

A validation study of the CirCom comorbidity score in an English cirrhosis population using the Clinical Practice Research Datalink

Colin J Crooks^{1,2}

Joe West^{1,2}

Peter Jepsen^{3,4}

¹Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK; ²Nottingham Digestive Diseases Biomedical Research Centre, School of Medicine, University of Nottingham, Nottingham, UK; ³Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; ⁴Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Purpose: The CirCom score has been developed from Danish data as a specific measure of comorbidity for cirrhosis to predict all-cause mortality. We compared its performance with the Charlson Comorbidity Index (CCI) in an English cirrhosis population.

Patients and methods: We used comorbidity scores in a survival model to predict mortality in a cirrhosis cohort in the Clinical Practice Research Datalink. The discrimination of each score was compared by age, gender, socioeconomic status, cirrhosis etiology, cirrhosis stage, and year after cirrhosis diagnosis. We also measured their ability to predict liver-related versus non-liver-related death.

Results: There was a small improvement in the C statistic from the model using the CirCom score ($C=0.63$) compared to the CCI ($C=0.62$), and there was an overall improvement in the net reclassification index of 1.5%. The improvement was more notable in younger patients, those with an alcohol etiology, and those with compensated cirrhosis. Both scores performed better (C statistic >0.7) for non-liver-related deaths than liver-related deaths (C statistic <0.6), as comorbidity was only weakly predictive of liver-related death.

Conclusion: The CirCom score provided a small improvement in performance over the CCI in the prediction of all-cause and non-liver mortality, but not liver-related mortality. Therefore, it is important to include a measure of comorbidity in studies of cirrhosis survival, alongside a measure of cirrhosis severity.

Keywords: cirrhosis, mortality, comorbidity, prognosis, cause of death, cohort

Plain language summary

Why was the study done? We assessed whether the effect of non-liver disease on survival in patients with liver disease scarring (called cirrhosis) is better captured by a cirrhosis-specific measure (the CirCom score) than by a generic measure (the Charlson Comorbidity Index [CCI]).

What did the researchers do and find? The CirCom score was better able to predict patients' survival times than the CCI, particularly in younger patients, patients with less severe cirrhosis, and patients whose cirrhosis was due to alcohol.

What do these results mean? This paper showed that the CirCom score is better than the CCI at describing the survival of English patients with liver cirrhosis. It also demonstrated the importance of accounting for non-liver disease in patients with liver cirrhosis.

Introduction

Patients with cirrhosis have a high mortality.¹ Their high mortality is partly due to comorbidity,² so adjustment for differences in the burden of comorbidity is important in studies that compare mortality among these patients. This is similar to what

Correspondence: Colin J Crooks
Division of Epidemiology and Public Health, Clinical Sciences Building,
University of Nottingham, Nottingham City Hospital, Nottingham, NG5 1PB, UK
Tel +44 115 823 1356
Email colin.crooks@nottingham.ac.uk

has been shown in end-stage renal failure, heart failure, and chronic obstructive pulmonary disease (COPD).³⁻⁵ For cirrhosis, Jepsen et al have developed a comorbidity score (CirCom) within a Danish cohort of patients with liver cirrhosis and shown it to be an improvement on the existing Charlson comorbidity score.⁶ However, the accompanying commentary recommended further external validation that included calculation of absolute risks, as well as discrimination and model fit.⁷

The most frequently validated method to date is the secondary care-derived CCI, published in 1987,⁸ developed using hospital chart data of medical inpatients to predict mortality in the 1-year postdischarge and validated in a cohort of breast cancer inpatients. However, this score assessed all medical inpatients rather than those with specific disease, thus failing to recognize that the prognostic effect of a specific comorbid disease (eg, COPD) might depend on the index disease (eg, ischemic heart disease versus cirrhosis). Furthermore, the management and prognosis of various diseases have changed greatly over the last two decades altering what is relevant to be contained in a score. In contrast, CirCom was derived specifically for cirrhotic patients and reassessed which comorbidities were associated with mortality in this context. It is simpler in that it includes less comorbidities overall compared to the CCI, but with some different comorbidities such as substance abuse (other than alcohol use) and epilepsy.⁶ We have previously extracted a validated and well-described cohort of cirrhotic patients with mixed etiology from linked primary care, secondary care, and death registry data within the Clinical Practice Research Datalink (CPRD).⁹ The purpose of this validation study of the CirCom score within this English cohort is to assess the performance of CirCom compared to the CCI in predicting mortality. By doing this assessment, we hope to provide evidence for its use (or nonuse) as the preferred measure of comorbidity adjustment in future population-based observational studies on cirrhosis mortality.

Materials and methods

Dataset

The CPRD consists of linked English Hospital Episodes Statistics data, primary care data, and the Office of National Statistics (ONS) death register. For this study, these data have linked records of all primary care events, hospital admissions, and causes of death from April 1997 to August 2010 for 3% of the English population (244 primary care practices).

Population

The cirrhosis cohort we used is one we have previously defined from the January 2011 static version of the CPRD (ISAC approved protocol number 09_065RA_4 and updated approval for this validation study 16_161).⁹ It consists of 5118 patients who were ≥ 18 years and had a diagnostic code for cirrhosis or a therapeutic code for cirrhosis, esophageal varices, or portal hypertension within either primary care or secondary care data within the CPRD between January 1, 1998 and December 31, 2009. These dates define the period when the linked data were available at the time of the initial study. The presence of cirrhosis was validated using secondary care, death registry, and free text data.¹ The study population was restricted to the 244 practices with the primary and secondary care linkages available within the January 2011 static version of the CPRD. For this cirrhosis cohort, the patient characteristics, etiology of the cirrhosis (alcohol, viral/autoimmune/metabolic, or unknown), cause of death, and 5-year survival have been well described.^{1,10} The observation period for patients within this cohort commenced on the latest of 1) 1 year after each patient's current registration date with an eligible practice, 2) the date that their practice's data were up to research standard, or 3) January 1, 1998, when the linkage of the CPRD to secondary care data was first available. The 1-year cutoff following registration was used to avoid including potential prevalent cases who were diagnosed before they were observable in the dataset. The period of observation in this cohort terminated for each patient on the earliest of 1) the date of their death, 2) the date the patient left the practice, 3) their practice's last data collection date, 4) the last date of the available linkage to secondary care (at the time of the study derivation) which was December 31, 2009. Within this observation period, the start of each patient's follow-up was defined as his or her first Read or ICD 10 code for cirrhosis within the observation period. Patients with a diagnosis of cirrhosis before the observation period were excluded as the CirCom score was defined from comorbidity present at the time of diagnosis of cirrhosis. Follow-up for each patient ended at the end of the observation period described above.

Ethics

The CPRD has obtained ethical approval from the National Research Ethics Service Committee (NRECS) for all purely observational research using anonymized CPRD data. Studies which do not include patient involvement are reviewed for scientific quality by the Independent Scientific Advisory Committee for the Medicines and Healthcare Products Regulatory Agency database research. Regulatory approval for this study was obtained under approval 16_161.

Sample size

Studies modeling required sample sizes for complex discriminatory models have indicated that a study like ours requires at least 500 deaths, and ideally 1000.¹¹ Two thousand five hundred sixty-four deaths occurred within our liver cirrhosis cohort within the follow-up time providing sufficient power overall. Within the stratified analysis, there were more than 500 deaths in each of the etiology groups when defined as Viral/Autoimmune/Metabolic, Alcoholic, or Unspecified, and within each of the age categories defined below.

Comorbidity scores

We defined the CirCom score as described by Jepsen et al.⁶ This score defines seven different weighted categories using ICD 10 codes. We also defined the CCI⁸ to provide a comparison similar to Jepsen et al's paper. We used the Read and ICD 10 codes for the individual comorbidities that we have previously defined for calculating the CCI in linked primary and secondary care data within the CPRD.¹² The Read codes for these comorbidities were also used to define the comorbidities for the CirCom score, apart from substance abuse, epilepsy, and COPD. For the latter two of these categories, we used published code lists from www.clinicalcodes.org,^{13,14} and for substance abuse, the Read codes are listed in Table S1. All comorbidities were defined using all diagnoses coded in the 5 years prior to the cirrhosis diagnosis date as was done in Jepsen et al's original paper.⁶

Other covariates included etiology, cirrhosis stage, year of follow-up, socioeconomic status, age, and gender. For the stratified analysis, we used the age bands we published in our original cohort (<45, 45–54, 55–64, 65–74, >75 years).¹⁰ Etiology was defined using the previously defined groups in the cohort as Alcoholic, Viral/Autoimmune/Metabolic, or Unspecified. Cirrhosis stage was defined as compensated or decompensated using the Baveno IV criteria already defined in the cohort.¹ Socioeconomic status was defined by quintile of deprivation as measured by the English Indices of Multiple Deprivation 2010.¹⁵ Each year of follow-up from the first to the fifth year after cirrhosis diagnosis was defined, similar to our previously published work on comorbidity scores.¹² Finally, we used cirrhosis and non-cirrhosis death outcomes as already defined in this cohort from previous work on cause of death from the linked ONS Death Registry.¹⁰ Specifically, we categorized deaths using the main ICD 10 chapter headings of K70–K77, C22, I85, I864, and I982 as liver related. This definition included bleeding from gastric and esophageal varices and hepatocellular carcinoma. All other ICD 10 codes were categorized as a non-liver death.

Statistical analysis

We described the cohort characteristics for each covariate to allow a comparison with numbers and proportions with the Danish Development cohort. We then fitted a Cox proportional hazards model including age, gender, and either the CCI as a categorical variable or the CirCom score as a categorical variable as in the Jepsen paper. To compare how well the Charlson and CirCom score models fitted the data, we calculated the Bayesian information criterion (BIC). This measure penalizes the likelihood of the model for the number of parameters it includes, and the model with the smaller BIC value is more likely to have a better fit. Discrimination was measured using the Harrell's C statistic, with 95% CIs calculated using the `somersD` command in Stata.¹⁶ We calculated the predicted absolute 1-year mortality risk from each model using cumulative incidence functions. These absolute predicted mortality risks were used to classify patients into 1-year mortality probabilities of $\leq 20\%$, 21%–50%, and $\geq 51\%$ to allow the net reclassification index (NRI) to be calculated. These were the categories used to assess the development of the CirCom score in the Danish cohort and were chosen to be clinically relevant.⁶

To assess the calibration of the two scores, the observed 1-year mortality, computed using the Kaplan–Meier method, was plotted against the 1-year mortality predicted by the Cox model.¹⁷ In addition, a decision curve analysis was performed assessing the net benefit of using each score compared to not using a score. The net benefit is calculated as the difference between the true positives (proportion of patients whose predicted risk was over a particular threshold who also died within 1 year of follow-up) and the false positives (proportion of patients whose predicted risk was over a particular threshold who did not die within 1 year of follow-up), for thresholds of predicted risk from 0% to 100%.¹⁸

A stratified analysis was then performed to assess the models' discrimination by age, gender, socioeconomic status, cirrhosis etiology, cirrhosis stage, and follow-up year as defined above. A final analysis assessed the models' discrimination in predicting liver-related death and non-liver-related death separately.

Results

Validation population characteristics

The validation cirrhosis cohort from the CPRD had fewer patients than that used in Denmark for the score's development and a shorter median follow-up time (1.9 years compared to 2.8 years, respectively), but a similar median age (59 years compared to 58 years, respectively). The CPRD cohort had a

Table 1 A comparison of the patient demographics of the Clinical Practice Research Datalink (CPRD) validation cohort and the original Danish Patient Registry derivation cohort

Characteristics of the validation cohort	CPRD cirrhosis cohort		Danish patient registry cohort	
	Patients (n)	Patients (%)	Patients (n)	Patients (%)
Number of patients	5,118		12,976	
Follow-up time (person years)	14,438		40,847	
Deaths during follow-up	2564	50.1	8911	68.7
Median follow-up time (years)	1.9		2.8	
1-year mortality	1516	29.6		34.5
5-year mortality	2332	45.6		80.5
Mean age (interquartile range)	59.1	49.4–70.0	57.9	50.3–65.3
Female	2153	42.1	4397	33.9
Male	2965	57.9	8579	66.1
Decompensated at presentation	2235	43.7		
Etiology				
Alcohol	2756	53.9		73.7
Viral/autoimmune/metabolic	1079	21.1		
Unknown	1283	25.1		
Most prevalent comorbidities				
Diabetes without complications	979	19.1	835	6.4
Rheumatological disease	705	13.8	422	3.3
Chronic obstructive pulmonary disease	445	8.7	951	7.3
Congestive cardiac disease	344	6.7	673	5.2
Cerebrovascular disease	256	5.0	720	5.5
Diabetes with complications	252	4.9	813	6.3
Hypothyroidism	250	4.9		
Peptic ulcer disease	239	4.7	1579	12.2
Cerebrovascular disease	234	4.6	720	5.5
Renal disease	231	4.5	67	0.5
CirCom score				
0	3120	61.0	9841	75.8
1+0	1384	27.0	2143	16.5
1+1	409	8.0	477	3.7
3+0	56	1.1	313	2.4
3+1	147	2.9	136	1.0
5+0	2	0.0	50	0.4
5+1	0	0	16	0.1
Charlson Comorbidity Index				
0	2644	51.7	7477	57.6
1	999	19.5	3034	23.4
2	617	12.1	1422	11.0
3	299	5.8	576	4.4
4	200	3.9	208	1.6
5	108	2.1	80	0.6
6	74	1.5	106	0.8
≥7	177	3.5	73	0.6

Note: Cells are left blank where information was not presented in the papers on the original cohort studies.

lower proportion with alcohol as an etiology, a lower proportion of men, and a lower mortality. This was despite a higher proportion of patients in the CPRD who had a comorbidity that contributed to the Charlson or CirCom score (Table 1).

Overall performance of comorbidity scores

The full models are shown for comparison in Table 2. The CirCom score provided a better model fit than the CCI with an improvement in the BIC (Table 2).

Measures of discrimination of the CCI and CirCom score models are shown in Table 3 compared to models with age and sex alone. Both scores showed an improvement when compared to age and sex alone with a small improvement in the C statistic from the model using the CirCom score compared to the CCI. This was also reflected in the 1.5% improvement of the CirCom score over the CCI in classifying 1-year mortality as measured by the categorical NRI (see Table 3). The addition of a covariate for decompensated or compensated liver disease further increased the

Table 2 Full models with the comorbidity scores in the Clinical Practice Research Datalink validation cohort

Covariate	Charlson Comorbidity Index		Covariate	CirCom score	
	Hazard ratio	95% CI		Hazard ratio	95% CI
<20 years	Reference	–		Reference	–
20–29 years	2.43	0.58–10.26		1.90	0.45–8.03
30–39 years	2.56	0.63–10.37		2.06	0.51–8.34
40–49 years	3.26	0.81–13.08		2.66	0.66–10.68
50–59 years	3.66	0.91–14.68		3.11	0.78–12.47
60–69 years	4.01	1.00–16.06		3.63	0.90–14.54
70–79 years	5.74	1.43–23.03		5.27	1.31–21.12
80–89 years	8.10	2.02–32.57		7.22	1.80–29.05
90–99 years	13.89	3.26–59.14		10.80	2.54, 46.01
Female	Reference	–		Reference	–
Male	1.28	1.18–1.39		1.24	1.15–1.35
Charlson Comorbidity Index				CirCom score	
0	Reference	–	0	Reference	–
1	1.09	0.98–1.21	1+0	1.43	1.31–1.57
2	1.27	1.12–1.43	1+1	1.88	1.64–2.15
3	1.53	1.31–1.79	3+0	2.29	1.67–3.14
4	1.46	1.20–1.77	3+1	2.95	2.44–3.56
5	1.63	1.27–2.09	5+0	13.00	3.24–52.24
6	1.62	1.21–2.17	5+1	No patients with a score of 5+1	
7	1.98	1.37–2.87			
8	3.09	2.40–3.98			
9	4.21	2.73–6.50			
10	5.22	2.94–9.25			
11	4.23	2.39–7.50			
12	1.70	0.55–5.29			
13	4.95	2.05–11.99			
15	4.46	0.63–31.74			
Total patients (N)	5118			5118	
BIC	40434			40294	

Note: Exponentiated coefficients.

Abbreviations: BIC, Bayesian information criterion; CI, confidence interval.

Table 3 Discrimination of the comorbidity models

Measured parameter	Age and sex	Age and sex + Charlson Comorbidity Index	Age and sex + CirCom score
C statistic	0.60	0.62	0.63
95% CIs	0.59–0.61	0.61–0.63	0.62–0.64
Mean 1-year predicted mortality risk			
1-year predicted mortality risk in patients who survived	28.6%	27.8%	27.7%
1-year predicted mortality risk in patients who died	33.4%	35.1%	35.3%
Net reclassification index (NRI) ($\leq 20\%$, $21\%–50\%$, $\geq 51\%$)			
NRI (compared to age and sex)	NA	6.4%	8.0%
NRI (CirCom versus Charlson index)	NA	NA	1.5%

Abbreviation: CI, confidence interval; NA, not applicable.

discrimination of the model containing the CirCom score ($C=0.67$, 95% confidence interval [0.66–0.68]). Calibration was similar between the two scores (Figure S1). The decision curve analysis showed similar results for both scores, with a net benefit in true over false positives when the threshold used for the predicted risk of 1-year mortality was between 20% and 60% for both the CCI and the CirCom score (Figure S2).

To assess whether the differences in performance were due to difference in numbers of parameters, we reassessed the CCI score collapsed to 0, 1, 2, 3, 4, and 5 or more. This reduced the BIC for the CCI to 40,369, but this was still greater than the BIC for the CirCom score (which remained the better fit). The discrimination for the CCI with only six parameters was not altered (C statistic= 0.62 [0.61–0.63]).

Stratified analysis

The CirCom score conferred a slight improvement in discrimination over the CCI in younger age groups, particularly in the <45-year-old age group (Table 4). Among the subgroups defined by cirrhosis etiology, the difference between the CCI and the CirCom score was most notable in the subgroup with alcoholic cirrhosis (Table 5). Both comorbidity scores performed better in those with autoimmune, viral, metabolic, or unknown causes, which reflected the older mean age in these groups and resultant higher prevalence of comorbidity. There was also a slight improvement in discrimination of the CirCom score over the CCI in those with compensated cirrhosis at presentation, but not in those with decompensated cirrhosis. The CirCom score performed better than the CCI in the first year of follow-up with similar discrimination in the subsequent years (Table 6). Discrimination reduced with increasing deprivation, but there was less of a reduction for the CirCom score (Table S2).

Both comorbidity scores had identically poor discrimination for liver-related death and identically good discrimination for non-liver-related death. The inclusion of a measure of decompensation improved the discrimination of a model with either score for liver-related death (Table 7).

Discussion

The CirCom score provided a small improvement in performance over the CCI when used to predict mortality in a large, population-based cohort of patients with cirrhosis of mixed etiology. Both scores showed good discriminative ability to predict deaths not related to the liver, which were almost half of the deaths, but poor ability to predict deaths related to the liver. However, the purpose of a comorbidity score is to adjust for factors other than the severity of cirrhosis and in this context it performs. Both the CCI and the CirCom score improved the performance of the model over using just demographic information, emphasizing

Table 4 Age-stratified discrimination of the comorbidity models

Age (years)	Patients (n)	Patients (%)	Charlson Comorbidity Index C statistic	95% CI	CirCom score C statistic	95% CI
<45	827	16	0.58	0.54–0.61	0.62	0.59–0.66
45–54	1182	23	0.54	0.52–0.57	0.56	0.54–0.59
55–64	1300	25	0.57	0.54–0.59	0.58	0.56–0.61
65–74	991	19	0.60	0.57–0.62	0.60	0.58–0.63
>74	818	16	0.57	0.54–0.59	0.56	0.53–0.58

Notes: Each estimate is also adjusted for gender.

Abbreviation: CI, confidence interval.

Table 5 Etiology- and compensation-stratified discrimination of the comorbidity models

Cirrhosis etiology or compensation state at start of study	Patients (n)	Patients (%)	Charlson Comorbidity Index C statistic	95% CI	CirCom score C statistic	95% CI
Alcohol	2756	54	0.57	0.56–0.59	0.59	0.57–0.60
Other ^a	1079	21	0.64	0.61–0.67	0.65	0.62–0.67
Unknown	1283	25	0.69	0.67–0.71	0.69	0.67–0.71
Compensated	2883	56	0.63	0.62–0.65	0.65	0.63–0.66
Decompensated	2235	44	0.62	0.60–0.63	0.62	0.60–0.64

Notes: ^aAutoimmune, viral, or metabolic. Each estimate is also adjusted for age and gender.

Abbreviation: CI, confidence interval.

Table 6 Follow-up-stratified discrimination of the comorbidity models

Age band	Patients (n)	Person years	Charlson Comorbidity Index C statistic	95% CI	CirCom score C statistic	95% CI
<1 year	5118	1320183	0.62	0.61–0.64	0.64	0.62–0.65
1–2 years	2963	2019508	0.62	0.58–0.65	0.59	0.56–0.62
2–3 years	2194	2297575	0.63	0.59–0.66	0.65	0.61–0.69
3–4 years	1639	2315506	0.63	0.58–0.68	0.63	0.59–0.68
4–5 years	1217	2163567	0.63	0.58–0.70	0.61	0.56–0.67

Notes: Each estimate is also adjusted for age and gender.

Abbreviation: CI, confidence interval.

Table 7 Cause of death—stratified and compensation-stratified discrimination of the comorbidity models

Cause of death	Patients (n)	Patients (%)	Charlson Comorbidity Index C statistic	95% CI	CirCom score C statistic	95% CI
Liver-related death	1301	25	0.56	0.54–0.57	0.56	0.54–0.57
Non-liver-related death	1263	25	0.72	0.71–0.74	0.72	0.71–0.74
Cause of death	Patients (n)	Patients (%)	Including measure of decompensation	95% CI	Including measure of decompensation	95% CI
Liver-related death	1301	25	0.64	0.63–0.66	0.64	0.63–0.66
Non-liver-related death	1263	25	0.73	0.72–0.75	0.73	0.72–0.75

Abbreviation: CI, confidence interval.

the importance of including a comorbidity measure in any comparative study of cirrhosis survival. In particular, this validation study supports the use of the CirCom score as a measure of non-cirrhosis-related or all-cause mortality in cirrhotic patients in the English population.

The importance of our work is not just that it shows the utility of the score in an international context beyond Denmark, but that it also shows that the score is translatable into other coding systems such as the Read codes used in the CPRD. Furthermore, the Danish data use secondary care outpatient data for longitudinal comorbidity coding, whereas the English data use both linked inpatient secondary care and general practitioner primary care comorbidity coding. The finding that the score showed a consistent improvement over the CCI in this different health care context confirms the score's generalizability, particularly as we demonstrated an even greater improvement in the C statistic than in the original Danish derivation cohort.

The strengths of this study are that it provides an in-depth analysis of the performance of the CirCom score and the CCI in an English population. The English CPRD has extensive linkages, and these have allowed the current cohort to be validated and its characteristics comprehensively described.^{1,9,10} Therefore, we are confident of the validity of the cirrhosis diagnosis from the primary and secondary care data, and the recording of death from the national death registry. Furthermore, the recording of comorbidity in the CPRD has previously been validated against anonymized case records in many studies (myocardial infarction,^{19,20} heart failure,^{21,22} cerebrovascular disease,^{23–25} dementia,^{26,27} respiratory disease,^{28–30} connective tissue disease,^{31–34} peptic ulcers,³⁵ liver disease,^{9,36} renal failure,³⁷ cancer,³⁸ leukemia, and lymphoma³⁹), and the sensitivity of definitions improved when defined from linked primary and secondary care records (eg, diabetes,^{40,41} cirrhosis,⁹ and acute myocardial infarction⁴²).

The Model for End-Stage Liver Disease and the Child-Pugh score outperformed both the CCI and the CirCom score

in predicting cirrhosis survival in a US Veteran cohort,⁴³ and the validation in the original CirCom score paper showed the same.⁶ However, these measures depend on laboratory values that were not available in the CPRD. We have previously shown that it was possible to derive a measure of cirrhosis stage using just diagnostic coding within the CPRD,⁹ and including this as a variable for decompensation in our current study greatly improved the discrimination for liver-related death, and consequently the overall discrimination of all-cause mortality for our model with the CirCom score. The value of a comorbidity score, therefore, is that it predicts the additional non-liver-related outcomes that are not predicted by measures of severity of cirrhosis, and it will have benefit when added to any measure of cirrhosis severity.

The higher prevalence of comorbidity in the English cohort compared to the Danish cohort might reflect the more extensive comorbidity coding in a comprehensive primary care system in the UK or might reflect the more varied etiology of the English cohort, which had a lower proportion with alcohol etiology. We have previously shown that those patients with a non-alcohol etiology survive longer than those with an alcohol etiology, and, therefore, will have had a longer period of care in which to develop comorbidities and non-liver-related deaths.⁴⁴ Finally, within the English cohort, the improvement with the CirCom score over the CCI was most noticeable in younger patients and in those with an alcohol etiology. This likely reflects the inclusion of epilepsy and substance abuse that have more importance in a cirrhotic cohort because of their association with a more hazardous lifestyle.⁴⁵

Conclusion

We have validated the CirCom score in the English-linked CPRD as a measure of the burden of comorbidity and found that its performance is better than the CCI. However, both the CCI and the CirCom score improved discrimination compared to a model containing only age and sex. This emphasizes the importance of including any measure of comorbidity in comparative studies of cirrhosis survival.

Author contributions

CJ Crooks is the guarantor of the article, planned and performed the analysis, and drafted and edited the paper. P Jepsen had the original concept, contributed to the study design and analysis, and edited the paper. J West contributed to the study design and analysis, and edited the paper. All authors have approved the final version and authorship list and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ratib S, Fleming KM, Crooks CJ, Aithal GP, West J. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998–2009: a large population study. *J Hepatol*. 2014;60(2):282–289.
2. Jepsen P, Vilstrup H, Andersen PK, Lash TL, Sørensen HT, Sørensen HT. Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. *Hepatology*. 2008;48(1):214–220.
3. Incalzi RA, Fusco L, De Rosa M, et al. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J*. 1997;10(12):2794–2800.
4. Lee CS, Chien CV, Bidwell JT, et al. Comorbidity profiles and inpatient outcomes during hospitalization for heart failure: an analysis of the U.S. Nationwide inpatient sample. *BMC Cardiovasc Disord*. 2014;14(1):73.
5. Liu J, Huang Z, Gilbertson DT, Foley RN, Collins AJ. An improved comorbidity index for outcome analyses among dialysis patients. *Kidney Int*. 2009;77(2):141–151.
6. Jepsen P, Vilstrup H, Lash TL. Development and validation of a comorbidity scoring system for patients with cirrhosis. *Gastroenterology*. 2014;146(1):147–156.
7. Younossi ZM, Henry L, Stepanova M. A new comorbidity model for predicting mortality in patients with cirrhosis: does it work? *Gastroenterology*. 2014;146(1):19–24.
8. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383.
9. Ratib S, West J, Crooks CJ, Fleming KM. Diagnosis of liver cirrhosis in England, a cohort study, 1998–2009: a comparison with cancer. *Am J Gastroenterol*. 2014;109(2):190–198.
10. Ratib S, Fleming KM, Crooks CJ, Walker AJ, West J. Causes of death in people with liver cirrhosis in England compared with the general population: a population-based cohort study. *Am J Gastroenterol*. 2015;110(8):1149–1158.
11. Peek N, Arts DGT, Bosman RJ, van der Voort PHJ, de Keizer NF. External validation of prognostic models for critically ill patients required substantial sample sizes. *J Clin Epidemiol*. 2007;60(5):491–501.
12. Crooks CJ, West J, Card TR. A comparison of the recording of comorbidity in primary and secondary care by using the Charlson Index to predict short-term and long-term survival in a routine linked data cohort. *BMJ Open*. 2015;5(6):e007974.
13. Quint JK, Mullerova H, DiSantostefano RL, et al. Validation of chronic obstructive pulmonary disease recording in the clinical practice research datalink (CPRD-GOLD). *BMJ Open*. 2014;4(7):e005540.
14. Kontopantelis E, Springate DA, Ashworth M, Webb RT, Buchan IE, Doran T. Investigating the relationship between quality of primary care and premature mortality in England: a spatial whole-population study. *BMJ*. 2015;350(1):h904.
15. Noble M, McLennan D, Wilkinson K. The English indices of deprivation 2010; 2010. Available from: <http://eprints.ioe.ac.uk/id/eprint/2461>. Accessed April 4, 2013.
16. Newson R. Efficient calculation of jackknife confidence intervals for rank statistics. *J Stat Softw*. 2006;15(1):1–10.
17. Royston P. Tools for checking calibration of a Cox model in external validation: prediction of population-averaged survival curves based on risk groups. *Stata J*. 2015;15(1):275–297.
18. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making*. 2016;36(6):565–574.
19. Hammad TA, McAdams MA, Feight A, Iyasu S, Dal Pan GJ. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the general practice research database. *Pharmacoepidemiol Drug Saf*. 2008;17(12):1197–1201.
20. Meier CR. Antibiotics and risk of subsequent first-time acute myocardial infarction. *JAMA J Am Med Assoc*. 1999;281(5):427–431.
21. Huerta C, Varas-Lorenzo C, Castellsague J, García Rodríguez LA. Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population. *Heart*. 2006;92(11):1610–1615.
22. Maru S, Koch GG, Stender M, et al. Antidiabetic drugs and heart failure risk in patients with type 2 diabetes in the U.K. primary care setting. *Diabetes Care*. 2005;28(1):20–26.
23. Derby LE, Myers MW, Jick H. Use of dexfenfluramine, fenfluramine and phentermine and the risk of stroke. *Br J Clin Pharmacol*. 2001;47(5):565–569.
24. Gibbs RGJ, Newson R, Lawrenson R, Greenhalgh RM, Davies AH. Diagnosis and initial management of stroke and transient ischemic attack across UK health regions from 1992 to 1996: experience of a national primary care database. *Stroke*. 2001;32(5):1085–1090.
25. Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology*. 2004;62(4):563–568.
26. Jick H, Zornberg G, Jick S, Seshadri S, Drachman D. Statins and the risk of dementia. *Lancet*. 2000;356(9242):1627–1631.
27. Imfeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: a population-based case-control study. *J Am Geriatr Soc*. 2012;60(5):916–921.
28. Soriano JB, Vestbo J, Pride NB, Kiri V, Maden C, Maier WC. Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. *Eur Respir J*. 2002;20(4):819–825.
29. Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the general practice research database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax*. 1999;54(5):413–419.
30. Hubbard R. Adult height and cryptogenic fibrosing alveolitis: a case-control study using the UK General Practice Research Database. *Thorax*. 2000;55(10):864–866.
31. Watts RA, Al-Taiar A, Scott DGI, Macgregor AJ. Prevalence and incidence of Wegener's granulomatosis in the UK general practice research database. *Arthritis Rheum*. 2009;61(10):1412–1416.
32. Watson DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch Intern Med*. 2002;162(10):1105–1110.
33. Thomas SL, Edwards CJ, Smeeth L, Cooper C, Hall AJ. How accurate are diagnoses for rheumatoid arthritis and juvenile idiopathic arthritis in the general practice research database? *Arthritis Rheum*. 2008;59(9):1314–1321.
34. Jick SS, Choi H, Li L, McInnes IB, Sattar N. Hyperlipidaemia, statin use and the risk of developing rheumatoid arthritis. *Ann Rheum Dis*. 2009;68(4):546–551.
35. Cai S, GarciaRodriguez LA, Massa-Gonzalez EL, Hernandez-Diaz S. Uncomplicated peptic ulcer in the UK: trends from 1997 to 2005. *Aliment Pharmacol Ther*. 2009;30(10):1039–1048.
36. Fleming KM, Aithal GP, Solaymani-Dodaran M, Card TR, West J. Incidence and prevalence of cirrhosis in the United Kingdom, 1992–2001: a general population-based study. *J Hepatol*. 2008;49(5):732–738.
37. Van Staa TP, Travis S, Leufkens HGM, Logan RF. 5-aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. *Gastroenterology*. 2004;126(7):1733–1739.

38. Dregan A, Moller H, Murray-Thomas T, Gulliford MC. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. *Cancer Epidemiol.* 2012;36(5):425–429.
39. Lewis JD, Bilker WB, Brensinger C, Deren JJ, Vaughn DJ, Strom BL. Inflammatory bowel disease is not associated with an increased risk of lymphoma. *Gastroenterology.* 2001;121(5):1080–1087.
40. Harvey JN. Estimation of the prevalence of diagnosed diabetes from primary care and secondary care source data: comparison of record linkage with capture-recapture analysis. *J Epidemiol Community Heal.* 2002;56(1):18–23.
41. Morgan CL, Currie CJ, Stott NCH, Smithers M, Butler CC, Peters JR. Estimating the prevalence of diagnosed diabetes in a health district of Wales: the importance of using primary and secondary care sources of ascertainment with adjustment for death and migration. *Diabet Med.* 2000;17(2):141–145.
42. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ.* 2013;346(3):f2350.
43. Kaplan DE, Dai F, Aytaman A, et al. Development and performance of an algorithm to estimate the child-turcotte-pugh score from a national electronic healthcare database. *Clin Gastroenterol Hepatol.* 2015;13(13):2333–2341.e6.
44. Jepsen P, Lash TL, Vilstrup H. The clinical course of alcoholic cirrhosis: development of comorbid diseases. A Danish nationwide cohort study. *Liver Int.* 2016;36(11):1696–1703.
45. Chapman BP, Weiss A, Fiscella K, Muennig P, Kawachi I, Duberstein P. Mortality risk prediction: can comorbidity indices be improved with psychosocial data? *Med Care.* 2015;53(11):909–915.

Supplementary materials

Table S1 Read code list for non-alcohol substance misuse

Read code	Description
I46C.00	Failed heroin detoxification
I46E.00	H/O: recreational drug use
I46F.00	H/O: drug abuse
IJI.00	Suspected drug abuse
IJI0.00	Suspected abuse soft drugs
IJI1.00	Suspected abuse hard drugs
IT.00	History of substance misuse
IT0.00	H/O heroin misuse
IT00.00	H/O daily heroin misuse
IT01.00	H/O weekly heroin misuse
IT02.00	Previous history of heroin misuse
IT03.00	H/O infrequent heroin misuse
IT1.00	H/O methadone misuse
IT10.00	H/O daily methadone misuse
IT11.00	H/O weekly methadone misuse
IT13.00	Previous history of methadone misuse
IT2.00	H/O ecstasy misuse
IT20.00	H/O daily ecstasy misuse
IT21.00	H/O weekly ecstasy misuse
IT22.00	H/O infrequent ecstasy misuse
IT23.00	Previous history of ecstasy misuse
IT3.00	H/O benzodiazepine misuse
IT30.00	H/O daily benzodiazepine misuse
IT31.00	H/O weekly benzodiazepine misuse
IT32.00	H/O infrequent benzodiazepine misuse
IT33.00	Previous history of benzodiazepine misuse
IT4.00	H/O amphetamine misuse
IT40.00	H/O daily amphetamine misuse
IT41.00	H/O weekly amphetamine misuse
IT42.00	H/O infrequent amphetamine misuse
IT43.00	Previous history of amphetamine misuse
IT5.00	H/O cocaine misuse
IT50.00	H/O daily cocaine misuse
IT51.00	H/O weekly cocaine misuse
IT52.00	H/O infrequent cocaine misuse
IT53.00	Previous history of cocaine misuse
IT6.00	H/O crack cocaine misuse
IT60.00	H/O daily crack cocaine misuse
IT61.00	H/O weekly crack cocaine misuse
IT62.00	H/O infrequent crack cocaine misuse
IT63.00	Previous history of crack cocaine misuse
IT7.00	H/O hallucinogen misuse
IT73.00	Previous history of hallucinogen misuse
IT8.00	H/O cannabis misuse
IT80.00	H/O daily cannabis misuse
IT81.00	H/O weekly cannabis misuse
IT82.00	H/O infrequent cannabis misuse
IT83.00	Previous history of cannabis misuse
IT9.00	H/O solvent misuse
IT90.00	H/O daily solvent misuse
IT91.00	H/O weekly solvent misuse
IT93.00	Previous history of solvent misuse
ITA.00	H/O barbiturate misuse
ITB0.00	H/O daily major tranquilizer misuse

(Continued)

Table S1 (Continued)

Read code	Description
ITD.00	H/O opiate misuse
ITD0.00	H/O daily opiate misuse
ITD1.00	H/O weekly opiate misuse
ITD2.00	H/O infrequent opiate misuse
ITD3.00	Previous history of opiate misuse
ITE.00	Uses heroin on top of substitution therapy
ITF.00	Does not use heroin on top of substitution therapy
IV.00	Drug misuse behavior
IV0.00	Misuses drugs
IV00.00	Occasional drug user
IV01.00	Long-term drug misuser
IV02.00	Poly-drug misuser
IV0C.00	Drug addict
IV0E.00	Health problem secondary to drug misuse
IV26.00	Misused drugs in past
IV3.00	Drug injection behavior
IV38.00	Sharing of drug-injecting equipment
IV6.00	Drug-related offending behavior
IV64.00	Illicit drug use
IV65.00	Heroin misuse
IV66.00	Ecstasy misuse
46Q5.00	Urine amphetamine
46Q5.11	Amphetamine in urine
46QA.00	Urine cocaine
63C6.00	Maternal drug abuse
8AA.00	Drug abuse monitoring
8H7x.00	Referral to drug abuse counselor
8HHL.00	Referral to community drug dependency team
8Hh1.00	Self-referral to substance misuse service
E240.11	Heroin dependence
E242.00	Cocaine type drug dependence
E242000	Cocaine dependence, unspecified
E242100	Cocaine dependence, continuous
E242200	Cocaine dependence, episodic
E242300	Cocaine dependence in remission
E242z00	Cocaine drug dependence NOS
E244.00	Amphetamine or other psychostimulant dependence
E244000	Amphetamine or psychostimulant dependence, unspecified
E244100	Amphetamine or psychostimulant dependence, continuous
E244200	Amphetamine or psychostimulant dependence, episodic
E244300	Amphetamine or psychostimulant dependence in remission
E244z00	Amphetamine or psychostimulant dependence NOS
E25.00	Nondependent abuse of drugs
E256.00	Nondependent cocaine abuse
E256000	Nondependent cocaine abuse, unspecified
E256100	Nondependent cocaine abuse, continuous
E256200	Nondependent cocaine abuse, episodic
E256300	Nondependent cocaine abuse in remission
E256z00	Nondependent cocaine abuse NOS
E257.00	Nondependent amphetamine or other psychostimulant abuse
E257000	Nondependent amphetamine/psychostimulant abuse, unspecified
E257100	Nondependent amphetamine/psychostimulant abuse, continuous
E257200	Nondependent amphetamine or psychostimulant abuse, episodic
E257300	Nondependent amphetamine/psychostimulant abuse in remission
E257z00	Nondependent amphetamine or psychostimulant abuse NOS
E259.00	Nondependent mixed drug abuse

(Continued)

Table S1 (Continued)

Read code	Description
E259000	Nondependent mixed drug abuse, unspecified
E259100	Nondependent mixed drug abuse, continuous
E259200	Nondependent mixed drug abuse, episodic
E259300	Nondependent mixed drug abuse in remission
E259z00	Nondependent mixed drug abuse NOS
E25y.00	Nondependent other drug abuse
E25y000	Nondependent other drug abuse, unspecified
E25y100	Nondependent other drug abuse, continuous
E25y200	Nondependent other drug abuse, episodic
E25y300	Nondependent other drug abuse in remission
E25yz00	Nondependent other drug abuse NOS
Eu11212	Heroin addiction
Eu14.00	Mental and behavioral disorders due to use of cocaine
Eu14000	Mental and behavior disorder due to use cocaine: acute intoxication
Eu14100	Mental and behavior disorder due to use of cocaine: harmful use
Eu14200	Mental and behavior disorder due to use of cocaine: dependence syndrome
Eu14211	Drug addiction – cocaine
Eu14300	Mental and behavior disorder due to use of cocaine: withdrawal state
Eu14500	Mental and behavior disorder due to use of cocaine: psychotic disorder
Eu1A.00	Mental and behavioral disorders due to use of crack cocaine
Eu1A000	Mental and behavioral disorders due to use of crack cocaine: acute intoxication
Eu1A100	Mental and behavioral disorders due to use of crack cocaine: harmful use
Eu1Az00	Mental and behavioral disorders due to use of crack cocaine: unspecified mental and behavioral disorder
R10B000	Finding of cocaine in blood
SL50100	Heroin poisoning
SL85000	Cocaine poisoning
TJ85000	Adverse reaction to cocaine
U205.11	Overdose – heroin
U608312	Adverse reaction to cocaine
Z1Q6214	Heroin maintenance
ZC16.00	Abuse of drugs to lose weight
ZV11500	Personal history of drug abuse by injection
ZV6D700	Drug abuse counseling and surveillance

Abbreviations: H/O, history of; NOS, not otherwise specified.

Table S2 Socioeconomic status (as per IMD 2010)-stratified discrimination of the comorbidity models

Quintile of socioeconomic status	Patients (n)	Patients (%)	Charlson Comorbidity Index C statistic	95% CI	CirCom index C statistic	95% CI
Missing socioeconomic status	19	0.00	0.71	0.48–0.94	0.62	0.36–0.88
1=least deprived	856	0.17	0.63	0.60–0.66	0.64*	0.62–0.67
2	987	0.19	0.65	0.62–0.67	0.64	0.62–0.67
3	986	0.19	0.61	0.59–0.64	0.62	0.60–0.65
4	1059	0.21	0.60	0.58–0.63	0.62	0.59–0.64
5=most deprived	1211	0.24	0.61	0.59–0.63	0.63**	0.61–0.65

Notes: * $p=0.03$ between discrimination for the Charlson Comorbidity Index and the CirCom score. ** $p=0.007$ between discrimination for the Charlson Comorbidity Index and the CirCom score. IMD, *The English Indices of Multiple Deprivation 2010*.²

Abbreviation: CI, confidence interval.

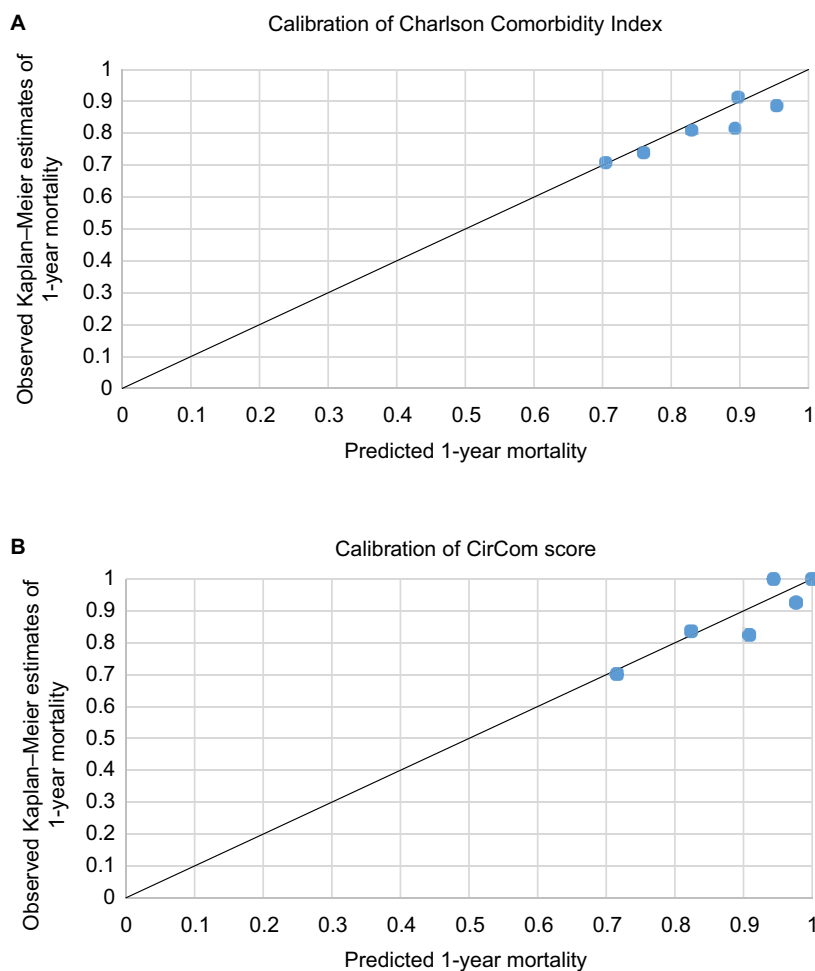


Figure S1 Calibration plots for observed 1-year mortality from Kaplan-Meier estimates against predicted 1-year mortality from the Cox proportional hazards model from the (A) Charlson Comorbidity Index and (B) CirCom score.

Note: Calculated using the `stcoxgrrp` ado program.³

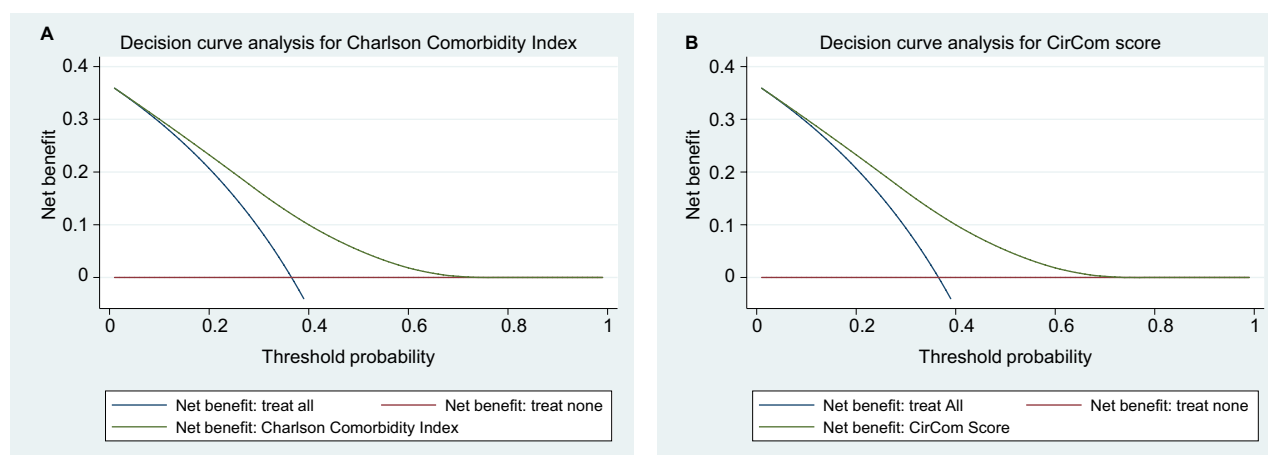


Figure S2 Decision curve analysis plots for (A) the Charlson Comorbidity Index and (B) the CirCom score.

Note: Calculated using the `dca` ado program.⁴

References

1. Quint JK, Mullerova H, DiSantostefano RL, et al. Validation of chronic obstructive pulmonary disease recording in the clinical practice research datalink (CPRD-GOLD). *BMJ Open*. 2014;4(7):e005540.
2. Department for Communities and Local Government [UK]; 2011. The English indices of deprivation 2010. Available from: <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010>. Accessed December 21, 2017.
3. Royston P. Tools for checking calibration of a Cox model in external validation: prediction of population-averaged survival curves based on risk groups. *Stata Journal*. 2015;15(1):275–297.
4. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making*. 2006;26(6):565–574.

Clinical Epidemiology

Publish your work in this journal

Clinical Epidemiology is an international, peer-reviewed, open access, online journal focusing on disease and drug epidemiology, identification of risk factors and screening procedures to develop optimal preventative initiatives and programs. Specific topics include: diagnosis, prognosis, treatment, screening, prevention, risk factor modification,

Submit your manuscript here: <https://www.dovepress.com/clinical-epidemiology-journal>

systematic reviews, risk and safety of medical interventions, epidemiology and biostatistical methods, and evaluation of guidelines, translational medicine, health policies and economic evaluations. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use.

Dovepress