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# Perform univariate and multivariate analysis on GBM Nature 2008
dataset (Suppl Data 5)

library('survival')
library('openxlsx')

#####
# load dataset and clinical information
#####

data <- read.xlsx('Suppl Table 5.xlsx')

#####
# SURVIVAL STATUS
# Assign 0,1 to overall survival status
# Deceased = 1, Living = 0
#####

data$status2 <- data$OS.Status
data[which(data$OS.Status == "DECEASED"),'status2'] <- 1
data[which(data$OS.Status == "LIVING"),'status2'] <- 0
data$status2 <- as.numeric(data$status2)

#####
# Perform Univariate Analysis - Clinical
#####

# Age
summary(coxph(Surv(data$OS.Months, status2 ) ~ Diagnosis.Age,
              data = data))

# Gender
# male = 1, female = 0
data$Sex2 <- 0
data[which(data$Sex == "Male"),'Sex2'] <- 1
summary(coxph(Surv(OS.Months, status2) ~ Sex2, data = data))

# KPS (Karnofsky performance Score)
summary(coxph(Surv(OS.Months, status2) ~ Karnofsky.Performance.Score,
              data = data))

# Subtype Classification
# Make subtypes as factors, with Mesenchymal as reference
data$subtype2 <- data$Gene.Expression.Subtype
data[which(data$Gene.Expression.Subtype == "Classical"),'subtype2'] <- 0
data[which(data$Gene.Expression.Subtype == "G-CIMP"),'subtype2'] <- 1
data[which(data$Gene.Expression.Subtype == "Mesenchymal"),'subtype2'] <-
2
data[which(data$Gene.Expression.Subtype == "Neural"),'subtype2'] <- 3
data[which(data$Gene.Expression.Subtype == "Proneural"),'subtype2'] <- 4

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data$subtype2 <- as.numeric(data$subtype2)

subtype_factor <- factor(data$Gene.Expression.Subtype,
                        levels = c("Mesenchymal", "Classical", "G-
CIMP", "Neural", "Proneural"))
summary(coxph(Surv(OS.Months, status2) ~ subtype_factor, data = data))

# IDH mutated
# mutated = 1, WT = 0
data$idh.mutated <- data$IDH1_STATUS
data[which(data$IDH1_STATUS == "R132H"), 'idh.mutated'] <- 1
data[which(data$IDH1_STATUS == "WT"), 'idh.mutated'] <- 0
class(data$idh.mutated) <- 'numeric'
summary(coxph(Surv(OS.Months, status2) ~ idh.mutated, data = data))

# MGMT Methylation
# methylation = 1, unmethylated = 0
data$methylated <- data$MGMT.Status
data[which(data$MGMT.Status == "METHYLATED"), 'methylated'] <- 1
data[which(data$MGMT.Status == "UNMETHYLATED"), 'methylated'] <- 0
class(data$methylated) <- 'numeric'
summary(coxph(Surv(OS.Months, status2) ~ methylated, data = data))

# Treatment (with TMZ)
# Treatment ("Nonstandard Radiation, TMZ Chemo ||
# Standard Radiation, TMZ Chemo || TMZ Chemo, TMZ Chemoradiation
# || TMZ Chemo) = 1
# Others = 0
data$Treatment <- 0
data[which( data$THERAPY_CLASS== "Nonstandard Radiation, TMZ Chemo" |
            data$THERAPY_CLASS == "Standard Radiation, TMZ Chemo" |
            data$THERAPY_CLASS == "TMZ Chemo" |
            data$THERAPY_CLASS == "TMZ Chemoradiation, TMZ
Chemo"), 'Treatment'] <- 1
summary(coxph(Surv(OS.Months, status2) ~ Treatment , data = data))

#####
# Perform Univariate Analysis - Gene Expression (High vs Low) by median
# High = 1, Low = 0
#####

# AHR
data$AHR_median <- 0
data[which(data$AHR > median(data$AHR, na.rm = T)), 'AHR_median'] <- 1
summary(coxph(Surv(OS.Months, status2) ~ AHR_median, data = data))

# ENTPD1
data$ENTPD1_median <- 0
data[which(data$ENTPD1 > median(data$ENTPD1, na.rm =
T)), 'ENTPD1_median'] <- 1
summary(coxph(Surv(OS.Months, status2) ~ ENTPD1_median, data = data))

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# KLF4
data$KLF4_median <- 0
data[which(data$KLF4 > median(data$KLF4, na.rm = T)), 'KLF4_median'] <- 1
summary(coxph(Surv(OS.Months, status2) ~ KLF4_median, data = data))

# CYP1A1
data$CYP1A1_median <- 0
data[which(data$CYP1A1 > median(data$CYP1A1, na.rm =
T)), 'CYP1A1_median'] <- 1
summary(coxph(Surv(OS.Months, status2) ~ CYP1A1_median, data = data))

# STAT1
data$STAT1_median <- 0
data[which(data$STAT1 > median(data$STAT1, na.rm = T)), 'STAT1_median']
<- 1
summary(coxph(Surv(OS.Months, status2) ~ STAT1_median, data = data))

# STAT3
data$STAT3_median <- 0
data[which(data$STAT3 > median(data$STAT3, na.rm = T)), 'STAT3_median']
<- 1
summary(coxph(Surv(OS.Months, status2) ~ STAT3_median, data = data))

# CCL2
data$CCL2_median <- 0
data[which(data$CCL2 > median(data$CCL2, na.rm = T)), 'CCL2_median'] <- 1
summary(coxph(Surv(OS.Months, status2) ~ CCL2_median, data = data))

# CCR2
data$CCR2_median <- 0
data[which(data$CCR2 > median(data$CCR2, na.rm = T) ), 'CCR2_median'] <-
1
summary(coxph(Surv(OS.Months, status2) ~ CCR2_median, data = data))

#####
# Multivariate Analysis
#####

summary(coxph(Surv(OS.Months, status2) ~ Diagnosis.Age +
            idh.mutated + Treatment + subtype2 + AHR_median, data =
data))
summary(coxph(Surv(OS.Months, status2) ~ Diagnosis.Age + Treatment +
            idh.mutated + subtype2 + ENTPD1_median, data = data))
summary(coxph(Surv(OS.Months, status2) ~ Diagnosis.Age + idh.mutated +
            Treatment + subtype2 + KLF4_median, data = data))
summary(coxph(Surv(OS.Months, status2) ~ Diagnosis.Age + idh.mutated +
            Treatment + subtype2 + CYP1A1_median, data = data))
summary(coxph(Surv(OS.Months, status2) ~ Diagnosis.Age + idh.mutated +

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summary(coxph(Surv(OS.Months, status2) ~ Diagnosis.Age + idh.mutated +
             Treatment + subtype2 + STAT1_median, data = data))
summary(coxph(Surv(OS.Months, status2) ~ Diagnosis.Age + idh.mutated +
             Treatment + subtype2 + CCL2_median, data = data))
summary(coxph(Surv(OS.Months, status2) ~ Diagnosis.Age + idh.mutated +
             Treatment + subtype2 + CCR2_median, data = data))
summary(coxph(Surv(OS.Months, status2) ~ Diagnosis.Age + idh.mutated +
             Treatment + subtype2 + STAT3_median, data = data))
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# Test the proportionality and goodness of fit for AHR expression
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fit <- coxph(Surv(OS.Months, status2) ~ Diagnosis.Age +
            idh.mutated + Treatment + subtype2 + AHR_median, data =
            data)
cox.zph(fit)
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