

A Biomarker approach for predicting survival using metabolite signature

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```
Eva <- read_excel("~/Documents/PHD/LUNGCANCER/SURVIVAL/WITHOUT_NOISE/DEFINITIVESETSURVIVALWITHOUTNOISY"  
## [1] "var5"  "var6"  "var7"  "var10" "var11" "var12" "var16" "var22"  
## [9] "var23" "var32" "var74"
```

INTRODUCTION

Goal of the study

- 56 lung cancer patients (Stage I and II = 12, Stage III and IV = 44)
- Survival data for cancer patients
- Metabolic data for estimating survival time
- Classify into high and low risk group
- This dataset will be used for validation

Characteristics of the data

- Survival data (survival time & censoring)
- Metabolic data (99 integration region from NMR spectrum after removing noise variables)
- Clinical covariates (BMI, Gender, Smoking, Age, Diabetes, Stage, Histology)

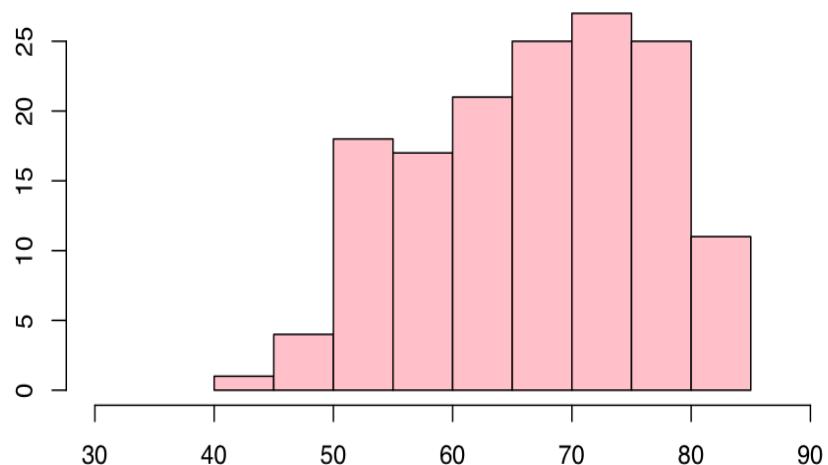
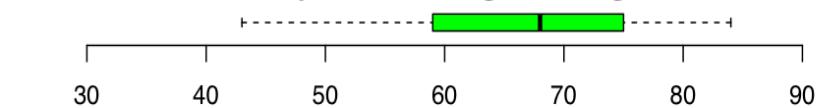
EXPLORATORY DATA ANALYSIS

The numerical variables

Age

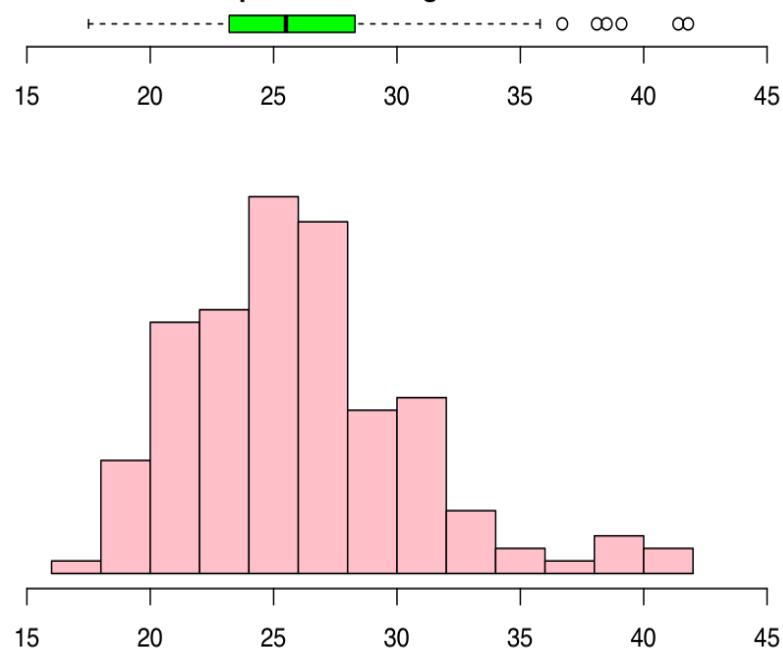
```
## [1] 67.1745  
## [1] 9.632947
```

Boxplot and Histogram of Age



```
BMI  
## [1] 26.06846  
## [1] 4.597459
```

Boxplot and Histogram of BMI

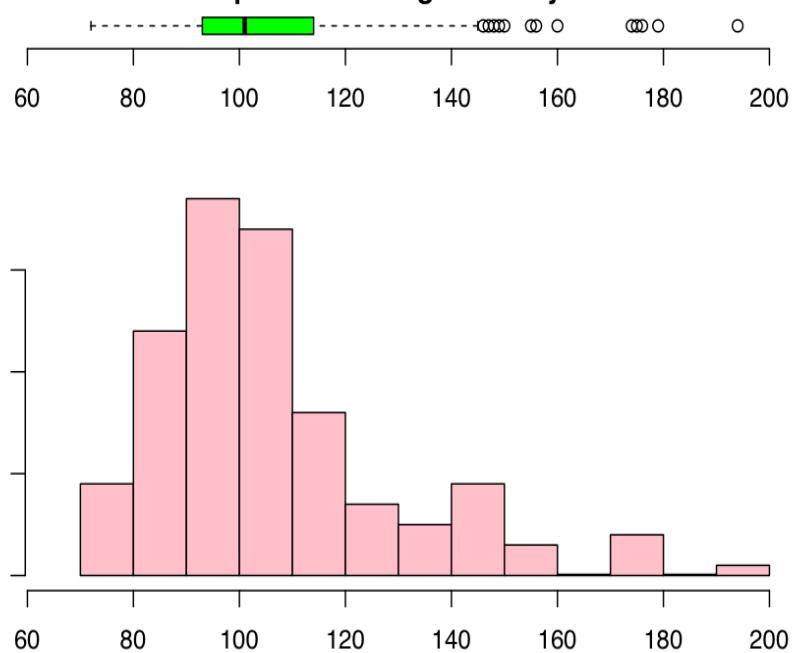


Glycemia

[1] 107.1477

[1] 23.02301

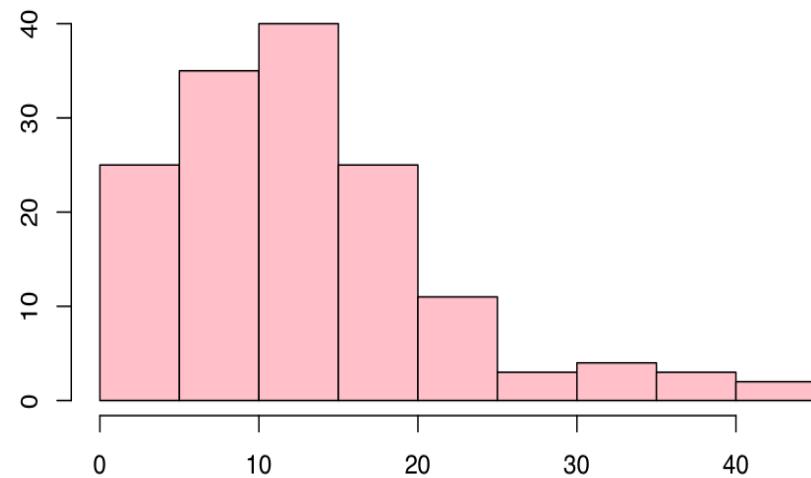
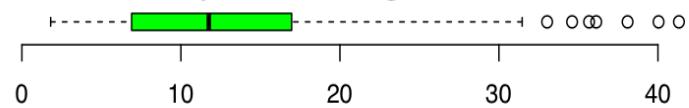
Boxplot and Histogram of Glycemia



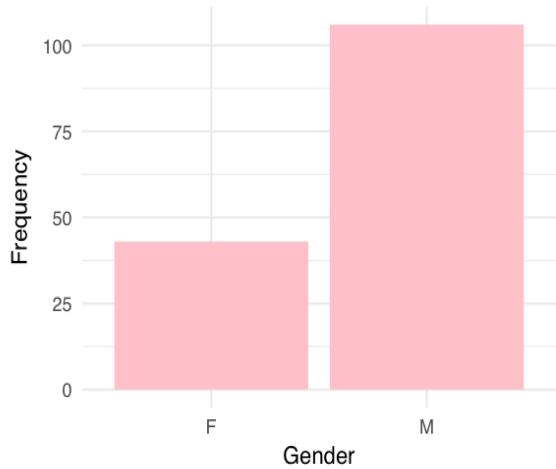
SUVMAX

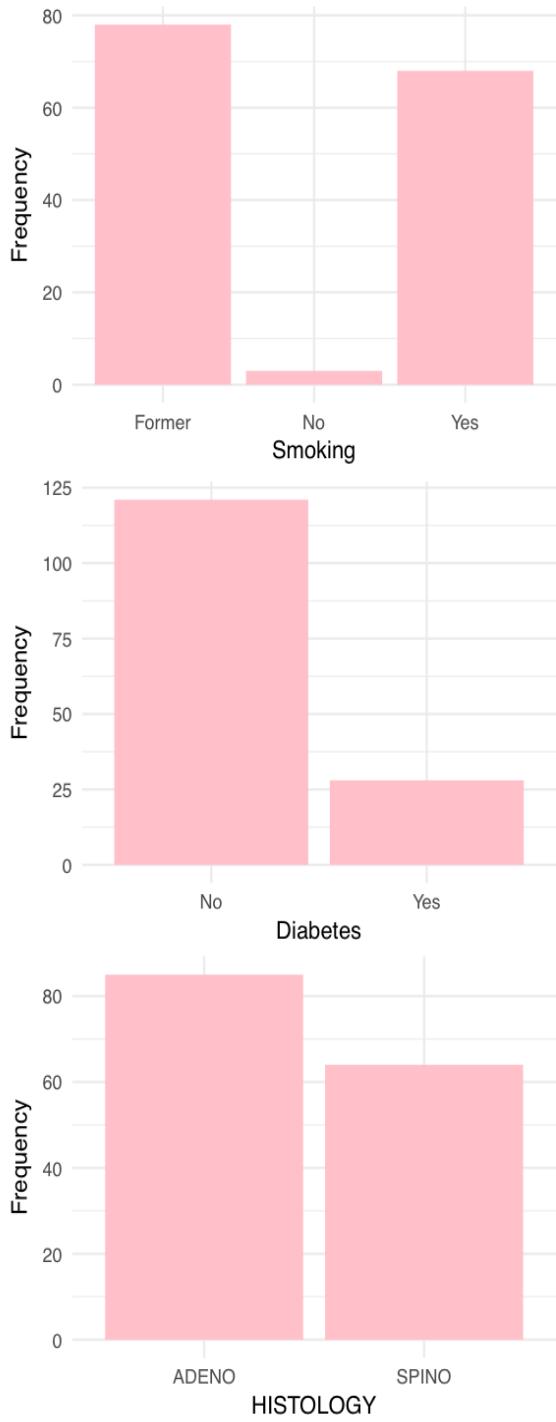
```
## [1] 12.98953  
## [1] 8.302056
```

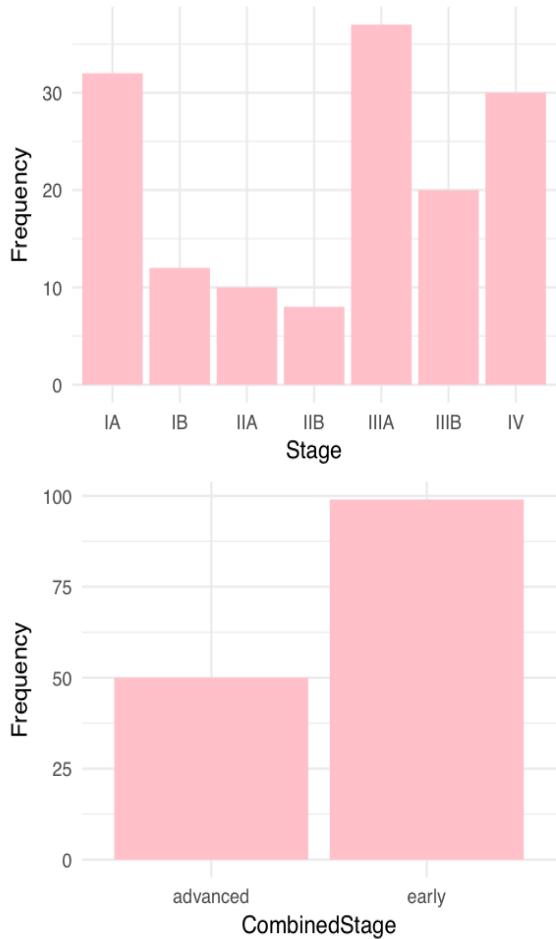
Boxplot and Histogram of SUVMAX



The categorical variables

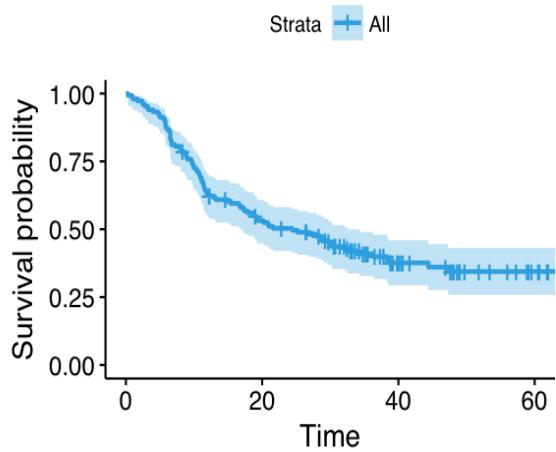




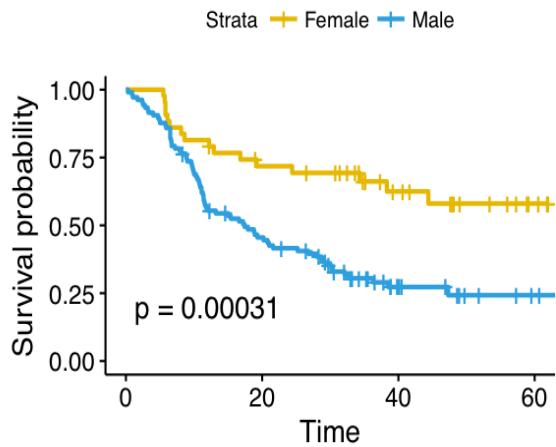


KAPLAN MEIER PLOT

For all the patients

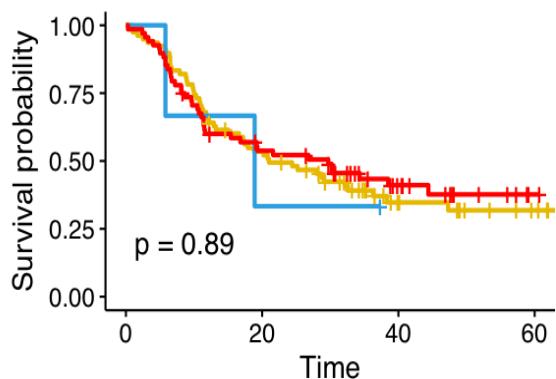


By gender



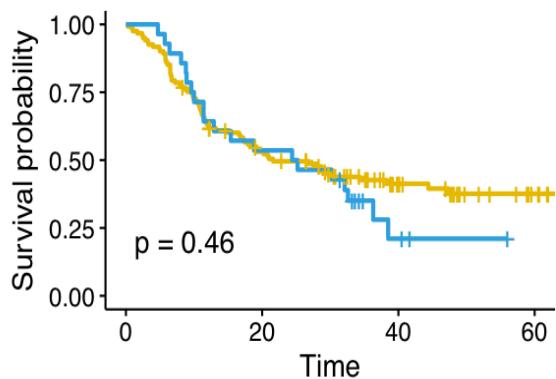
By smoking status

Strata Former No Yes



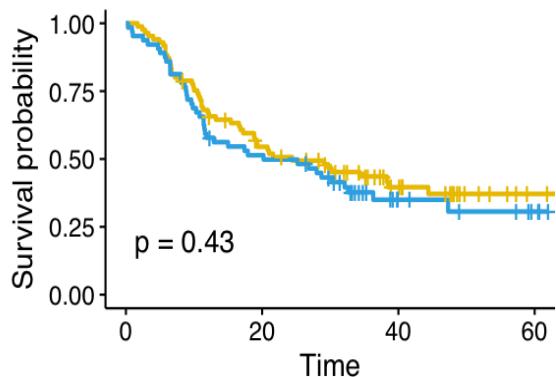
By diabetes status

Strata No Yes



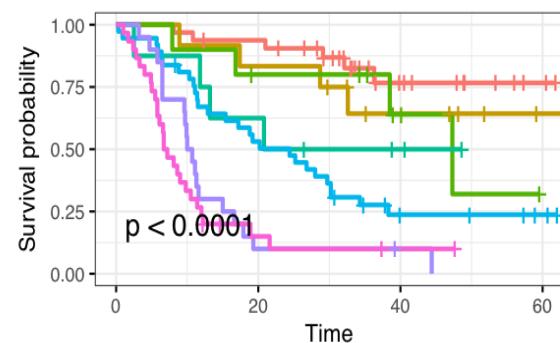
By histology status

Strata ADENO SPINO

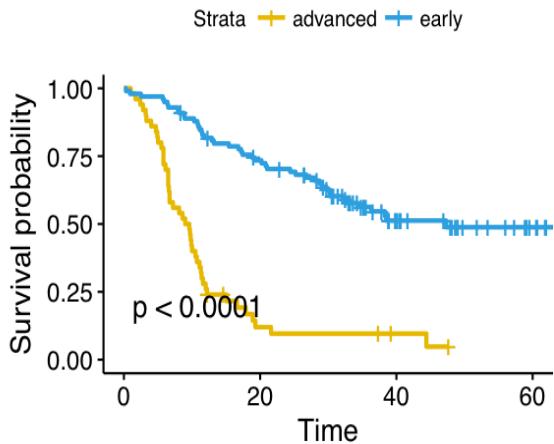


By Cancer stage

Strata IA IIA IIIA IV
IB IIB IIIB



By combined cancer stage



COXPH OF EACH OF THE CLINICAL COVARIATES (UNIVARIATE)

```
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## SUVMAX  0.03311852 1.033673 0.01077702 3.073068 0.002118705
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## Age     0.01995234 1.020153 0.01177923 1.693857 0.09029237
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## glycemia 0.003817722 1.003825 0.00448451 0.8513131 0.3945955
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## BMI    -0.01104295 0.9890178 0.0226375 -0.487817 0.6256795
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## SeksM   0.9660475  2.627539 0.2777509 3.478107 0.0005049678
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## SmokingNo 0.16785004 1.1827592 0.7219403 0.2324985 0.8161508
## SmokingYes -0.08243946 0.9208672 0.2148195 -0.3837616 0.7011551
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## DiabetesYes 0.1875769  1.206323 0.2543023 0.7376138 0.4607492
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## HISTOLOGYSPINO 0.1656035  1.180105 0.2118066 0.781862 0.4342957
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## Stage2early -1.636208  0.1947171 0.2230423 -7.335864 2.20296e-13
```

COXPH OF ALL CLINICAL COVARIATES (MULTIVARIATE)

Selecting those that are significant univariately to further use in the multivariate cox ph model. GENDER , STAGE and SUVMAX are significant.

```
##           coef exp(coef)    se(coef)      z   Pr(>|z|)
## SeksM      1.126110 3.0836367 0.2863767 3.932267 8.414836e-05
## Stage2early -1.771623 0.1700568 0.2360801 -7.504330 6.174335e-14
##           coef exp(coef)    se(coef)      z   Pr(>|z|)
## SeksM      1.09484210 2.9887107 0.28614831 3.826135 1.301708e-04
## Stage2early -1.71296972 0.1803295 0.23918856 -7.161587 7.974833e-13
## SUVMAX     0.02172431 1.0219620 0.01216952 1.785140 7.423858e-02
```

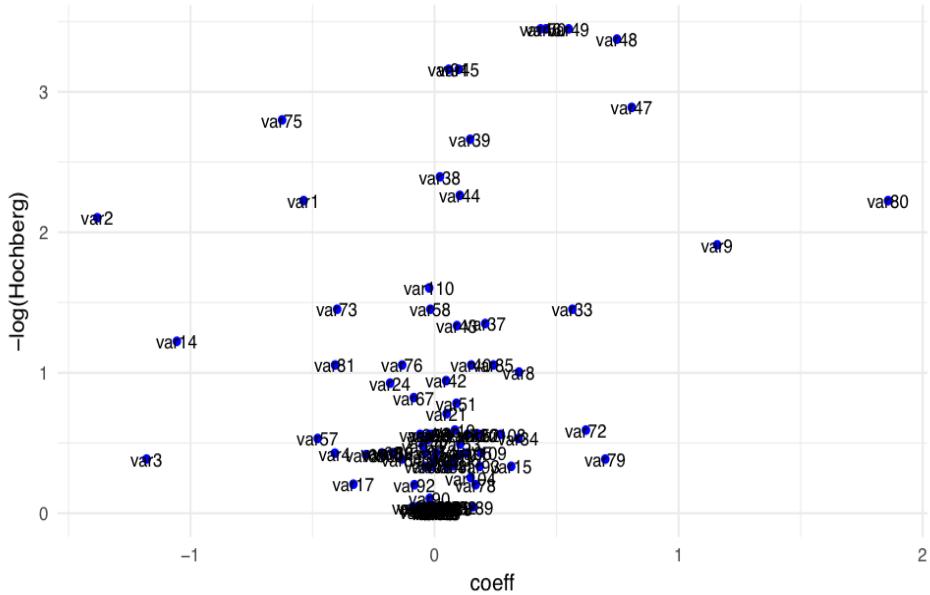
The three covariates were still significant univariately

COXPH OF EACH OF THE METABOLITES

This are the significant metabolites, multiplicity adjustment using BH which is the last column. 19 was significant before adjustment and None of the metabolites was significant after adjustment

```
##       rawpvalue     coeff      HR Hochberg adjusted
## var50  0.000628  0.45620 1.57800  0.0318 3.448289
## var49  0.000803  0.54940 1.73220  0.0318 3.448289
## var46  0.000965  0.43450 1.54410  0.0318 3.448289
## var48  0.001380  0.74720 2.11100  0.0342 3.375530
## var91  0.002340  0.05776 1.05950  0.0424 3.160607
## var45  0.002570  0.09862 1.10360  0.0424 3.160607
## var47  0.003930  0.80770 2.24280  0.0556 2.889572
## var75  0.004910 -0.62480 0.53535  0.0608 2.800165
## var39  0.006350  0.14540 1.15650  0.0698 2.662121
## var38  0.009210  0.02187 1.02210  0.0912 2.394700
## var44  0.011500  0.10320 1.10870  0.1040 2.263364
```

GRAPHICALLY EXPRESSION OF THE ADJUSTED PVALUES

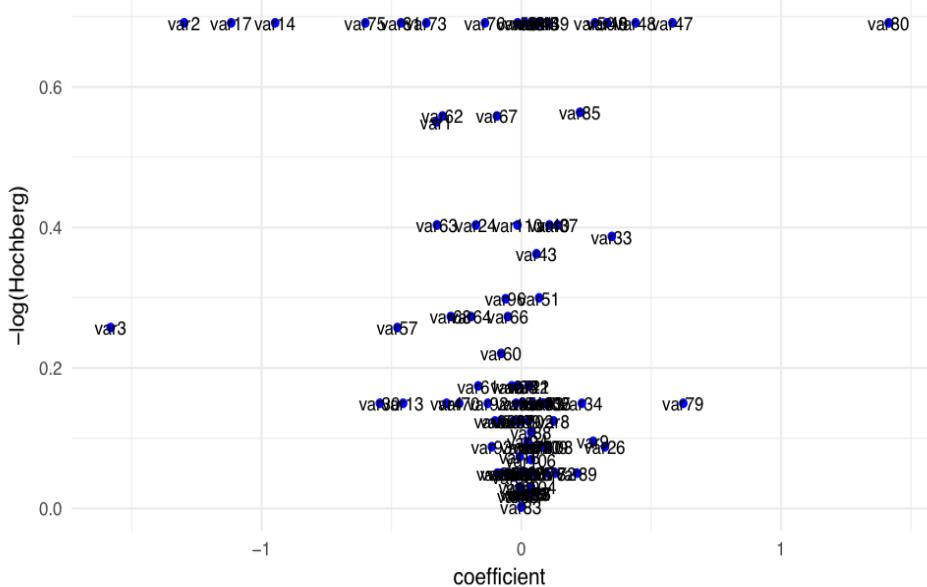


COXPH OF EACH OF THE METABOLITES WITH THE SIGNIFICANT METABOLITES

The Cox ph analysis of each metabolite with Gender , Stage. SUVMax not used because it is not of interest. 9 was significant before adjustment and None of the metabolites was significant after adjustment

##	metnames	coefficient	HR	rawpvale	Hochberg	adjusted
## 64	var75	-0.60050	0.54853	0.00743	0.501	0.6911492
## 36	var46	0.33060	1.39180	0.01180	0.501	0.6911492
## 2	var2	-1.29800	0.27312	0.01990	0.501	0.6911492
## 80	var91	0.04441	1.04540	0.02620	0.501	0.6911492
## 40	var50	0.28290	1.32700	0.02690	0.501	0.6911492
## 39	var49	0.33020	1.39120	0.03800	0.501	0.6911492
## 37	var47	0.58160	1.78890	0.03810	0.501	0.6911492
## 35	var45	0.06344	1.06550	0.04410	0.501	0.6911492
## 29	var39	0.10600	1.11190	0.04880	0.501	0.6911492
## 38	var48	0.43980	1.55250	0.05470	0.501	0.6911492
## 69	var80	1.41400	4.11050	0.06070	0.501	0.6911492

GRAPHICALLY EXPRESSION OF THE ADJUSTED PVALUES



CLASSIFICATION OF SUBJECT BY STAGE

```
nrow(early)
## [1] 99
nrow(advanced)
## [1] 50
length(Eva[15:113])
## [1] 99
```

COXPH OF EACH OF THE CLINICAL COVARIATES BY STAGE (UNIVARIATE)

Note : First row is the early stage and the second row is the advanced stage

SUVMAX

```
##          coef exp(coef)   se(coef)      z Pr(>|z|)
## SUVMAX 0.02314140  1.023411 0.01591087 1.454440 0.1458244
## SUVMAX 0.02434832  1.024647 0.01763576 1.380622 0.1673952
```

AGE

```
##           coef exp(coef)    se(coef)      z Pr(>|z|)  
## Age  0.04085263 1.041699 0.01736327 2.3528197 0.01863166  
## Age -0.00725423 0.992772 0.01628258 -0.4455209 0.65594335
```

GLYCEMIA

```
##           coef exp(coef)    se(coef)      z Pr(>|z|)  
## glycemia 0.009725176 1.009773 0.005839602 1.665383 0.09583627  
## glycemia 0.008065276 1.008098 0.007327538 1.100680 0.27103586
```

BMI

```
##           coef exp(coef)    se(coef)      z Pr(>|z|)  
## BMI  0.01593295 1.0160606 0.03147484 0.5062121 0.6127078  
## BMI -0.02740559 0.9729665 0.02967237 -0.9236065 0.3556912
```

SEKS

```
##           coef exp(coef)    se(coef)      z Pr(>|z|)  
## SeksM 1.0169211 2.764669 0.3915203 2.597365 0.009394203  
## SeksM 0.9902089 2.691797 0.4262583 2.323025 0.020177798
```

SMOKING

```
##           coef exp(coef)    se(coef)      z Pr(>|z|)  
## SmokingNo       NA       NA 0.0000000       NA       NA  
## SmokingYes -0.57002186 0.5655131 0.3223555 -1.76830205 0.07701042  
## SmokingNo  -0.89171750 0.4099511 0.7573912 -1.17735386 0.23905430  
## SmokingYes -0.03016768 0.9702828 0.3219874 -0.09369214 0.92535372
```

DIABETES

```
##           coef exp(coef)    se(coef)      z Pr(>|z|)  
## DiabetesYes 0.6224869 1.863557 0.3181916 1.9563272 0.05042663  
## DiabetesYes 0.3810854 1.463873 0.4849650 0.7857998 0.43198479
```

HISTOLOGY

```
##           coef exp(coef)    se(coef)      z Pr(>|z|)  
## HISTOLOGYSPINO 0.5665452 1.762169 0.3022555 1.8743913 0.06087651  
## HISTOLOGYSPINO 0.2452616 1.277956 0.3201189 0.7661576 0.44358253
```

COXPH OF ALL CLINICAL COVARIATES FOR EARLY STAGE (MULTI-PLE)

Selecting those that are significant univariately to further use in the multivariate cox ph model. AGE and GENDER are significant.

```

##           coef exp(coef)   se(coef)      z Pr(>|z|)
## SeksM 1.016921  2.764669 0.3915203 2.597365 0.009394203

```

COXPH OF EACH OF ALL CLINICAL COVARIATES FOR ADVANCED STAGE (MULTIPLE)

Selecting those that are significant univraitely to further use in the multirivariate cox ph model. GENDER is significant.

```

##           coef exp(coef)   se(coef)      z Pr(>|z|)
## SeksM 0.9902089  2.691797 0.4262583 2.323025 0.0201778

```

In both cases, Seks was significant.

COXPH ON EACH OF THE METABOLITES IN THE EARLY STAGE

This are the significant metabolites, multiplicity adjustment using BH which is the last column. None of the metabolites were significant after adjustment.

```

##       erawpvalue ecoeff      eHR eHochberg eadjusted
## var75    0.00436 -0.8523 0.42643     0.356 1.0328245
## var31    0.00720  0.8991 2.45740     0.356 1.0328245
## var76    0.01130 -0.2682 0.76478     0.373 0.9861769
## var1     0.01520 -0.7626 0.46647     0.376 0.9781661
## var58    0.02440 -0.0267 0.97365     0.464 0.7678707
## var2     0.02910 -1.9150 0.14735     0.464 0.7678707
## var91    0.03280  0.0553 1.05690     0.464 0.7678707
## var46    0.04830  0.3705 1.44850     0.560 0.5798185

```

COXPH ON EACH OF THE METABOLITES IN THE ADVANCED STAGE

This are the significant metabolites, multiplicity adjustment using BH which is the last column. None of the metabolites were significant after adjustment.

```

##       arawpvalue acoeff      aHR aHochberg aadjusted
## var24    0.0070 -0.49680 0.60846     0.247 1.398367
## var105   0.0188  0.50110 1.65050     0.247 1.398367
## var26    0.0193  2.60000 13.45700    0.247 1.398367
## var31    0.0199 -0.87420 0.41718     0.247 1.398367
## var27    0.0207  2.32100 10.18600    0.247 1.398367
## var25    0.0237 -0.78950 0.45409     0.247 1.398367
## var69    0.0313 -0.17470 0.83970     0.247 1.398367
## var47    0.0352  0.86990 2.38660     0.247 1.398367
## var107   0.0357  0.35750 1.42980     0.247 1.398367
## var46    0.0376  0.39760 1.48820     0.247 1.398367
## var85    0.0382  0.42860 1.53510     0.247 1.398367
## var50    0.0412  0.37010 1.44790     0.247 1.398367
## var103   0.0433  0.45690 1.57920     0.247 1.398367
## var82    0.0465  0.98940 2.68950     0.247 1.398367
## var38    0.0478  0.02210 1.02230     0.247 1.398367
## var77    0.0480  1.00500 2.73120     0.247 1.398367
## var18    0.0499 -0.04522 0.95579     0.247 1.398367

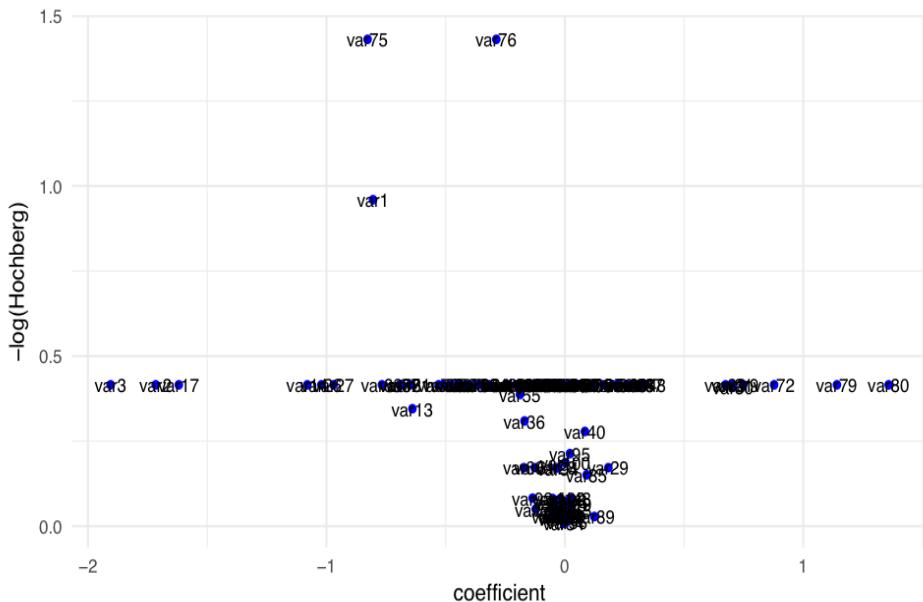
```

COXPH OF EACH OF THE METABOLITES WITH THE SIGNIFICANT METABOLITES IN THE EARLY STAGE

The Cox ph analysis of each metabolite with Gender. None of the metabolites was significant

```
##   metnames coefficient      HR rawpvale Hochberg adjusted
## 64  var75    -0.82730 0.43723  0.00465   0.239 1.4312917
## 65  var76    -0.28760 0.75008  0.00482   0.239 1.4312917
## 1   var1     -0.80450 0.44733  0.01160   0.383 0.9597203
## 22  var31     0.70250 2.01870  0.03620   0.660 0.4155154
## 70  var81    -0.64900 0.52257  0.04150   0.660 0.4155154
## 80  var91     0.05161 1.05300  0.04570   0.660 0.4155154
## 48  var58    -0.02357 0.97670  0.04690   0.660 0.4155154
```

GRAPHICALLY EXPRESSION OF THE ADJUSTED PVALUES IN EARLY STAGE

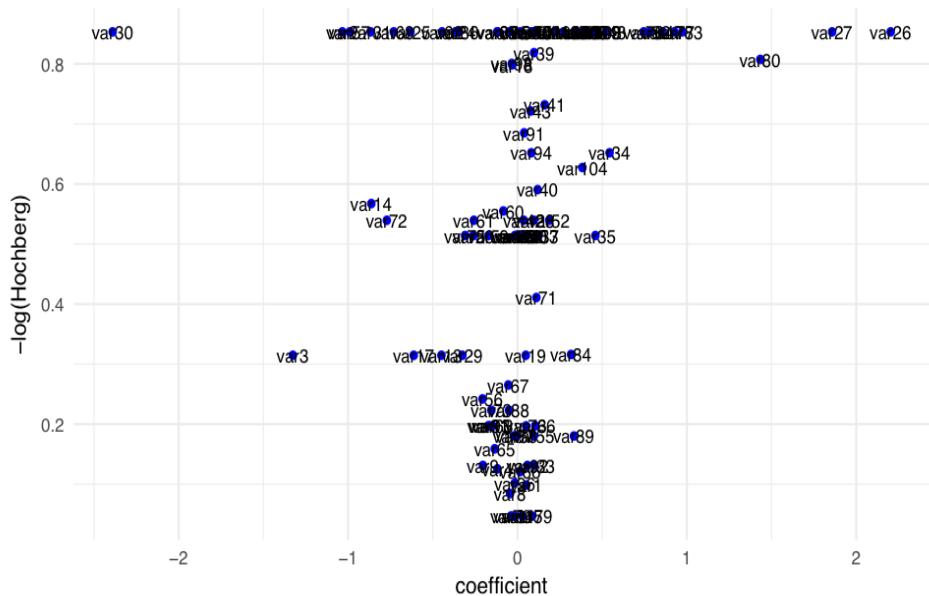


COXPH OF EACH OF THE METABOLITES WITH THE SIGNIFICANT METABOLITES IN THE ADVANCED STAGE

The Cox ph analysis of each metabolite with Gender. None of the metabolites was significant

```
##   metnames coefficient      HR rawpvale Hochberg adjusted
## 22  var31    -0.8666 0.420370  0.0207   0.426 0.8533159
## 36  var46     0.4145 1.513600  0.0256   0.426 0.8533159
## 37  var47     0.8566 2.355100  0.0354   0.426 0.8533159
## 21  var30    -2.3900 0.091587  0.0384   0.426 0.8533159
## 40  var50     0.3548 1.425900  0.0400   0.426 0.8533159
## 90  var101    0.1113 1.117800  0.0419   0.426 0.8533159
```

GRAPHICALLY EXPRESSION OF THE ADJUSTED PVALUES IN ADVANCED STAGE



MODELLING FRAMEWORK

- Model clinical and metabolic variables

$$h(t) = h_o(t) \exp^u$$

$$\mu = \sum_{m=1}^M \alpha_m C_m + \sum_{n=1}^N \beta_n X_n$$

- Obtain a risk score based on the coefficient and data of the metabolites

$$R_i = \sum_{n=1}^N \hat{\beta}_n x_n$$

- Obtain the risk group (G) using the median as cutoff

$$\text{Low risk} = R_i < \text{median}(R_i)$$

$$\text{high risk} = R_i > \text{median}(R_i)$$

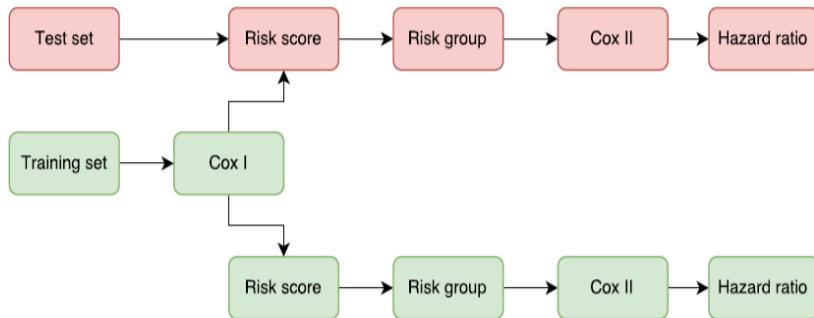
- Model the clinical covariates and the risk group to obtain the hazard ratio and survival in the risk group

$$h(t) = h_o(t) \exp^u$$

$$\mu = \sum_{m=1}^M \alpha_m C_m + \gamma G$$

CROSS VALIDATION WORKFLOW

- Divide the data into training and test set based on the specified fold
- Use the training set to fit the model (clinical covariates and all the metabolites) and select the nonzero metabolites
- Use the nonzero metabolites to obtain the risk score based in the training set as well as the test set using its coefficient and the respective set
- Model the clinical covariates and the risk group to obtain the hazard ratio and survival of the risk group in the training and test set



SHRINKAGE METHOD (LASSO)

The lasso is cross validated in 1000 loops with Gender and stage. The HR of the risk group is reported.

LASSO CROSS VALIDATION FOR ALL THE PATIENTS

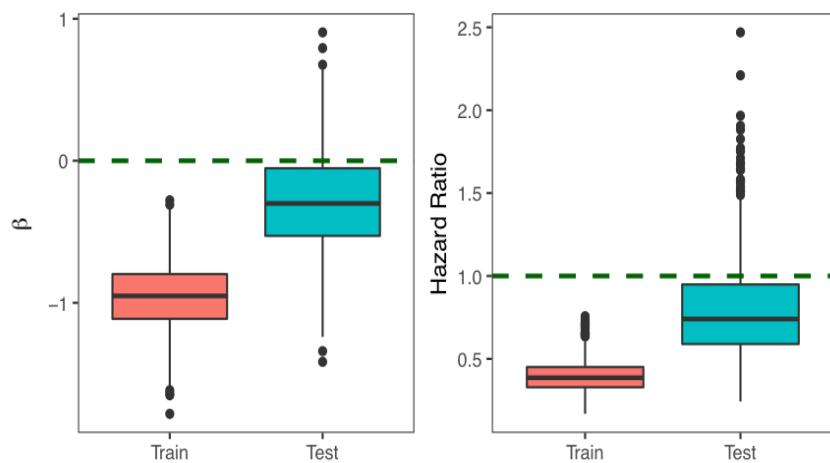
coefficient

All subjects survival result

```
##          Training      Test
## Mean   -0.9544202 -0.2890539
## Median -0.9515429 -0.3005168
## SD     0.2385981  0.3568691
##          Training      Test
## Mean   0.39610260 0.7982325
## Median 0.38614478 0.7404355
## SD     0.09530597 0.2942590
```

GRAPHICAL OUTPUT

Model with gender and stage Boxplot of the coefficient of test, training set.



LASSO CROSS VALIDATION FOR EARLY STAGE

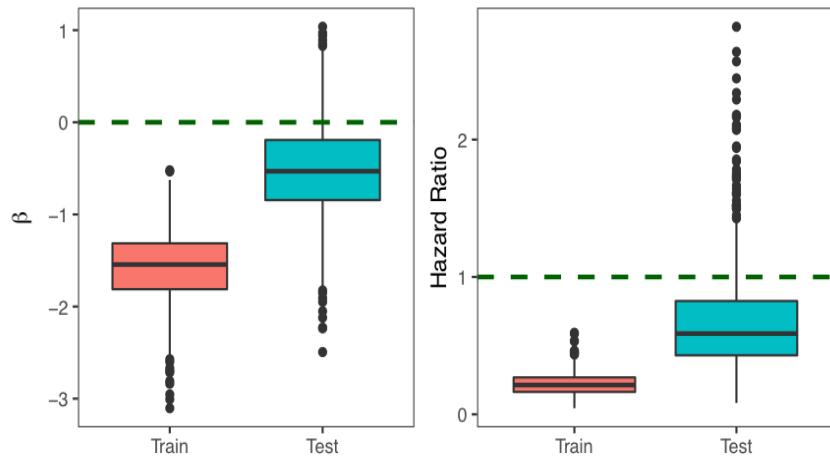
coefficient

hazard ratio

```
##          Training      Test
## Mean   -1.5662119 -0.5214210
## Median -1.5438466 -0.5312890
## SD     0.3716885  0.5009248
##          Training      Test
## Mean   0.22303180 0.6734808
## Median 0.21355806 0.5878468
## SD     0.07997575 0.3670268
```

GRAPHICAL OUTPUT FOR THE EARLY STAGE

Model with gender, Boxplot of the coefficient of test, training set.



LASSO CROSS VALIDATION FOR ADVANCED STAGE

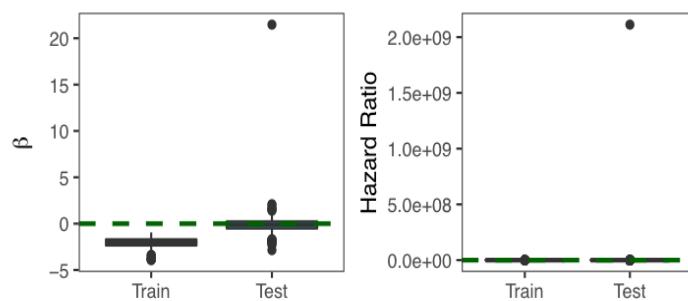
coefficient

hazard ratio

```
##           Training      Test
## Mean    -2.046487 -0.1235610
## Median -2.006048 -0.1227002
## SD      0.490006  0.9132481
##           Training      Test
## Mean    0.14429929 2.112137e+06
## Median  0.13451927 8.845293e-01
## SD      0.06613037 6.679161e+07
```

GRAPHICAL OUTPUT FOR THE ADVANCED STAGE WITH THE OUTLYING VALUE

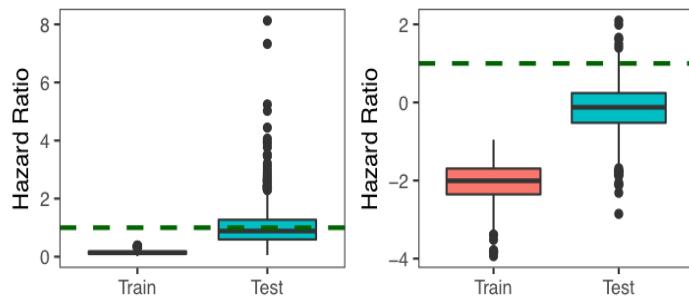
Model with gender, Boxplot of the coefficient of test, training set.



GRAPHICAL OUTPUT FOR THE ADVANCED STAGE WITHOUT THE OUTLYING VALUE

Model with gender, Boxplot of the coefficient of test, training set. That is without 1299

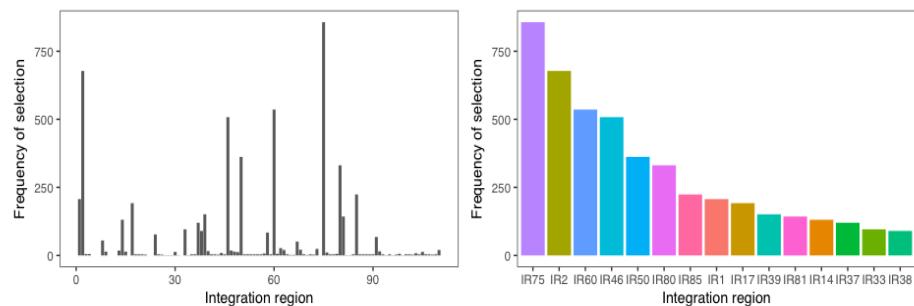
```
## [1] 1299
```



TOP 15 metabolites using all subjects

```
## [1] "IR75" "IR2" "IR60" "IR46" "IR50" "IR80" "IR85" "IR1" "IR17" "IR39"  
## [11] "IR81" "IR14" "IR37" "IR33" "IR38"
```

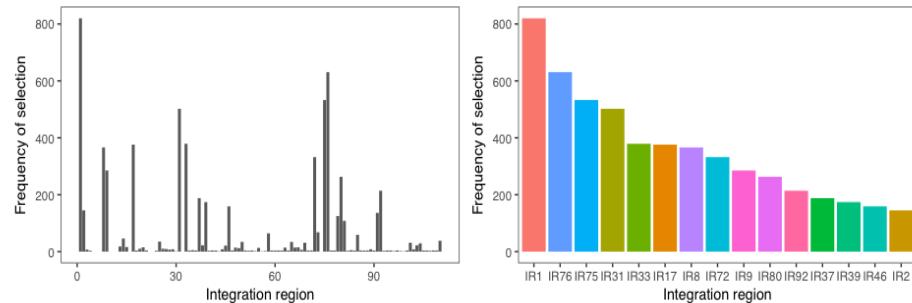
THE FREQUENCY OF SELECTION IN THE 1000 CV FOR ALL SUBJECT



TOP 15 metabolites using early subjects

```
## [1] "IR1" "IR76" "IR75" "IR31" "IR33" "IR17" "IR8" "IR72" "IR9" "IR80"  
## [11] "IR92" "IR37" "IR39" "IR46" "IR2"
```

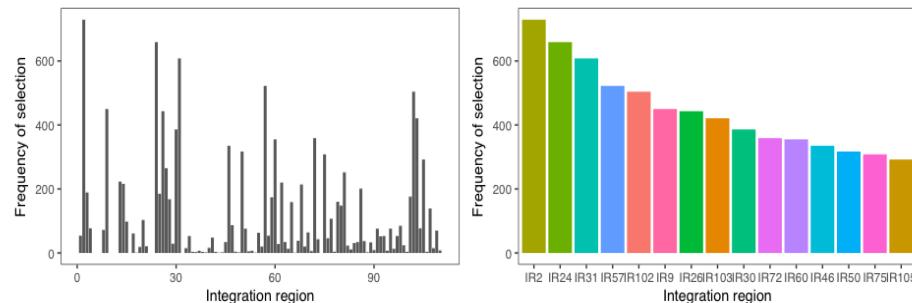
THE FREQUENCY OF SELECTION IN THE 1000 CV FOR EARLY SUBJECT



TOP 15 metabolites using advanced subjects

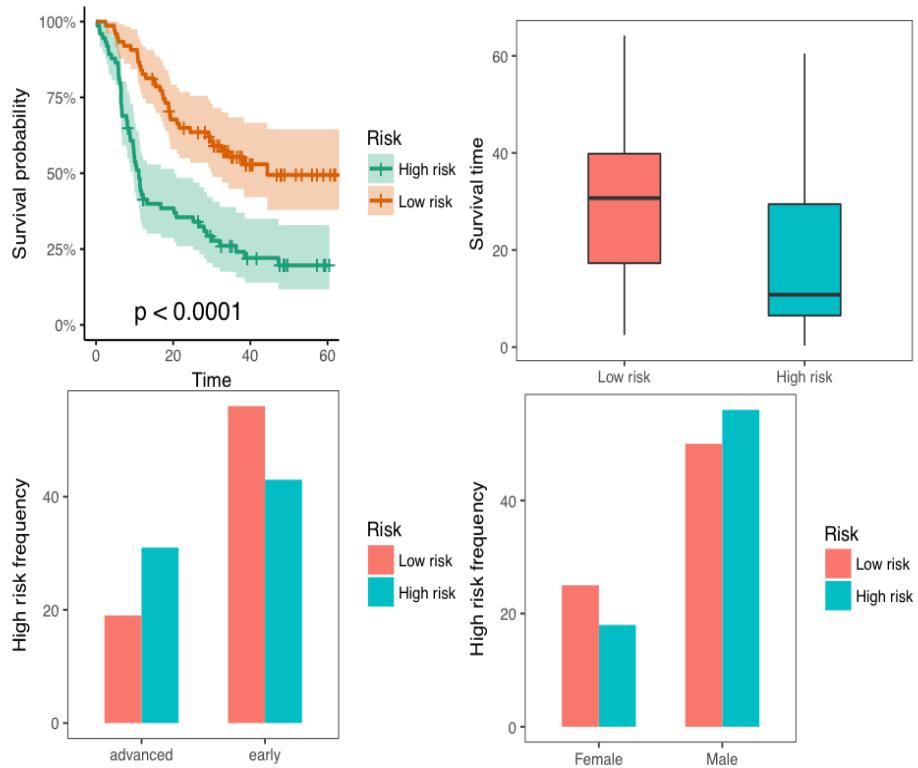
```
## [1] "IR2"   "IR24"  "IR31"  "IR57"  "IR102" "IR9"   "IR26"  "IR103"
## [9] "IR30"  "IR72"  "IR60"  "IR46"  "IR50"  "IR75"  "IR105"
```

THE FREQUENCY OF SELECTION IN THE 1000 CV FOR ADVANCED SUBJECT



COXPH USING TOP 5 MOST SELECTED METABOLITES USING ALL THE SUBJECTS(FIXED ANALYSIS)

```
##           coef exp(coef)  se(coef)      z    Pr(>|z|)
## SeksM     1.03147897 2.8052116 0.29537895 3.4920531 4.793230e-04
## Stageearly -1.90992685 0.1480912 0.25377126 -7.5261749 5.224835e-14
## var75     -0.65167079 0.5211743 0.26748205 -2.4363159 1.483772e-02
## var2      -1.45043454 0.2344684 0.59661450 -2.4311084 1.505271e-02
## var60     -0.09567864 0.9087560 0.08723763 -1.0967588 2.727468e-01
## var46      0.17175522 1.1873872 0.30398709  0.5650083 5.720681e-01
## var50      0.23333395 1.2628031 0.29346750  0.7950930 4.265594e-01
##
##           coef exp(coef)  se(coef)      z    Pr(>|z|)
## SeksM     1.276167 3.5828793 0.2948314 4.328463 1.501536e-05
## Stageearly -1.835999 0.1594542 0.2446609 -7.504257 6.177779e-14
## riskgroupLow risk -1.009858 0.3642706 0.2249205 -4.489845 7.127502e-06
```

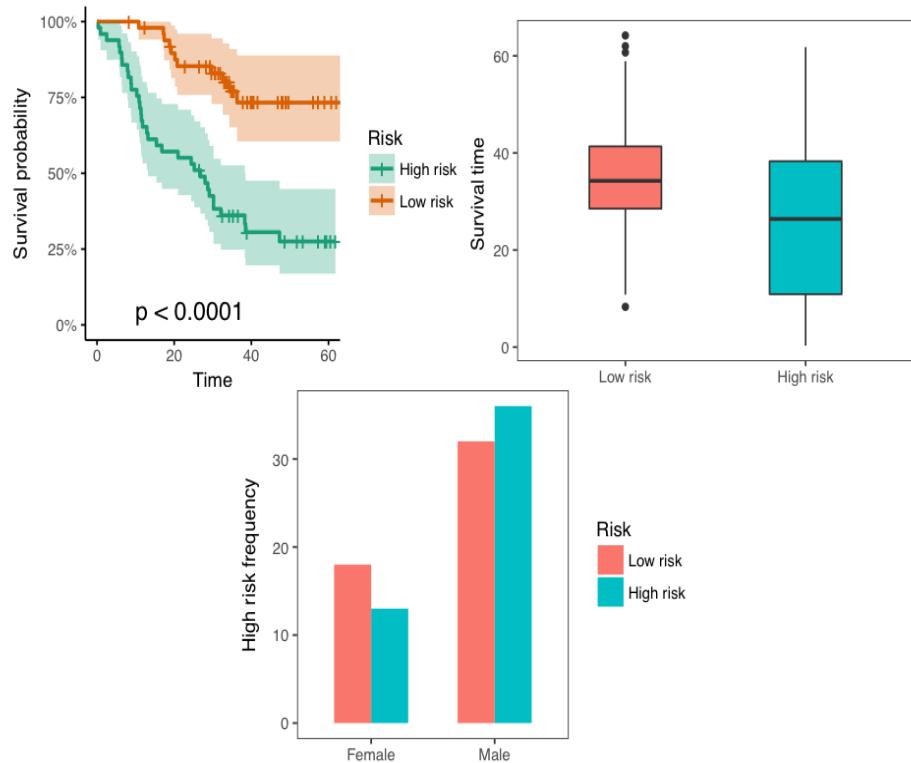


COXPH USING TOP 5 MOST SELECTED METABOLITES USING EARLY STAGE SUBJECTS (FIXED ANALYSIS)

```

##           coef exp(coef)  se(coef)      z Pr(>|z|)
## SeksM  0.72274073 2.0600716 0.4320002 1.67301002 0.09432532
## var1   -0.77145458 0.4623401 0.3258594 -2.36744643 0.01791131
## var76  -0.02055597 0.9796539 0.2418420 -0.08499751 0.93226337
## var75  -0.89004414 0.4106376 0.6940559 -1.28238112 0.19970898
## var31   0.54079837 1.7173774 0.3614169  1.49632846 0.13456808
## var33   1.05544035 2.8732401 0.4650301  2.26961738 0.02323081
##           coef exp(coef)  se(coef)      z Pr(>|z|)
## SeksM      0.9278607 2.5290928 0.3921795  2.365908 1.798590e-02
## riskgroupLow risk -1.4397909 0.2369773 0.3482240 -4.134669 3.554664e-05

```

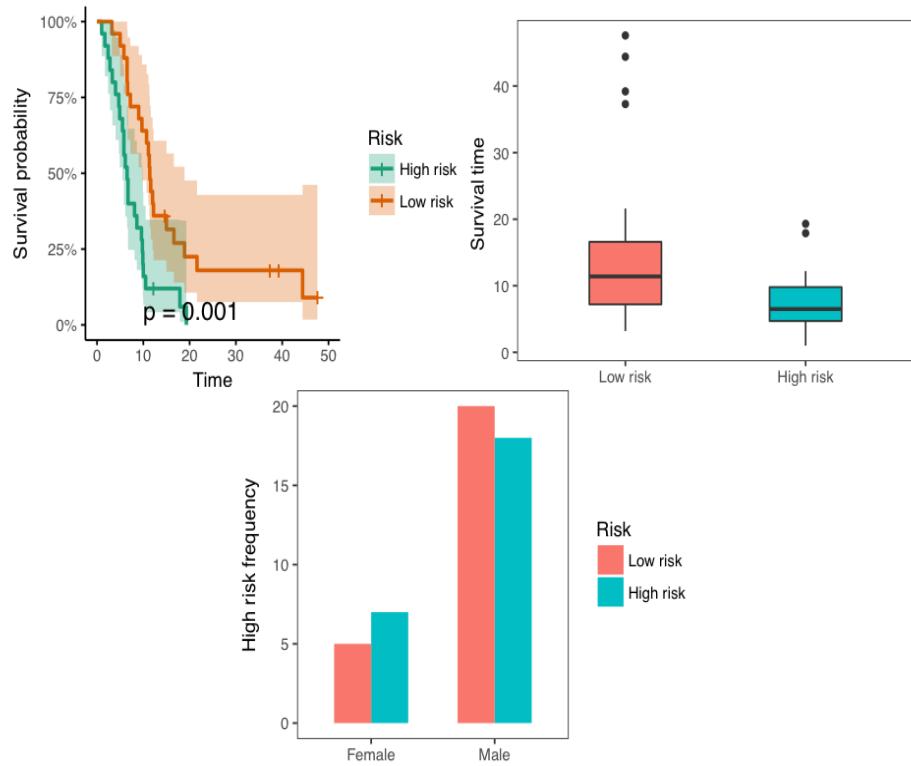


COXPH USING TOP 5 MOST SELECTED METABOLITES USING ADVANCED STAGE SUBJECTS (FIXED ANALYSIS)

```

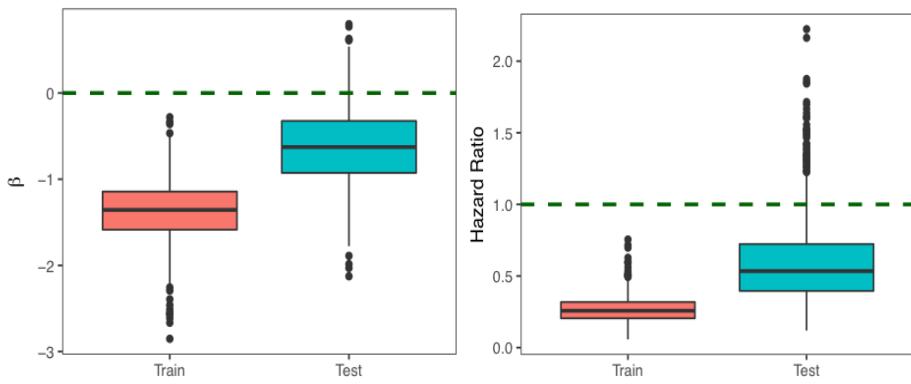
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## SeksM    0.79420374 2.2126784 0.45560736 1.7431758 0.08130291
## var2     -1.98654815 0.1371681 0.88807407 -2.2369172 0.02529175
## var24    -0.13771750 0.8713448 0.20972835 -0.6566471 0.51140788
## var31    -1.07387544 0.3416818 0.43015130 -2.4965063 0.01254234
## var57    -0.60738017 0.5447762 0.72839537 -0.8338606 0.40435957
## var102   0.04612836 1.0472088 0.07930893 0.5816288 0.56081674
##
##           coef exp(coef)   se(coef)      z Pr(>|z|)
## SeksM    0.9226299 2.5158983 0.4235589  2.178280 0.02938521
## riskgroupLow risk -0.9518822 0.3860138 0.3142389 -3.029167 0.00245229

```



TOP 10 CROSS VALIDATION FOR THE EARLY STAGE

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

```
##          Training      Test
## Mean -1.3669551 -0.6177602
```

```

## Median -1.3563922 -0.6273375
## SD      0.3346197  0.4625716

```

SUMMARY RESULT FOR THE HAZARD RATIO

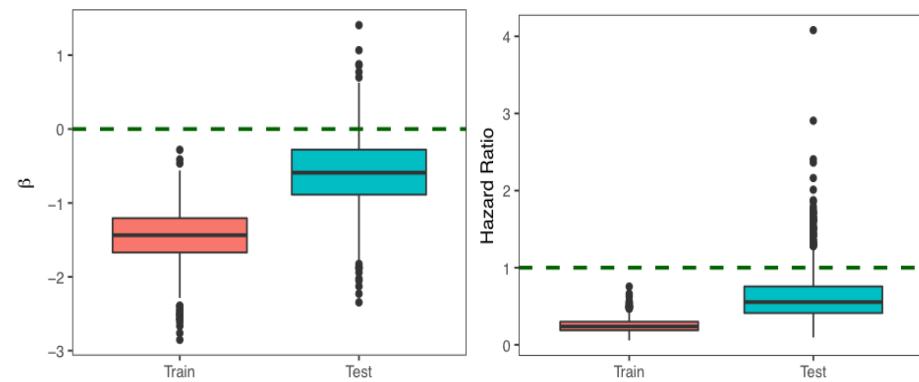
```

##          Training     Test
## Mean    0.26905507 0.6005352
## Median 0.25758859 0.5340117
## SD     0.08900012 0.2966315

```

TOP 15 CROSS VALIDATION FOR THE EARLY STAGE

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

```

##          Training     Test
## Mean    -1.4525399 -0.5861704
## Median -1.4366563 -0.5904550
## SD      0.3609106  0.4847118

```

SUMMARY RESULT FOR THE HAZARD RATIO

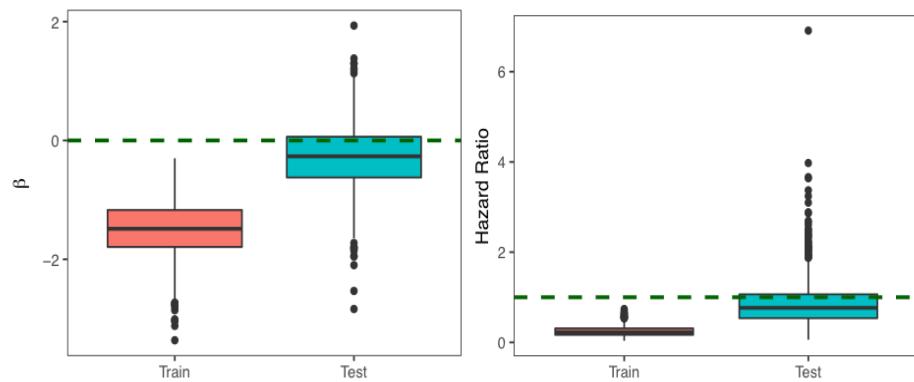
```

##          Training     Test
## Mean    0.2491150 0.6270269
## Median 0.2377214 0.5540752
## SD     0.0882902 0.3414526

```

TOP 10 CROSS VALIDATION FOR THE ADVANCED STAGE

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

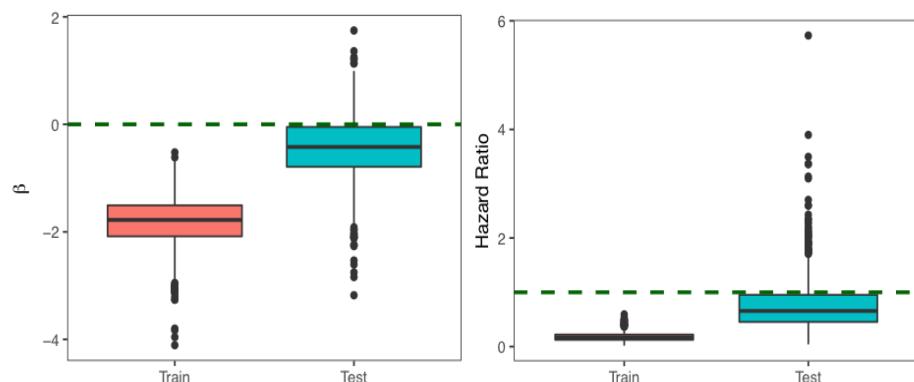
```
##          Training      Test
## Mean    -1.502514 -0.2815683
## Median -1.486255 -0.2669308
## SD      0.471263  0.5531735
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##          Training      Test
## Mean    0.2470794 0.8768150
## Median 0.2262183 0.7657261
## SD      0.1116208 0.5315927
```

TOP 15 CROSS VALIDATION FOR THE ADVANCED STAGE

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

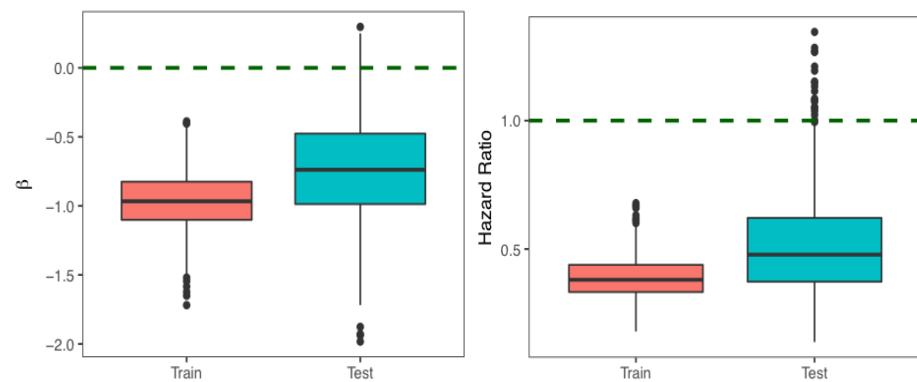
```
##          Training      Test
## Mean   -1.810783 -0.4485844
## Median -1.778124 -0.4206581
## SD     0.477290  0.6223543
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##          Training      Test
## Mean   0.1816324 0.7659802
## Median 0.1689547 0.6566148
## SD     0.0824193 0.4989649
```

FIXED 5 METABOLITES WITH NO SELECTION FOR ALL THE PATIENTS (CROSS VALIDATION)

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

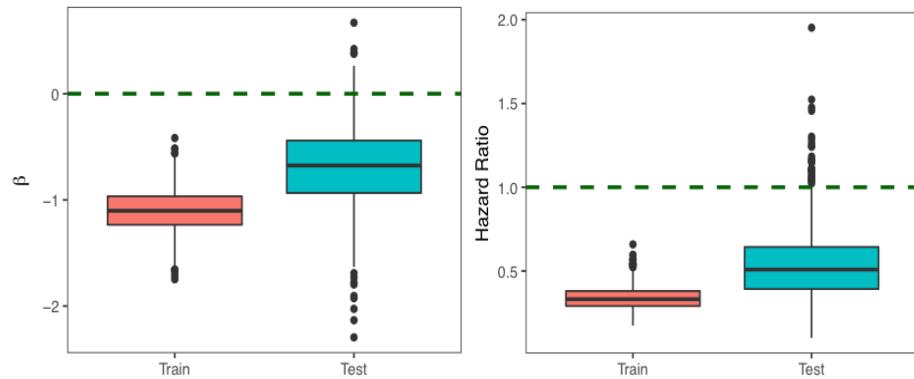
```
##          Training      Test
## Mean   -0.9685472 -0.7390378
## Median -0.9666055 -0.7381915
## SD     0.2077426  0.3742399
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##          Training      Test
## Mean   0.38780668 0.5117700
## Median 0.38037204 0.4779776
## SD     0.07996639 0.1939423
```

FIXED 10 METABOLITES WITH NO SELECTION FOR ALL THE PATIENTS (CROSS VALIDATION)

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

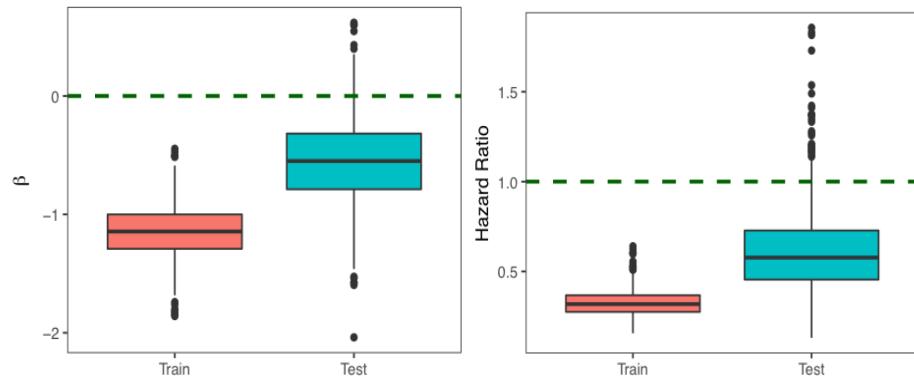
```
##           Training      Test
## Mean    -1.1012469 -0.6861020
## Median   -1.1024793 -0.6760349
## SD       0.2059857  0.3833477
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##           Training      Test
## Mean     0.33958536 0.5416047
## Median   0.33204682 0.5086298
## SD       0.07085415 0.2146154
```

FIXED 15 METABOLITES WITH NO SELECTION FOR ALL THE PATIENTS (CROSS VALIDATION)

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

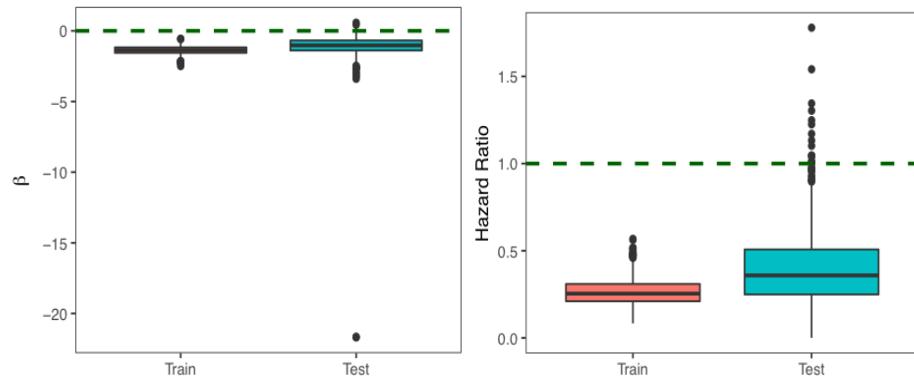
```
##           Training      Test
## Mean    -1.1503180 -0.5522712
## Median   -1.1443615 -0.5494740
## SD       0.2168441  0.3562486
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##           Training      Test
## Mean     0.32398472 0.6133106
## Median   0.31842717 0.5772533
## SD       0.07014235 0.2270141
```

FIXED 5 METABOLITES WITH NO SELECTION FOR THE EARLY PATIENTS (CROSS VALIDATION)

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

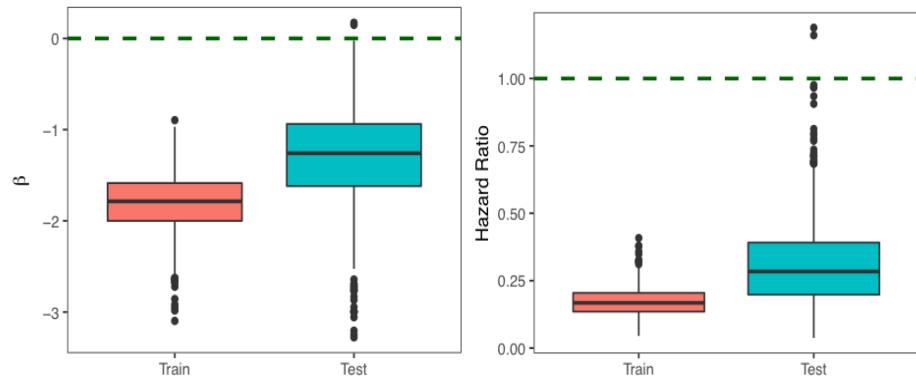
```
##           Training      Test
## Mean    -1.3701876 -1.099594
## Median   -1.3702425 -1.025913
## SD       0.3016709  1.071675
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##           Training      Test
## Mean     0.26566843 0.3976967
## Median   0.25404536 0.3584690
## SD       0.07981209 0.2106820
```

FIXED 10 METABOLITES WITH NO SELECTION FOR THE EARLY PATIENTS (CROSS VALIDATION)

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

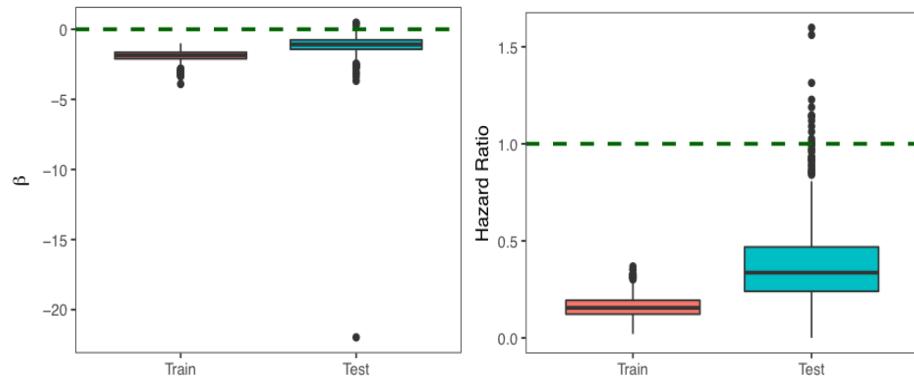
```
##           Training      Test
## Mean    -1.8056754 -1.2958908
## Median   -1.7860413 -1.2587377
## SD       0.3162652  0.5287447
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##           Training      Test
## Mean     0.17242014 0.3114302
## Median   0.16762250 0.2840123
## SD       0.05255191 0.1577604
```

FIXED 15 METABOLITES WITH NO SELECTION FOR THE EARLY PATIENTS (CROSS VALIDATION)

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

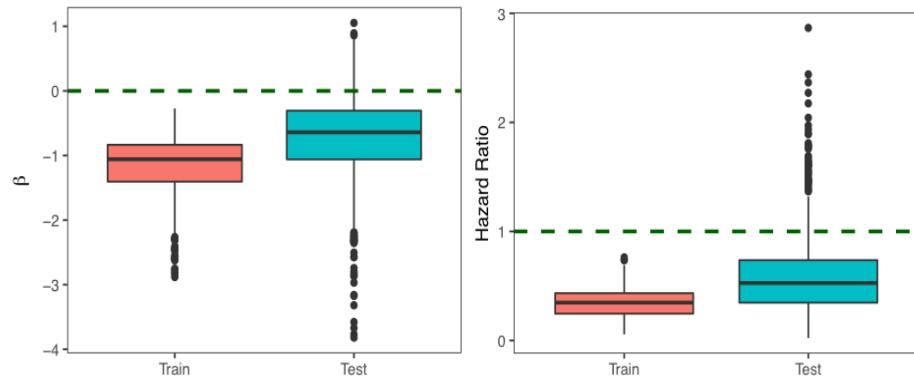
```
##           Training      Test
## Mean    -1.8886496 -1.1338006
## Median   -1.8644814 -1.0898056
## SD       0.3653839  0.8511991
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##           Training      Test
## Mean     0.16092091 0.3758726
## Median   0.15497655 0.3362821
## SD       0.05477195 0.2003592
```

FIXED 5 METABOLITES WITH NO SELECTION FOR THE ADVANCED PATIENTS (CROSS VALIDATION)

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

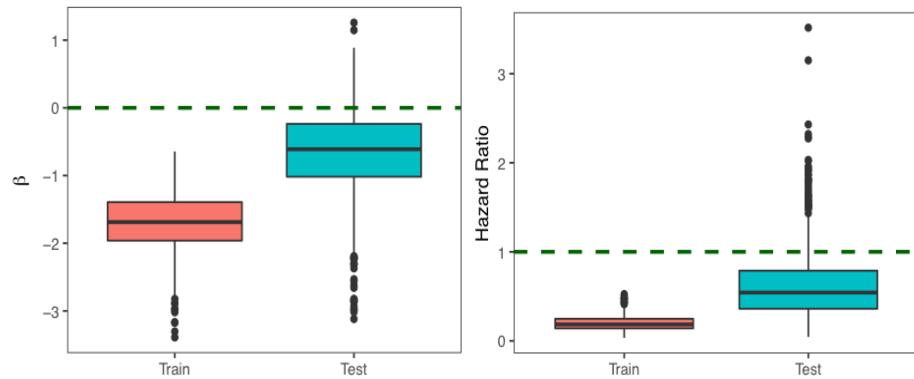
```
##           Training      Test
## Mean    -1.1502981 -0.7168734
## Median   -1.0575724 -0.6404751
## SD       0.4499097  0.6688212
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##           Training      Test
## Mean     0.3459660 0.5921717
## Median   0.3472979 0.5270420
## SD      0.1338466 0.3649520
```

FIXED 10 METABOLITES WITH NO SELECTION FOR THE ADVANCED PATIENTS (CROSS VALIDATION)

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

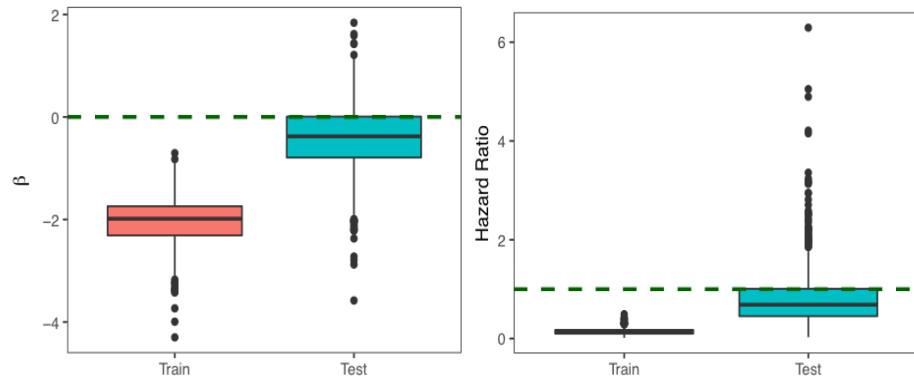
```
##           Training      Test
## Mean    -1.6990157 -0.6551011
## Median   -1.6873144 -0.6110547
## SD       0.4158383  0.6439568
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##           Training      Test
## Mean     0.19842969 0.6262806
## Median   0.18501574 0.5427781
## SD      0.07905433 0.3922349
```

FIXED 15 METABOLITES WITH NO SELECTION FOR THE ADVANCED PATIENTS (CROSS VALIDATION)

GRAPHICAL OUTPUT



SUMMARY RESULT FOR THE COEFFICIENT

```
##           Training      Test
## Mean    -2.0380596 -0.4066227
## Median   -1.9853803 -0.3782013
## SD       0.4430618  0.6523366
```

SUMMARY RESULT FOR THE HAZARD RATIO

```
##           Training      Test
## Mean     0.14272759 0.8171418
## Median   0.13732839 0.6850934
## SD       0.06033518 0.5886112
```