

The Effect of Adding the Chronic Disease Score to the Charlson Comorbidity Score in Predicting Mortality in Type – 2 Diabetes Mellitus Patients: An Application of Reclassification Measures

Hemalkumar Mehta¹, Vinay Mehta², Zhiwen Liu², Cynthia Girman²

¹College of Pharmacy, University of Houston

²Epidemiology, Merck Sharp & Dohme

Abstract:

Risk adjustment models such as Charlson Comorbidity Score (CCS) and Chronic Disease Score (CDS) are used to control for confounding and predicting outcomes in epidemiologic studies. A traditional statistical measure such as concordance (c) statistics has been used widely in literature for comparison of different risk adjustment models. Recently, new measures have been introduced for comparison of such models, including reclassification methods such as reclassification tables and calibration statistics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI). In the current study, in addition to c-statistics, we show the application of novel reclassification measures in comparing risk adjustment models. We compared CCS and CCS + CDS models in predicting one-year mortality in type 2 diabetes mellitus patients using the Clinical Practice Research Database (CPRD) database. Descriptive statistics was used to describe the cohort. Logistic regression models were applied to predict mortality; all analyses were adjusted for age and gender. Reclassification tables and calibration statistics, NRI and IDI were calculated. All data manipulation and statistical analyses were performed using SAS 9.3. Results showed that both CCS and CDS were predictive of 1-year mortality (c-statistics: 0.791, 0.788, respectively). The addition of CDS to a model with the CCS score improved c-statistics slightly (C-statistics: 0.803). The NRI and IDI values were positive for CCS + CDS model compared to CCS model which demonstrated that the CCS + CDS model performed significantly better compared to CCS model. These results suggest that the combined use of the CCS and CDS may be useful to adjust for comorbidity in outcome models of mortality in patients with type 2 diabetes mellitus.

Introduction:

Comorbidity scores are useful tools to control for confounding or to predict outcomes in epidemiologic analyses. To date, several comorbidity measures have been developed for outcomes such as mortality, hospitalization, length of stay and healthcare expenditure.

Commonly used comorbidity scores include Charlson Comorbidity Score (CCS) and Chronic Disease Score (CDS). CCS is a diagnosis-based comorbidity index which has been adapted to administrative claims data using ICD-9-CM codes. The adapted CCS included 17 disease categories and weights are assigned to each of these disease categories. All weights are summed to obtain a numeric comorbidity score (range: 0 to 33) for particular patient. (Charlson, 1987; Deyo, 1992) CDS is a prescription-based comorbidity index; outpatient pharmacy dispensing data are used to identify specific disease categories. Weights are given to these disease categories and summed to obtain a continuous numeric score (range: -2.72 to 13.69). (Clark, 1995)

Prior studies have compared these two commonly used comorbidity scores (CCS and CDS) in predicting different outcomes. (Schneeweiss, 2001) Studies have also included both comorbidity scores in a single model to predict outcomes with an assumption that inclusion of both comorbidity score predicts outcome better compared to individual comorbidity score. A commonly used statistical measure to compare two models is the c-statistic for binary outcomes and adjusted R^2 for continuous outcomes. The c-statistic has been criticized for its insensitivity: "The use of a single, somewhat insensitive, measure of model fit such as the c-statistic can erroneously eliminate important clinical risk predictors for consideration in scoring algorithms". (Cook, 2007) To overcome the limitations of traditional c-statistic measures, new methods based on risk stratification have recently been proposed to compare predictive models. Such methods include the reclassification calibration statistic, the net reclassification improvement, and the integrated discrimination improvement. (Cook, 2006; Cook, 2009)

Objective:

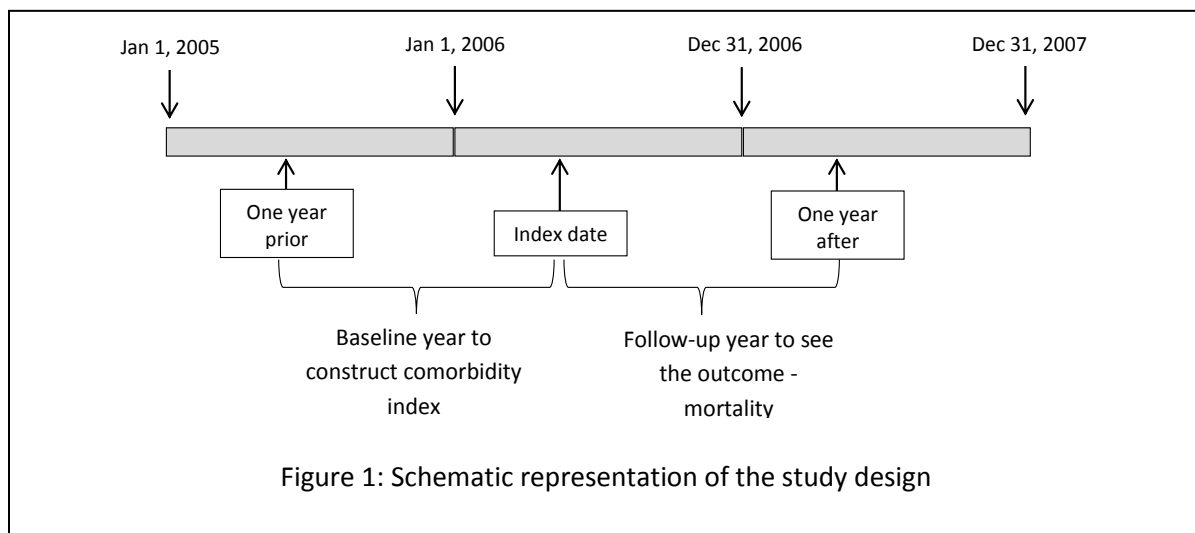
In this paper, we assessed whether a combined model with both comorbidity scores outperformed a model with only one score, by applying the newly introduced reclassification measures, in addition to traditional c-statistics, in predicting one year mortality outcomes in in type 2 diabetes mellitus patients.

Methods:

Data Source and Study Design

A retrospective longitudinal cohort study design was employed using the Clinical Practice Research Database (CPRD) database. The CPRD is world's largest source of anonymised longitudinal data from general practices in UK and the database is widely used in epidemiological studies.

The study included all adult patients (between ages 18 to 115 years) who were diagnosed with type 2 diabetes mellitus between Jan 1, 2006 and Dec 31, 2006. Index date was defined as the date of type 2 diabetes mellitus diagnosis between the Jan 1 and Dec 31, 2006. Information from diagnosis and prescription information during the baseline year (one year prior to the index date) was used to construct comorbidity scores. All patients were followed one year from the index date to observe the mortality outcome.



Statistical Analysis

Descriptive statistics was used to describe the study cohort. The following SAS commands were used for this purpose: **Proc Means**, **Proc Freq** and **Proc Corr**.

Logistic regression (**Proc Logistic**) was used to predict the mortality outcome in this patient population. The dependent variable for the analysis was mortality (yes/no). All logistic models included age and gender as baseline covariates. Three logistic models were developed: (i) baseline covariates + CCS (ii) baseline covariates + CDS and (iii) baseline covariates + CCS + CDS.

In order to derive CCS and CDS, comorbidities and prescription drugs were identified from the diagnosis and prescription files. Appropriate weights (Table 1) were given to the disease category and then weights were summed to obtain a continuous numeric score for each comorbidity index.

Table 1: Weights for Charlson comorbidity Score (CCS) and Chronic Disease Score (CDS)

Charlson comorbidity score weights	
Charlson Disease category	Original Charlson weights (Charlson,1987)
1. Myocardial Infarction	1
2. Congestive heart failure	1
3. Peripheral vascular disease	1
4. Cerebrovascular disease	1
5. Dementia	1
6. Chronic pulmonary disease	1
7. Rheumatologic disease	1
8. Peptic ulcer disease	1
9. Mild liver disease	1
10. Diabetes	1
11. Diabetes with chronic complications	2
12. Hemiplegia or paraplegia	2
13. Renal disease	2
14. Any malignancy, including lymphoma and leukemia	2
15. Moderate or severe liver disease	3
16. Metastatic solid tumor	6
17. AIDS	6
Maximum Charlson comorbidity score a patient can have	33

Chronic disease score weights	
Chronic Disease Score category	Original CDS weights (Clark, 1993)
1. Coronary and peripheral vascular disease	0.61
2. Epilepsy	0.29
3. Hypertension	0.34
4. HIV	3.53
5. Tuberculosis	0.59
6. Rheumatologic condition	0.71
7. Hyperlipidemia	0.32
8. Malignancies	-0.10
9. Parkinson's disease	0.45
10. Renal disease	-0.46
11. End Stage Renal Disease (ESRD)	-1.17
12. Cardiac disease ASCVD	0.40
13. CHF	0.40
14. Diabetes	0.91
15. Glaucoma	0.18
16. Cystic fibrosis	0.10
17. Liver failure	0.33
18. Acid peptic disease	0.54
19. Transplantation	-0.99
20. Respiratory illness, asthma	0.60
21. Thyroid disorders	0.23
22. Gout	0.07

23. Crohn's and ulcerative disease	0.14
24. Pain and inflammation	0.48
25. Pain	0.46
26. Depression	0.67
27. Psychotic illness	0.50
28. Bipolar disorders	0.32
29. Anxiety and tension	0.52
Maximum Chronic disease score a patient can have	13.69

Reclassification measures included reclassification tables, reclassification calibration statistics, net reclassification improvement (NRI) and integrated discrimination index (IDI). SAS macros to calculate reclassification measures available in Cook et al.'s paper were applied. (Cook, 2009)

Reclassification tables and recalibration statistics were calculated using **%RECLASS** macro. Reclassification tables classify individuals among clinically meaningful risk strata. The median rounded predicted probability value for one-year mortality among cases and controls were used to make low, medium and high risk categories; the median value was 0.019 among cases and 0.069 among controls. So, three risk categories were defined as follows: low (0 to <0.019), medium (0.019 to <0.069) and high (0.069 to 1). Observed and average predicted mortality rates for cells with at least 20 observations can be compared on the basis of a chi-square goodness-of-fit test within reclassified categories for each model separately. This is similar to well-known Hosmer–Lemeshow goodness-of-fit statistic, but applied to reclassified categories, and therefore referred to as the reclassification calibration statistic.

Reclassification table and calibration macro:

%macro

```
RECLASS (DSNAME, DETAIL, STATVAR, PROB1, PROB2, NCAT, C1, C2, C3, C4, C5, C6, C7, C8, C9) ;
```

```
* Macro to compute calibration statistics for KxK (K=NCAT) table;
* Formed using categs of predicted probs (eg 0, 5, 10, 20%);
* Counts categs for DF;
* Computes statistics for all and for cells with n>=20;
* Allows up to 10 categories (usually 3 or 4);
* Variables:
* DSNAME = dataset name;
* DETAIL = 2 for detailed printout, 1 for limited, 0 for none;
* STATVAR = outcome variable (coded 0,1);
* PROB1 = probability for model 1;
* PROB2 = probability for model 2;
* NCAT = number of categories in classification;
```

* C1-C9 = category cutpoints (there should be ncat-1 cutpoints);

The NRI assesses risk reclassification and is the difference in proportions moving up and down risk strata among case patients versus control participants; that is, those who did or did not develop the disease during follow-up year.

		New model			
		Low	Medium	High	Total
Old model	Low	**			
	Medium		**		
	High			**	
	Total				

The net reclassification improvement is then the sum of reclassification improvements for cases and controls. NRI can be calculated using **%NRICAT** macro.

$$NRI = \Pr\left(\frac{up}{cases}\right) - \Pr\left(\frac{down}{cases}\right) + \Pr\left(\frac{down}{controls}\right) - \Pr\left(\frac{up}{controls}\right)$$

Net reclassification improvement macro:

%macro

NRICAT (DSNAME, DETAIL, STATVAR, PROB1, PROB2, NCAT, C1, C2, C3, C4, C5, C6, C7, C8, C9) ;

* Macro to compute Net Reclassification Index (NRI) of Pencina, Stat Med 2007;

* Uses up to 10 categories with cutpoints c1-c9;

* Variables:

* DSNAME = dataset name;

* DETAIL = 2 for detailed printout, 1 for limited, 0 for none;

* STATVAR = outcome variable (coded 0,1);

* PROB1 = probability for model 1;

* PROB2 = probability for model 2;

* NCAT = number of categories in classification;

* C1-C9 = category cutpoints (should have ncat-1 cutpoints);

The IDI is the difference in Yates, or discrimination, slopes between two models, in which the Yates slope is the mean difference in \hat{p} cases - \hat{p} controls. The difference in slopes is a measure of improvement in the model. IDI can be calculated using **%IDIMAC** macro.

$$IDI = (ave \hat{p}_{cases} - ave \hat{p}_{controls})_{new\ model} - (ave \hat{p}_{cases} - ave \hat{p}_{controls})_{old\ model}$$

Integrated discrimination index macro:

```
%macro IDIMAC (DSNAME, DETAIL, PROB1, PROB2, OUT01);  
  
* Macro to compute difference in Yates slopes or  
  integrated discrimination improvement (IDI) from Pencina, 2007;  
  
* Variables:  
* DSNAME = dataset name;  
* DETAIL = 1 or 2 for limited printout, 0 for none;  
* PROB1 = probability for model 1;  
* PROB2 = probability for model 2;  
* OUT01 = outcome variable (coded 0,1) (if 1,2 alter signs);
```

SAS Codes and Accompanying Results:

```
Title "Descriptive Stat";  
Proc means data = RAfinal.Objective1_1_one;  
  var age;  
run;
```

```
Title "Descriptive Stat";  
Proc freq data = RAfinal.Objective1_1_one;  
  Tables gender oneyeardeath;  
run;
```

Table 2: Baseline and outcome characteristics of the cohort

	Type 2 DM patients
N	26,191
Age , mean (SD)	64.76 (13.39)
Male, %	54.44
One year Mortality N (%)	920 (3.51)

Table 2 Interpretation: The cohort consisted of 26,191 patients with type 2 diabetes mellitus. The mean age of the cohort was 64.76 (\pm 13.39) and more than half of the patients were males. 3.51% patients died in the one year after the index date.

```

Title "Distribution of comorbidity scores in Diabetes patients - By age
category";
Proc means data = RAfinal.Objective1_1_one;
  class age_cat3;
  var Deyo_Charlson      Original_CDS;
run;

```

Figure 2: Mean comorbidity scores by age group in type 2 diabetes mellitus patients

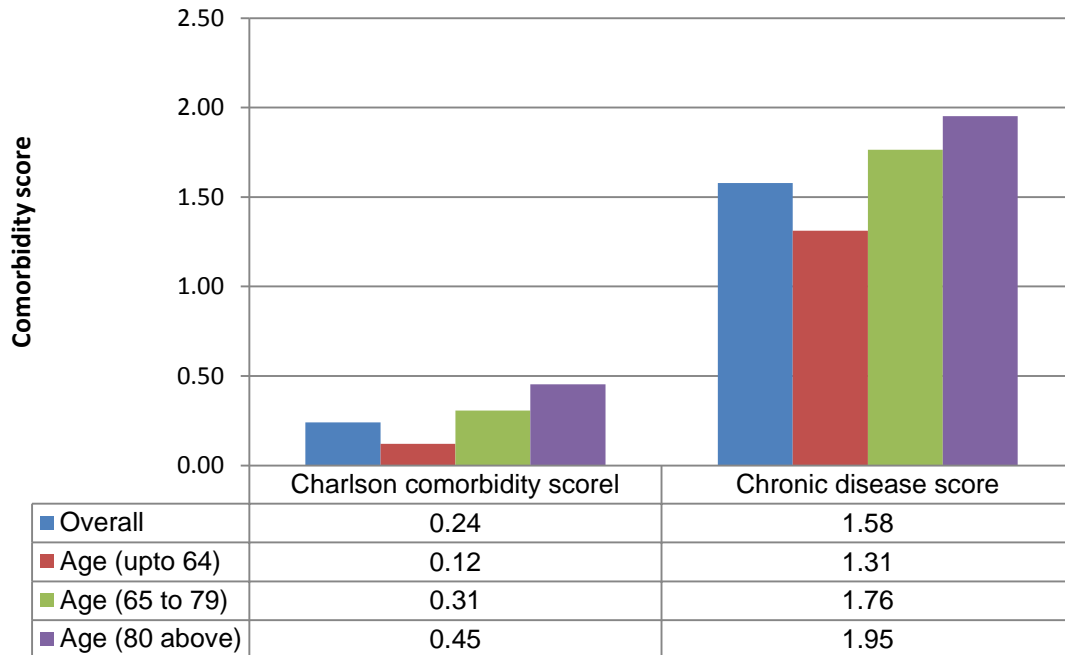


Figure 2 Interpretation: The mean Charlson comorbidity score (CCS) and Chronic disease score (CDS) were 0.24 and 1.58 units, respectively. Both comorbidity scores increase with increasing age, as evident from figure 2.

```

Title "Distribution of comorbidity scores in Diabetes patients ";
Proc means data = RAfinal.Objective1_1_one N mean std min max median p75 p95;
  var Deyo_Charlson  Original_CDS;
run;

```

```

Title "Number of pts with 0 value";
Proc freq data = RAfinal.Objective1_1_one;
  Tables Deyo_Charlson_zero Original_CDS_zero;
run;

```


Table 3: Descriptive statistics of comorbidity scores in type 2 diabetes mellitus patients

	Type 2 diabetes mellitus patients				
	Mean (SD)	% with 0	Median	75 th percentile	Maximum
Charlson comorbidity score	0.24 (0.67)	85.77	0	0	10
Chronic disease score	1.58 (1.06)	7.49	1.46	2.27	5.83

Table 3 Interpretation: Table 3 reports the descriptive statistics of the comorbidity scores. More than 85% patients had Charlson comorbidity score of zero. The maximum Charlson score was 10 with a median of 0. In contrast, only approximately 7% patients had a chronic disease score of zero; the maximum chronic disease score was 5.38 with a median of 1.46.

```
Title "Spearman Correlation coefficient";
Proc corr data = RAfinal.Objective1_1_one spearman;
    var Deyo_Charlson Original_CDS;
run;
```

Table 4: Spearman correlation coefficient

	Charlson Original	CDS Original
Charlson comorbidity score	1	
Chronic disease score	0.24	1

Table 4 Interpretation: The spearman correlation coefficient between Charlson comorbidity score and chronic disease score was 0.24 indicating quite modest correlation.

```
Title "C-statistics for Deyo_Charlson";
Proc logistic data = SUGI.Objective1_1_one;
    class gender;
    model oneyeardeath (event = '1') = gender age Deyo_Charlson;
    output out= DChar1 (keep = patid Dchar1) pred=DChar1;
    roc;
run;
```

```

Title "C-statistics for Original_CDS";
Proc logistic data = SUGI.Objectivel_1_one;
  class gender;
  model onyeardeath (event = '1') = gender age Original_CDS;
  output out= Ocds1 (keep = patid Ocds1) pred= Ocds1;
  roc;
run;

Title "C-statistics for Deyo_Charlson and Original_CDS";
Proc logistic data = SUGI.Objectivel_1_one;
  class gender;
  model onyeardeath (event = '1') = gender age Deyo_Charlson
                                         Original_CDS;
  output out= DChar_Ocds1 (keep = patid DChar_Ocds1) pred= DChar_Ocds1;
  roc;
run;

```

Table 5: Prediction of one year mortality by comorbidity scores in type2 diabetes mellitus patients

Comorbidity scores	C-index with 95% CI*
Charlson comorbidity score	0.791 (0.777-0.805)
Chronic disease score	0.788 (0.774-0.802)
Charlson comorbidity score + Chronic disease score	0.803 (0.789-0.817)

* All models included age and gender.

Table 5 Interpretation: Table 5 reports c-statistics for the two comorbidity scores. A general guideline to evaluate different models based on c-statistics is as follows (Hosmer, 2000):

- 0.5 - chance prediction
- 0.7-0.8 - acceptable
- 0.8-0.9 - excellent
- 1.0 - perfect prediction

Charlson comorbidity score and chronic disease score model showed acceptable c-statistics values, whereas the combined model showed an excellent c-statistic. However, the difference in c-statistics between models with single scores and the model with both scores was marginal. This means that the CCS + CDS model performed slightly better in predicting one year mortality outcome in type 2 diabetes mellitus patients compared to CCS or CDS model alone.

Preparing dataset for Reclassification measures

Proc SQL;

```
Create table Rafinal.Objective1_1_one_phat as
  select *
  from Dchar1 a1, Ocds1 d1, Dchar_Ocds1 f1
  where a1.patid = d1.patid = f1.patid;
quit;
```

Proc sql;

```
create table RAfinal.reclass_obj1_one as
  select *
  from rafinal.Objective1_1_one (keep = patid onyeardeath) a ,
  Rafinal.Objective1_1_one_phat b
  where a.patid = b.patid;
quit;
```

Reclassification Measures

1. Reclassification tables and reclassification calibration statistics

```
%Include "C:\Users\hbmehta2\Desktop\shared\Projects\SCSUG_SUGI 2012_13
Project\macrolib\reclass.txt";
```

```
%reclass(SUGI.reclass_obj1_one,2, onyeardeath, dchar1, dchar_ocds1, 3,
0.019, 0.069);
```

Table 6: Reclassification table comparing one-year mortality risk strata for the Charlson comorbidity score vs. Chronic disease score

Charlson (CCS) Model	CCS + CDS Model			Total, n(%)	Reclassified into new risk category, n(%)		
	Low	Medium	High		Lower	Higher	Total
Low							
Persons included, n(%)	11,850 (94.1)	737 (5.9)	0 (0)	12,587 (48.1)	...	5.9	5.9
Case patients (deaths), n(%)	92	16	0	108	...	14.8	14.8
Control patients (No deaths), n(%)	11,758	721	0	12,479	...	5.8	5.8
Observed risk, %	0.78	2.17
Medium							
Persons included, n(%)	1,311 (13.2)	7,861 (79.1)	763 (7.7)	9,935 (37.9)	13.2	7.7	20.9
Case patients (deaths), n(%)	4	295	70	369	1.1	19.0	20.1
Control patients (No deaths), n(%)	1,307	7,566	693	9,566	13.7	7.2	20.9
Observed risk, %	0.31	3.75	9.17	
High							
Persons included, n(%)	0 (0)	665 (18.1)	3,004 (81.9)	3,669 (14.0)	18.1	...	18.1
Case patients (deaths), n(%)	0	41	402	443	9.3	...	9.3
Control patients (No deaths), n(%)	0	624	2,602	3,226	19.3	...	19.3
Observed risk, %	...	6.17	13.38	
Total							
Persons included, n(%)	13,161 (50.25)	9,263 (35.37)	3,767 (14.38)	26,191 (100)
Case patients (deaths), n(%)	96	352	472	920
Control patients (No deaths), n(%)	13,065	8,911	3,295	25,271
Observed risk, %	0.73	3.8	12.53	3.51

Table 6 Interpretation: The CCS model classified 48.1%, 37.9% and 14% patients into low medium and high risk category, respectively. The CCS+CDS model classified approximately similar proportions of patients into low, medium and high risk categories. The table cells highlighted in blue color indicates that both models, i.e. CCS and CCS+CDS, classified patients into same risk category. So, we can say that 45.24% (11,850/26,191) patients were classified in low risk category whereas 11.47 (3,004/26,191) were classified in high risk category. As compared to CCS model, CCS+CDS model classified 3,476 patients (737+0+1,311+763+0+665) into newer risk categories indicating that 13.27% (3,476/26,191) were reclassified. Red color indicates increase in risk categories whereas green color indicates decrease in risk categories. Rather than simple reclassification, the important issue is a comparison of observed and expected rates within each cross-classified category. This determines whether individuals are reclassified correctly or whether the changes are due to chance. Observed and predicted average mortality within each cell is compared using chi-square statistics for cell size ≥ 20 . A statistically significant value indicates poor fit: the chi-square value was 48.02 (p value: <0.0001) for CCS model and 15.36 (p value: 0.009) for CCS + CDS model. Both models indicated lack of fit but CCS+CDS model fitted data better compared to CCS model. This means that addition of CDS to a model with CCS improves model fit.

2. Net Reclassification Improvement (NRI)

```
%Include "C:\Users\hbmehta2\Desktop\shared\Projects\SCSUG_SUGI 2012_13
Project\macrolib\nri.txt";
```

```
%nricat (SUGI.reclass_obj1_one,2, oneyeardeath, dchar1, dchar_ocds1,3,
0.019, 0.069);
```

Table 7: Net Reclassification Index

%NRI (p-value)	Charlson comorbidity score	Charlson comorbidity score + Chronic disease score
Charlson original	0	6.50 (<0.001)

Table 7 Interpretation: Net Reclassification Index (NRI) indicates proportion of patients correctly reclassified by the new score compared to the old score. The combined model (CCS+CDS) reclassified 6.50% patients into correct strata compared to the Charlson comorbidity score (p-value: <0.001). This means that combined model (CCS + CDS) performed better compared to CCS alone.

Hand calculation of NRI from reclassification table (table 6) is as follows:

$$\begin{aligned}
 NRI &= \Pr\left(\frac{up}{cases}\right) - \Pr\left(\frac{down}{cases}\right) + \Pr\left(\frac{down}{controls}\right) - \Pr\left(\frac{up}{controls}\right) \\
 &= \left(\frac{16 + 70}{920}\right) - \left(\frac{4 + 41}{920}\right) + \left(\frac{1,307 + 624}{25,271}\right) - \left(\frac{721 + 693}{25,271}\right) \\
 &= 0.04456 + 0.02045 \\
 &= 0.0650 \\
 &= 6.50\%
 \end{aligned}$$

3. Integrated Discrimination Index (IDI)

```
%Include "C:\Users\hbmehta2\Desktop\shared\Projects\SCSUG_SUGI 2012_13
Project\macrolib\idi.txt";
```

```
%IDIMAC (SUGI.reclass_obj1_one,2, dchar1, dchar_ocds1, oneyeardeath );
```

Table 8: Integrated Discrimination Index

	Charlson comorbidity score	Charlson comorbidity score + Chronic disease score
Charlson comorbidity score	0	0.43 (<0.001)

Table 8 Interpretation: Integrated discrimination index (IDI), the difference in slopes between two models, is a measure of improvement in the model. The positive value of IDI indicates improvement in the model. The integrated discrimination improvement for chronic disease score

is 0.43%. This means that the difference in average predicted probabilities between case patients and control participants increased by 0.0043 when chronic disease score was added to the model.

Conclusions:

In this paper, we have applied of reclassification measures in evaluating the performance of two comorbidity scores in predicting one-year mortality outcome in type 2 diabetes mellitus patients. C-statistics results suggest that the addition of the chronic disease score somewhat improved the prediction of mortality over that of the Charlson comorbidity score alone. Results from reclassification calibration statistics, NRI and IDI reached the same conclusion. In addition to c-statistics, reclassification measures such as reclassification tables and calibration statistics, NRI and IDI can be added to the armamentarium of risk adjustment model comparisons.

References:

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Contact Information:

Your comments and questions are valued and encouraged. Contact the author at:

Hemalkumar B. Mehta, MS

PhD Student (Pharmacy Administration),
Department of Clinical Sciences and Administration,
College of Pharmacy, University of Houston,
1441Moursund Street,
Houston, TX 77030



Phone: 718-607-4967

E-mail: hbmehta3@uh.edu

Web: www.mehtahemal.com

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