BIOSTAT III: Survival Analysis for Epidemiologists: Take-home examination

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Instructions

- **The examination is individual-based: you are not allowed to cooperate with anyone**, although you are encouraged to consult the available literature. The examiner will use Urkund in order to assess potential plagiarism.
- The examination will be made available by noon on Wednesday 17 February 2021 and **the examination is due by 17:00 on Wednesday 24 February 2021**.
- The examination will be graded and results returned to you by Wednesday 3 March 2021.
- The examination is in two parts. To pass the examination, you need to score at least 7/13 for Part 1 focused on rates and general regression modelling and 11/21 for Part 2 on survival analysis.
- Do not write answers by hand: please use Word, LaTeX, Markdown or a similar format for your examination report and submit the report **as a PDF file**.
- Motivate all answers in your examination report. Define any notation that you use for equations. The examination report should be written in English.
- Email the examination report containing the answers **as a PDF file** to gunilla.nilsson.roos@ki.se. **Write your name in the email, but do NOT write your name or otherwise reveal your identity in the document containing the answers.**

1 Description of the data

In this exam, we will use the colon cancer data presented in the course. We will specifically focus on the variable subsite as the exposure of interest (this variable has not been given a lot of focus during the course). It gives information about in which part of the colon the tumour was detected and has 4 levels, 'Coecum and ascending', 'Transverse', 'Descending and sigmoid', and 'Other and not otherwise specified (NOS)'. A few extra variabes have also been created that are not included in the dataset used for the computer lab. Below is a description of the variables used in this exam, and output from stset with time since diagnosis as the time-scale and death due to colon cancer as the outcome.

```
-------------------------------------------------------------------------------------
agegrp                                                             Age in 4 categories
-------------------------------------------------------------------------------------

                  type:  numeric (byte)
                 label:  agegrp
```

```
          range:  [0,3]                        units:  1
  unique values:  4                        missing .:  0/13,208

     tabulation:  Freq.   Numeric  Label
                    652         0  0-44
                  2,106         1  45-59
                  5,735         2  60-74
                  4,715         3  75+

-----------------------------------------------------------------------------------------------
year8594                                                     Indicator for diagnosed during 1985-94
-----------------------------------------------------------------------------------------------

           type:  numeric (byte)
          label:  year8594

          range:  [0,1]                        units:  1
  unique values:  2                        missing .:  0/13,208

     tabulation:  Freq.   Numeric  Label
                  5,434         0  Diagnosed 75-84
                  7,774         1  Diagnosed 85-94

-----------------------------------------------------------------------------------------------
sex                                                                                         Sex
-----------------------------------------------------------------------------------------------

           type:  numeric (byte)
          label:  sex

          range:  [1,2]                        units:  1
  unique values:  2                        missing .:  0/13,208

     tabulation:  Freq.   Numeric  Label
                  5,455         1  Male
                  7,753         2  Female

-----------------------------------------------------------------------------------------------
subsite                                                               Anatomical subsite of tumour
-----------------------------------------------------------------------------------------------

           type:  numeric (byte)
          label:  colonsub

          range:  [1,4]                        units:  1
  unique values:  4                        missing .:  0/13,208

     tabulation:  Freq.   Numeric  Label
                  4,820         1  Coecum and ascending
                  2,365         2  Transverse
                  5,391         3  Descending and sigmoid
                    632         4  Other and NOS

-----------------------------------------------------------------------------------------------
stage                                                                Clinical stage at diagnosis
-----------------------------------------------------------------------------------------------
```

```
                 type:  numeric (byte)
                label:  stage

                range:  [1,3]                        units:  1
        unique values:  3                        missing .:  0/13,208

           tabulation:  Freq.   Numeric  Label
                        6,274         1  Localised
                        1,787         2  Regional
                        5,147         3  Distant

-----------------------------------------------------------------------------------------------
d                                           Indicator for death due to colon cancer, 1=yes, 0=no
-----------------------------------------------------------------------------------------------

                 type:  numeric (float)

                range:  [0,1]                        units:  1
        unique values:  2                        missing .:  0/13,208

           tabulation:  Freq.  Value
                        6,022  0
                        7,186  1

-----------------------------------------------------------------------------------------------
y                                                    Follow-up time in exact years (#days/365.24)
-----------------------------------------------------------------------------------------------

                 type:  numeric (float)

                range:  [.04380681,20.961559]        units:  1.000e-09
        unique values:  439                      missing .:  0/13,208

                 mean:   3.76028
             std. dev:    4.4187

          percentiles:        10%       25%       50%       75%       90%
                          .125945   .542109   1.87548   5.45942   10.5438

-----------------------------------------------------------------------------------------------

. stset y, fail(d==1) exit(time 10)

     failure event:  d == 1
obs. time interval:  (0, y]
 exit on or before:  time 10

------------------------------------------------------------------------------
     13,208  total observations
          0  exclusions
------------------------------------------------------------------------------
     13,208  observations remaining, representing
      7,122  failures in single-record/single-failure data
 43,966.874  total analysis time at risk and under observation
                                                at risk from t =         0
                                     earliest observed entry t =         0
                                          last observed exit t =        10
```

Part 1

Q 1

Below is the output from a Poisson model with colon cancer death as the outcome and subsite and age group at diagnosis as explanatory variables.

```
. poisson d i.subsite i.agegrp, exp(y)

Iteration 0:   log likelihood = -23913.572
Iteration 1:   log likelihood = -23913.443
Iteration 2:   log likelihood = -23913.443

Poisson regression                              Number of obs     =     13,208
                                                LR chi2(6)        =     759.97
                                                Prob > chi2       =     0.0000
Log likelihood = -23913.443                     Pseudo R2         =     0.0156

------------------------------------------------------------------------------------------
                       d |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------------+-----------------------------------------------------------------
                subsite |
            Transverse  |   .2477318   .0333812     7.42   0.000     .1823057    .3131578
Descending and sigmoid  |   .0171663   .0272406     0.63   0.529    -.0362244    .0705569
         Other and NOS  |   .1345189   .0572765     2.35   0.019      .022259    .2467788
                        |
                 agegrp |
                 45-59  |   .1326942   .0638993     2.08   0.038     .0074539    .2579345
                 60-74  |   .4641152   .0586528     7.91   0.000     .3491579    .5790725
                   75+  |   .9398427   .0589442    15.94   0.000     .8243141    1.055371
                        |
                  _cons |  -2.518287   .0577151   -43.63   0.000    -2.631406   -2.405167
                  ln(y) |          1  (exposure)
------------------------------------------------------------------------------------------

. est store A
```

a) Interpret the parameter for subsite 'Transverse' in the output above, including a statement about statistical significance. (2 pt)

b) Interpret the parameter for subsite 'Descending and sigmoid' in the output above, including a statement about statistical significance. (2 pt)

c) What is the hazard ratio comparing a patient with subsite 'Transverse' and diagnosed aged 45-59 to a patient with subsite 'Coecum and ascending' and diagnosed in the youngest age group? (2 pt)

d) In this example, subsite is the exposure. We know that the distribution of age differs across subsites, and it is also known that colon cancer-specific mortality differs by age. Will this be a problem when you interpret the effect of subsite in the output above? Motivate your answer. (2 pt)

Q 2

A second Poisson model is fitted, including interaction terms between subsite and age group. The model is also compared with the model fitted in Q1 using a likelihood-ratio test.

```
. poisson d i.subsite##i.agegrp, exp(y)

Iteration 0:   log likelihood = -23889.634
Iteration 1:   log likelihood = -23889.332
Iteration 2:   log likelihood = -23889.332

Poisson regression                              Number of obs     =     13,208
                                                LR chi2(15)       =     808.19
                                                Prob > chi2       =     0.0000
Log likelihood = -23889.332                     Pseudo R2         =     0.0166

-----------------------------------------------------------------------------------------------
                            d |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------------------+----------------------------------------------------------------
                      subsite |
                   Transverse |   .5488913   .1544657     3.55   0.000     .2461441    .8516385
        Descending and sigmoid |   .6811782   .1331186     5.12   0.000     .4202706    .9420859
                Other and NOS | -.0742398   .2957184    -0.25   0.802    -.6538373    .5053576
                              |
                       agegrp |
                        45-59 |   .5470006   .1164724     4.70   0.000     .3187188    .7752824
                        60-74 |   .7903322   .1070393     7.38   0.000     .5805391    1.000125
                          75+ |   1.216963   .1070192    11.37   0.000     1.007209    1.426716
                              |
               subsite#agegrp |
             Transverse#45-59 |  -.5168524   .1779356    -2.90   0.004    -.8655997    -.168105
             Transverse#60-74 |  -.3242193   .1629553    -1.99   0.047    -.6436058   -.0048329
               Transverse#75+ |  -.2336096   .1632869    -1.43   0.153     -.553646    .0864268
Descending and sigmoid#45-59 |  -.7688978   .1514086    -5.08   0.000    -1.065653   -.4721424
Descending and sigmoid#60-74 |  -.7094681   .1393483    -5.09   0.000    -.9825857   -.4363505
  Descending and sigmoid#75+ |  -.6571303   .1402717    -4.68   0.000    -.9320578   -.3822029
          Other and NOS#45-59 |  -.2616855   .3438992    -0.76   0.447    -.9357156    .4123446
          Other and NOS#60-74 |   .1961377   .3089865     0.63   0.526    -.4094648    .8017402
            Other and NOS#75+ |   .3896897    .307874     1.27   0.206    -.2137323    .9931117
                              |
                        _cons |  -2.820275   .1025978   -27.49   0.000    -3.021363   -2.619187
                        ln(y) |          1  (exposure)
-----------------------------------------------------------------------------------------------

. lrtest A

Likelihood-ratio test                                 LR chi2(9)  =     48.22
(Assumption: A nested in .)                           Prob > chi2 =    0.0000
```

a) What is the hazard ratio when comparing subsite 'Transverse' to 'Coecum and ascending' among patients diagnosed in the youngest age group. (2 pt)

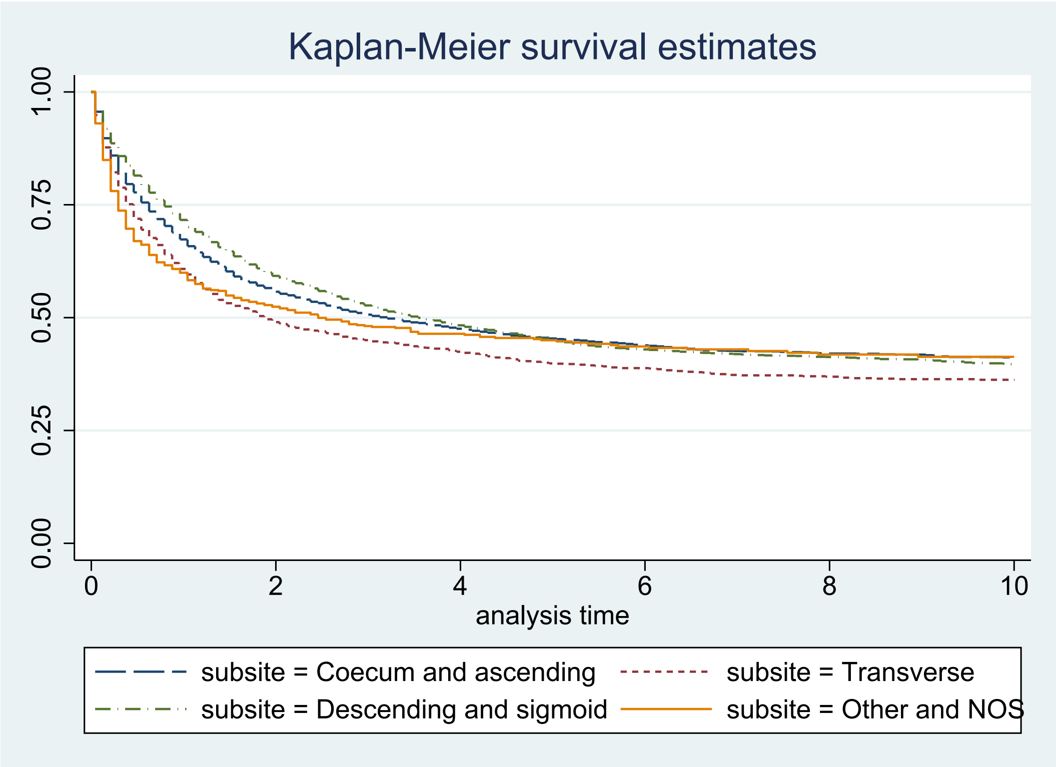
b) What is the hazard ratio when comparing subsite 'Transverse' to 'Coecum and ascending' among patients diagnosed in the ages 60-74? (2 pt)

c) Is there evidence of effect modification by age? Motivate your answer. (1 pt)

Part 2

Q 3

Here is a Kaplan-Meier graph of the survivor function for the 4 subsites, and the output from a log rank test.




```
. sts test subsite

         failure _d:  d == 1
   analysis time _t:  y
  exit on or before:  time 10


Log-rank test for equality of survivor functions

                       |   Events         Events
subsite                |  observed       expected
-----------------------+-------------------------
Coecum and ascending   |      2557        2605.52
Transverse             |      1374        1180.68
Descending and sigmoid |      2850        3021.69
Other and NOS          |       341         314.12
-----------------------+-------------------------
Total                  |      7122        7122.00

                             chi2(3) =      45.86
                             Pr>chi2 =     0.0000
```

a) Based on the Kaplan-Meier graph, what is the 1-year survival for each of the 4 subsites (approximately)? (2 pt)

b) Based on the Kaplan-Meier graph, what can you conclude about the hazard rate of death due to colon cancer for the 4 subsites? (3 pt)

c) Would you say that the proportional hazards assumption is reasonable? Motivate your answer. (2 pt)

d) Would you conclude that there is evidence of a difference in the cancer-specific mortality across subsites? (1 pt)

e) Why is it better to answer the question above using a regression model instead of a log-rank test? (2 pt)

Q 4

Below is the output from a Cox model, and test of the proportional hazards assumption based on the Schoenfelds residuals from this model.

```
. stcox i.subsite i.agegrp

         failure _d:  d == 1
   analysis time _t:  y
  exit on or before:  time 10

Iteration 0:   log likelihood = -64476.566
Iteration 1:   log likelihood =  -64358.24
Iteration 2:   log likelihood = -64357.746
Iteration 3:   log likelihood = -64357.746
Refining estimates:
Iteration 0:   log likelihood = -64357.746

Cox regression -- Breslow method for ties

No. of subjects =       13,208                Number of obs    =     13,208
No. of failures =        7,122
Time at risk    =  43966.87383
                                               LR chi2(6)       =     237.64
Log likelihood  =   -64357.746                Prob > chi2      =     0.0000

------------------------------------------------------------------------------------------
                     _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------------+-----------------------------------------------------------------
                subsite |
             Transverse |   1.213999   .0406689     5.79   0.000      1.13685    1.296384
Descending and sigmoid  |    .986004   .0269601    -0.52   0.606     .9345541    1.040286
          Other and NOS |   1.121014   .0646428     1.98   0.048     1.001213    1.255148
                        |
                 agegrp |
                  45-59 |   1.046113   .0671159     0.70   0.482     .9225032    1.186287
                  60-74 |   1.240406   .0731012     3.66   0.000     1.105095    1.392285
                    75+ |    1.60553   .0951475     7.99   0.000     1.429468    1.803278
------------------------------------------------------------------------------------------

. estat phtest, detail

      Test of proportional-hazards assumption
```

```
Time:  Time
-----------------------------------------------------------------
            |       rho            chi2       df       Prob>chi2
------------+----------------------------------------------------
1b.subsite  |          .              .        1             .
2.subsite   |    -0.02292          3.74        1         0.0530
3.subsite   |     0.06947         34.54        1         0.0000
4.subsite   |    -0.04271         12.99        1         0.0003
0b.agegrp   |          .              .        1             .
1.agegrp    |    -0.01304          1.21        1         0.2704
2.agegrp    |    -0.00981          0.69        1         0.4071
3.agegrp    |    -0.03354          7.99        1         0.0047
------------+----------------------------------------------------
global test |                    109.14        6         0.0000
-----------------------------------------------------------------
```

a) Is this model equivalent to the Poisson model in question 1 (Q1)? Motivate your answer. (2 pt)

b) What is the hazard ratio comparing subsite 'Other and NOS' to 'Coecum and ascending' for patients aged 75+ at diagnosis? (2 pt)

c) Write out the model formulation (linear predictor) of the model. (2 pt)

d) Is there evidence of non-proportional hazards for the covariate of interest, subsite? (1 pt)

e) Why would a stratified Cox model, stratifying by subsite, not be suitable in this study? (1 pt)

Q 5

a) Descibe a study where you would choose attained age as the time-scale. Motivate your answer. (2pt)

b) Describe an approach (other than stratified Cox model) of allowing for non-proportional hazards. (1 pt)