SEVERITY ANALYSIS USING RIDITS

Mary A. Marion, U.S. EPA

Abstract.

The United States Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances, Office of Pesticide Programs has been given the task of reviewing chemical registrant data and analyses some of which use the statistical technique of ridits. The technique of ridit analysis used in severity analysis was studied for its feasibility for use at the EPA. The two data sets chosen were that of one study evaluating the severity of glomerulonephropathy in male rat kidneys with dose increments of the chemical being reviewed and another of mononuclear cell leukemia, also in male rats.

Introduction.

This is in response to a request for computer validation of a ridit analysis done by hand. A generic SAS program to calculate the ridits, mean ridits by group, the overall population mean ridit and a chi-square statistic to test hypotheses of no dose difference with respect to the control dose was developed for use with multiple dose levels. The reference group was the population although the control group can also be specified.

Two data sets were examined. The evaluation of severity of glomerulonephrophy in male rat kidneys with dose increments of the pesticide X and a second evaluation of severity of mononuclear cell leukemia with dose increments of the pesticide Y were reported.

On the basis of the severity distributions in Tables 1 and 2, a statistical analysis by means of RIDIT (Relative to an Identified Distribution -developed by Bross, 1958) analysis was calculated for each dose group in terms of its weighted ordered severity score. This score is called the mean ridit for a dose group.

Ridit analysis is a way of making comparisons among different samples of the endpoint selected by intervals. The endpoint selected in this study is the number of animals falling into severity codes (no disease, minimum, mild, moderate, and severe) by dose group samples. The intervals consist of the severity codes.

The primary sampling unit is an animal, from it is determined a level of severity based upon a continuous random variable which is divided into ordinal categories. Associated with each animal from the identified distribution is a numerical quantity (ridit) which is a measure of degree of injury. The ridit calculated for the jth severity code is the proportion of all animals from the reference group falling at or below the midpoint of the jth severity code. The reference group is a composite of all the dose groups.

A dose level's MEAN RIDIT is an estimate of the probability that a randomly selected animal from it has a value on the underlying continuous variable greater than or equal to the value for a randomly selected animal from the control group (Fleiss, 1986, p.81). It is an estimate of the chance that an animal in a given dose group is "worse off" than an animal in the reference group.

The pairwise comparison of mean RIDITS of control and each dose group is evaluated by a chi-square statistic modified for the number of ties associated with
each severity code.

**Analysis of Severity.**

**TABLE 1**

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>GRP1</th>
<th>GRP2</th>
<th>GRP3</th>
<th>GRP4</th>
<th>ONE</th>
<th>RIDIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>21</td>
<td>0.03666</td>
</tr>
<tr>
<td>minimum</td>
<td>20</td>
<td>25</td>
<td>16</td>
<td>13</td>
<td>74</td>
<td>0.20139</td>
</tr>
<tr>
<td>mild</td>
<td>21</td>
<td>13</td>
<td>18</td>
<td>13</td>
<td>65</td>
<td>0.44271</td>
</tr>
<tr>
<td>moderate</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>14</td>
<td>56</td>
<td>0.65278</td>
</tr>
<tr>
<td>severe</td>
<td>10</td>
<td>15</td>
<td>19</td>
<td>26</td>
<td>72</td>
<td>0.87500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RBAR1</th>
<th>RBAR2</th>
<th>RBAR3</th>
<th>RBAR4</th>
<th>POPRIDIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.45419</td>
<td>0.46161</td>
<td>0.49867</td>
<td>0.58553</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Group1 vs Group2

<table>
<thead>
<tr>
<th>Degrees</th>
<th>Scheffe of ChiSquare</th>
<th>Freedom</th>
<th>p_value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.025126</td>
<td>3</td>
<td>0.99695</td>
</tr>
</tbody>
</table>

Group1 vs Group3

<table>
<thead>
<tr>
<th>Degrees</th>
<th>Scheffe of ChiSquare</th>
<th>Freedom</th>
<th>p_value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.99525</td>
<td>3</td>
<td>0.82657</td>
</tr>
</tbody>
</table>

Group1 vs Group4

<table>
<thead>
<tr>
<th>Degrees</th>
<th>Scheffe of ChiSquare</th>
<th>Freedom</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.81355</td>
<td>3</td>
<td>0.05026</td>
</tr>
</tbody>
</table>

The mean ridit (rbar1) of .45419 is an indication of the probability that a randomly selected subject from group 1 (the control group) will have a more extreme value than a randomly selected animal from the reference group. Since this number is less than .5, we would infer that its animals tend to have less extreme values than the subjects of the reference group.

The mean ridit for group 4 is .58553 and is the probability that a randomly selected animal from it has a value indicating greater severity or seriousness than a randomly selected individual from the standard group.

The evaluation of severity of glomerulonephropathy in male rat kidneys with dose increments of the pesticide X resulted in a statistically significant difference in the comparison of the controls and the highest dose group (1250 ppm) at the 10% level. The actual p_value was .050026.
### TABLE 2

**MONONUCLEAR CELL LEUKEMIA ANALYSIS - PESTICIDE Y**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>SEVERITY</th>
<th>CODE0</th>
<th>CODE1</th>
<th>CODE2</th>
<th>CODE3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GRP1</td>
<td>39</td>
<td>30</td>
<td>29</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>GRP2</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>GRP3</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>ONE</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>RIDIT</td>
<td>0.32667</td>
<td>0.69000</td>
<td>0.78000</td>
<td>0.91667</td>
</tr>
</tbody>
</table>

|            | RBAR1    | 50    | 50    | 50    | 150   |
|            | RBAR2    |       |       |       |       |
|            | RBAR3    |       |       |       |       |
|            | POFRIDIT | 0.43287 | 0.52633 | 0.5408 | 0.5   |

**Group 1 vs Group 2**

<table>
<thead>
<tr>
<th>Degrees</th>
<th>Degrees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheffe</td>
<td>ChiSquare</td>
</tr>
<tr>
<td>3.88969</td>
<td>2</td>
</tr>
</tbody>
</table>

**Group 1 vs Group 3**

<table>
<thead>
<tr>
<th>Degrees</th>
<th>Degrees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheffe</td>
<td>ChiSquare</td>
</tr>
<tr>
<td>5.08331</td>
<td>2</td>
</tr>
</tbody>
</table>

The mean ridit (rbar1) of .43287 is an indication of the probability that a randomly selected subject from group 1 (the control group) will have a more extreme value than a randomly selected animal from the reference group. Since this number is less than .5, we would infer that its animals tend to have less extreme values than the subjects of the reference group.

The mean ridit for group 4 is .5408 and is the probability that a randomly selected animal from it has a value indicating greater severity or seriousness than a randomly selected individual from the reference group.

The evaluation of severity of mononuclear cell leukemia in male rats with dose increments of pesticide Y (Data Set 2) resulted in a statistically significant difference in the comparison of the controls and the highest dose group at the 10% level. The actual p_value was .078736 insignificant at the 5% level.

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**Mathematical Background with an Example.**

Bross [1958] has developed the use of Ridit analysis for ordered but not interval scaled data such as injury severity categories. Ridit analysis is primarily a test of differences in location.

We know that a given percentile is that value which divides the range of a set of data into two parts such that a given percentage of the measures lies below this value. It is therefore a probability. Ridit analysis transforms ordinal data to a probability scale. The ridit score for each category is a percentile rank of a subject in the reference population and is equal to the number of subjects in all lower categories plus one-half the number of items in the subject category, all divided by the population size. The score (ridit) given to a
severity category is the relative frequency up to the midpoint of that category in the reference group.

Once the ridits for each category have been determined, they are considered as a dependent variable for the other groups to which it is compared and the usual normal probability distribution family of statistics can be applied in calculating means, standard deviations etc. The mean ridits calculated in this way will be approximately normal for reasonable sample sizes.

The mean ridit for the comparison group is determined as follows. If an item X, is selected at random from the reference population (control group) and an item Y, is selected at random from the comparison group, then the mean ridit is an estimate of P(X≤Y), that is, of the probability that X is less seriously injured than Y. The control group mean ridit is always .5 under this definition.

Let the reference group be group 1. This is in conformance to the SAS program RIDITS referenced in the bibliography. Let \( P_{ij} \) be the proportion in severity category \( j=1,...,k \) of the group \( i \) and define the ridit for a severity category by

\[
R_j = \sum_{n=1}^{j-1} \frac{P_{nj}}{P_{nj} + P_{nj}/2}.
\]

If \( X \) denotes the injury severity for a subject selected at random from the reference population, and \( Y \) denotes the injury severity for a subject within a particular group (dose), then the mean ridit for that group (dose)

\[
\bar{R}_i = \sum_{j=1}^{k} R_j P_{ij}
\]

can be interpreted as an estimate that a subject from the reference group would be in a less severe severity classification code than a dosed subject. More precisely,

\[ \bar{R}_i \text{ estimates } P[X<Y] + \frac{1}{2} P[X=Y] \]

The standard error of the mean ridit of a group of size \( N \) is approximately (Fleiss, 1967, p.105)

\[ \text{S.E.}(\bar{R}_i) = \frac{1}{2\sqrt{N_i}} \]

The population mean ridit \( \bar{R} \) is calculated as

\[ \bar{R} = \sum \frac{\bar{R}_i N_i}{\sum N_i} \]

It is the probability that for a subject selected at random from the population the subject would be in a less severe severity code level than a subject which has been dosed by a pesticide. Comparisons on the basis of mean ridits have used t-tests and analysis of variance.

RIDITS output for the above theoretical problem adapted from Scott et al. and presented by Jairus D. Flora, Jr. in the Encyclopedia of Statistical Sciences
is given in Table 3. Replacing the control dose group is the nonbelted group entered as group one to conform with the SAS macro RIDITS.SAS. It is used as the reference group in computing the ridits as opposed to combining the groups within each of the severity categories. Each method will yield different results.

TABLE 3

<table>
<thead>
<tr>
<th>Injury Severity</th>
<th>Restraint Use</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEVERITY</td>
<td>GRP1</td>
<td>GRP2</td>
</tr>
<tr>
<td>none</td>
<td>minor</td>
<td>357</td>
<td>417</td>
</tr>
<tr>
<td>minor</td>
<td>moderate</td>
<td>540</td>
<td>330</td>
</tr>
<tr>
<td>moderate</td>
<td>serious</td>
<td>53</td>
<td>33</td>
</tr>
<tr>
<td>serious</td>
<td></td>
<td>35</td>
<td>17</td>
</tr>
</tbody>
</table>

\[ \text{Rbar}_1 = 0.41815 \quad \text{Rbar}_2 = 0.46339 \quad \text{P} = 0.0288 \]

In this analysis the reference group was taken to be the non seatbelt users. The mean ridit \( \text{Rbar}_i \) is an indication that a randomly selected subject from group \( i \) will have a more extreme value (greater severity) than a randomly selected subject from the reference group.

\[ \text{Rbar}_1 = 0.500 \rightarrow \text{a randomly chosen subject in the control group of non seat belt users is equally likely to be in a more severe injury category than the reference group.} \]

\[ \text{Rbar}_2 = 0.418 \rightarrow \text{the seat belt users are less likely to be in a more severe injury category than the reference group of non seat belt users. If I look at the population as a whole, a randomly selected subject will be in a more severe injury category with probability of 0.46339.} \]

A chi-square statistic expressing the statistical significance of the difference between seat and non seat belt users is very significant with a p-value of 3x10^-11.

The seat belt users are less likely to be in a more severe injury category than the reference group making the use of seat belts more attractive to the public.

SAS Code.

The SAS code developed to analyze the above data sets is below. Both call a macro ridits for the ridit analysis. Inputs to the macro are explained in the beginning of the macro itself.
Posters

Data set #1.

%let mtitle=\n%str(GLOMERULONEPHROPATHY SEVERITY ANALYSIS -PESTICIDE X));
%let compgrp=2;
%let one=sum(of Grpl-Grp&nogrp);

data d;
input severity $ Grp1-Grp&nogrp @@;
one=x=one;
cards;
none 05 05 07 04
minimum 20 25 16 13
mild 21 13 18 13
moderate 16 14 12 14
severe 10 15 19 28
;
%ridits(d,&nogrp,&codeno,&mtitle,&one);

Data set #2

%let mtitle=\n%str(MONONUCLEAR CELL LEUKEMIA SEVERITY ANALYSIS -Data Set 2);
%let compgrp=2;
%let one=sum(of Grpl-Grp&nogrp);

data d;
input severity $ Grp1-Grp&nogrp @@;
one=x=one;
cards;
code0 39 30 29
code1 04 05 02
code2 02 05 09
code3 05 10 10
;
%ridits(d,&nogrp,&codeno,&mtitle,&one);

Seatbelt Analysis of 1974 Cars

%let mtitle=\n%str(Injury Severity for Belted and Nonbelted Occupants of 1974 Cars);
%let one=Grpl;

data d;
input severity $ Grpl-Grp&nogrp @@; one=one; cards: none 357 417 minor 540 330 moderate 53 33 serious 35 17 ;

%ridits(d,&nogrp,&codeno,&mtitle,&one);

%macro ridits(dsname,nogrp,codeno,mtitle,one);

/***************************************************************************
 */ A RIDIT ANALYSIS
 */ Written by Mary A. Marion while at the U.S. EPA, July 22, 1995
 */
 */ References:
 */
 */ Fleiss, Joseph L. (1973)
 */ Statistical Methods for Rates and Proportions, 102-108
 */
 */ Fleiss, Joseph L. (1986)
 */ The Design and Analysis of Clinical Experiments, 76-90
 */
 */ Kotz, Samuel, Johnson, Norman L. And Read, Campbell B. (1982),
 */ Encyclopedia of Statistical Science, V8, pages 136-139,
 */
 */ SAS Language Reference v6 First Edition, 491
 */
 */ Macros called: dosums, mmeans2, loop, mout, compgrp
 */
 */ Inputs:
 */
 */ NOGRP = Number of groups
 */ CODENO = No of severity codes (levels)
 */ MTITLE = title of the experiment
 */ DSNAME = Input data matrix of severity codes by group
 */ ONE = reference population
 */
 */ Constraints:
 */
 */ Scheffé-type comparisons between groups always compare to Grpl.
 */ Thus always enter the control group as Grpl
 */
***************************************************************************/

data d; set &dsname;
one=one;
two=one/2;

/* THREE (Column 3) Computation */
proc transpose data=d out=td; var one; run;
%dosums(&codeno);
proc transpose data=td out=td2; var sum1-sum&codeno; run;
data ridit; merge td2 d; rename col=three;
keep severity one two coll dum Grpl-Grp\&nogrp;
dum=1;
run;

/* RIDIT Calculations */
%mmeans2(ridit,one,sum);
data ridit; merge ridit meansout; by dum;
data ridit; set ridit; drop sum;
sun=0=sum;
four=two+three;
ridit=four/sum0;

/* CONTROL Group Calculations */
data ridit; set ridit;
product1=Grpl*ridit;
%mmeans2(ridit,Grpl,sum);
data ridit; merge ridit meansout; by dum;
data ridit; set ridit; drop sum;
sun=0;

%mmeans2(ridit,product1,sum);
data calculat; merge ridit meansout; by dum;
data calculat; set calculat; drop sum;
sun=0;
rbar1=sun/prod1; run;
proc print data=calculat noobs;
var one two three four ridit product1 sunsun pro1 rbar1;
title2 'Calculations -Group 1';
run cancel;

/* OTHER Group Calculations */
&loop;

/* Output of Basic Table */
proc print data=calculat noobs;
var severity Grpl-Grp\&nogrp; run cancel;
title &mtitle;
options formdlim=' ' nonumber;
title;

/* Output of Basic Ridit Calculations */
proc print data=calculat noobs;
var one two three four ridit; run cancel;
%mout;

/* OUTPUT of table of dose group X severity levels +
ridits for the severity categories */
options formdlim='';
options nonumber;
proc print data=calculat noobs;
var severity grpl-grp\&nogrp one ridit;
sun grpl-grp\&nogrp one;
title &mtitle; run;

/* CALCULATION OF POPULATION MEAN RIDIT */
/* Step 1  CDF type calculations of group totals */
data calculat; set calculat;
%macro total(nogrp);
/ * Step 2  Computing group totals and putting them into new3 as max&j */
%macro total2;
%local j;
%do j=1 %to &nogrp;
%means2(calculat,total&j,max); run;
data new&j; set meansout;
keep max; rename max=max&j; run;
%end;
data new3;
merge %do j=1 %to &nogrp;
new&j %end; ;
%mend;
%total2;

proc transpose data=new3 out=new3out; run;
data new3out; set new3out; keep coll;
rename coll=grpwts;
run;

/* another way of doing ...*/
data calculat; set calculat;
retain total1 0;
total1=sum(total1,grpl); */
data new; set calculat; keep rbar1-rbar&nogrp;
if _n_ eq 1 then output; run;
data new2; set new;
proc transpose data=new2 out=newout; run;
data newout; set newout; keep coll;
rename coll=rbars; run;
data allout; merge new newout new3out;
proc means data=allout mean noprint;
var rbars;
weight grpwts;
output out=allouto mean=PopRidit;
run;
data new; merge new allouto;
keep rbar1-rbar&nogrp PopRidit;
run;

/* OUTPUT of rbars + Population Mean Ridit */
options formdlim=' '; title;
proc print data=new noobs; run;

/* OUTPUT of Scheffe'-type Group Comparisons to the control group Grpl */
%macro generate(nogrp);
%do i=2 %to &nogrp;
%compgrp(\$i); %end;
%mend;
%generate(\$nogrp);

%mend;

%macro dosums(codeno);
/* start=3 always sum3(of coll-col2)
 stop = number of severity code levels + 1 */
options source mprint symbolgen;
%local i ii stop;
data td; set td; keep sum1-sum\$codeno;
sum1=0;
sum2=sum(coll);
%let stop=&codeno+1;
%do i=3 %to &stop;
 %do ii=i-2 %to i-2; %end;
sum&i=sum(of coll-col&ii);
%end;
options source mprint;
%mend;

%macro mmeans2(dsname, varlst, stat);
/* Written by Mary A. Marion while at the EPA - Nov'93 */
options nosource nomprint;
proc datasets library=work; delete meansout; run;
proc means data=&dsname noprint;
var &varlst;
output out=meansout
n=n nmiss=nmiss mean=mean std=std min=min max=max range=range
sum=sum var=var uuss=uss css=css stderr=stderr cv=cv
/* skewness=skewness kurtosis=kurtosis sumwgt=sumwgt */
t=t prt=prt;
run;
data meansout; set meansout;
dum=1;
keep &stat dum; run;
options source mprint;
%mend mmeans2;

%macro loop;
%local j;
%do j=2 %to \$nogrp;
%mmeans2(calculate,Grp&j,sum);
data calculate; merge calculate meansout by dum;
data calculate; set calculate; drop sum;
sum&j=sum;
product&j=Grp&j*ridit;
proc print data=calculate noobs;
var severity grp1-grp\$nogrp
 one two three four ridit
 product&j sum&j;
title2 "sum&j and product &j calculation"; run cancel;
%mmeans2(calculate,product&j,sum);
data calculat; merge calculat meansout; by dum;
data calculat; set calculat; drop sum;
sumprod&j=sum;
rbar&j=sumprod&j/sum&j;
proc print data=calculat noobs;
var severity Grp1-Grp&nogrp one two four ridit
  product1-product&j sum1-sum&j sumprod1-sumprod&j rbar1-rbar&j;
title2 "Calculations -&nogrp Groups";
run cancel;
%end;
%mend loop;

%macro mout;
%local j;
%do j=l %to &nogrp;
proc print data=calculat noobs:
var product&j sum&j sumprod&j rbar&j; run cancel;
%end;
%mend mout;

%macro compgrp(compgrp);
options nosource nomprint;
/* TIE Group and F Statistic Calculations */
/* Fleiss, Design and Analysis of Clinical Experiments page 77 (3.37) */
data fO; set calculat; keep dum tie ndot fnum1 fdenom1;
tie=grpl+qrp+compgrp;
ndot=sum1+sum+compgrp;
fnum1=tie*(tie-l)*(tie+l);
fdenom1=ndot*(ndot-l)*(ndot+l);
%mmeans2(fO,fnum1,sum);
data fO; merge fO meansout; by dum;
fnum=sum;
%mmeans2(fO,fdenom1,sum);
data fO; merge fO meansout; by dum;
fdenom=max;
data f; set fO; keep dum ndot fnum fdenom F;
if _N_ > l then delete;
F=1-(fnum/fdenom);
/* ChiSquare Calculation */
/* Fleiss, Design and Analysis of Clinical Experiments page 82 (3.43) */
data scheffe; merge new3 new f;
above=12 * max1 * max&compgrp * (rbar1-rbar&compgrp)**2;
below= ( max1 + max&compgrp + 1 ) * F;
Chi=above/below;
df=&nogrp-l;
p_value=1-probchi(Chi,df);
/* OUTPUT of Scheffe ChiSquare */
proc print data=scheffe split='*' noobs; var Chi df p_value;
label Chi="Scheffe ChiSquare" df='Degrees of Freedom' p_value='p_value' ;
title "Group1 vs Group&compgrp": run;

/* CALCULATION CHECKING */
options formdlim='';
proc print data=calculat;
var severity grpl-grp&nogrp one two three four ridit one
     product1-product&nogrp sum1-sum&nogrp sumprod1-sumprod&nogrp
     rbar1-rbar&nogrp tota11-total&nogrp;
title1 &mtitle; title2 'Calculation Checking': run cancel;

/* OUTPUT of calculations */
options formdlim='';
title1 &mtitle;
proc print data=f0; title2 'f0'; run cancel;
options formdlim='';
proc print data=f; title2 'f'; run cancel;
proc print data=scheffe; title2 "scheffe": run cancel;
%mend;

Acknowledgements.

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technical accuracy of this paper. My supervisor Hugh Pettigrew provided the
time to write the macros and test the techniques.

The analyses were done using SAS macros developed by the author using SAS 6.10 for
windows on a NEC workstation at the U.S. EPA.

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14, pages 18-38.

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pages 263-264.

Bross, Irwin D. J. (1956), Ridit Analysis of Automotive Crash Injuries, Cornell
University Medical College, Department of Public Health and Preventive Medicine,
Division of Automotive Crash Injury Research.

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