TUGAS KELOMPOK CASE STUDY COX REGRESSION



Anggota Kelompok 4:

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Model Survival B DEPARTEMEN MATEMATIKA FAKULTAS MATEMATIKA DAN ILMU PENGETAHUAN ALAM UNIVERSITAS INDONESIA TAHUN AJARAN 2022/2023

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Tabel Kontribusi

Anggota	Jenis Kontribusi	Persentase Kontribusi
Divaya Syifa Susilobudi – 2106650790	Aktif terlibat dalam diskusi. Membuat latar belakang, tujuan, rumusan masalah, dan informasi data, serta membuat format laporan	100%
Favian Sulthan Wafi – 2106706205	Aktif terlibat dalam diskusi. Mencari dataset. Membuat hasil dan pembahasan bagian uji hipotesis k-sampel dan analisis model regresi cox-PH, serta membuat kesimpulan dan daftar pustaka	100%
Wulan Akhsah – 2106637100	Aktif terlibat dalam diskusi. Membuat hasil dan pembahasan bagian preprocessing dan analisis deskriptif, serta merapikan format laporan	100%

BAB 1

Pendahuluan

1.1 Latar Belakang

Primary biliary cirrhosis (PBC) adalah penyakit hati autoimun kronis yang secara utama mempengaruhi saluran empedu kecil di dalam hati. Penyakit ini ditandai dengan kerusakan progresif pada saluran empedu tersebut, menyebabkan gangguan aliran empedu, peradangan, dan akhirnya sirosis hati. Gejalanya dapat meliputi kelelahan, gatal-gatal, kuning pada kulit dan mata (jaundice), dan nyeri perut. PBC lebih sering terjadi pada wanita di usia pertengahan. Gejalanya bisa berupa kelelahan, gatal-gatal, kulit dan mata kuning, serta nyeri perut. Prevalensi PBC di seluruh dunia berkisar antara 0,5 hingga 40 kasus per 100.000 orang, namun angka ini dapat bervariasi di berbagai wilayah dan kelompok populasi.

Analisis survival/analisis data ketahanan hidup adalah suatu metode yang berhubungan dengan waktu suatu individu / subjek mulai dari awal pengamatan sampai terjadinya kejadian. Kejadian yang diamati seperti kematian, timbul atau kambuhnya penyakit, rusak atau kembali bekerjanya sebuah mesin, dan kejadian pada individu yang berhenti atau mendapatkan pekerjaan (Kleinbaum & Klein, 2005: 4). Salah satu contoh analisis survival dalam bidang kesehatan adalah untuk menguji perbedaan resiko pada pasien kelompok tertentu dengan kelompok lainnya.

Terdapat beberapa cara untuk menganalisis data survival. Salah satunya adalah menggunakan metode parametrik, metode non-parametrik, dan metode semiparametrik. Metode parametrik mengasumsikan bahwa waktu survival mengikuti distribusi tertentu seperti Weibull, gamma, atau eksponensial. Metode non-parametrik digunakan jika data tidak mengikuti distribusi tertentu. Selain itu, analisis regresi juga dapat digunakan untuk memahami data survival. Regresi adalah metode statistik yang mempelajari hubungan antara beberapa variabel. Regresi Cox adalah salah satu metode regresi yang populer dalam analisis data survival. Metode ini merupakan metode semiparametrik di mana model hazard dasar mengikuti pola nonparametrik, sementara variabel independen mengikuti model parametrik. Tujuan dari regresi Cox adalah memahami hubungan antara waktu survival dan variabel-variabel yang mempengaruhinya. Regresi Cox juga dikenal sebagai

regresi Cox Proporsional Hazard karena mengasumsikan tingkat kematian tetap seiring berjalannya waktu, yang merupakan asumsi penting dalam metode ini.

Pada kasus ini, kami akan menggunakan metode Cox Proportional Hazard untuk mengetahui apakah ada perbedaan resiko kematian penderita PBC pada stadium yang berbeda.

1.2 Tujuan

Untuk mengetahui perbedaan risiko kematian penderita PBC dengan stadium yang berbeda menggunakan model regresi Cox-PH.

1.3 Rumusan Masalah

- 1. Apakah ada perbedaan risiko kematian penderita PBC pada stadium 1, 2, 3, dan 4?
- 2. Apakah risiko kematian penderita PBC meningkat seiring meningkatnya stadium?

1.4 Informasi Data

Data yang akan kami gunakan adalah dataset Primary Biliary Cirrhosis (PBC). Sumber dataset akan kami lampirkan di daftar pusaka. Berikut adalah detail mengenai variabel yang akan kami gunakan.

- age: usia dalam tahun
- **albumin**: serum albumin (g/dl)
- alk.phos: alkalin fosfatase (U/liter)
- ascites: keberadaan asites
- ast: aspartat aminotransferase (U/ml)
- **bili**: serum bilirunbin (mg/dl)
- **chol**: serum kolesterol (mg/dl)
- **copper**: tembaga dalam urine (ug/day)
- edema:
 - \circ 0 = tidak ada edema
 - \circ 0,5 = tidak diobati atau berhasil diobati
 - o 1 = edema meskipun terapi diuretik
- hepato: keberadaan hepatomegali atau pembesaran hati
- id: nomor kasus

- platelet: jumlah platelet
- protime: waktu darah menggumpal yang terstandardisasi
- sex: m/f
- spiders: malformasi pembuluh darah di kulit
- **stage**: stadium histologis penyakit (butuh biopsy)
- status: status di titik akhir
 - \circ 0 = tersensor
 - 1 = transplantasi
 - \circ 2 = kematian
- **time** = jumlah hari antara pendaftaran dan awal kematian, transplantasi, atau analisis studi pada Juli 1986
- trt:
 - 1 = D-penicilmain
 - \circ 2 = plasebo
 - o NA = tidak dirandomisasi
- **trig**: trigliserida (mg/dl)

BAB 2

Hasil dan Pembahasan

2.1 Preprocessing dan Analisis Deskriptif

2.1.1 Preprocessing

Sebelum melakukan uji, akan dilakukan *preprocessing* pada data. Pertama dilakukan pemasukkan data setelah mengunduh dalam bentuk file .csv, kemudian dimuatkan ke dalam variabel "pbc". Setelah itu, akan dilihat dimensi dari data untuk melihat jumlah kolom dan baris, serta akan ditampilkan tipe data sebagai berikut.

```
> pbc <- read.csv("C:/Users/ASUS/Downloads/pbc.csv") #mengimport dataset melalui device
> dim(pbc)
[1] 419 20
```

Ditampilkan enam contoh data:

```
> head(pbc)
                        age sex ascites hepato spiders edema bili chol albumin copper alk.phos
  id time status trt
                1 58.76523
                                                                               156 1718.0 137.95
                                                                                                   172
 1 400
              2
                                     1
                                            1
                                                   1 1.0 14.5 261
                                                                        2.60
  2 4500
              0
                 1 56, 44627
                                      0
                                                    1
                                                        0.0 1.1 302
                                                                        4.14
                                                                                 54
                                                                                      7394.8 113.52
                                                                                                     88
  3 1012
                 1 70.07255
3
              2
                                      0
                                            0
                                                    0
                                                       0.5 1.4 176
                                                                        3.48
                                                                                210
                                                                                      516.0 96.10
                              m
                                                                                                     55
                 1 54.74059
                                                    1 0.5 1.8 244
4 4 1925
                                      0
                                                                        2.54
                                                                                 64
                                                                                      6121.8 60.63
                                                                                                     92
                                            1
                 2 38.10541
                                                       0.0 3.4 279
                                                                                143
                                                                                      671.0 113.15
                                                                                                     72
  5 1504
                                      0
                                                                        3.53
                 2 66.25873
6 6 2503
                                                    0 0.0 0.8 248
                                                                                      944.0 93.00
 platelet protime stage
      190
             12.2
      221
             10.6
3
      151
             12.0
                     4
4
      183
             10.3
                     4
5
      136
             10.9
                      3
6
             11.0
       NA
```

Akan dilihat apakah ada *missing values* pada kolom yang dianalisis.

```
> sum(is.na(pbc$stage)) ; sum(is.na(pbc$status)) ; sum(is.na(pbc$time))
[1] 6
[1] 0
[1] 0
```

Berdasarkan *output* tersebut terdapat *missing value*, maka akan dihapus terlebih dahulu dan dicek kembali apakah masih ada *missing value*.

```
> pbc <- pbc[!(is.na(pbc$stage)), ] ; pbc <- pbc[!(is.na(pbc$stage)), ] ; pbc <- pbc[!(is.na(pbc$stage)), ]
> sum(is.na(pbc$stage)) ; sum(is.na(pbc$status)) ; sum(is.na(pbc$time))
[1] 0
[1] 0
[1] 0
```

Karena sudah tidak ada, maka preprossessing dilanjutkan. Untuk memudahkan perhitungan, waktu akan diubah dari hari menjadi tahun. Kemudian, untuk data status *transplant* dijadikan tersensor karena pasien masih hidup setelah mendapatkan *transplant*.

```
> pbc$time <- pbc$time / 365
> pbc$status[pbc$status == 1] <- 0
> pbc$status[pbc$status == 2] <- 1
> table(pbc$status)

0  1
256 157
> attach(pbc)
The following objects are masked from pbc (pos = 3):
    age, albumin, alk.phos, ascites, ast, bili, chol, copper, edema, hepato, id, platelet, protime, sex, spiders, stage, status, time, trig, trt
```

Fungsi attach digunakan untuk memanggil variabel-variabel pbc, tanpa perlu memanggil pbc.

2.1.2 Analisis Deskriptif

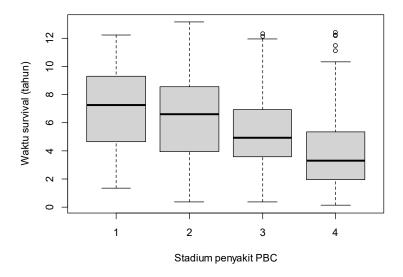
Setelah melakukan *preprocessing*, akan dibuat analisis deskriptifnya. Pada subbab ini akan dilihat perbedaan survival experience dari setiap stage pbc dan akan dilihat apakah ada tren dari fungsi hazard tiap stagenya. Pertama akan dilihat tipe data dan ringkasan dari *dataframe* pbc.

```
> str(pbc)
'data.frame':
               413 obs. of 20 variables:
          : int 1 2 3 4 5 6 7 8 9 10 ...
          : num
               1.1 12.33 2.77 5.27 4.12 ...
               1011010111...
 $ status : num
               1111222212...
$ trt
          : int
                58.8 56.4 70.1 54.7 38.1 ...
          : num
                "f" "f" "m" "f" ...
          : chr
$ sex
 $ ascites : int
                1000000001...
$ hepato : int
                1101111000...
$ spiders : int
               1101100011...
          : num 1 0 0.5 0.5 0 0 0 0 0 1 ...
$ edema
          : num 14.5 1.1 1.4 1.8 3.4 0.8 1 0.3 3.2 12.6 ...
$ bili
$ chol
          : int 261 302 176 244 279 248 322 280 562 200 ...
$ albumin : num 2.6 4.14 3.48 2.54 3.53 3.98 4.09 4 3.08 2.74 ...
 $ copper : int
                156 54 210 64 143 50 52 52 79 140 ...
$ alk.phos: num 1718 7395 516 6122 671 ...
                137.9 113.5 96.1 60.6 113.2 ...
          : num
          : int
$ trig
               172 88 55 92 72 63 213 189 88 143 ...
$ platelet: int 190 221 151 183 136 NA 204 373 251 302 ...
 $ protime : num 12.2 10.6 12 10.3 10.9 11 9.7 11 11 11.5 ...
 $ stage : int 4 3 4 4 3 3 3 3 2 4 ...
```

```
> summary(pbc)
       id
                       time
                                         status
                                                             trt
                                                                                              sex
                                                                              age
Min.
           1.0
                  Min.
                         : 0.1123
                                     Min.
                                            :0.0000
                                                       Min.
                                                               :1.000
                                                                        Min.
                                                                                :26.28
                                                                                          Length:413
        :
1st Qu.:104.0
                                                       1st Ou.:1.000
                  1st Ou.: 2.9918
                                     1st Ou.: 0.0000
                                                                        1st Ou.: 42.74
                                                                                          Class :character
Median :207.0
                  Median: 4.6630
                                     Median :0.0000
                                                       Median :1.000
                                                                        Median :51.00
                                                                                                :character
                                                                                          Mode
Mean
       :208.3
                  Mean
                        : 5.2454
                                     Mean
                                            :0.3801
                                                       Mean
                                                               :1.494
                                                                        Mean
                                                                                :50.65
 3rd Qu.:310.0
                  3rd Qu.: 7.1479
                                     3rd Qu.: 1.0000
                                                        3rd Qu.: 2.000
                                                                         3rd Qu.:58.00
Max.
        :419.0
                  Max.
                         :13.1370
                                             :1.0000
                                                       Max.
                                                               :2.000
                                                                        Max.
                                                                                :78.44
                                     Max.
                                                        NA'S
                                                               :101
                                         spiders
                                                             edema
    ascites
                                                                                bili
                                                                                                  chol
                        hepato
                                                                                             Min.
                                                                :0.0000
                                                                           Min.
Min.
        :0.00000
                    Min.
                            :0.0000
                                      Min.
                                              :0.0000
                                                        Min.
                                                                                  : 0.300
                                                                                                     : 120.0
 1st Qu.: 0.00000
                    1st Qu.: 0.0000
                                      1st Qu.: 0.0000
                                                         1st Qu.: 0.0000
                                                                           1st Qu.: 0.800
                                                                                             1st Qu.: 249.5
Median :0.00000
                    Median :1.0000
                                      Median :0.0000
                                                        Median :0.0000
                                                                           Median : 1.400
                                                                                             Median:
                                                                                                       309.5
        :0.07692
                                                                                             Mean
                                                                                                      369.5
Mean
                    Mean
                           :0.5128
                                      Mean
                                             :0.2885
                                                        Mean
                                                                :0.1017
                                                                           Mean
                                                                                    3.221
 3rd Qu.: 0.00000
                    3rd Qu.:1.0000
                                      3rd Qu.:1.0000
                                                         3rd Qu.: 0.0000
                                                                           3rd Qu.: 3.400
                                                                                             3rd Qu.: 400.0
        :1.00000
                                              :1.0000
                                                                :1.0000
                                                                                  :28.000
                                                                                                     :1775.0
Max.
                    Max.
                            :1.0000
                                      Max.
                                                        Max.
                                                                           Max.
                                                                                             Max.
        :101
                    NA'S
                                      NA'S
                                                                                             NA'S
                                                                                                     :129
 NA'S
                            :101
                                              :101
    albumin
                     copper
                                      alk.phos
                                                            ast
                                                                              trig
                                                                                              platelet
Min.
        :1.96
                 Min.
                           4.00
                                   Min.
                                              289.0
                                                      Min.
                                                                26.35
                                                                        Min.
                                                                                : 33.00
                                                                                           Min.
                                                                                                  : 62.0
1st Qu.:3.25
                 1st Qu.: 41.25
                                   1st Qu.:
                                              871.5
                                                      1st Qu.: 80.60
                                                                        1st Qu.: 84.25
                                                                                           1st Qu.:188.2
                                                                                           Median :249.0
Median:3.53
                 Median: 73.00
                                   Median: 1259.0
                                                      Median :114.70
                                                                        Median :108.00
Mean
        :3.50
                 Mean
                        : 97.65
                                   Mean
                                            1982.7
                                                      Mean
                                                              :122.56
                                                                        Mean
                                                                                :124.70
                                                                                           Mean
                                                                                                  :255.9
 3rd Qu.:3.78
                 3rd Qu.:123.00
                                   3rd Qu.: 1980.0
                                                      3rd Qu.:151.90
                                                                         3rd Qu.:151.00
                                                                                           3rd Qu.:317.8
        :4.64
                        :588.00
                                           :13862.4
                                                              :457.25
                                                                        Max.
                                                                                :598.00
                                                                                           Max.
                                                                                                  :563.0
                                   Max.
                                                      Max.
Max.
                 Max.
                 NA'S
                        :103
                                   NA'S
                                           :101
                                                      NA'S
                                                              :101
                                                                         NA'S
                                                                                :131
                                                                                           NA'S
                                                                                                  :11
    protime
                      stage
Min.
        : 9.00
                  Min.
                         :1.000
1st Qu.:10.00
                  1st Ou.: 2.000
Median :10.60
                  Median :3.000
Mean
        :10.74
                  Mean
                         :3.024
 3rd Qu.:11.10
                  3rd Qu.:4.000
Max.
        :18.00
                  Max.
                         :4.000
NA'S
        : 2
```

Selanjutnya akan ditetapkan bahwa hanya akan digunakan stage sebagai variabel penjelas untuk waktu hingga terjadi kematian. Akan dicek boxplot dan perbandingan pasien yang hidup dan meninggal dari setiap stage.

> boxplot(time~stage,data=pbc,xlab="Stadium penyakit PBC", ylab="Waktu survival (tahun)")



Berdasarkan boxplot, terlihat bahwa terdapat kecenderungan pasien dengan tingkat stage (stadium) tinggi memiliki waktu survival yang lebih pendek daripada tingkat stage

yang lebih rendah. Seperti pada stage 4, memiliki waktu survival yang lebih pendek dibandingkan pasien pada tiga stage yang lainnya.

```
> table(pbc$status,pbc$stage)
```

```
1 2 3 4
0 19 69 108 60
1 2 23 48 84
```

Berdasarkan tabel perbandingan, jumlah pasien yang masih bertahan hidup dan yang meninggal di masing-masing stage, diperoleh 2 dari 21 pasien stage 1 meninggal, 23 dari 92 pasien stage 2 meninggal, 48 dari 156 pasien stage 3 meninggal, dan untuk stage 4 terdapat 84 dari 144 pasien meninggal.

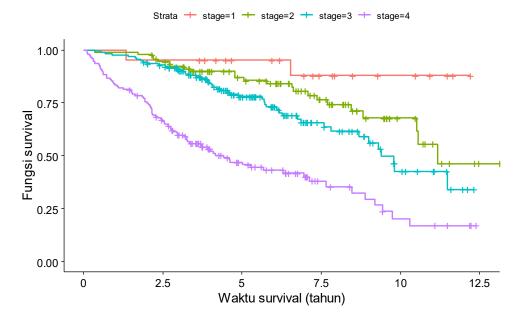
Kemudian akan dibuat estimasi fungsi survival dengan menggunakan Kaplan-Meier dan dibuat visualisasi sebagai berikut.

```
> st.stage <- survfit(Surv(time, status)~stage, data=pbc, conf.type="log-log")
> summary(st.stage)
Call: survfit(formula = Surv(time, status) ~ stage, data = pbc, conf.type = "log-log")
              stage=1
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
 1.34
        21
               1
                     0.952 0.0465
                                  0.707
 6.54
                     0.879 0.0824
                                        0.585
                                                    0.970
              stage=2
  time n.risk n.event survival std.err lower 95% CI upper 95% CI
 0.356
          92 1 0.989 0.0108
                                    0.925
                                                  0.998
                      0.978 0.0152
 1.712
          91
                  1
                                         0.916
                                                     0.995
 2.167
          89
                  1
                      0.967
                             0.0186
                                         0.902
                                                     0.989
 2.189
          88
                  1
                      0.956 0.0214
                                         0.888
                                                     0.983
          86
 2.337
                  1
                      0.945 0.0238
                                         0.873
                                                     0.977
 2.712
          84
                  1 0.934 0.0261
                                         0.859
                                                     0.970
 2.737
          82
                  1 0.923 0.0281
                                         0.844
                                                     0.962
 3.200
          78
                  1 0.911 0.0302
                                         0.829
                                                     0.954
          75
 3.384
                 1 0.899 0.0321
                                         0.814
                                                     0.946
          64
                 1 0.885 0.0345
                                                     0.936
 4.770
                                         0.795
          63
61
                  1 0.870 0.0367
 4.784
                                         0.777
                                                     0.926
 5.060
                  1
                      0.856
                             0.0388
                                          0.759
                                                     0.916
          57
                      0.841
 5.784
                  1
                             0.0409
                                         0.741
                                                     0.905
          47
 6.575
                  1
                      0.823
                             0.0438
                                          0.717
                                                     0.892
 6.627
          46
                  1
                      0.805
                             0.0464
                                         0.695
                                                     0.879
          41
                                         0.670
 7.077
                      0.786 0.0492
                  1
                                                     0.865
 7.367
          38
                      0.765 0.0521
                                         0.644
                  1
                                                     0.850
 7.704
          34
                      0.743 0.0552
                                         0.615
                                                     0.833
                 1
 8.455
          25
                      0.713 0.0605
                 1
                                         0.575
                                                     0.813
 8.827
          21
                 1
                      0.679 0.0664
                                         0.530
                                                     0.790
 10.518
          11
                 1
                      0.617 0.0843
                                         0.431
                                                     0.758
          10
                                                     0.718
                      0.555 0.0958
                                          0.352
 10.556
                  1
 11.175
          6
                  1 0.463 0.1163
                                          0.232
                                                     0.666
```

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4. 208	4.049	103	1	0.833	0.03138		0.761		0.885
4.318 95 1 0.808 0.03360 0.732 0.865 4.540 88 1 0.799 0.03445 0.721 0.857 4.630 85 1 0.789 0.03530 0.710 0.849 4.893 80 1 0.780 0.03621 0.698 0.841 5.630 64 1 0.767 0.03764 0.683 0.832 5.701 63 1 0.755 0.03896 0.669 0.822 5.726 62 1 0.743 0.04020 0.654 0.812 5.767 61 1 0.731 0.04134 0.640 0.802 6.093 54 1 0.717 0.04273 0.624 0.792 6.181 52 1 0.704 0.04408 0.607 0.780 6.268 51 1 0.690 0.04532 0.591 0.769 6.756 43 1 0.674 0.04702 0.572 0.756 6.858 42 1 0.658 0.04856 0.553 0.743 7.586 32 1 0.637 0.05121 0.528 0.728 7.800 30 1 0.616 0.05372 0.502 0.711 8.685 24 1 0.590 0.05729 0.469 0.692 8.992 21 1 0.562 0.06107 0.4344 0.672 9.301 18 1 0.531 0.06517 0.396 0.649 9.392 16 1 0.498 0.06903 0.357 0.623 9.792 15 1 0.466 0.07566 0.277 0.567 9.311 144 1 0.993 0.00692 0.9517 0.999 0.118 143 1 0.986 0.09975 0.9456 0.993 0.195 141 1 0.972 0.01369 0.9277 0.567 11.482 5 1 0.341 0.09729 0.163 0.527 Stage=4 time n.risk n.event survival std.err lower 95% CI upper 95% CI 0.112 144 1 0.993 0.00692 0.9517 0.999 0.118 143 1 0.986 0.09975 0.9456 0.993 0.195 141 1 0.972 0.01369 0.9277 0.989 0.118 143 1 0.986 0.00975 0.9456 0.993 0.195 141 1 0.972 0.01369 0.9277 0.989 0.211 140 1 0.965 0.01526 0.9186 0.985 0.258 139 1 0.958 0.01665 0.9096 0.981 0.301 138 1 0.951 0.01792 0.9007 0.977 0.304 137 1 0.944 0.01909 0.8920 0.977 0.304 137 1 0.944 0.01909 0.8920 0.972 0.313 138 1 0.951 0.01792 0.9007 0.977 0.304 137 1 0.944 0.01909 0.8920 0.972 0.359 136 1 0.938 0.02017 0.8833 0.967 0.490 135 1 0.938 0.02017 0.8833 0.967 0.523 133 1 0.917 0.02303 0.8579 0.952 0.524 130 1 0.896 0.02546 0.8814 0.941 0.592 130 1 0.896 0.02546 0.8814 0.941	4.074	102	1	0.825	0.03212		0.751		0.878
4.540 88 1 0.799 0.03445 0.721 0.857 4.630 85 1 0.789 0.03530 0.710 0.849 4.893 80 1 0.780 0.03621 0.698 0.841 5.630 64 1 0.767 0.03764 0.683 0.832 5.701 63 1 0.755 0.03896 0.669 0.822 5.726 62 1 0.743 0.04020 0.654 0.812 5.767 61 1 0.731 0.04134 0.640 0.802 6.093 54 1 0.717 0.04273 0.624 0.792 6.181 52 1 0.704 0.04532 0.591 0.768 6.268 51 1 0.690 0.04532 0.591 0.766 6.756 43 1 0.674 0.04702 0.572 0.756 6.858 42 1 0.658 0.04856 0.553 0.743 7.586 32 1 0.637 0.05121 0.528 0.728 7.800 30 1 0.616 0.05372 0.502 0.711 8.685 24 1 0.590 0.05729 0.469 0.692 8.992 21 1 0.562 0.06107 0.434 0.672 9.301 18 1 0.531 0.06517 0.396 0.649 9.392 16 1 0.498 0.06903 0.357 0.623 9.792 15 1 0.465 0.07196 0.320 0.597 9.819 12 1 0.426 0.07566 0.277 0.567 11.482 5 1 0.341 0.09729 0.163 0.527 **stage=4** **time n.risk n.event survival std.err lower 95% CI upper 95% CI 0.112 144 1 0.993 0.00692 0.9517 0.999 0.118 143 1 0.986 0.00975 0.9456 0.997 0.140 142 1 0.979 0.01190 0.9368 0.993 0.195 141 1 0.972 0.01369 0.9277 0.587 0.140 142 1 0.979 0.01190 0.9368 0.993 0.195 141 1 0.955 0.01526 0.9186 0.985 0.258 139 1 0.958 0.01665 0.9096 0.981 0.301 138 1 0.951 0.01792 0.9007 0.977 0.304 137 1 0.944 0.01909 0.8920 0.972 0.304 137 1 0.944 0.01909 0.8920 0.972 0.359 136 1 0.938 0.02017 0.8833 0.997 0.450 134 1 0.994 0.0213 0.8663 0.957 0.523 133 1 0.917 0.02303 0.8579 0.952 0.521 10.0 134 1 0.924 0.0213 0.8663 0.957 0.522 130 1 0.896 0.02546 0.8332 0.936	4.208	100	1	0.817	0.03284		0.742		0.872
4.630 85 1 0.789 0.03530 0.710 0.849 4.893 80 1 0.780 0.03621 0.698 0.841 5.630 64 1 0.767 0.03764 0.683 0.832 5.701 63 1 0.755 0.03896 0.669 0.822 5.726 62 1 0.743 0.04020 0.654 0.812 5.767 61 1 0.731 0.04134 0.640 0.802 6.093 54 1 0.717 0.04273 0.624 0.792 6.181 52 1 0.704 0.04408 0.607 0.780 6.268 51 1 0.690 0.04532 0.591 0.769 6.756 43 1 0.674 0.04702 0.572 0.756 6.858 42 1 0.637 0.05121 0.528 0.728 7.586 32 1 0.637 0.05121 0.528 0.728 7.800 30 1 0.616 0.05372 0.502 0.711 8.685 24 1 0.590 0.05729 0.469 0.692 8.992 21 1 0.562 0.06107 0.434 0.672 9.301 18 1 0.531 0.06517 0.396 0.649 9.392 16 1 0.498 0.06903 0.357 0.624 9.392 16 1 0.498 0.06903 0.357 0.629 9.792 15 1 0.465 0.07196 0.320 0.597 9.819 12 1 0.426 0.07566 0.277 0.567 11.482 5 1 0.341 0.09729 0.163 0.527 stage=4 time n.risk n.event survival std.err lower 95% CI upper 95% CI 0.112 144 1 0.993 0.00692 0.9517 0.999 0.118 143 1 0.986 0.00975 0.9456 0.997 0.140 142 1 0.979 0.01190 0.9368 0.993 0.195 141 1 0.972 0.01369 0.9277 0.989 0.211 140 1 0.965 0.01526 0.9186 0.985 0.258 139 1 0.958 0.01665 0.9096 0.981 0.301 138 1 0.951 0.01792 0.9007 0.977 0.304 137 1 0.944 0.01909 0.8920 0.972 0.304 137 1 0.944 0.01909 0.8920 0.972 0.319 134 1 0.994 0.0213 0.8663 0.997 0.490 135 1 0.931 0.02118 0.8748 0.962 0.510 134 1 0.924 0.02213 0.8663 0.957 0.523 133 1 0.917 0.02303 0.8579 0.952 0.524 1 0.900 0.02586 0.8414 0.941 0.592 130 1 0.896 0.02546 0.8414 0.941 0.592 130 1 0.896 0.02546 0.8432 0.936	4.318	95	1	0.808	0.03360		0.732		0.865
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0.005 129 1 0.889 0.02619 0.8250 0.930									
	0.605	129	1	0.889	0.02619		0.8250		0.930

0.611	128	1	0.882	0.02689	0.8170	0.925
0.723	127	2			0.8010	0.914
0.833	125	1			0.7930	0.908
0.879	124	1	0.854	0.02941	0.7852	0.902
0.915	123	1	0.847	0.02998	0.7773	0.897
0.953	122	1		0.03053	0.7695	0.891
0.984	121	1			0.7617	0.885
1.063	120	1		0.03156	0.7540	0.879
1.096 1.260	119	1		0.03205	0.7463	0.873
1.504	118 116	1		0.03253 0.03299	0.7386 0.7309	0.867
1.512	115	1		0.03233	0.7232	0.855
1.532	114	1			0.7155	0.849
1.636	113	1		0.03429	0.7079	0.843
1.844	111	1			0.7002	0.837
1.901	110	1	0.770	0.03510	0.6925	0.831
1.926	109	1	0.763	0.03548	0.6849	0.825
1.940	108	1		0.03585	0.6773	0.818
1.992	107	1		0.03620	0.6697	0.812
2.055	106	1		0.03654	0.6621	0.806
2.088	105	1		0.03687	0.6546	0.800
2.107	104	1		0.03719	0.6471	0.793
2.132 2.151	103	1		0.03749 0.03779	0.6396 0.6321	0.787
2.153	101	1		0.03779	0.6247	0.774
2.164	100	1		0.03834	0.6173	0.768
2.184	99	1		0.03860	0.6099	0.761
2.258	98	1		0.03884	0.6025	0.755
2.329	96	1	0.678	0.03909	0.5950	0.748
2.438	95	1	0.671	0.03933	0.5876	0.742
2.477	93	1	0.664	0.03956	0.5801	0.735
2.548	92	1			0.5726	0.728
2.562	91	1		0.04000	0.5652	0.722
2.660	90	1		0.04020	0.5577	0.715
2.685	88	1			0.5502	0.708
2.740	87	1		0.04059	0.5427	0.701
2.773 2.841	86 83	1		0.04077 0.04096	0.5352 0.5276	0.695
2.951	82	1		0.04113	0.5199	0.681
2.967	81	1		0.04130	0.5123	0.674
3.192	77	1		0.04149	0.5043	0.666
3.263	75	2		0.04185	0.4882	0.652
3.279	73	1	0.567	0.04201	0.4802	0.644
3.334	72	1		0.04215	0.4722	0.637
3.699	62	1		0.04243	0.4629	0.628
3.715	61	1		0.04268	0.4536	0.620
3.929	57	1		0.04297	0.4437	0.611
4.005	53	1		0.04331	0.4332	0.602
4.088 4.159	52 51	1		0.04363 0.04391	0.4228 0.4125	0.593 0.584
4.427	48	1		0.04422	0.4017	0.574
4.608	46	1		0.04452	0.3906	0.564
4.630	45	1		0.04479	0.3797	0.554
5.005	40	1	0.458	0.04519	0.3675	0.543
5.274	38	1	0.446	0.04557	0.3550	0.532
5.674	34	1		0.04608	0.3412	0.520
6.293	30	1		0.04675	0.3259	0.508
6.959	24	1		0.04793	0.3067	0.493
7.118 7.660	19	1		0.04984	0.2827	0.476
8.466	15 12	1		0.05255 0.05585	0.2533 0.2192	0.457
8.888	11	1		0.05806	0.1877	0.411
9.200	10	1		0.05929	0.1583	0.386
9.438	9	1		0.05960	0.1310	0.359
9.756	7	1		0.05988	0.1007	0.329
0.307	6	1		0.05864	0.0736	0.297

Estimasi Kaplan-Meier



Berdasarkan hasil visualisasi fungsi survival berdasarkan stage, terlihat bahwa terdapat perbedaan antara fungsi suvival untuk empat stage tersebut. Hal ini mengindikasikan bahwa stage merupakan calon variabel penjelas yang cukup baik untuk waktu terjadinya kematian (*event*). Pada plot tersebut juga terlihat bahwa pada mayoritas titik waktu pengamatan, fungsi survival untuk stage 1 lebih tinggi daripada stage 2. Namun, fungsi survival stage 2 lebih tinggi dari fungsi survival stage 3 dan fungsi survival stage 3 lebih tinggi dari fungsi survival stage 4. Hal ini mengimplikasikan bahwa pasien penderita pbc stage 4 lebih cepat atau memiliki resiko yang lebih besar untuk mengalami kematian (*event*) dibandingkan stage 3, stage 2, dan stage 1. Atau dapat disimpulkan bahwa semakin tinggi tingkatan stagenya, maka akan semakin beresiko untuk mengalami kematian (*event*).

2.2 Uji K-Sampel

Berdasarkan hasil analisis deskriptif, agar lebih yakin bahwa memang terdapat perbedaan fungsi survival yang signifikan dari setiap stadium, akan dilakukan uji k-sampel menggunakan bantuan *software* R untuk melihat apakah terdapat perbedaan risiko kematian penderita PBC dengan stadium yang berbeda (1,2,3,4). Hipotesis yang diajukan adalah sebagai berikut:

 H_0 : $h_1(t) = h_2(t) = h_3(t) = h_4(t)$, untuk $t \le \tau$ (tidak ada perbedaan resiko kematian dari setiap stadium)

 H_1 : $h_j(t) \neq h_k(t)$, untuk beberapa $t \leq \tau, j \neq k$, j, k = 1,2,3,4 (setidaknya terdapat satu staidum dengan risiko kematian yang berbeda)

Dengan menggunakan bantuan *software* R, dapat dilakukan uji log-rank test dengan hasil yang didapatkan sebagai berikut.

```
> survdiff(Surv(time,status)~stage, data=pbc)
survdiff(formula = Surv(time, status) ~ stage, data = pbc)
          N Observed Expected (O-E)^2/E (O-E)^2/V
                         11.4
                                   7.77
                                              8.45
stage=1 21
                   2
stage=2 92
                  23
                         44.1
                                  10.08
                                             14.20
stage=3 156
                  48
                         61.4
                                   2.92
                                              4.81
                  84
                                   48.00
stage=4 144
                         40.1
                                             65.51
 Chisq= 70.3 on 3 degrees of freedom, p= 4e-15
```

Dari hasil di atas, terlihat bahwa stadium 1, 2, dan 3 memiliki nilai *expected* yang lebih tinggi dari *observed*. Sedangkan, untuk stadium 4, ternyata nilai *observed*nya lebih tinggi dari nilai *expected*. Secara tidak langsung, hasil ini memberikan informasi bahwa terdapat perbedaan risiko kematian antarbeberapa stadium penderita PBC.

Hal ini dikonfirmasi dengan nilai p-valuenya $(p = 4 \times 10^{-15})$ yang lebih kecil dari taraf signifikansi $(\alpha = 0.05)$ sehingga H_0 ditolak. Berarti, dapat disimpulkan bahwa terdapat perbedaan risiko kematian dari penderita PBC dengan stadium yang berbeda.

2.3 Analisis Model Regresi Cox-PH

Setelah mengetahui bahwa terdapat perbedaan risiko kematian dari pasien PBC dengan stadium yang berbeda, ingin diketahui lebih lanjut risiko kematian dari stadium

manakah yang lebih tinggi ataupun lebih rendah. Untuk menganalisis hal tersebut, akan dilakukan analisis dari model regresi Cox-PH.

Pertama-tama, akan dibentuk model regresi Cox-PH terlebih dahulu. Karena variabel stadium merupakan variabel kategorik, akan dibentuk variabel dummy Z_2 , Z_3 , dan Z_4 dengan stadium=1 merupakan kategori acuan(baseline), sebagai berikut.

$$Z_{2} = \begin{cases} 1, & stadium = 2 \\ 0, & stadium \neq 2 \end{cases}$$

$$Z_{3} = \begin{cases} 1, & stadium = 3 \\ 0, & stadium \neq 3 \end{cases}$$

$$Z_{4} = \begin{cases} 1, & stadium = 4 \\ 0, & stadium \neq 4 \end{cases}$$

Sehingga model Cox-PH yang dibentuk adalah

$$h(t,x) = h_o(t)e^{\beta_2 Z_2 + \beta_3 Z_3 + \beta_4 Z_4}$$

i = 2, 3, 4 = baseline hazard yang bergantung waktu t

 β_i = koefisien regresi yang bersesuaian dengan variabel penjelas, i = 2, 3, 4

 Z_i = variabel penjelas (stadium), i = 2, 3, 4

Dengan menggunakan bantuan *software* R, didapatkan estimasi parameter β dari model Cox-PH yang telah dibentuk menggunakan metode Breslow, sebagai berikut.

```
> summary(coxph(Surv(time, status)~factor(stage), data=pbc, method="breslow"))
Call:
coxph(formula = Surv(time, status) ~ factor(stage), data = pbc,
    method = "breslow")
  n= 413, number of events= 157
                  coef exp(coef) se(coef)
                                               z Pr(>|z|)
factor(stage)2 1.1028 3.0125 0.7374 1.496 0.134777
factor(stage)3 1.5291
                          4.6142 0.7224 2.117 0.034287
factor(stage)4 2.5313 12.5699 0.7168 3.532 0.000413
factor(stage)2
factor(stage)3 *
factor(stage)4 ***
Signif. codes:
0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
               exp(coef) exp(-coef) lower .95 upper .95
factor(stage)2
                  3.013
                           0.33195
                                     0.710
                                                   12.78
factor(stage)3
                  4.614
                             0.21672
                                         1.120
                                                   19.01
factor(stage)4
                12.570
                             0.07956
                                         3.085
                                                   51.22
Concordance= 0.694 (se = 0.02)
Likelihood ratio test= 65.16 on 3 df,
                                         p=5e-14
Wald test = 59.6 on 3 df, p=7e-13
Score (logrank) test = 70.25 on 3 df, p=4e-19
                                        p=4e-15
```

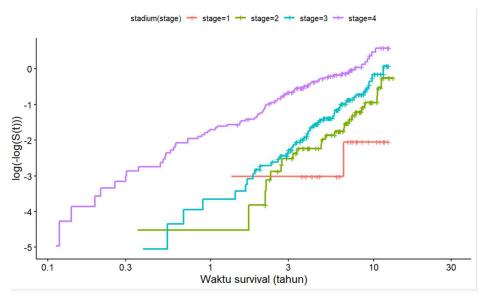
Dari hasil di atas, terlihat bahwa:

- Penderita PBC stadium 2 memiliki risiko kematian $\exp(\beta_2) = 3.0125$ kali dari penderita PBC stadium 1
- Penderita PBC stadium 3 memiliki risiko kematian $\exp(\beta_3) = 4.6142$ kali dari penderita PBC stadium 1
- Penderita PBC stadium 4 memiliki risiko kematian $\exp(\beta_4) = 12.5699$ kali dari penderita PBC stadium 1

Yang berarti terdapat keterurutan dari fungsi hazard penderita PBC, dengan stadium 1 memiliki risiko kematian yang paling rendah dan stadium 4 memiliki risiko kematian paling tinggi.

2.4 Pengecekan Asumsi Proportional Hazard(PH)

Untuk memastikan apakah benar stadium merupakan variabel penjelas yang signifikan terhadap risiko kematian, perlu dilakukan pengecekan asumsi PH menggunakan plot fungsi log(H(t)) sebagai berikut.



Terlihat dari grafik bahwa stadium 2, 3, dan 4 memperlihatkan keparalelan yang cukup baik, terutama di tengah sampai akhir waktu. Akan tetapi, stadium 1 memperlihatkan ketidaksejajaran dengan setiap stadium lainnya. Hal ini mungkin disebabkan karena data pasien stadium yang terlalu sedikit. Oleh karena itu, jika ingin menggunakan hasil dari model Cox-PH ini, penggunaannya harus dibatasi pada waktu tengah dan akhir pengamatan saja, serta perlu ditambahkan data pasien stadium 1.

BAB 3

Penutup

3.1 Kesimpulan

Dari hasil analisis survival dataset Primary Biliary Cirrhosis (PBC), didapatkan kesimpulan sebagai berikut:

- Terdapat perbedaan risiko kematian penderita PBC dengan stadium yang berbeda (1, 2, 3, 4).
- 2. Terdapat keterurutan dari fungsi hazard penderita PBC, yaitu stadium 1 memiliki risiko kematian yang paling rendah. dilanjutkan dengan stadium 2, kemudian 3, dan stadium 4 memiliki risiko kematian paling tinggi.
- 3. Penggunaan hasil dari model Cox-PH ini harus dibatasi di waktu tengah sampai akhir pengamatan saja, serta perlu ditambahkan data pasien stadium 1.

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