

SUPPLEMENTARY MATERIAL

Closed Testing of Each Group Versus the Others Combined in a Multiple Group Analysis

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This Supplement Contains the following Materials:

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2. Computation of Power by Numerical Integration
3. Numerical Results for Logistic Regression Model Simulations
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1 Computations for Simple Examples

The following program computed the hierarchical tests for the two simple examples of differences in means or proportions among four groups.

```
%macro assoc;
data two; set one end=eof;
drop i muk SEk;
array mus (&Levels) mu1-mu&Levels;
array SEs (&Levels) SE1- SE&Levels;
retain mu1-mu&Levels SE1- SE&Levels;
mus(i) = muk;
SEs(i) = SEk;
if eof then output;
data tests; set two;
data mus; set tests (keep = mu1-mu&Levels);
data SEs; set tests (keep = SE1- SE&Levels);
proc iml;
use mus;
read all into mus;
use SEs;
read all into SEs;
var = diag( SEs##2);
**** test of H01+H02+H03;
**** equal to test of H01+H02+H03+H04, also H01+H02+H04, H01+H03+H04, H02+H03+H04;
c123 = {3 -1 -1 -1, -1 3 -1 -1, -1 -1 3 -1}/3;
```

```

CH123 = (mus*c123')* inv(c123*var*c123') * (c123*mus');
pCh123 = 1 - Probchi(CH123, 3);
Print "test of H01 and H02 and H03";
print ch123 pch123;
**** test of H01+H02;
c12 = {3 -1 -1 -1, -1 3 -1 -1}/3;
CH12 = (mus*c12')* inv(c12*var*c12') * (c12*mus');
pCh12 = 1 - Probchi(CH12, 2);
Print "test of H01 and H02";
print ch12 pch12;
run;
**** test of H01+H03;
c13 = {3 -1 -1 -1, -1 -1 3 -1}/3;
CH13 = (mus*c13')* inv(c13*var*c13') * (c13*mus');
pCh13 = 1 - Probchi(CH13, 2);
print "test of H01 and H03";
print ch13 pch13;
**** test of H01+H04;
c14 = {3 -1 -1 -1, -1 -1 -1 3}/3;
CH14 = (mus*c14')* inv(c14*var*c14') * (c14*mus');
pCh14 = 1 - Probchi(CH14, 2);
print "test of H01 and H04";
print ch14 pch14;
**** test of H02+H03;
c23 = {-1 3 -1 -1, -1 -1 3 -1}/3;
CH23 = (mus*c23')* inv(c23*var*c23') * (c23*mus');
pCh23 = 1 - Probchi(CH23, 2);
print "test of H02 and H03";
print ch23 pch23;
**** test of H02+H04;
c24 = {-1 3 -1 -1, -1 -1 -1 3}/3;
CH24 = (mus*c24')* inv(c24*var*c24') * (c24*mus');
pCh24 = 1 - Probchi(CH24, 2);
print "test of H02 and H04";
print ch24 pch24;
**** test of H03+H04;
c34 = {-1 -1 3 -1, -1 -1 -1 3}/3;
CH34 = (mus*c34')* inv(c34*var*c34') * (c34*mus');
pCh34 = 1 - Probchi(CH34, 2);
print "test of H03 and H04";
print ch34 pch34;
**** test of H01;
c1= {3 -1 -1 -1}/3;
mul0 = mus*{0 1 1 1}'/3;
CH1= (mus*c1')* inv(c1*var*c1') * (c1*mus');

```

```

pCh1= 1 - Probchi(CH1, 1);
print "test of H01";
print ch1 pch1;
**** test of H02;
c2= {-1 3 -1 -1}/3;
mu2o = mus*{1 0 1 1}'/3;
CH2= (mus*c2')* inv(c2*var*c2') * (c2*mus');
pCh2= 1 - Probchi(CH2, 1);
print "test of H02";
print ch2 pch2;
**** test of H03;
c3= {-1 -1 3 -1}/3;
mu3o = mus*{1 1 0 1}'/3;
CH3= (mus*c3')* inv(c3*var*c3') * (c3*mus');
pCh3= 1 - Probchi(CH3, 1);
print "test of H03";
print ch3 pch3;
**** test of H04;
c4= {-1 -1 -1 3}/3;
mu4o = mus*{1 1 1 0}'/3;
CH4= (mus*c4')* inv(c4*var*c4') * (c4*mus');
pCh4= 1 - Probchi(CH4, 1);
print "test of H04";
print ch4 pch4;
quit;
%mend assoc;
data one; input i muk SEk;
Title McMillan 4 diets;
cards;
1 4.2 0.6
2 5.5 0.5
3 6.2 0.4
4 4.8 0.7
;
%let Levels = 4;
%assoc; run;
data one; input i muk nk;
Title Treiman 4 proportions;
SEk = sqrt(muk*(1-muk)/nk);
cards;
1 0.436 101
2 0.649 97
3 0.582 91
4 0.558 95
;

```

```
%let Levels = 4;
%assoc; run;
```

2 Computation of Power by Numerical Integration

The relative power of the closed versus Bonferroni-corrected t -test was computed as follows. As in the simulations assume that the sample size is $n = 200$ where $X_i \sim N(\mu_i, \sigma_i^2)$, $\sigma_i = 5$ ($i = 1, 2, 3$). For specified mean values (μ_1, μ_2, μ_3) , the probability that a test would be significant is computed as

$$\int_{x_1} \int_{x_2} \int_{x_3} I[t(x_1, x_2, x_3)] \phi_1(x_1) \phi_2(x_2) \phi_3(x_3) dx_1 dx_2 dx_3$$

where $t(x_1, x_2, x_3)$ denotes the test statistic as a function of the observed values, $I(t)$ is the indicator function to denote whether t reaches the criteria for significance and $\phi_j(x_j)$ is the normal density for the j th group. For closed testing $I(t)$ denotes whether both the 2 df F -test of $H_{0,123} : \mu_1 = \mu_2 = \mu_3$ and the t -test of $H_{0,1:23} : \mu_1 = (\mu_2 + \mu_3)/2$ are significant at the 0.05 level. Likewise, the probability of significance of the Bonferroni-corrected t -test is obtained using the indicator function $I(t)$ to denote a t -test p -value $\leq 0.05/3$.

3 Numerical Results for Logistic Regression Model Simulations

Consider the case of three treatment groups $G = 1, 2, 3$ and a binary outcome $Y = 0, 1$, where

$$\text{logit}[P(Y = 1|G)] = \alpha + \beta_{2:1} \cdot I(G = 2) + \beta_{3:1} \cdot I(G = 3),$$

where $\beta_{i:1}$ is the log odds ratio for comparing group i versus 1, $i = 2, 3$. The table below reports the probability of rejection for the comparison of group 1 versus the others (i.e., H_{01}) at level 0.05 for various combinations of the parameters $\alpha, \beta_{2:1}$ and $\beta_{3:1}$ for $n = 200$ per group (i.e., a total sample size of 600) and using 5,000 simulations. The results are reported first without (Unadjusted) and then with adjustment for multiple testing using the Bonferroni, Holm, Hommel and the closed testing procedure approaches.

	α	$\beta_{2:1}$	$\beta_{3:1}$	Unadjusted	Bonferroni	Holm	Hommel	Closed Testing
1	1	0.0	0.0	0.0534	0.0208	0.0216	0.0224	0.0282
2	1	0.2	-0.2	0.0492	0.0176	0.0252	0.0264	0.0446
3	1	0.5	-0.5	0.0462	0.0130	0.0376	0.0410	0.0462
4	1	0.0	0.5	0.2446	0.1314	0.1656	0.1706	0.2216
5	1	0.2	0.5	0.4594	0.2968	0.3130	0.3214	0.3644
6	1	0.5	0.5	0.6932	0.5286	0.5368	0.5438	0.5640

The first three simulation scenarios correspond to the null hypothesis H_{01} . While all four adjustments for multiplicity control the type I error probability, the Bonferroni, Holm and Hommel procedures are more conservative (i.e., lower p -values) than the closed testing procedure. The last three simulations correspond to the alternative hypothesis, and the results show that the closed testing procedure provides higher power than the other three approaches.

4 Numerical Results for Cox PH Model Simulations

Consider the case of three treatment groups $G = 1, 2, 3$ and an exponentially distributed time-to-event outcome Y with log hazard rate given by

$$\log(\lambda(t|G)) = \alpha + \beta_{2:1} \cdot I(G = 2) + \beta_{3:1} \cdot I(G = 3),$$

where $\beta_{i:1}$ is the log hazard ratio for comparing group i versus 1, $i = 2, 3$. The simulations considered administrative censoring of the event times larger than 0.5 censored at 0.5. The table below reports the probability of rejection for the comparison of group 1 versus the others (i.e., H_{01}) at level 0.05 for various combinations of the parameters $\alpha, \beta_{2:1}$ and $\beta_{3:1}$ for $n = 200$ per group (i.e., a total sample size of 600) and using 5,000 simulations. The rejection probabilities are reported first without (Unadjusted) and then with adjustment for multiple testing using the Bonferroni, Holm, Hommel and the closed testing procedure approaches.

	α	$\beta_{2:1}$	$\beta_{3:1}$	Unadjusted	Bonferroni	Holm	Hommel	Closed Testing
1	1	0	0	0.0522	0.0206	0.0216	0.0222	0.0254
2	1	$\log(1.3)$	$\log(0.7)$	0.0502	0.0206	0.0492	0.0494	0.0502
3	1	$\log(1.5)$	$\log(0.5)$	0.0536	0.0210	0.0536	0.0536	0.0536
4	1	1	$\log(1.3)$	0.2258	0.0916	0.1282	0.1376	0.2216
5	1	$\log(1.3)$	$\log(1.3)$	0.6882	0.4638	0.4906	0.5020	0.6302
6	1	$\log(1.3)$	$\log(1.5)$	0.9002	0.7608	0.8004	0.8072	0.8840

The first three simulation scenarios correspond to the null hypothesis H_{01} . While all four adjustments for multiplicity control the type I error, the Bonferroni, Holm and Hommel procedures are more conservative (i.e., lower p-values) than the closed testing procedure. The last three simulations correspond to the alternative hypothesis, and the results show that the closed testing procedure provides higher power than the other three approaches.

5 Logistic Models in SAS

A logistic regression model for three groups could be conducted using the following SAS statements:

```
proc logistic descending;
title2 individual groups with contrast tests of one-versus-others;
class group / descending param=ref;
model Y = group / expb;
contrast 'H01' group 1 1;
contrast 'H02' group 2 -1;
contrast 'H03' group -1 2;
run;
```

Thus, for example, H_{02} refers to the contrast $2\beta_{2:1} - \beta_{3:1} = 0$. The 2-*df* model Wald (or likelihood ratio) test would provide a test of the joint null hypothesis $H_{01} \cap H_{02} \cap H_{03}$. If significant at level α then each of the elemental hypotheses could then be tested at level α .

For a four group analysis, additional contrasts could be included in the program with contrasts as shown in the text. For example, for the higher order hypothesis $H_{02} \cap H_{03}$, the contrast would be of the form

```
contrast 'H02 and H03' group 3 -1 1, group -1 3 -1;
```

6 Cox PH Models for Three Groups in SAS

With three groups, the 2-df test of the joint null hypothesis, and tests of the elemental hypotheses H_{01} , H_{02} , and H_{03} , can be obtained using the SAS procedure PHREG as follows. The variable *group* is coded such as 0, 1 or 2 with group 0 as the reference;

```
ods output Estimates=betas;
proc phreg;
class group / descending param=ref;
model time*event(0) = group / rl;
estimate 'H01' group 0 1, group 1 0 / cov;
estimate 'H02' group 0 -1, group 1 -1 / cov;
estimate 'H03' group -1 0, group -1 1 / cov;run;
```

In our paper the coefficients are labeled as $B_{2:1}$ and $B_{3:1}$ and the other coefficients are computed as contrasts of the vector $(B_{2:1} \ B_{3:1})$. These contrasts are computed in the estimate statements. However, the SAS ODS provides the coefficients in the order $B_{3:1}$ then $B_{2:1}$. Thus, the coefficients in each in each row of the transformation matrix for each estimate must be reversed from what is presented in the text in order to obtain the other coefficients as a function of $(B_{3:1} \ B_{2:1})$.

Additional statements then compute the tests of the three hypotheses.

```
Data h1 h2 h3; set betas;
keep estimate cov1 cov2;
If StmtNo = 1 and Label = "H01" then output h1;
If StmtNo = 1 and Label ne "H01" then output h1;
If StmtNo = 2 and Label = "H02" then output h2;
If StmtNo = 2 and Label ne "H02" then output h2;
If StmtNo = 3 and Label = "H03" then output h3;
If StmtNo = 3 and Label ne "H03" then output h3;

%macro domore;
PROC IML;
  USE &dsin;
  READ ALL INTO Xin ; ** estimates in first column, covariances in next 2 columns;
  betas = Xin[1:2, 1];
  covin = Xin[1:2, 2:3];
  expb = exp(betas);
  J = J(1, 2, 1);
  stat = J*expb -2;
```

```

HROthervj = J*expb/2;
HRjvothervj = 1/HROthervj; **** approximate;
vstat = expb'*covin*expb;
c2d = stat**2/vstat;
df = 1;
P2={1} - PROBCHI(C2D, 1);    *** 2-sided p;
print "&dsin" HROthervj stat vstat c2d df p2;
quit; run;
%mend domore;

title test of h1; %let dsin=h1; %domore; run;
title test of h2; %let dsin=h2; %domore; run;
title test of h3; %let dsin=h3; %domore; run;

```

7 Testing One vs. the Others Combined in a Cox PH Model with Four Groups

Consider the case of $K = 4$ groups for a time-to-event outcome. The elementary hypotheses for comparing each group versus the others combined are given by

$$H_{01} : \exp\{\beta_{2:1}\} + \exp\{\beta_{3:1}\} + \exp\{\beta_{4:1}\} = 3 \quad (1)$$

$$H_{02} : \exp\{\beta_{1:2}\} + \exp\{\beta_{3:2}\} + \exp\{\beta_{4:2}\} = 3 \quad (2)$$

$$H_{03} : \exp\{\beta_{1:3}\} + \exp\{\beta_{2:3}\} + \exp\{\beta_{4:3}\} = 3 \quad (3)$$

$$H_{04} : \exp\{\beta_{1:4}\} + \exp\{\beta_{2:4}\} + \exp\{\beta_{3:4}\} = 3. \quad (4)$$

Let $\beta_{(1)} = (\beta_{2:1} \ \beta_{3:1} \ \beta_{4:1})^T$. Then fitting a Cox PH model with group 1 as the reference group yields an estimate $\hat{\beta}_{(1)}$ for $\beta_{(1)}$ along with a consistent estimate of its variance-covariance matrix, denoted by $\Sigma_{(1)}$. Note that the estimate $\hat{\beta}_{(2)}$ for $\beta_{(2)} = (\beta_{1:2} \ \beta_{3:2} \ \beta_{4:2})^T$ is obtained as

$$\hat{\beta}_{(2)} = \begin{bmatrix} -1 & 0 & 0 \\ -1 & 1 & 0 \\ -1 & 0 & 1 \end{bmatrix} \cdot \hat{\beta}_{(1)}. \quad (5)$$

Let

$$f(\beta_{(1)}) = \begin{pmatrix} \exp\{\beta_{2:1}\} + \exp\{\beta_{3:1}\} + \exp\{\beta_{4:1}\} - 3 \\ \exp\{-\beta_{2:1}\} + \exp\{\beta_{3:1} - \beta_{2:1}\} + \exp\{\beta_{4:1} - \beta_{2:1}\} - 3 \\ \exp\{-\beta_{3:1}\} + \exp\{\beta_{2:1} - \beta_{3:1}\} + \exp\{\beta_{4:1} - \beta_{3:1}\} - 3 \\ \exp\{-\beta_{4:1}\} + \exp\{\beta_{2:1} - \beta_{4:1}\} + \exp\{\beta_{3:1} - \beta_{4:1}\} - 3 \end{pmatrix}, \quad \beta_{(1)} = (\beta_{2:1}, \beta_{3:1}, \beta_{4:1}). \quad (6)$$

The gradient of f , denoted by ∇f has rows given by:

$$\begin{pmatrix} \exp\{\beta_{2:1}\}, \exp\{\beta_{3:1}\}, \exp\{\beta_{4:1}\} \\ -\exp\{-\beta_{2:1}\} - \exp\{\beta_{3:1} - \beta_{2:1}\} - \exp\{\beta_{4:1} - \beta_{2:1}\}, \exp\{\beta_{3:1} - \beta_{2:1}\}, \exp\{\beta_{4:1} - \beta_{2:1}\} \\ \exp\{\beta_{2:1} - \beta_{3:1}\}, -\exp\{-\beta_{3:1}\} - \exp\{\beta_{2:1} - \beta_{3:1}\} - \exp\{\beta_{4:1} - \beta_{3:1}\}, \exp\{\beta_{4:1} - \beta_{3:1}\} \\ \exp\{\beta_{2:1} - \beta_{4:1}\}, \exp\{\beta_{3:1} - \beta_{4:1}\}, -\exp\{-\beta_{4:1}\} - \exp\{\beta_{2:1} - \beta_{4:1}\} - \exp\{\beta_{3:1} - \beta_{4:1}\} \end{pmatrix}. \quad (7)$$

Then intersection hypotheses can be tested using their corresponding rows of f and ∇f .

For example, the intersection hypothesis $H_{01} \cap H_{02}$ corresponds to the first two rows of f . Using the delta method, $H_{01} \cap H_{02}$ can be tested using

$$f_{12}(\hat{\beta}_{(1)})^T \cdot \left(\nabla f_{12}(\hat{\beta}_{(1)}) \cdot \Sigma_{(1)} \cdot \nabla f_{12}(\hat{\beta}_{(1)})^T \right)^{-1} \cdot f_{12}(\hat{\beta}_{(1)}), \quad (8)$$

which under the null follows a chi-square distribution with $2\text{-}df$, where f_{12} and ∇f_{12} , denote the first two components of the function f and its gradient ∇f , respectively. One can show that any intersection of three individual hypotheses is equivalent to the joint hypothesis $\beta_{2:1} = \beta_{3:1} = \beta_{4:1} = 0$ which can be tested using a test with $3\text{-}df$ using the last 3 rows of f and ∇f as in (8).

8 Additional R Program for a Cox Model for Three Groups

In addition, the following pages display the program Cox3group.Rnw that is a Latex document with embedded R program code that applies the closed-versus-others testing to a simulated data set using a Cox PH model for three groups. Copy the contents into a text document and change the file type to .Rnw and place it in a folder. Download the Sweave.sty file and save it in the same folder as the .Rnw program.

To run the program, submit the following two lines in the R terminal:

```
\quad setwd("PATH TO FOLDER CONTAINING THE PROGRAM ")
\quad Sweave("Cox3group.rnw",syntax="SweaveSyntaxNoweb")
```

Note that R uses / as a delimiter rather than the usual \.

This will generate a .tex file that you can then compile to get the pdf output file. The contents of this output file are also presented below.


```

%Cox3group.Rnw
\documentclass[12pt]{article}

\usepackage{amsmath}
\usepackage[noae]{Sweave}
\usepackage{amscd}
\usepackage[tableposition=top]{caption}
\usepackage{ifthen}
\usepackage{color}
\SweaveOpts{echo=FALSE}
\usepackage[margin=0.93in]{geometry}

\begin{document}
\SweaveOpts{concordance=TRUE}

\title{Closed Testing of Each Group Versus the Others
Combined in a Multiple Group Analysis}
\author{John M. Lachin, Ionut Bebu\\
\vspace{0.4cm}
\texttt{ibebu@bsc.gwu.edu}}
\maketitle
%\tableofcontents

\abstract{A time-to-event example using simulated data is
presented in R.}
%Utils
<<utils>>=
library(MASS)
tt = Sys.time()
library(survival)
library(car)
@

\section{Main}

\begin{itemize}
\item{Consider  $K=3$  groups and generate exponentially
distributed time-to-event data with  $n=200$  participants per
group (for a total of 600 participants),  $\alpha=1$ ,  $\beta_{2:1}
=\log(1.3)$  and  $\beta_{3:1}=\log(0.7)$ , and administrative
censoring at  $t_0=0.5$ .
<<generate data>>=
generate_data_function = function(n,a,b21,b31)
{
  set.seed(1234)
  r_a = exp(a)
  r_b21 = exp(a + b21)
  r_b31 = exp(a + b31)

  aa = data.frame(Y = c(rexp(n,r_a),rexp(n,r_b21),rexp
(n,r_b31)),

```

```

      G = as.factor(c(rep(1,n),rep(2,n),rep(3,n)))
      c_ind = which(aa$Y>0.5)
      aa$Y[c_ind] = 0.5
      aa$C = 1
      aa$C[c_ind] = 0
      aa
    }

aa = generate_data_function(n=200,a=1,b21=log(1.3),b31=log(0.7))
@
}
  \item{Look at the first five rows of the data:
<<look at the first five rows>>=
#   aa$G = as.factor(aa$G)
    aa[1:5,]
@
$Y$ is the time-to-event or censoring outcome, $G$ is group (with
three levels), and $C$ is censoring (1=event, 0=censoring).
}
  \item{Fit a Cox model and get the estimates for  $\beta_{2:1}$ 
and  $\beta_{3:1}$  and their variance-covariance matrix:
<<fit Cox model>>=
  m = coxph(Surv(Y,C) ~ G, data=aa)
  summary(m)$coeff
  list(beta_23_1=coef(m),Sigma_23_1=vcov(m))
@
}
  \item{Likewise, get the estimates and their variance-
covariance matrix for  $\beta_{1:2}$ ,  $\beta_{3:2}$  and  $\beta_{1:3}$ ,
 $\beta_{2:3}$ 
<< vs two>>=
  A2 = rbind(c(-1,0),c(-1,1))
  A3 = rbind(c(0,-1),c(1,-1))

  list(beta_13_2=A2%%coef(m),Sigma_13_2=A2%%vcov(m)%%t(A2))
  list(beta_12_3=A3%%coef(m),Sigma_12_3=A3%%vcov(m)%%t(A3))
@
}
  \item{These estimates and their variance-covariance matrices
were obtained by matrix manipulations from the Cox model fit with
 $G=1$  as the reference group. One can check the results for
 $\beta_{1:2}$ ,  $\beta_{3:2}$  by fitting the Cox model using  $G=2$ 
as the reference group:
<<check vs two>>=
  m2 = coxph(Surv(Y,C) ~ relevel(G,ref="2"), data=aa)
  list(beta_13_2=coef(m2),Sigma_13_2=vcov(m2))
@
}
  \item{Consider the null hypothesis:
\begin{equation}\label{null}
\exp(\beta_{2:1})+\exp(\beta_{3:1})=2\,,.
\end{equation}
```

Using the delta method, run the unadjusted test for ([\ref{null}](#)) and obtain the p-value (p_{value}), $\exp(\hat{\beta}_{2:1}) + \exp(\hat{\beta}_{3:1}) - 2$ (difference) and its standard error (SE):

```
<<tests>>=
single_test_function = function(mu,Sigma)
{
  A = diag(exp(mu))
  est = sum(exp(mu)) - 2
  #ste = sqrt(c(1,1)%*%A%*%Sigma%*%t(A)%*%c(1,1))
  ste = sqrt(exp(mu)%*%Sigma%*%exp(mu))
  c(p_value=2*(1-pnorm(abs(est/ste))),difference=est,SE=ste)
}
single_test_function(coef(m),vcov(m))
@
}
\item{The same for testing
\begin{equation}\label{null2}
\exp(\beta_{1:2})+\exp(\beta_{3:2})=2\,,.
\end{equation}
<<test two>>=
single_test_function(c(A2%*%coef(m)),A2%*%vcov(m)%*%t(A2))
@
and for
\begin{equation}\label{null3}
\exp(\beta_{1:3})+\exp(\beta_{2:3})=2\,,.
\end{equation}
<<test three>>=
single_test_function(c(A3%*%coef(m)),A3%*%vcov(m)%*%t(A3))
@
}
\item{Now test (\ref{null}) and report the \it adjusted p-values (i.e., adjusted for also testing group 2 vs. groups 1 \& 3 combined, and group 3 vs. groups 1 \& 2 combined):
<<multiplicity>>=
#linear.Hypothesis(m1,c(0,1,1))
pp = c(single_test_function(coef(m),vcov(m))[1],
single_test_function(c(A2%*%coef(m)),A2%*%vcov(m)%*%t(A2))
[1],
single_test_function(c(A3%*%coef(m)),A3%*%vcov(m)%*%t(A3))
[1])
p_all = linearHypothesis(m,rbind(c(1,0),c(0,1)))[[4]][2]

res = c(Unadjusted=pp[1],
Bonferroni=p.adjust(pp, method=c("bonferroni"))[1],
Holm=p.adjust(pp, method=c("holm"))[1],
Hommel=p.adjust(pp, method=c("hommel"))[1],
Joint=p_all)
out = c(res)
names(out) = c
("Unadjusted","Bonferroni","Holm","Hommel","Joint")
round(out,digits=c(4,4,4,4,4))
```

@
 The "Joint" p-value corresponds to the 2 DF test for $\beta_{2:1} = \beta_{3:1} = 0$. While the joint hypothesis $\beta_{2:1} = \beta_{3:1} = 0$ is rejected ($p < 0.0001$), the unadjusted p-value for testing ($\text{\ref{null}}$) is larger than 0.05, so the closed testing procedure fails to reject ($\text{\ref{null}}$). All adjustments yield p-values larger than 0.05.

Note that the true $\beta_{2:1}$ and $\beta_{3:1}$ values correspond to the null hypothesis ($\text{\ref{null}}$).

```
\end{itemize}

%\begin{thebibliography}{99}

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```

Closed Testing of Each Group Versus the Others Combined in a Multiple Group Analysis

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Abstract

A time-to-event example using simulated data is presented in R.

1 Main

- Consider $K = 3$ groups and generate exponentially distributed time-to-event data with $n = 200$ participants per group (for a total of 600 participants), $\alpha = 1$, $\beta_{2:1} = \log(1.3)$ and $\beta_{3:1} = \log(0.7)$, and administrative censoring at $t_0 = 0.5$.
- Look at the first five rows of the data:

```
      Y G C
1 0.500000000 1 0
2 0.090777520 1 1
3 0.002421367 1 1
4 0.500000000 1 0
5 0.142436512 1 1
```

Y is the time-to-event or censoring outcome, G is group (with three levels), and C is censoring (1=event, 0=censoring).

- Fit a Cox model and get the estimates for $\beta_{2:1}$ and $\beta_{3:1}$ and their variance-covariance matrix:

```
      coef exp(coef) se(coef)      z Pr(>|z|)
G2  0.3188619 1.3755613 0.1130170  2.821362 0.004782025
G3 -0.3290651 0.7195962 0.1217573 -2.702632 0.006879289
```

```
$beta_23_1
      G2      G3
0.3188619 -0.3290651
```

```
$Sigma_23_1
      G2      G3
G2 0.012772845 0.006668631
G3 0.006668631 0.014824831
```

- Likewise, get the estimates and their variance-covariance matrix for $(\beta_{1:2}, \beta_{3:2})$ and $(\beta_{1:3}, \beta_{2:3})$

```
$beta_13_2
      [,1]
[1,] -0.3188619
[2,] -0.6479269

$Sigma_13_2
      [,1]      [,2]
[1,] 0.012772845 0.006104214
[2,] 0.006104214 0.014260414

$beta_12_3
      [,1]
[1,] 0.3290651
[2,] 0.6479269

$Sigma_12_3
      [,1]      [,2]
[1,] 0.01482483 0.00815620
[2,] 0.00815620 0.01426041
```

- These estimates and their variance-covariance matrices were obtained by matrix manipulations from the Cox model fit with $G = 1$ as the reference group. One can check the results for $(\beta_{1:2}, \beta_{3:2})$ by fitting the Cox model using $G = 2$ as the reference group:

```
$beta_13_2
relevel(G, ref = "2")1 relevel(G, ref = "2")3
      -0.3188619      -0.6479269

$Sigma_13_2
      relevel(G, ref = "2")1 relevel(G, ref = "2")3
relevel(G, ref = "2")1      0.012772845      0.006104214
relevel(G, ref = "2")3      0.006104214      0.014260414
```

- Consider the null hypothesis:

$$\exp(\beta_{2:1}) + \exp(\beta_{3:1}) = 2. \quad (1)$$

Using the delta method, run the unadjusted test for (1) and obtain the p-value (*p_value*), $\exp(\hat{\beta}_{2:1}) + \exp(\hat{\beta}_{3:1}) - 2$ (*difference*) and its standard error (*SE*):

```
p_value difference      SE
0.6539053 0.0951575 0.2122424
```

- The same for testing

$$\exp(\beta_{1:2}) + \exp(\beta_{3:2}) = 2. \quad (2)$$

```
p_value      difference      SE
1.333006e-09 -7.498949e-01 1.236763e-01
```

and for

$$\exp(\beta_{1:3}) + \exp(\beta_{2:3}) = 2. \quad (3)$$

p_value	difference	SE
0.0002205703	1.3012421362	0.3522381368

- Now test (1) and report the *adjusted* p-values (i.e., adjusted for also testing group 2 vs. groups 1 & 3 combined, and group 3 vs. groups 1 & 2 combined):

Unadjusted	Bonferroni	Holm	Hommel	Joint
0.6539	1.0000	0.6539	0.6539	0.0000

The "Joint" p-value corresponds to the 2 DF test for $\beta_{2:1} = \beta_{3:1} = 0$. While the joint hypothesis $\beta_{2:1} = \beta_{3:1} = 0$ is rejected ($p < 0.0001$), the unadjusted p-value for testing (1) is larger than 0.05, so the closed testing procedure fails to reject (1). All adjustments yield p-values larger than 0.05.

Note that the true $\beta_{2:1}$ and $\beta_{3:1}$ values correspond to the null hypothesis (1).