Cox Proportional Hazards and Random Survival Forests

Welcome to the final assignment in Course 2! In this assignment you'll develop risk models using survival data and a combination of linear and non-linear techniques. We'll be using a dataset with survival data of patients with Primary Biliary Cirrhosis (pbc). PBC is a progressive disease of the liver caused by a buildup of bile within the liver (cholestasis) that results in damage to the small bile ducts that drain bile from the liver. Our goal will be to understand the effects of different factors on the survival times of the patients. Along the way you'll learn about the following topics:

- Cox Proportional Hazards
 - Data Preprocessing for Cox Models.
- Random Survival Forests
 - Permutation Methods for Interpretation.

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- 6. Hazard ratio
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1. Import Packages

We'll first import all the packages that we need for this assignment.

- sklearn is one of the most popular machine learning libraries.
- numpy is the fundamental package for scientific computing in python.
- pandas is what we'll use to manipulate our data.
- matplotlib is a plotting library.
- lifelines is an open-source survival analysis library.

```
In [1]: import sklearn
import numpy as np
import pandas as pd
import matplotlib.pyplot as plt

from lifelines import CoxPHFitter
from lifelines.utils import concordance_index as cindex
from sklearn.model_selection import train_test_split

from util import load_data
```

2. Load the Dataset

Run the next cell to load the data.

```
In [2]: df = load_data()
```

3. Explore the Dataset

In the lecture videos time was in months, however in this assignment, time will be converted into years. Also notice that we have assigned a numeric value to sex, where female = 0 and male = 1.

Next, familiarize yourself with the data and the shape of it.

```
In [3]: print(df.shape)
# df.head() only outputs the top few rows
df.head()
(258, 19)
```

Out[3]:

	time	status	trt	age	sex	ascites	hepato	spiders	edema	bili	chol	а
0	1.095890	1.0	0.0	58.765229	0.0	1.0	1.0	1.0	1.0	14.5	261.0	
1	12.328767	0.0	0.0	56.446270	0.0	0.0	1.0	1.0	0.0	1.1	302.0	
2	2.772603	1.0	0.0	70.072553	1.0	0.0	0.0	0.0	0.5	1.4	176.0	
3	5.273973	1.0	0.0	54.740589	0.0	0.0	1.0	1.0	0.5	1.8	244.0	
6	5.019178	0.0	1.0	55.534565	0.0	0.0	1.0	0.0	0.0	1.0	322.0	

Take a minute to examine particular cases.

```
In [4]:
         i = 20
         df.iloc[i, :]
                       11.175342
Out[4]: time
                        1.000000
        status
        trt
                        0.000000
                       44.520192
         age
         sex
                        1.000000
         ascites
                        0.00000
        hepato
                        1.000000
         spiders
                        0.000000
        edema
                        0.000000
        bili
                        2.100000
        chol
                      456.000000
        albumin
                        4.000000
        copper
                      124.000000
        alk.phos
                     5719.000000
                      221.880000
        ast
        trig
                      230.000000
        platelet
                       70.000000
        protime
                        9.900000
        stage
                        2.000000
        Name: 23, dtype: float64
```

Now, split your dataset into train, validation and test set using 60/20/20 split.

```
In [5]: np.random.seed(0)
    df_dev, df_test = train_test_split(df, test_size = 0.2)
    df_train, df_val = train_test_split(df_dev, test_size = 0.25)

    print("Total number of patients:", df.shape[0])
    print("Total number of patients in training set:", df_train.shape[0])
    print("Total number of patients in validation set:", df_val.shape[0])

    print("Total number of patients in test set:", df_test.shape[0])

Total number of patients: 258
    Total number of patients in training set: 154
    Total number of patients in validation set: 52
    Total number of patients in test set: 52
```

Before proceeding to modeling, let's normalize the continuous covariates to make sure they're on the same scale. Again, we should normalize the test data using statistics from the train data.

```
In [6]: continuous_columns = ['age', 'bili', 'chol', 'albumin', 'copper', '
    alk.phos', 'ast', 'trig', 'platelet', 'protime']
    mean = df_train.loc[:, continuous_columns].mean()
    std = df_train.loc[:, continuous_columns].std()
    df_train.loc[:, continuous_columns] = (df_train.loc[:, continuous_columns] - mean) / std
    df_val.loc[:, continuous_columns] = (df_val.loc[:, continuous_columns] - mean) / std
    df_test.loc[:, continuous_columns] = (df_test.loc[:, continuous_columns] - mean) / std
```

Let's check the summary statistics on our training dataset to make sure it's standardized.

In [7]: df_train.loc[:, continuous_columns].describe()

Out[7]:

	age	bili	chol	albumin	copper	alk.ŗ
count	1.540000e+02	1.540000e+02	1.540000e+02	1.540000e+02	1.540000e+02	1.540000€
mean	9.833404e-16	-3.258577e- 16	1.153478e-16	1.153478e-16	5.767392e-18	1.326500
std	1.000000e+00	1.000000e+00	1.000000e+00	1.000000e+00	1.000000e+00	1.000000€
min	-2.304107e+00	-5.735172e- 01	-1.115330e+00	-3.738104e+00	-9.856552e- 01	-7.8821
25%	-6.535035e-01	-4.895812e- 01	-5.186963e-01	-5.697976e-01	-6.470611e- 01	-5.1864
50%	-6.443852e-03	-3.846612e- 01	-2.576693e-01	5.663556e-02	-3.140636e- 01	-3.4160
75%	5.724289e-01	2.977275e-02	1.798617e-01	6.890921e-01	3.435366e-01	-4.6205
max	2.654276e+00	5.239050e+00	6.243146e+00	2.140730e+00	5.495204e+00	4.869263€

4. Cox Proportional Hazards

Our goal is to build a risk score using the survival data that we have. We'll begin by fitting a Cox Proportional Hazards model to your data.

Recall that the Cox Proportional Hazards model describes the hazard for an individual i at time t as

$$\lambda(t, x) = \lambda_0(t)e^{\theta^T X_i}$$

The λ_0 term is a baseline hazard and incorporates the risk over time, and the other term incorporates the risk due to the individual's covariates. After fitting the model, we can rank individuals using the person-dependent risk term $e^{\theta^T X_i}$.

Categorical variables cannot be used in a regression model as they are. In order to use them, conversion to a series of variables is required.

Since our data has a mix of categorical (stage) and continuous (wblc) variables, before we proceed further we need to do some data engineering. To tackle the issue at hand we'll be using the Dummy Coding technique. In order to use Cox Proportional Hazards, we will have to turn the categorical data into one hot features so that we can fit our Cox model. Luckily, Pandas has a built-in function called get_dummies that will make it easier for us to implement our function. It turns categorical features into multiple binary features.

	Α	В	С
w	1	0	0
Χ	0	0	1
Υ	0	1	0
Z	0	0	0

Exercise 1

In the cell below, implement the to one hot(...) function.

▶ Hints

```
In [8]: # UNQ C1 (UNIQUE CELL IDENTIFIER, DO NOT EDIT)
        def to_one_hot(dataframe, columns):
            Convert columns in dataframe to one-hot encoding.
            Args:
                dataframe (dataframe): pandas dataframe containing covariat
        es
                columns (list of strings): list categorical column names to
        one hot encode
            Returns:
                one hot df (dataframe): dataframe with categorical columns
        encoded
                                     as binary variables
            111
            ### START CODE HERE (REPLACE INSTANCES OF 'None' with your code
        ) ###
            one hot df = pd.get dummies(dataframe,columns=columns, drop fir
        st = True, dtype=np.float64)
            ### END CODE HERE ###
            return one hot df
```

Now we'll use the function you coded to transform the training, validation, and test sets.

```
In [9]: # List of categorical columns
to_encode = ['edema', 'stage']

one_hot_train = to_one_hot(df_train, to_encode)
one_hot_val = to_one_hot(df_val, to_encode)
one_hot_test = to_one_hot(df_test, to_encode)

print(one_hot_val.columns.tolist())
print(f"There are {len(one_hot_val.columns)} columns")

['time', 'status', 'trt', 'age', 'sex', 'ascites', 'hepato', 'spid ers', 'bili', 'chol', 'albumin', 'copper', 'alk.phos', 'ast', 'tri g', 'platelet', 'protime', 'edema_0.5', 'edema_1.0', 'stage_2.0', 'stage_3.0', 'stage_4.0']
There are 22 columns
```

Expected output

```
['time', 'status', 'trt', 'age', 'sex', 'ascites', 'hepato', 'spiders', 'bili', 'chol', 'albumin', 'copper', 'alk.phos', 'ast', 'trig', 'platel et', 'protime', 'edema_0.5', 'edema_1.0', 'stage_2.0', 'stage_3.0', 'stage_4.0']
There are 22 columns
```

Look for new features

Now, let's take a peek at one of the transformed data sets. Do you notice any new features?

```
In [10]: print(one_hot_train.shape)
  one_hot_train.head()
  (154, 22)
```

Out[10]:

	time	status	trt	age	sex	ascites	hepato	spiders	bili	chol
279	3.868493	0.0	0.0	-0.414654	0.0	0.0	0.0	0.0	-0.300725	-0.096081
137	3.553425	1.0	0.0	0.069681	1.0	0.0	1.0	0.0	0.895363	0.406085
249	4.846575	0.0	1.0	-0.924494	0.0	0.0	1.0	0.0	-0.510565	-0.225352
266	0.490411	1.0	0.0	1.938314	0.0	1.0	1.0	1.0	0.748475	-0.608191
1	12.328767	0.0	0.0	0.563645	0.0	0.0	1.0	1.0	-0.405645	-0.210436

5 rows × 22 columns

5. Fitting and Interpreting a Cox Model

Run the following cell to fit your Cox Proportional Hazards model using the lifelines package.

```
In [11]: cph = CoxPHFitter()
cph.fit(one_hot_train, duration_col = 'time', event_col = 'status',
step_size=0.1)
```

Out[11]: clifelines.CoxPHFitter: fitted with 154 total observations, 90 rig
 ht-censored observations>

You can use cph.print_summary() to view the coefficients associated with each covariate as well as confidence intervals.

```
In [12]: cph.print_summary()
```

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> model lifelines.CoxPHFitter duration col 'time' event col 'status' number of observations 154 number of events observed 64 partial log-likelihood -230.82 time fit was run 2021-02-03 05:25:40 UTC

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	z	р	loţ
trt	-0.22	0.80	0.30	-0.82	0.37	0.44	1.45	-0.73	0.46	
age	0.23	1.26	0.19	-0.13	0.60	0.88	1.82	1.26	0.21	
sex	0.34	1.41	0.40	-0.45	1.14	0.64	3.11	0.84	0.40	
ascites	-0.10	0.91	0.56	-1.20	1.01	0.30	2.75	-0.17	0.86	
hepato	0.31	1.36	0.38	-0.44	1.06	0.64	2.89	0.81	0.42	
spiders	-0.18	0.83	0.38	-0.94	0.57	0.39	1.77	-0.47	0.64	
bili	0.05	1.05	0.18	-0.29	0.39	0.75	1.48	0.29	0.77	
chol	0.19	1.20	0.15	-0.10	0.47	0.91	1.60	1.28	0.20	
albumin	-0.40	0.67	0.18	-0.75	-0.06	0.47	0.94	-2.28	0.02	
copper	0.30	1.35	0.16	-0.01	0.61	0.99	1.84	1.91	0.06	
alk.phos	-0.22	0.80	0.14	-0.49	0.05	0.61	1.05	-1.62	0.11	
ast	0.21	1.24	0.16	-0.10	0.53	0.91	1.69	1.34	0.18	
trig	0.20	1.23	0.16	-0.11	0.52	0.89	1.68	1.27	0.21	
platelet	0.14	1.15	0.15	-0.16	0.43	0.86	1.54	0.92	0.36	
protime	0.36	1.43	0.17	0.03	0.69	1.03	1.99	2.15	0.03	
edema_0.5	1.24	3.47	0.46	0.35	2.14	1.42	8.50	2.72	0.01	
edema_1.0	2.02	7.51	0.60	0.84	3.20	2.31	24.43	3.35	<0.005	1
stage_2.0	1.21	3.35	1.08	-0.92	3.33	0.40	28.06	1.11	0.27	
stage_3.0	1.18	3.27	1.09	-0.96	3.33	0.38	27.86	1.08	0.28	
stage_4.0	1.41	4.10	1.15	-0.85	3.67	0.43	39.43	1.22	0.22	

Concordance 0.83

Log-likelihood ratio test 97.63 on 20 df, -log2(p)=38.13

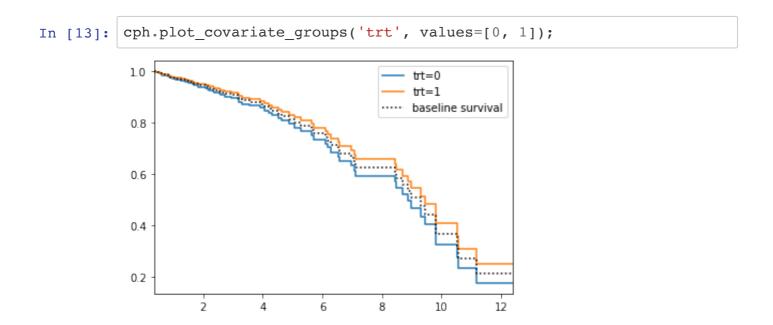
Question:

- According to the model, was treatment trt beneficial?
- What was its associated hazard ratio?
 - Note that the hazard ratio is how much an incremental increase in the feature variable changes the hazard.

► Check your answer!

We can compare the predicted survival curves for treatment variables. Run the next cell to plot survival curves using the plot_covariate_groups() function.

- The y-axis is th survival rate
- The x-axis is time



Notice how the group without treatment has a lower survival rate at all times (the x-axis is time) compared to the treatment group.

6. Hazard Ratio

Recall from the lecture videos that the Hazard Ratio between two patients was the likelihood of one patient (e.g smoker) being more at risk than the other (e.g non-smoker).

$$\frac{\lambda_{smoker}(t)}{\lambda_{nonsmoker}(t)} = e^{\theta(X_{smoker} - X_{nonsmoker})^T}$$

Where

$$\lambda_{smoker}(t) = \lambda_0(t)e^{\theta X_{smoker}^T}$$

and

$$\lambda_{nonsmoker}(t) = \lambda_0(t)e^{\theta X_{nonsmoker}^T}$$

Exercise 2

In the cell below, write a function to compute the hazard ratio between two individuals given the cox model's coefficients.

▶ Hints

Now, evaluate it on the following pair of indivduals: i = 1 and j = 5

```
In [15]: i = 1
    case_1 = one_hot_train.iloc[i, :].drop(['time', 'status'])

j = 5
    case_2 = one_hot_train.iloc[j, :].drop(['time', 'status'])

print(hazard_ratio(case_1.values, case_2.values, cph.params_.values
))

15.029017732492221
```

Expected Output:

15.029017732492221

Question:

Is case_1 or case_2 at greater risk?

► Check your answer!

Inspect different pairs, and see if you can figure out which patient is more at risk.

```
In [16]: i = 4
    case_1 = one_hot_train.iloc[i, :].drop(['time', 'status'])

    j = 7
    case_2 = one_hot_train.iloc[j, :].drop(['time', 'status'])

    print("Case 1\n\n", case_1, "\n")
    print("Case 2\n\n", case_2, "\n")
    print("Hazard Ratio:", hazard_ratio(case_1.values, case_2.values, c ph.params_.values))
```

Case 1

trt	0.000000
age	0.563645
sex	0.000000
ascites	0.000000
hepato	1.000000
spiders	1.000000
bili	-0.405645
chol	-0.210436
albumin	1.514297
copper	-0.481961
alk.phos	2.173526
ast	-0.144699
trig	-0.531125
platelet	-0.450972
protime	-0.139881
edema_0.5	0.000000
edema_1.0	0.000000
stage_2.0	0.000000
stage_3.0	1.000000
stage_4.0	0.000000
Name: 1, dty	pe: float64

Case 2

trt	0.000000
age	0.463447
sex	0.000000
ascites	0.000000
hepato	1.000000
spiders	0.00000
bili	-0.489581
chol	-0.309875
albumin	-1.232371
copper	-0.504348
alk.phos	2.870427
ast	-0.936261
trig	-0.150229
platelet	3.190823
protime	-0.139881
edema_0.5	0.00000
$edema_1.0$	0.000000
stage_2.0	0.00000
stage_3.0	0.00000
stage_4.0	1.000000
Name: 38,	dtype: float64

Hazard Ratio: 0.1780450006997129

► Check your answer!

7. Harrell's C-index

To evaluate how good our model is performing, we will write our own version of the C-index. Similar to the week 1 case, C-index in the survival context is the probability that, given a randomly selected pair of individuals, the one who died sooner has a higher risk score.

However, we need to take into account censoring. Imagine a pair of patients, A and B.

Scenario 1

- A was censored at time t_A
- B died at t_B
- $t_A < t_B$.

Because of censoring, we can't say whether A or B should have a higher risk score.

Scenario 2

Now imagine that $t_A > t_B$.

- A was censored at time t_A
- B died at t_B
- $t_A > t_B$

Now we can definitively say that B should have a higher risk score than A, since we know for a fact that A lived longer.

Therefore, when we compute our C-index

- We should only consider pairs where at most one person is censored
- If they are censored, then their censored time should occur after the other person's time of death.

The metric we get if we use this rule is called **Harrel's C-index**.

Note that in this case, being censored at time t means that the true death time was some time AFTER time t and not at t.

- Therefore if $t_A = t_B$ and A was censored:
 - Then *A* actually lived longer than *B*.
 - This will effect how you deal with ties in the exercise below!

Exercise 3

Fill in the function below to compute Harrel's C-index.

▶ Hints

```
In [18]: # UNQ_C3 (UNIQUE CELL IDENTIFIER, DO NOT EDIT)
         def harrell c(y true, scores, event):
             Compute Harrel C-index given true event/censoring times,
             model output, and event indicators.
             Args:
                 y_true (array): array of true event times
                 scores (array): model risk scores
                 event (array): indicator, 1 if event occurred at that index
         , 0 for censorship
             Returns:
                 result (float): C-index metric
             n = len(y true)
             assert (len(scores) == n and len(event) == n)
             concordant = 0.0
             permissible = 0.0
             ties = 0.0
             result = 0.0
             ### START CODE HERE (REPLACE INSTANCES OF 'None' and 'pass' wit
         h your code) ###
             # use double for loop to go through cases
             for i in range(n):
                 # set lower bound on j to avoid double counting
                 for j in range(i+1, n):
                     # check if at most one is censored
                     if not (event[i] == 0 and event[j] == 0):
                         # check if neither are censored
                         if event[i] == 1 and event[j] == 1:
                              permissible += 1
                              # check if scores are tied
                              if y true[i] == y true[j]:
                                  ties += 1
```

```
# check for concordant
                    elif y true[i] > y true[j] and scores[i] < scor</pre>
es[j]:
                        concordant += 1
                    elif y_true[i] < y_true[j] and scores[i] > scor
es[j]:
                        concordant += 1
                # check if one is censored
                elif event[i] == 0 or event[j] == 0:
                    # get censored index
                    censored = i
                    uncensored = i
                    if event[i] == 0:
                        censored = i
                        uncensored = j
                    # check if permissible
                    # Note: in this case, we are assuming that cens
ored at a time
                    # means that you did NOT die at that time. That
is, if you
                    # live until time 30 and have event = 0, then y
ou lived THROUGH
                    # time 30.
                    if y true[censored] >= y true[uncensored]:
                        permissible += 1
                        # check if scores are tied
                        if scores[i] == scores[j]:
                            # update ties
                            ties += 1
                        # check if scores are concordant
                        if y true[censored] >= y true[uncensored] a
nd scores[censored] < scores[uncensored]:</pre>
                            concordant += 1
    # set result to c-index computed from number of concordant pair
    # number of ties, and number of permissible pairs (REPLACE 0 wi
th your code)
    result = (concordant + 0.5 * ties) / permissible
    ### END CODE HERE ###
    return result
```

You can test your function on the following test cases:

```
In [19]: y true = [30, 12, 84, 9]
         # Case 1
         event = [1, 1, 1, 1]
         scores = [0.5, 0.9, 0.1, 1.0]
         print("Case 1")
         print("Expected: 1.0, Output: {}".format(harrell c(y true, scores,
         event)))
         # Case 2
         scores = [0.9, 0.5, 1.0, 0.1]
         print("\nCase 2")
         print("Expected: 0.0, Output: {}".format(harrell c(y true, scores,
         event)))
         # Case 3
         event = [1, 0, 1, 1]
         scores = [0.5, 0.9, 0.1, 1.0]
         print("\nCase 3")
         print("Expected: 1.0, Output: {}".format(harrell_c(y_true, scores,
         event)))
         # Case 4
         y true = [30, 30, 20, 20]
         event = [1, 0, 1, 0]
         scores = [10, 5, 15, 20]
         print("\nCase 4")
         print("Expected: 0.75, Output: {}".format(harrell c(y true, scores,
         event)))
         # Case 5
         y true = list(reversed([30, 30, 30, 20, 20]))
         event = [0, 1, 0, 1, 0]
         scores = list(reversed([15, 10, 5, 15, 20]))
         print("\nCase 5")
         print("Expected: 0.583, Output: {}".format(harrell c(y true, scores
         , event)))
         # Case 6
         y_{true} = [10, 10]
         event = [0,1]
         scores = [4,5]
         print("\nCase 6")
         print(f"Expected: 1.0 , Output:{harrell c(y true, scores, event):.4
         f}")
```

Now use the Harrell's C-index function to evaluate the cox model on our data sets.

Train: 0.8265139116202946 Val: 0.8544776119402985 Test: 0.8478543563068921

What do these values tell us?

8. Random Survival Forests

This performed well, but you have a hunch you can squeeze out better performance by using a machine learning approach. You decide to use a Random Survival Forest. To do this, you can use the RandomForestSRC package in R. To call R function from Python, we'll use the r2py package. Run the following cell to import the necessary requirements.

```
In [21]: %load_ext rpy2.ipython
%R require(ggplot2)

from rpy2.robjects.packages import importr
# import R's "base" package
base = importr('base')

# import R's "utils" package
utils = importr('utils')

# import rpy2's package module
import rpy2.robjects.packages as rpackages

forest = rpackages.importr('randomForestSRC', lib_loc='R')

from rpy2 import robjects as ro
R = ro.r

from rpy2.robjects import pandas2ri
pandas2ri.activate()
```

R[write to console]: Loading required package: ggplot2

Instead of encoding our categories as binary features, we can use the original dataframe since trees deal well with raw categorical data (can you think why this might be?).

Run the code cell below to build your forest.

```
In [22]: model = forest.rfsrc(ro.Formula('Surv(time, status) ~ .'), data=df_
train, ntree=300, nodedepth=5, seed=-1)
```

```
In [23]:
         print(model)
                                   Sample size: 154
                             Number of deaths: 64
                               Number of trees: 300
                    Forest terminal node size: 15
                Average no. of terminal nodes: 6.54
         No. of variables tried at each split: 5
                       Total no. of variables: 17
                Resampling used to grow trees: swor
             Resample size used to grow trees: 97
                                      Analysis: RSF
                                        Family: surv
                                Splitting rule: logrank *random*
                Number of random split points: 10
                                    Error rate: 19.07%
```

Finally, let's evaluate on our validation and test sets, and compare it with our Cox model.

Your random forest model should be outperforming the Cox model slightly. Let's dig deeper to see how they differ.

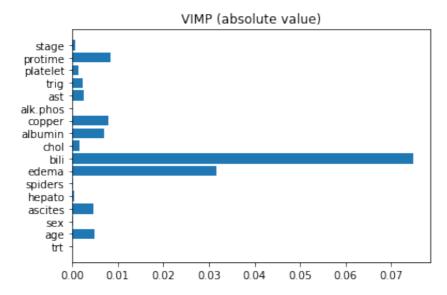
9. Permutation Method for Interpretation

We'll dig a bit deeper into interpretation methods for forests a bit later, but for now just know that random surival forests come with their own built in variable importance feature. The method is referred to as VIMP, and for the purpose of this section you should just know that higher absolute value of the VIMP means that the variable generally has a larger effect on the model outcome.

Run the next cell to compute and plot VIMP for the random survival forest.

```
In [26]: vimps = np.array(forest.vimp(model).rx('importance')[0])

y = np.arange(len(vimps))
plt.barh(y, np.abs(vimps))
plt.yticks(y, df_train.drop(['time', 'status'], axis=1).columns)
plt.title("VIMP (absolute value)")
plt.show()
```



Question:

How does the variable importance compare to that of the Cox model? Which variable is important in both models? Which variable is important in the random survival forest but not in the Cox model? You should see that edema is important in both the random survival forest and the Cox model. You should also see that bili is important in the random survival forest but not the Cox model.

Congratulations!

You've finished the last assignment in course 2! Take a minute to look back at the analysis you've done over the last four assignments. You've done a great job!