Generating Receiver Operating Characteristic (ROC) curve using SAS® Macros

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ABSTRACT

Early identification of responsiveness to treatments has significant clinical and economic implications. The Receiver Operating Characteristic (ROC) curve is a key tool for diagnostic test and has been used in identification of early clinical responses that could predict long-term outcomes. [1,2] Youden's Index is often used in conjunction with ROC analysis[3], and the maximum value of Youden's index may be used as a criterion for selecting the optimum cut-off point[4]. Based on the reported method[1,2], this paper illustrates how to generate ROC curves and Youden's index using SAS® Macros and simulated data. This visual method could help research scientist to estimate the predictive accuracy easily.

INTRODUCTION

Early improvements in disease activity have been associated with improved long-term clinical outcomes in methotrexate-treated rheumatoid arthritis patients, as well as patients with other autoimmune diseases. Early improvement in Psoriasis Area and Severity Index (PASI) can be evaluated as a predictor for a clinical response at a later time using Receiver Operating Characteristic (ROC) curve. ROC curve is based on univariate logistic regressions. [1,2] The area under the ROC curve (AUC-ROC) at different time points is used to assess overall predictability at each time point. Youden's Index is an important summary measure of the ROC curve. The index is defined for all points of an ROC curve, and maximizing it allows to find an optimal cut-off point independently from the prevalence. [4]

MATERIALS AND METHODS

Statistical Methods

Data for this analysis were generated from simulation according to the clinical trials reported[1,2] for patients with psoriasis. In general, patients are randomized to receive either placebo or active treatment at Weeks 0, 2, 4, 8, 12 of the induction phase.

Psoriasis Area and Severity Index (PASI) improvement at weeks 2, 4 and 6, 8, and 12 are collected. PASI improvement in early weeks of 2, 4, and 6 are used to predict PASI responses at Week 12. The overall utility of PASI improvements observed at Weeks 2, 4, and 6 for predicting a PASI75 response at Week 12 is evaluated using ROC curves based on univariate logistic regressions of PASI75 at Week 12 (dependent variable) and PASI improvements from baseline to Weeks 2, 4, and 6 (independent variable). The area under the ROC curve (AUC-ROC) at Weeks 2, 4, and 6 was used to assess overall predictability at each time point. Negative predictive value (NPV), positive predictive value (PPV), sensitivity, specificity, as well as Youden Index (YI), calculated at each percent of PASI improvement, are used to determine the range of PASI responses that had the greatest predictive value.

Statistical Measures
    1. **Sensitivity, Specificity, PPV and NPV**

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	With Disease	Without Disease	
Test Positive	True Positive (TP) A	False Positive (FP) B	A+B
Test Negative	False Negative (FN) C	True Negative (TN) D	C+D
	A+C	B+D	

> NPV is the probability of a patient won't have the disease given the test result is negative
> NPV = TN / (FN + TN) = D/(C+D)
> PPV is the probability of a patient will have the disease given the test result is positive
> PPV = TP / (TP + FP) = A/(A+B)
> Sensitivity is the probability of a test will be positive given a patient with the disease
> Sensitivity = TP/(TP+FN) = A/(A+C)
> Specificity is the probability of a test will be negative given a patient without the disease
> Specificity = TN/(TN+FP) = D/(B+D)

2. ROC
The ROC curve is created by plotting the Sensitivity against the 1-Specificity at various threshold settings.

3. Youden's Index
YI(c) = Sensitivity(c) + Specificity(c) -1

SAS Macros
The following four SAS Macros (LOGREG, COMBINE, ROCPLOT and YINDEX macros) show how we fitted the logistic regression model, manipulated the data table and prepared the ROC dataset, generated ROC curve, and generated Youden's Index table for plot gradually.

STEP 1: LOGREG macro - fits logistic regression to produce ROC data and classification table

%LOGREG (dv =, iv =, weeknum1 =, weeknum2 =, setnum =);

 where

dv   Dependent Variable PASI75 value at week12

iv   Independent Variable PASI percent change from baseline to week 2, 4 and 6

weeknum1 Week number 12 (the week to be predicted)

weeknum2 Week number 2, 4 or 6 (early responder week)

```
*********************************************************************************
ROC curves, optimal cutoff points of PASI percent improvement from baseline to week 2, 4 and 6 to
predict PASI75 at week 12
********************************************************************************;
%macro LOGREG(dv=,iv=,weeknum1=,weeknum2=,setnum=);
%put ***  Now executing macro LOGREG ***;
* Logistic regression to produce ROC data and classification table *;
* Input dataset basedata includes PASI percent improvement from baseline to week 2, 4 and 6 *;
ods listing close;
ods output association=auc oddsratios=or parameterestimates=pe;
```

```
proc logistic data=basedata descending;
    model &dv=&iv / outroc=rocdata;
run;
ods listing;

* Set macro values based on ROC data *;
proc sql noprint;
    select nvalue2 format 6.4 into :c
    from auc
    where label2='c';  *  c-Statistic  *;

    select oddsratioest format 5.3 into :o
    from or;  *  Odds ratio  *;

    select lowercl format 5.3 into :l
    from or;  *  Lower limit of odds ratio  *;

    select uppercl format 5.3 into :u
    from or;  *  Upper limit of odds ratio  *;

    select estimate into :est1-:est2
    from pe;  *  Estimates needed to convert probabilities back to percent improvement  *;
quit;

* Set all values needed for display based on ROC data *
data rocdata&setnum;
    length Time $100;
    set rocdata;
    _spec_=1-_1mspec_; *  Calculate specificity  *;
    prob=put(_prob_,6.4); *  Format probability  *;
    tp=compress(put(_pos_,best.)); *  Format true positive  *;
    tn=compress(put(_neg_,best.)); *  Format true negative  *;
    fp=compress(put(_falpos_,best.)); *  Format false positive  *;
    fn=compress(put(_falneg_,best.)); *  Format false negative *;
    sn=put(_sensit_,6.4); *  Format sensitivity  *;
    sp=put(1-_1mspec_,6.4); *  Format specificity  *;
    msp=put(_1mspec_,6.4); *  Format 1-specificity  *;
    diff_snsp=abs(input(substr(sp,1),6.4)-input(substr(sn,1),6.4));  *  Difference between sensitivity and
specificity  *;
    interc=&est1;
    xest=&est2;  *  Estimates needed to convert probabilities back to percent change  *;
    yindex=input(substr(sn,1),6.4)+input(substr(sp,1),6.4)-1; *  Calculate Youden's Index  *;
    if input(substr(tp,1),best.)+input(substr(fp,1),best.)^=0 then
        ppv = input(substr(tp,1),best.)/(input(substr(tp,1),best.)+input(substr(fp,1),best.)); *  Calculate ppv  *;
    ppred=put(ppv,6.4);
    if input(substr(tn,1),best.)+input(substr(fn,1),best.)^=0 then
        npv = input(substr(tn,1),best.)/(input(substr(tn,1),best.)+input(substr(fn,1),best.)); *  Calculate npv  *;
    npred=put(npv,6.4)
    if 0<input(substr(prob,1),6.4)<1 then
        pctchg = (log(input(substr(prob,1),6.4)/(1-input(substr(prob,1),6.4)))-interc)/xest; *  Calculate PASI
percent improvement  *;
    auc=&c; *  AUC  *;
    or=&o; *  Odds ratio  *;
    orlcl=&l; *  Lower limit of odds ratio  *;
    orucl=&u; *  Upper limit of odds ratio  *;
    pctchgwk=&weeknum2; *  Early responder week  *;
```

```sas
    pasi75wk=&weeknum1; * Week to be predicted  *;
    Time='PASI 75% Improvement at Week '||compress(put(pasi75wk,best.))||' [AUC:'||compress(put (auc,
6.4 ))||']';
    indexnum=&setnum;
 run;

proc sort data=rocdata&setnum out=sortroc;
    by indexnum yindex descending diff_snsp;
run;  *  Sort by ascending Youdens Index and descending difference between sensitivity & specificity  *;

data roccutpts&setnum;
  set sortroc;
  by indexnum yindex descending diff_snsp;
  if last.indexnum;  *  This is the optimal cutoffpoint based on max Youdens Index and smallest difference
between sensitivity & specificity  *;
  cuttype='OPT';
run;
%mend LOGREG;


*  PASI percent improvement to week 2, PASI75 at week 12  *;
% LOGREG (dv=pasi75_v8,iv=pasits_pctchgv2v4,weeknum1=12,weeknum2=2,setnum=1);
*  PASI percent improvement to week 4, PASI75 at week 12  *;
% LOGREG (dv=pasi75_v8,iv=pasits_pctchgv2v5,weeknum1=12,weeknum2=4,setnum=3);
*  PASI percent improvement to week 6, PASI75 at week 12  *;
% LOGREG (dv=pasi75_v8,iv=pasits_pctchgv2v6,weeknum1=12,weeknum2=6,setnum=5);
```

STEP 2: COMBINE macro - Combines and manipulates the datasets generated in LOGREG macro

```sas
%macro COMBINE;

%put **  Now executing macro 'combine'  **;
data final_roc;
  length time2 $200;
  set
   %do i=1 %to 6;
          rocdata&i
   %end;
  ;
  time2='PASI Change to Week '||compress(put(pctchgwk,best.))||', '||time; * Set additional time point for
'cutoff points' output *;
run;

data final_cutpts;
  length time2 $200 cutpoint $50;
  set
    %do i=1 %to 4;
          roccutpts&i
    %end;
  ;
  time2='PASI Change to Week '||compress(put(pctchgwk,best.))||', '||time; * Set additional time point for
'optimal cutoff points' output *;
  if cuttype='OPT' then cutpoint='Optimal ('||compress(put(round(pctchg),best.))||'% Improvement)';
run;
%mend COMBINE;


%COMBINE;
```

STEP 3: ROCPLOT macro – Generates ROC curves

% ROCPLOT (week =);

  Where

week the week number to be predicted

```
%macro ROCPLOT(week=);
proc sql noprint;
  select distinct auc into: auc_ separated by ' '
    from final_roc
    where pasi75wk=&week;
  quit;


%let auc2=%scan(&auc_,1,' ');
%let auc4=%scan(&auc_,2,' ');
%let auc6=%scan(&auc_,3,' ');

title;
footnote;
options nodate nocenter nonumber mautosource  missing=' ' mrecall formchar='|----|+|---+=|-/\<>*' ls =
133 ps = 47;
ods path show;
ods path(prepend) work.templat(update);

proc template;
  define style mystyle;
  style usertext from usertext /
    font=("Arial")
    protectspecialchars = off
    outputwidth=100%
    just=c
    backgroundcolor = white;
  end;
run;

options orientation=landscape papersize=("11in", "8.5in") leftmargin= "1.0 in" rightmargin="1.0 in"
        topmargin="1.0 in" bottommargin="1.0 in" nodate nonumber;
goptions reset=all device = emf  ftext=simplex ftitle=simplex cback = white ctext = black
        htext = 3.0 ymax=4in  xmax=11in vsize=5in hsize=5in htitle=2 gsflen=80 gunit = pct display
        gsfmode = replace noborder;

data anno;
    function='move'; xsys='1'; ysys='1'; x=0; y=0; output;
    function='draw'; xsys='1'; ysys='1'; color='black'; x=98; y=98; output;
run;

axis1 label=(h=3 a=90 j=c "Sensitivity") order = (0 to 1 by 0.1) value=(h=3 )  minor=none ;
axis2 label=(h=3 j=c "1-Specificity") order = (0 to 1 by 0.1)  value=(h=3 )  minor=none major=none;

legend1 label=none
```

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```
        value=(h=8 pt "Week 2 (AUC=&auc2)" "Week 4 (AUC=&auc4)" "Week 6 (AUC=&auc6)")
        position=(bottom right inside) down=3 mode=share;

   symbol  i=j c=cx82786f  l=1 h=2 w=2;
   symbol2 i=j c=cxd52b1e  l=1 h=2 w=2;
   symbol3 i=j c=cx263f6a  l=1 h=2 w=2;

title h=2 "PASI Percent Improvement from baseline to weeks 2, 4 and 6 (observed) to Predict PASI75 at
Week &week" ;

 proc gplot data=final_roc(where=(pasi75wk=&week));
      plot _sensit_*_1mspec_=pctchgwk/autovref
            cautovref=ltgray noframe anno=anno legend=legend1   vaxis=axis1 haxis=axis2;
 run;
 quit;
%mend ROCPLOT;

% ROCPLOT (week=12);
```
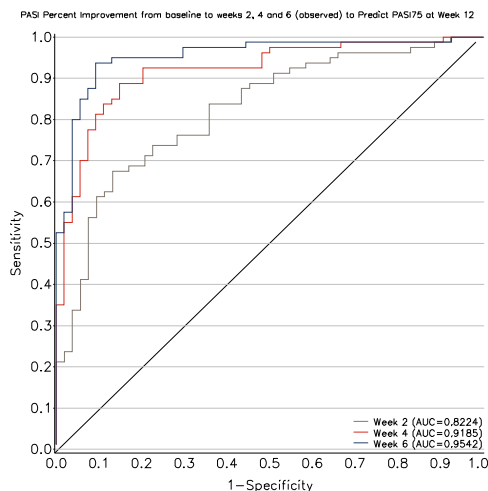
Below are the ROC plot generated from the ROCPLOT macro:

PASI Percent Improvement from baseline to weeks 2, 4 and 6 (observed) to Predict PASI75 at Week 12

- The accuracy of a test is measured by AUC (Area Under the Curve).

- AUC is the area between the curve and the x axis.

- The closer the curve goes to the top left corner, the more accurate the test.

- An area of 1 represents a perfect test, while an area of 0.5 represents a worthless test.

- Statistically, more area under the curve means that it is identifying more true positives while minimizing the number/percent of false positives.

STEP 4: YINDEX macro - Generates the dataset for the figures of Youden's Index, sensitivity, and specificity versus each percent of PASI improvement

% YINDEX (setnum =);

  where

setnum the same as in LOGREG macro

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```
%macro YINDEX (setnum = );
data yindex&setnum;
    merge final_roc(where=(indexnum=3) keep=time2 _sensit_ _spec_ yindex pctchg indexnum)
          final_cutpts(where=(indexnum=3 and cuttype='OPT') keep=time2 pctchg yindex indexnum
cuttype rename=(yindex=peak_Youden_Index pctchg=opt_cutpt));
    by time2;
    rename time2=time
    _sensit_=Sensitivity
    _spec_=Specificity
    yindex=Youden_Index
    pctchg=cutpt;
  drop indexnum cuttype;
run;
%mend YINDEX;
% YINDEX (setnum=1);
% YINDEX (setnum=2);
% YINDEX (setnum=3);
% YINDEX (setnum=4);
% YINDEX (setnum=5);
% YINDEX (setnum=6);
```
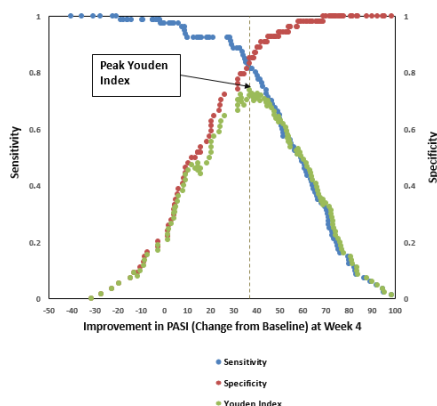
Here is part of one data table created by the YINDEX macro.

	time	Sensitivity	Specificity	Youden_Index	cutpt	peak_Youden_Inde	opt_cutpt
1	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.0125	1	0.0125	98.29224888716...	0.7394	32.66416258667...
2	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.025	1	0.024999999999...	94.838574793079	0.7394	32.66416258667...
3	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.0375	1	0.037500000000...	94.41087900974...	0.7394	32.66416258667...
4	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.05	1	0.05	91.74842097576...	0.7394	32.66416258667...
5	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.0625	1	0.0625	89.38352060026...	0.7394	32.66416258667...
6	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.075	1	0.075	86.64674865856...	0.7394	32.66416258667...
7	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.0875	1	0.087499999999...	82.86549986916...	0.7394	32.66416258667...
8	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.1	1	0.1	82.51341183009...	0.7394	32.66416258667...
9	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.1125	1	0.1125	82.34072996391...	0.7394	32.66416258667...
10	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.125	1	0.125	80.12823753335...	0.7394	32.66416258667...
11	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.1375	1	0.1375	79.91112910872...	0.7394	32.66416258667...
12	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.15	1	0.15	79.55676266334...	0.7394	32.66416258667...
13	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.1625	1	0.1625	76.21872464212...	0.7394	32.66416258667...
14	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.175	1	0.175	75.26398592254...	0.7394	32.66416258667...
15	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.1875	1	0.1875	75.01002062213...	0.7394	32.66416258667...
16	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.2	1	0.2	74.71125257997...	0.7394	32.66416258667...
17	PASI Change to Week 4, PASI 75% Improvement at Week 12 [AUC: 0.9185]	0.2125	1	0.2125	73.57629352530...	0.7394	32.66416258667...

……..

Based on the Youden's index, Sensitivity and Specificity values in this data table, the figure below could be created in Excel to help the statistician to find out the best cutoff point.

CONCLUSIONS

This paper describes the methods for (1) choosing the most appropriate cut-off for a test; (2) evaluating the accuracy of a diagnostic test using AUC value (C statistics in logistic model) to discriminate the diseased cases from normal cases; (3) comparing the performance of two or more classifiers via a visual method. The SAS Macros presented in this paper are very useful to perform ROC curve analyses. Furthermore, the ability to predict subsequent clinical response in patients helps the decision-making.

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