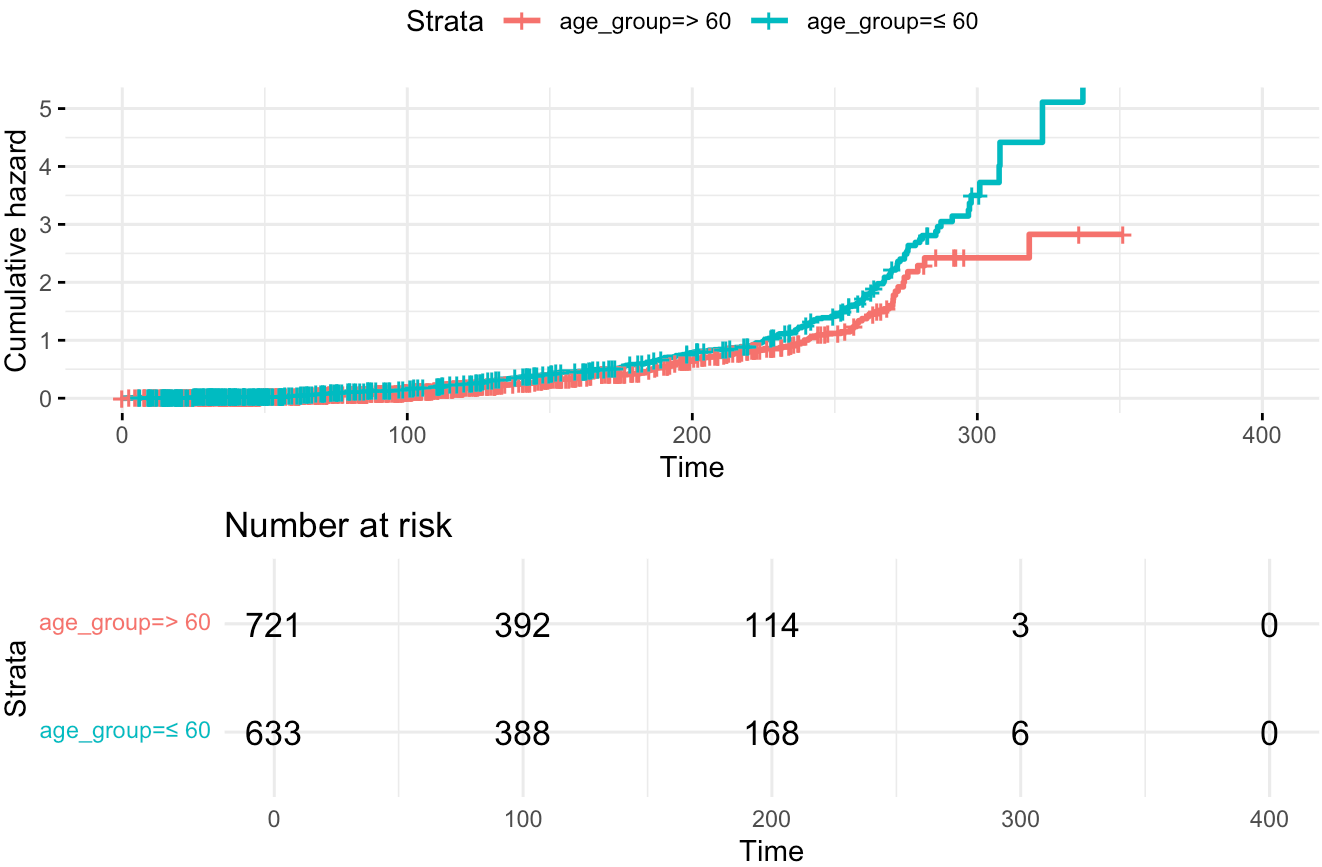
Number at risk

tumor_stage_grp=Early	458	327	142	3	0
tumor_stage_grp=Intermediate	776	414	130	6	0
tumor_stage_grp=Late	120	39	10	0	0

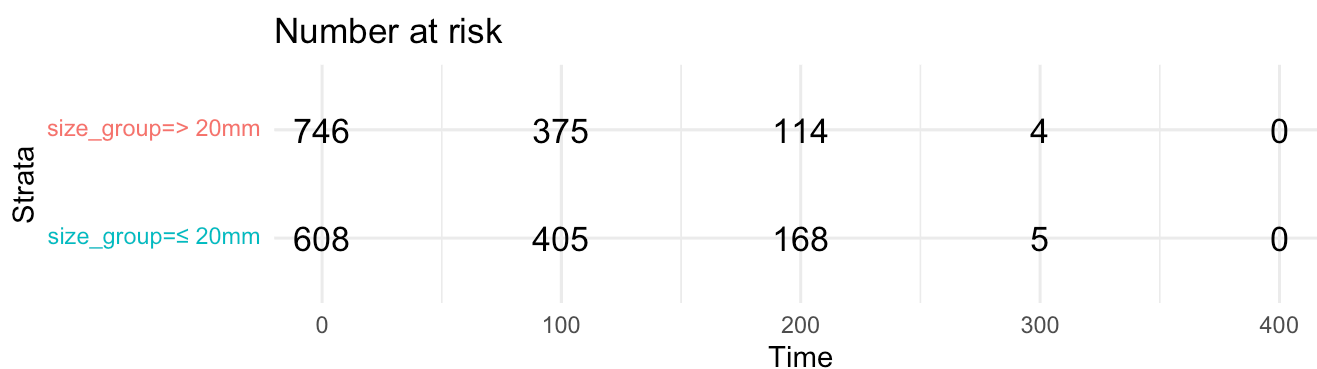
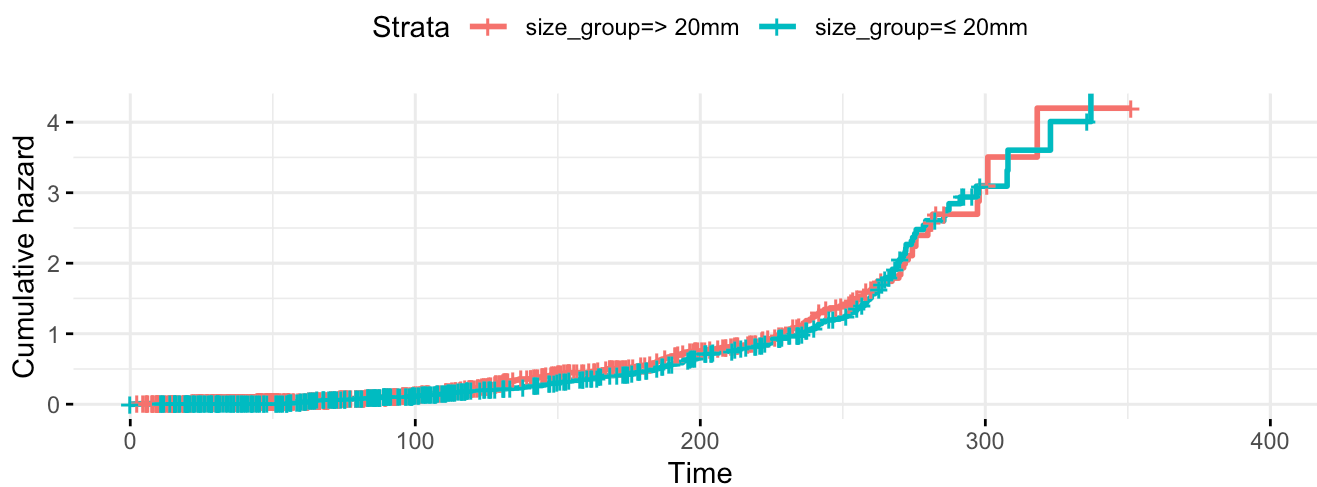
Strata

Time

KM curve by age_group



KM curve by size_group



```
get_cox <- function(var, df){
  formula <- as.formula(paste("Surv(overall_survival_months, overall_survival) ~", var))
  model <- coxph(formula, data = df_model)
  var1 <- rownames(summary(model)$coefficients)
  p_value <- summary(model)$coefficients[, "Pr(>|z|)"]
  hr <- summary(model)$coefficients[, "exp(coef)"]
  return(list(variable = var1,
              p_value = p_value,
              harzed_ratio = hr))
}

cox_var <- c(
  "age_at_diagnosis", "tumor_size", "tumor_stage_grp", "neoplasm_histologic_grade",
  "er_status", "pr_status", "her2_status", "type_of_breast_surgery", "chemotherapy",
  "hormone_therapy", "radio_therapy", "tp53", "tp53_mut_bin", "age_group", "size_group"
)
cox_result <- lapply(cox_var, get_cox, df = df_model)
cox_result_df <- do.call(rbind, lapply(cox_result, as.data.frame))
```

```
cox_result_df
```

	variable
1	age_at_diagnosis
2	tumor_size
tumor_stage_grpIntermediate	tumor_stage_grpIntermediate
tumor_stage_grpLate	tumor_stage_grpLate
neoplasm_histologic_grade2	neoplasm_histologic_grade2
neoplasm_histologic_grade3	neoplasm_histologic_grade3
11	er_statusPositive
12	pr_statusPositive
13	her2_statusPositive
type_of_breast_surgeryBREAST CONSERVING	type_of_breast_surgeryBREAST CONSERVING
type_of_breast_surgeryMASTECTOMY	type_of_breast_surgeryMASTECTOMY
14	chemotherapy1
15	hormone_therapy1
16	radio_therapy1
17	tp53
18	tp53_mut_bin1
19	age_group≤ 60
110	size_group≤ 20mm

	p_value	harzed_ratio
1	1.603294e-02	0.9914464
2	6.605071e-01	1.0015440
tumor_stage_grpIntermediate	1.169882e-01	1.1426042
tumor_stage_grpLate	1.128365e-01	1.3599931
neoplasm_histologic_grade2	5.205099e-01	0.9137327
neoplasm_histologic_grade3	5.289992e-01	0.9163688
11	1.536674e-01	0.8688951
12	2.656370e-01	0.9123345
13	1.915166e-02	1.3680895
type_of_breast_surgeryBREAST CONSERVING	4.538662e-04	0.2338315
type_of_breast_surgeryMASTECTOMY	5.837651e-05	0.1888122
14	2.499391e-10	1.8317210
15	1.155988e-08	1.6316368
16	7.050152e-05	1.4387202
17	1.933130e-04	1.1674635
18	3.865868e-01	0.9255697
19	1.558315e-03	1.3101685
110	2.446481e-01	0.9082791

```
df_cox <- df_model %>% select(-age_group,-size_group,-tp53_mut_bin,-tumor_stage)
cox_fit_total <- coxph(Surv(overall_survival_months,overall_survival) ~ ., data = df_cox)
summary(cox_fit_total)
```

Call:

```
coxph(formula = Surv(overall_survival_months, overall_survival) ~
      ., data = df_cox)
```

n= 1354, number of events= 596

coef	exp(coef)	se(coef)	z
------	-----------	----------	---

age_at_diagnosis	-0.0038330	0.9961743	0.0042129	-0.910
tumor_size	-0.0032810	0.9967244	0.0041428	-0.792
neoplasm_histologic_grade2	-0.1216521	0.8854564	0.1421567	-0.856
neoplasm_histologic_grade3	-0.3504253	0.7043884	0.1500841	-2.335
chemotherapy1	0.8790028	2.4084967	0.1412044	6.225
hormone_therapy1	0.7612930	2.1410429	0.1012790	7.517
radio_therapy1	0.1317201	1.1407890	0.1178195	1.118
er_statusPositive	-0.0002493	0.9997508	0.1444976	-0.002
pr_statusPositive	-0.1148094	0.8915361	0.1017957	-1.128
her2_statusPositive	0.0930050	1.0974672	0.1464554	0.635
type_of_breast_surgeryBREAST CONSERVING	-1.3092310	0.2700276	0.4256437	-3.076
type_of_breast_surgeryMASTECTOMY	-1.5042121	0.2221923	0.4212916	-3.570
tp53	0.1894068	1.2085324	0.0433754	4.367
tumor_stage_grpIntermediate	-0.2442978	0.7832543	0.1045932	-2.336
tumor_stage_grpLate	-0.2046972	0.8148940	0.2403548	-0.852

Pr(>|z|)

age_at_diagnosis	0.362905
tumor_size	0.428386
neoplasm_histologic_grade2	0.392130
neoplasm_histologic_grade3	0.019551 *
chemotherapy1	4.81e-10 ***
hormone_therapy1	5.61e-14 ***
radio_therapy1	0.263575
er_statusPositive	0.998624
pr_statusPositive	0.259387
her2_statusPositive	0.525402
type_of_breast_surgeryBREAST CONSERVING	0.002099 **
type_of_breast_surgeryMASTECTOMY	0.000356 ***
tp53	1.26e-05 ***
tumor_stage_grpIntermediate	0.019507 *
tumor_stage_grpLate	0.394411

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

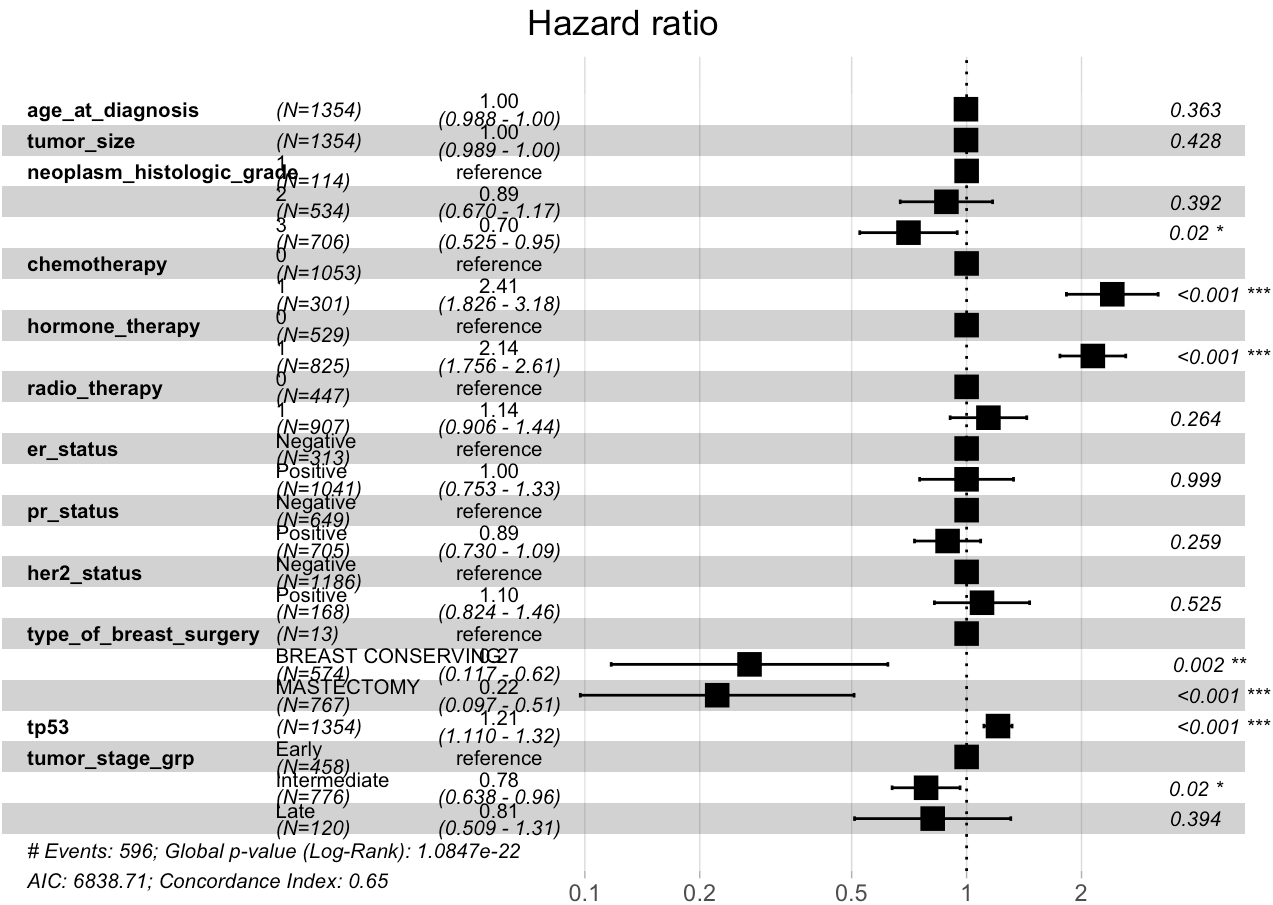
	exp(coef)	exp(-coef)	lower .95
age_at_diagnosis	0.9962	1.0038	0.9880
tumor_size	0.9967	1.0033	0.9887
neoplasm_histologic_grade2	0.8855	1.1294	0.6701
neoplasm_histologic_grade3	0.7044	1.4197	0.5249
chemotherapy1	2.4085	0.4152	1.8262
hormone_therapy1	2.1410	0.4671	1.7556
radio_therapy1	1.1408	0.8766	0.9056
er_statusPositive	0.9998	1.0002	0.7532
pr_statusPositive	0.8915	1.1217	0.7303
her2_statusPositive	1.0975	0.9112	0.8236
type_of_breast_surgeryBREAST CONSERVING	0.2700	3.7033	0.1172
type_of_breast_surgeryMASTECTOMY	0.2222	4.5006	0.0973
tp53	1.2085	0.8274	1.1100
tumor_stage_grpIntermediate	0.7833	1.2767	0.6381
tumor_stage_grpLate	0.8149	1.2272	0.5088

upper .95

age_at_diagnosis	1.0044
tumor_size	1.0049
neoplasm_histologic_grade2	1.1700
neoplasm_histologic_grade3	0.9453
chemotherapy1	3.1764
hormone_therapy1	2.6112
radio_therapy1	1.4371
er_statusPositive	1.3271
pr_statusPositive	1.0884
her2_statusPositive	1.4624
type_of_breast_surgeryBREAST CONSERVING	0.6219
type_of_breast_surgeryMASTECTOMY	0.5074
tp53	1.3158
tumor_stage_grpIntermediate	0.9615
tumor_stage_grpLate	1.3052

Concordance= 0.651 (se = 0.013)
Likelihood ratio test= 141.7 on 15 df, p=<2e-16
Wald test = 149.5 on 15 df, p=<2e-16
Score (logrank) test = 155.1 on 15 df, p=<2e-16

```
ggforest(cox_fit_total, data = df_model)
```



```
#这个我感觉没啥用可以删了
df_lasso <- df_model[df_model$overall_survival_months > 0, ]
df_lasso <- na.omit(df_lasso)
X <- model.matrix(Surv(overall_survival_months, overall_survival) ~ ., data = df_lasso)[,
y <- Surv(df_lasso$overall_survival_months, df_lasso$overall_survival)
cox_lasso <- cv.glmnet(X, y, family = "cox", alpha = 1)
selected_vars <- rownames(coef(cox_lasso))[
  as.vector(coef(cox_lasso, s = "lambda.min")) != 0
]
selected_vars
```

```
[1] "tumor_size"                "tumor_stage1"
[3] "neoplasm_histologic_grade3" "chemotherapy1"
[5] "hormone_therapy1"          "radio_therapy1"
[7] "pr_statusPositive"         "her2_statusPositive"
[9] "tp53_mut_bin1"             "type_of_breast_surgeryMASTECTOMY"
[11] "tp53"                      "age_group≤ 60"
```

```
reg_feature <- c("overall_survival_months", "overall_survival", "tumor_stage", "neoplasm_hi
df_data <- df_model %>%
  select(all_of(reg_feature)) %>%
  filter(overall_survival_months > 0) %>%
  na.omit()
```

```
aft_formula <- as.formula(paste("Surv(overall_survival_months, overall_survival) ~",
  paste(reg_feature[-c(1,2)], collapse = " + ")))
```

```
model_lognormal <- survreg(aft_formula, data = df_data, dist = "lognormal")
model_weibull <- survreg(aft_formula, data = df_data, dist = "weibull")
model_exponential <- survreg(aft_formula, data = df_data, dist = "exponential")
model_loglogistic <- survreg(aft_formula, data = df_data, dist = "loglogistic")
```

```
AIC(model_lognormal, model_weibull, model_exponential, model_loglogistic)
```

	df	AIC
model_lognormal	13	7724.989
model_weibull	13	7283.647
model_exponential	12	7916.010
model_loglogistic	13	7420.526

```
sapply(list(lognormal = model_lognormal,
  weibull = model_weibull,
  exponential = model_exponential,
  loglogistic = model_loglogistic), logLik)
```

lognormal	weibull	exponential	loglogistic
-3849.494	-3628.823	-3946.005	-3697.263

```
km_fit <- survfit(Surv(overall_survival_months, overall_survival) ~ 1, data = df_data)
fit_exp <- flexsurvreg(Surv(overall_survival_months, overall_survival) ~ 1, data = df_da
fit_weib <- flexsurvreg(Surv(overall_survival_months, overall_survival) ~ 1, data = df_da
fit_ln <- flexsurvreg(Surv(overall_survival_months, overall_survival) ~ 1, data = df_da
fit_ll <- flexsurvreg(Surv(overall_survival_months, overall_survival) ~ 1, data = df_da

t_grid <- seq(0, max(df_data$overall_survival_months), length.out = 200)

df_pred <- data.frame(
  time = t_grid,
  exponential = summary(fit_exp, t = t_grid)[[1]]$est,
  weibull = summary(fit_weib, t = t_grid)[[1]]$est,
  lognormal = summary(fit_ln, t = t_grid)[[1]]$est,
  loglogistic = summary(fit_ll, t = t_grid)[[1]]$est
)

df_long <- tidyr::pivot_longer(df_pred, -time, names_to = "model", values_to = "surv")

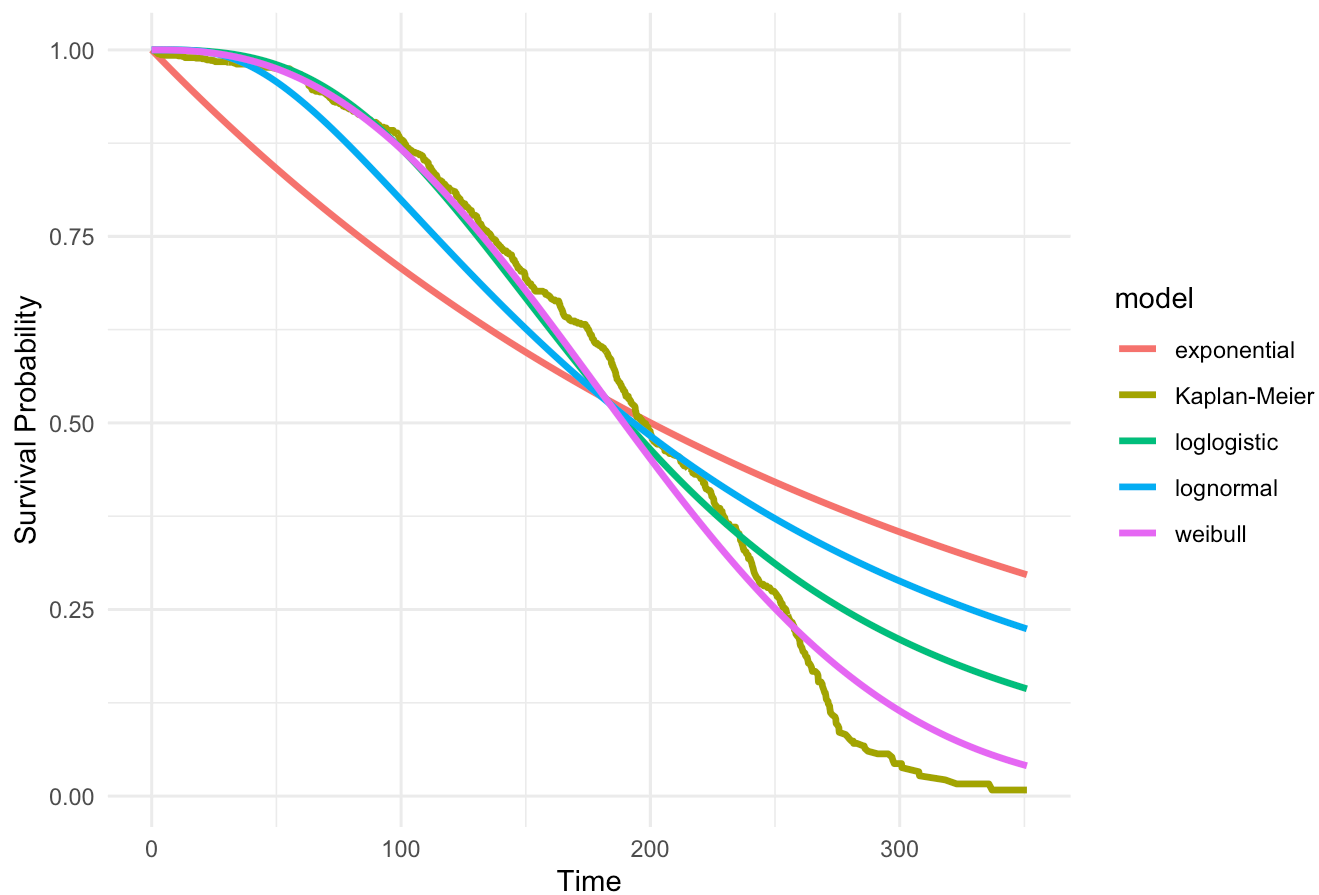
km_df <- data.frame(time = km_fit$time,
  surv = km_fit$surv,
  model = "Kaplan-Meier")

plot_df <- rbind(df_long, km_df)

ggplot(plot_df, aes(x = time, y = surv, color = model)) +
  geom_line(size = 1.2) +
  labs(title = "Survival Curves: KM vs Parametric Models",
    x = "Time", y = "Survival Probability") +
  theme_minimal()
```

Warning: Using `size` aesthetic for lines was deprecated in ggplot2 3.4.0.
i Please use `linewidth` instead.

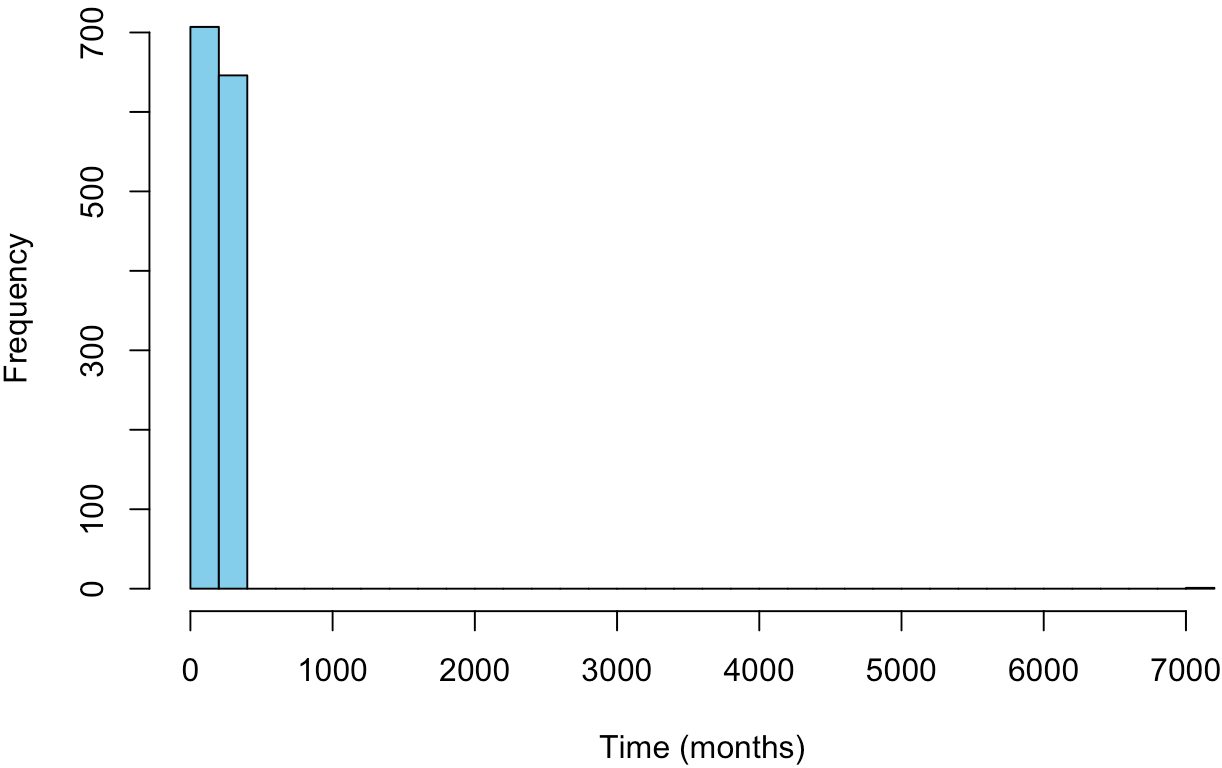
Survival Curves: KM vs Parametric Models



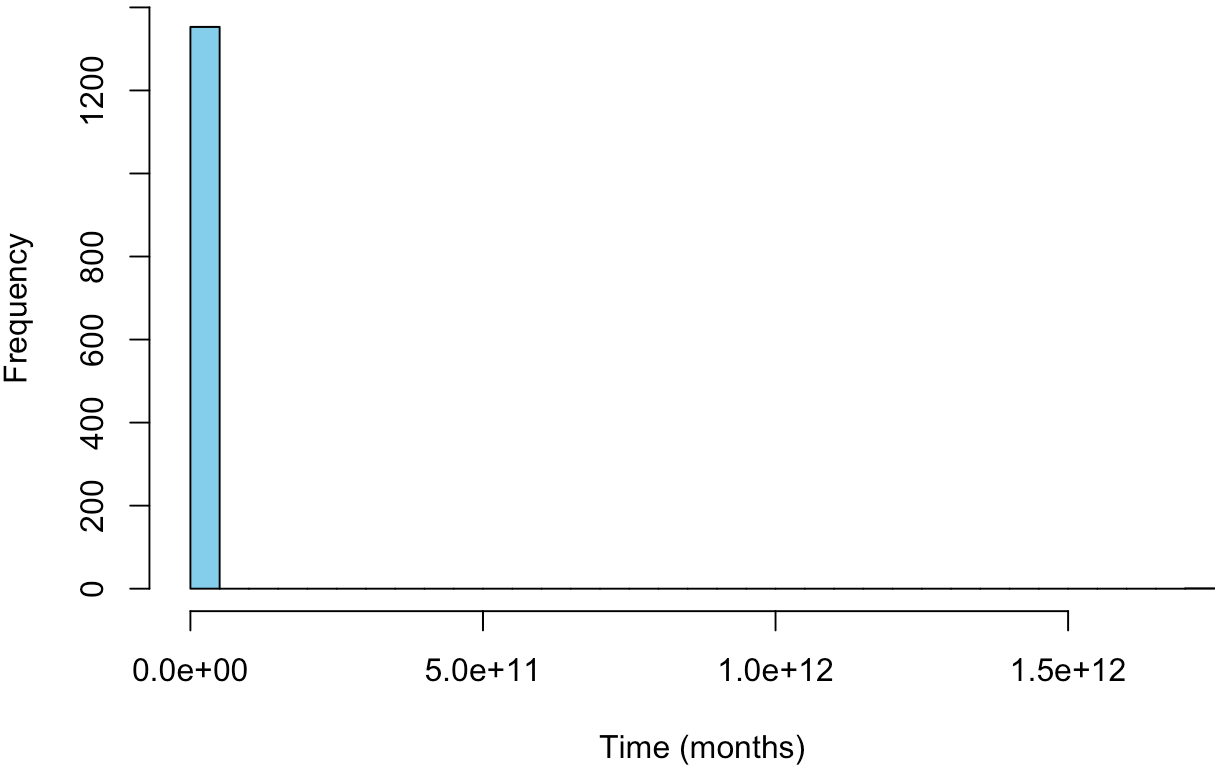
```
pred_result <- list(lognormal = 0, weibull = 0, exponential = 0, loglogistic = 0)
for (name in names(pred_result)) {
  model_obj <- get(paste0("model_", name))
  model_pred <- predict(model_obj, type = "response")
  pred_result[[name]] <- model_pred
}
```

```
for(name in names(pred_result)){
  hist(pred_result[[name]], main = paste(name,"Predicted Survival Time"),
       xlab = "Time (months)",col = "skyblue" ,breaks = 30)
}
```

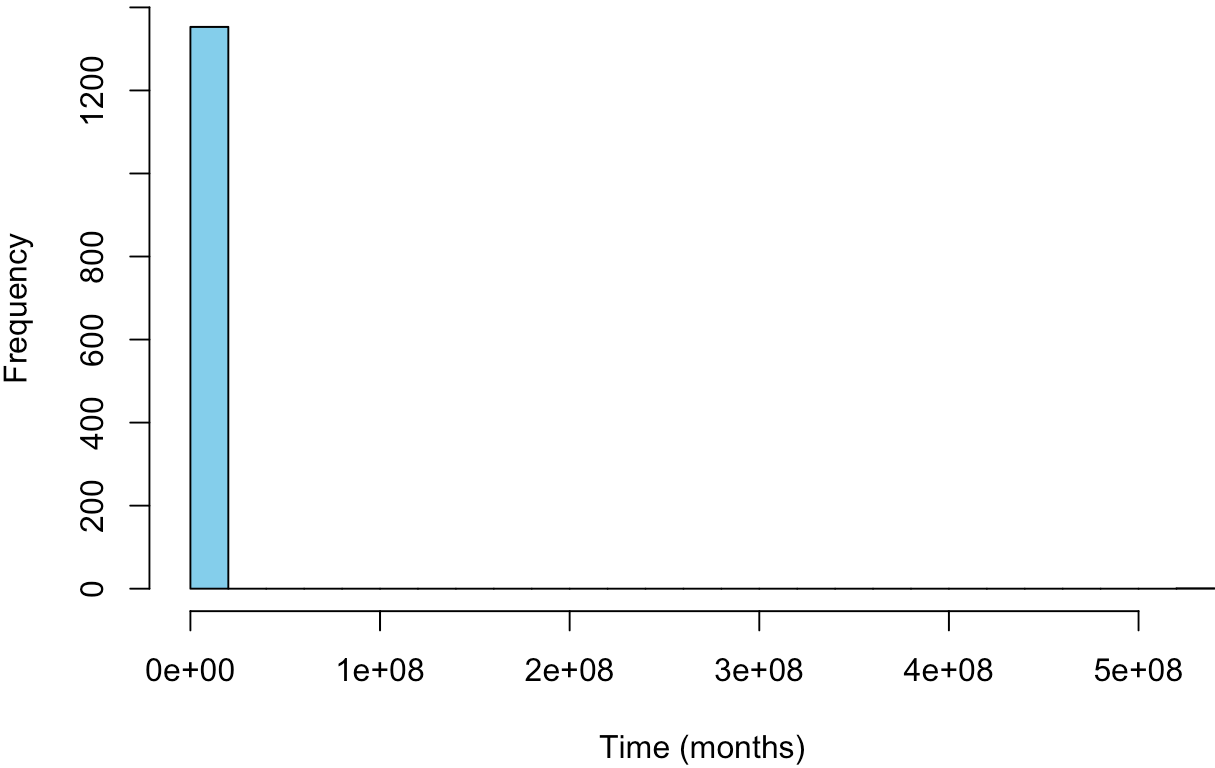
lognormal Predicted Survival Time



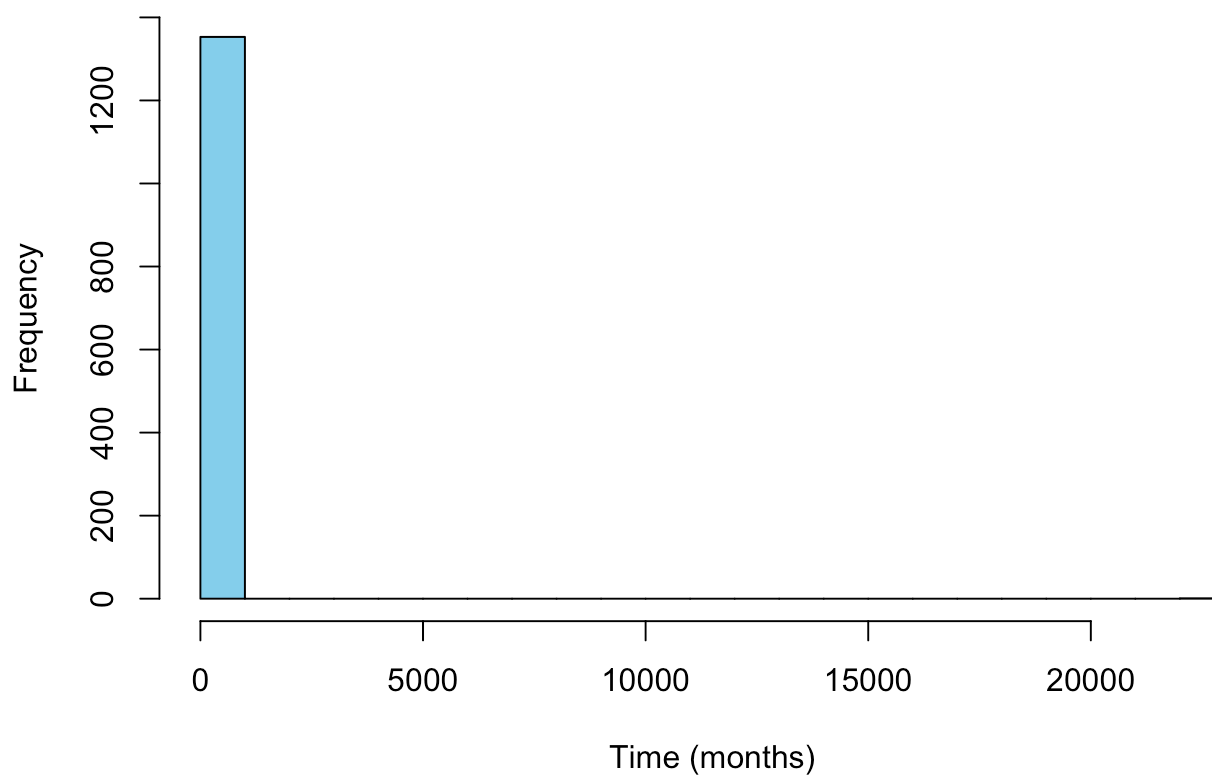
weibull Predicted Survival Time



exponential Predicted Survival Time



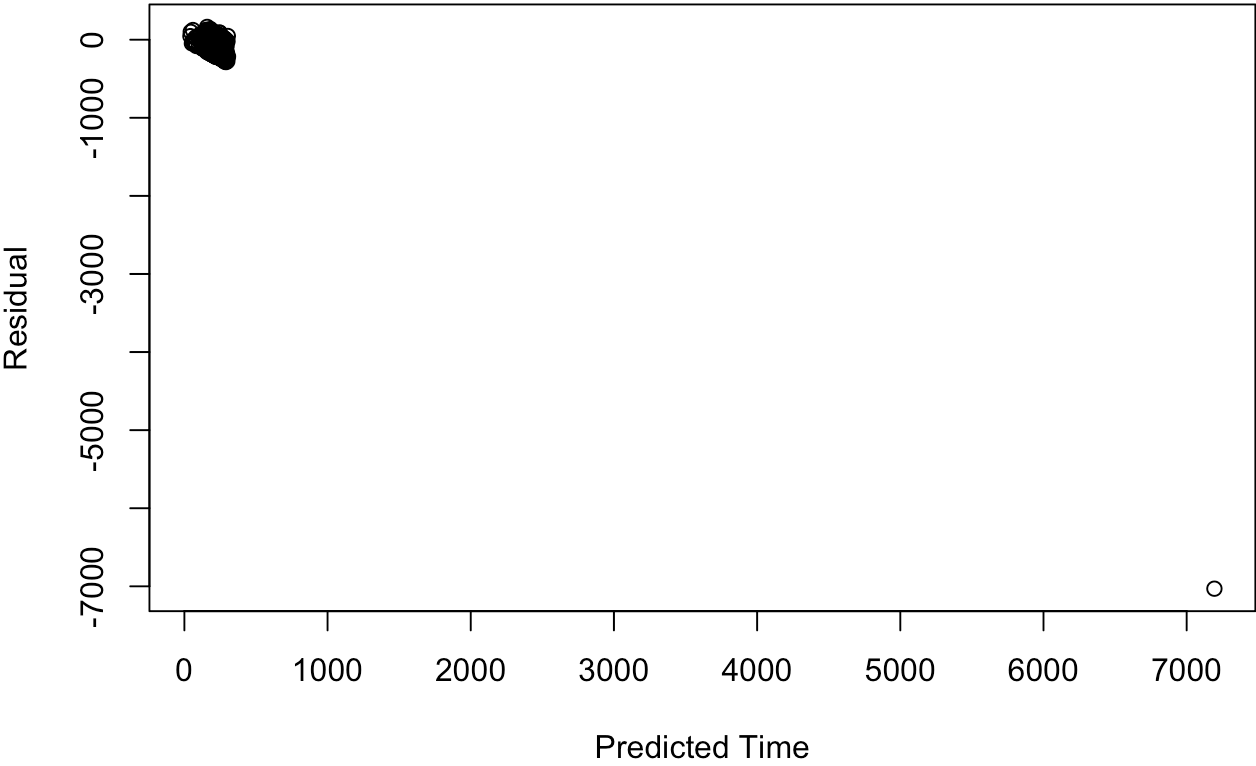
loglogistic Predicted Survival Time



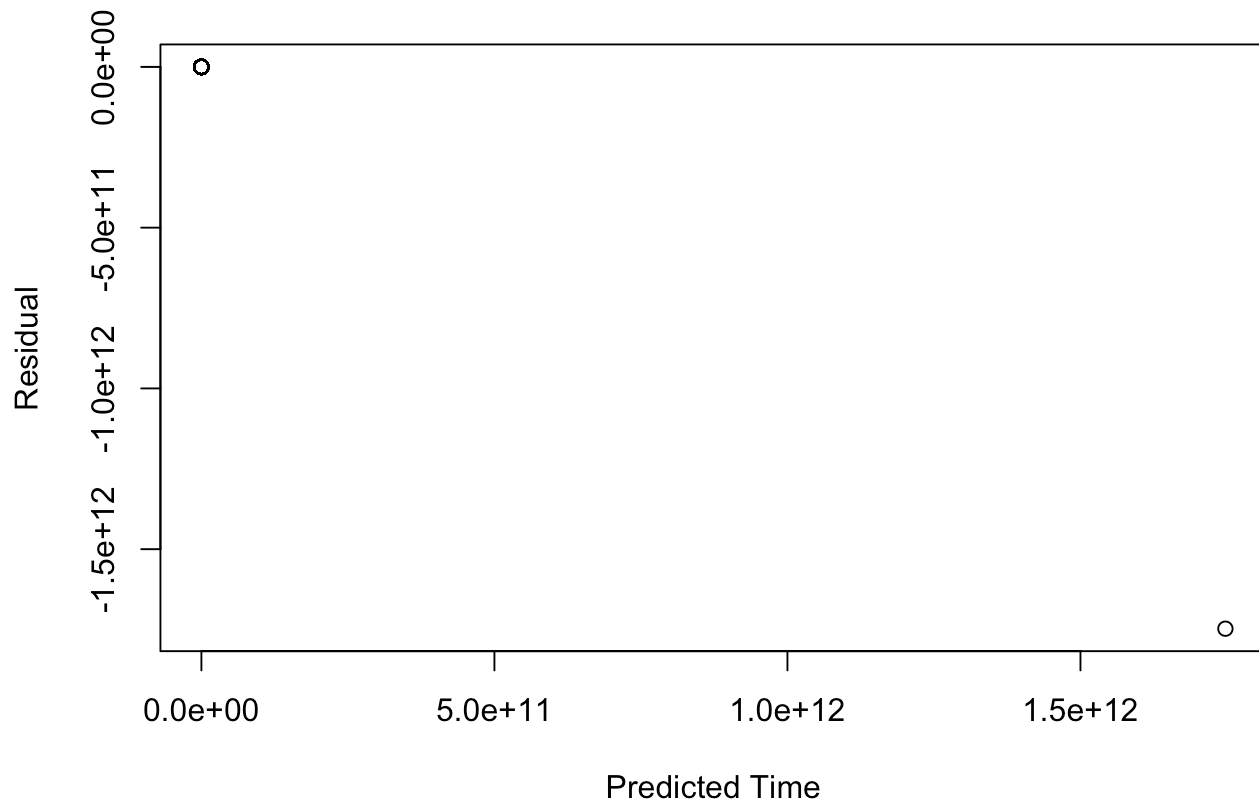
```
resid_result <- list(lognormal = 0, weibull = 0, exponential = 0, loglogistic = 0)
for (name in names(resid_result)) {
  model_obj <- get(paste0("model_", name))
  model_resid <- resid(model_obj, type = "response")
  resid_result[[name]] <- model_resid
}
```

```
for(name in names(resid_result)){
  plot(pred_result[[name]], resid_result[[name]],
       xlab = "Predicted Time", ylab = "Residual",
       main = paste(name, "Model Residuals"))
}
```

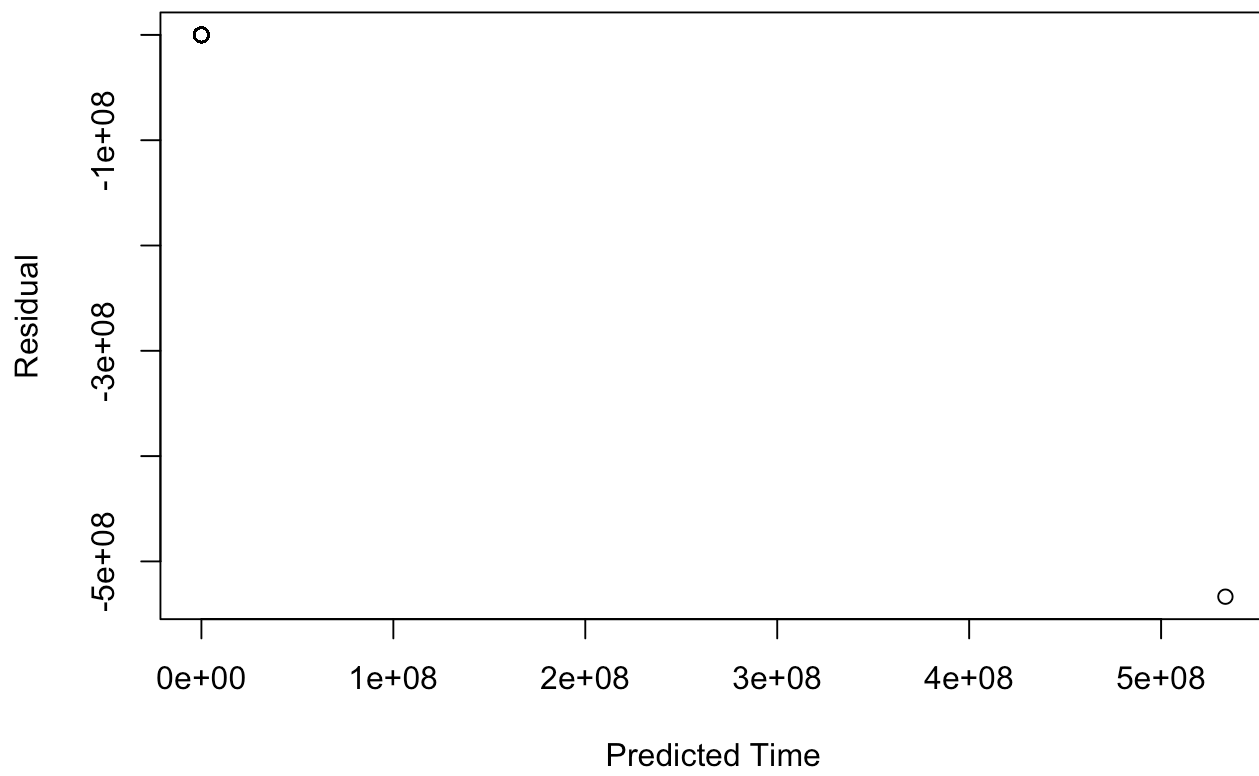
lognormal Model Residuals



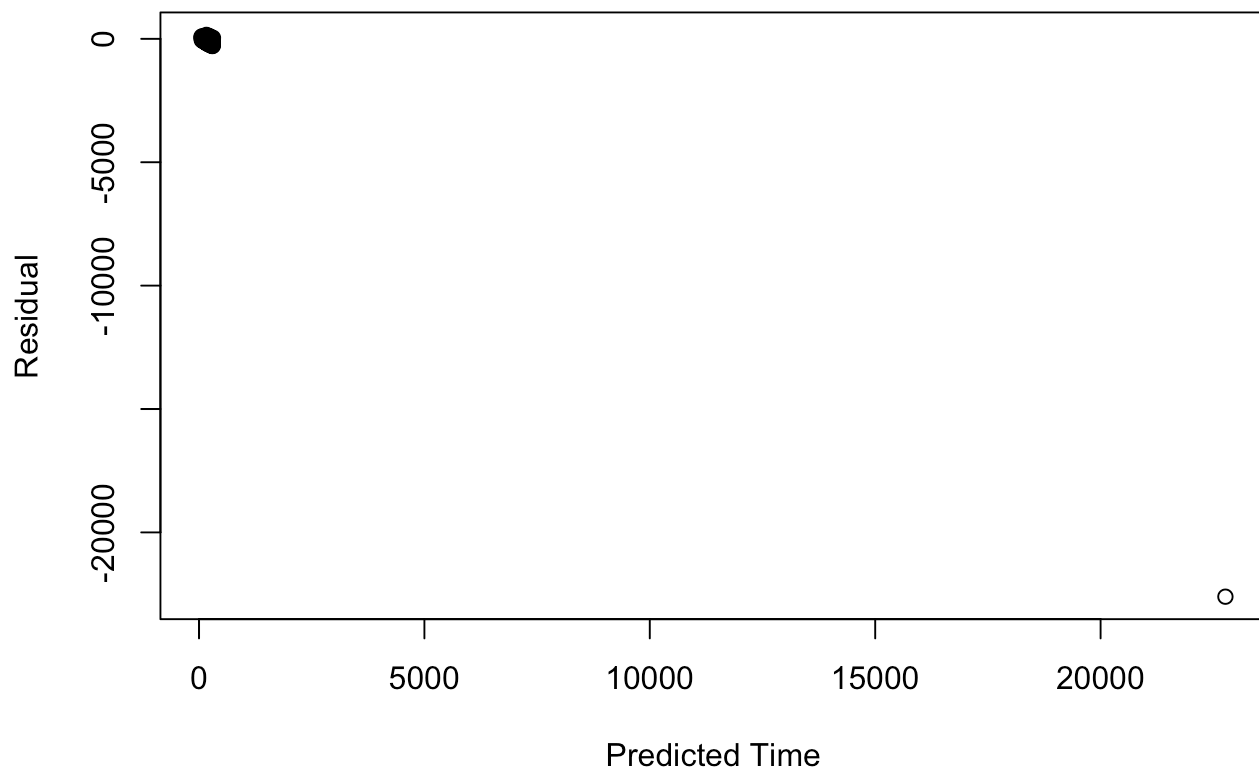
weibull Model Residuals



exponential Model Residuals

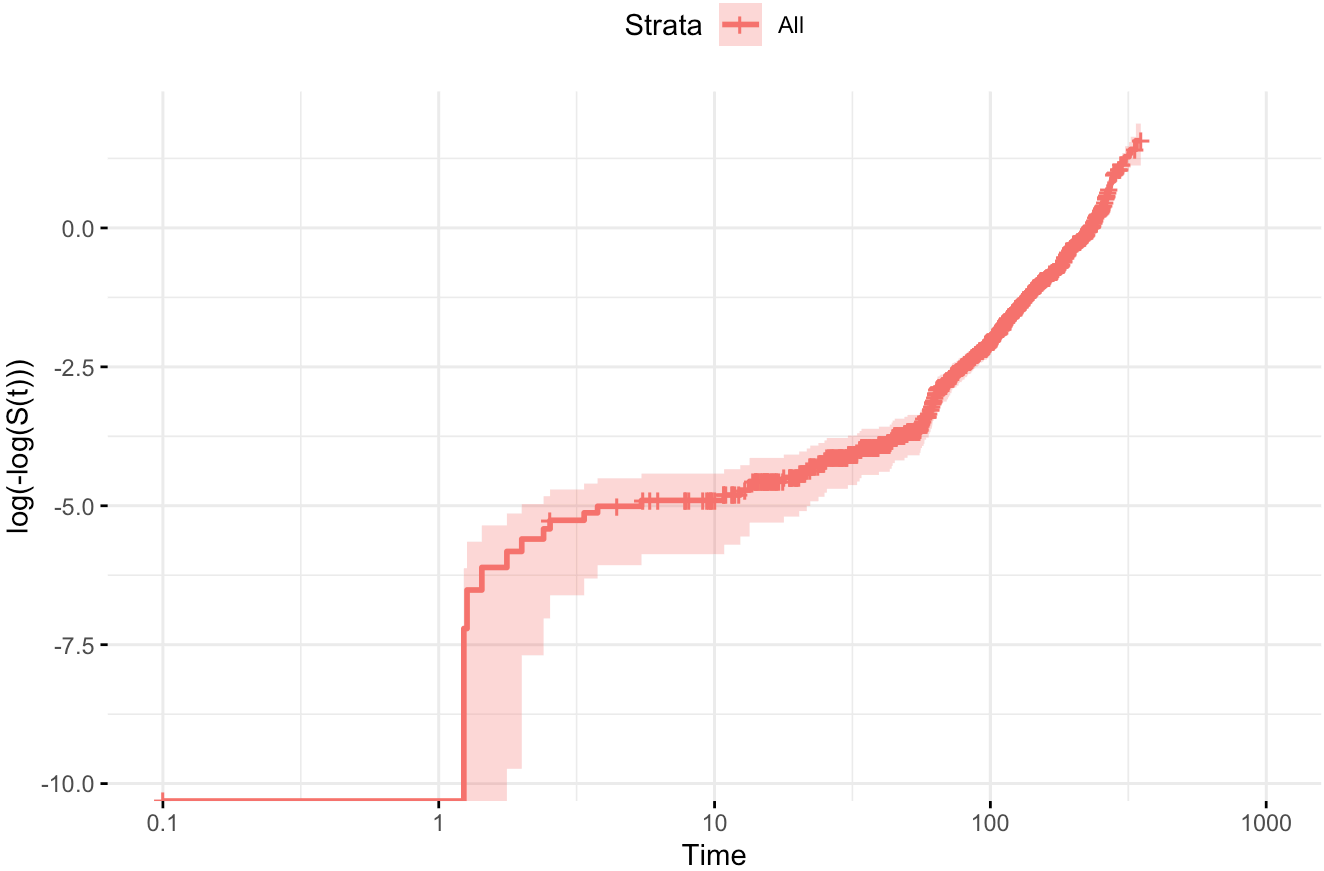


loglogistic Model Residuals



```
km_fit <- survfit(Surv(overall_survival_months, overall_survival) ~ 1,  
                  data = df_data)  
ggsurvplot(km_fit, fun = "cloglog",  
            title = "log(-log(Survival)) vs log(Time)",  
            ggtheme = theme_minimal())
```

log(-log(Survival)) vs log(Time)



```
survdif(Surv(overall_survival_months, overall_survival) ~ tp53_mut_bin,  
data = df_model)
```

Call:
survdif(formula = Surv(overall_survival_months, overall_survival) ~
tp53_mut_bin, data = df_model)

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
tp53_mut_bin=0	886	416	406	0.238	0.751
tp53_mut_bin=1	468	180	190	0.510	0.751

Chisq= 0.8 on 1 degrees of freedom, p= 0.4