**Elixhauser outperforms Charlson comorbidity index in prognostic value after ACS: insights from a national registry**

**Running title:** Charlson and Elixhauser comorbidity measures comparison in ACS

Fangyuan Zhang1, Yida Chiu3, Joie Ensor1, 2, Mohamed O. Mohamed1,4, George Peat2, Mamas A. Mamas1,4

1 Keele Cardiovascular Research Group, Centre for Prognosis Research, Institutes of Applied Clinical Science and Primary Care and Health Sciences, Keele University, UK

2 School of Medicine, Keele University, UK

3 Papworth Trials Unit Collaboration, Royal Papworth Hospital, Cambridge, UK

4 Department of Cardiology, Royal Stoke University Hospital, Stoke-on-Trent, UK

Correspondence to:

Mamas A. Mamas

Professor of Cardiology

Keele Cardiovascular Research Group,

Centre for Prognosis Research,

Institute for Primary Care and Health Sciences,

Keele University, UK

mamasmamas1@yahoo.co.uk

Word count (including abstract and references): 4464

# Abstract

**Objective:** To compare the performance of risk adjustment models using the Elixhauser and Charlson comorbidity scores in predicting in-hospital outcomes of ACS patients from a nationwide administrative database.

**Study design and Setting:** All hospitalisations for ACS in the United States between 2004 and 2014 (n=7,201,900) were retrospectively analysed. We used ECS and CCI score based on ICD-9 codes to define comorbidity variables. Logistic regression models were fitted to three in-hospital outcomes, including mortality, Major Acute Cardiovascular & Cerebrovascular Events (MACCE) and bleeding. The prognostic values of ECS and CCI after adjusting for known confounders, were compared using the C-statistic, Akaike information criterion (AIC) and Bayesian information criterion (BIC).

**Results:** The statistical performance of models predicting all in-hospital outcomes demonstrated that the ECS had superior prognostic value compared to the CCI, with higher C-statistics and lower AIC and BIC values associated with the former.

**Conclusion:** This is the first study that compared the prognostic value of the ECS and CCI scores in predicting multiple ACS outcomes, based on their scoring systems. Better discrimination and goodness of fit was achieved with the Elixhauser method across all in-hospital outcomes studied.

**Key words:** acute coronary syndrome, comorbidity index, Charlson Score, Elixhauser score, model performance, model comparison.

# Introduction

Acute coronary syndrome (ACS) accounts for approximately 13% of deaths a year in the United States 1 and is commonly encountered in elderly populations who are increasingly multi-morbid, due to increases in life expectancy and advances in medical care.2-4 Comorbidity is defined as the coexistence of multiple conditions that co-exist with an index medical condition at an individual patient level.5 ACS rarely occurs in isolation, with patients often having more than one additional co-morbid condition.6-8 The burden of comorbidity is important in patients admitted with ACS, as it may impact on their outcomes and the treatments that they are offered.6,9,10 There is increasing interest in using measures of comorbidity burden in developing risk-stratification tools in patients with ACS.11

The Charlson Comorbidity Index (CCI)12,13 and the Elixhauser Comorbidity Score (ECS)14,15 are well-validated measures of comorbid burden, and both have been broadly used for risk assessment in patients with ACS.6,7 Whilst a small number of studies have compared the performance of the ECS and CCI in patients with ACS, with studies reporting that ECS might outperform than CCI in the prediction of ACS outcomes,16,17 these studies are limited for several reasons. Most of these studies are derived from patient populations with small sample sizes or come from cohorts that are of historical interest.17 Many of these studies have used component comorbidities of the CCI and ECS as binary prognostic factors in the predictive models, prior to the development of the ECS scoring system16-18 which limits their applicability in contemporary practice, particularly when both scoring systems are well established and in widespread use. The primary objective of this analysis was to compare the prognostic value of the CCI and ECS in predicting clinical outcomes using their scoring systems in a national cohort of patients admitted with an ACS, to improve the risk-adjustment methods in assessing ACS outcomes.

# Method

## Data source

All hospital discharges with ACS in the United States (US) from the year 2004-2014 were extracted from the National Inpatient Sample (NIS), which is the largest publicly available all-payer inpatient healthcare database in the United States and is sponsored by the Agency for Health Research and Quality (AHRQ).19 The NIS contains more than 7 million hospital discharges annually in the US. From 2012, the NIS database includes a 20% stratified sample of hospitalizations from all participating hospitals to improve national estimates. Weights were recorded for each discharge record, which were applied in the analysis to obtain national estimates.

## Study population and design

The study period was from January 2004 to December 2014. All patients aged 18 years or older with a principal diagnosis of ACS were included and identified by International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes of 410.xx (acute myocardial infarction (MI)) and 4111 (Unstable Angina (UA)).

Baseline patient characteristics include age, gender, race, admission day (weekday or weekend), median household income for patient’s ZIP code, Charlson comorbidities, Elixhauser comorbidities, other clinically relevant comorbidities (smoking, atrial fibrillation, long-term use of anticoagulants, previous percutaneous coronary intervention (PCI), previous coronary artery bypass grafting (CABG)), and procedural characteristics such as PCI, coronary angiography (CA), CABG, thrombolysis and intra-aortic balloon pump (IABP). The NIS database includes up to 30 diagnosis codes and 15 procedure codes, which were used to identify relevant conditions, procedures and comorbidities. A list of ICD-9-CM codes used to extract this information is provided in **Supplementary Table 1**.

## Study outcomes

In-hospital mortality, MACCE (Major Acute Cardiovascular & Cerebrovascular Events) and major bleeding were treated as the primary clinical outcomes. Outcomes were identified using ICD-9-CM codes (**Supplementary Table 2**). MACCE was defined as in-hospital mortality, cardiac complications, acute ischemic stroke, and vascular complications (vascular injury). Major bleeding included any gastrointestinal, intracranial, retroperitoneal and procedure-related haemorrhage. Cardiac complications were defined as a composite of pericardial effusion, cardiac tamponade, coronary dissection or need for pericardiocentesis).

## Charlson/Deyo and Elixhauser

In this analysis, the Deyo definition of the Charlson comorbidity index (CCI)12 was used, which included 17 comorbidities. The Elixhauser comorbidity score (ECS) developed by Van Walraven et al.14 was utilized and included 29 comorbidities. The CCI and ECS were developed by assigning a weighting to each included comorbid condition based on its observed association with 1-year all-cause mortality (**Supplementary Table 1**). These weightings are then used to provide an overall score for each patient representing their comorbidity burden. Total CCI scores for each patient were categorised into four commonly used levels:12 “0” no comorbidity, “1” mild comorbid condition, “2” moderate condition, “≥3” severe comorbid burden. ECS scores were categorized into five commonly used levels14 that correspond to ECS<0, =0, 1-5, 6-13, ≥14.

## Statistical analysis

Description of the data is presented using the median and interquartile ranges (IQR) for continuous variables and number and percentage for categorical variables. Multiple imputation by chained equations (MICE) was conducted to impute missing data in age, sex, race, household income and mortality variables, with the number of imputation datasets equal to the highest proportion of missing for any particular variable.20,21 Model parameters and performance statistics were estimated within imputation datasets and combined using Rubin’s Rules.22 All variables included in the analysis model, potential confounders and outcomes were included in the imputation model to ensure congeniality between analysis and imputation models.23

A series of multivariable logistic regression models were utilized to compare the relative contribution of the CCI and ECS to the prediction of in-hospital adverse outcomes including mortality, major bleeding and MACCE, after adjusting for variables with known clinical importance and potential confounders. Seven logistic regression models were fitted for each of the outcomes, resulting in a total of 21 models: 1) the basic model only included patient demographic information, which provided a baseline measurement for evaluating the relative contribution of controlling for comorbidities; 2) based on the basic model, the second model entered a block of other specific risk factors; 3) in the third model, procedural variables were added; 4-7) based on the third model, the CCI and ECS scores were added independently. Both the CCI and ECS were treated as categorical variables (as commonly used in practice and proposed by the original authors), and as continuous variables assuming linearity. For example, the following seven models were compared for the outcome in-hospital mortality:

* Model 1: Age, gender, race, median income, day of admission, year
* Model 2: Model 1 + type of ACS, smoking, atrial fibrillation, long-term use of anticoagulants, prior PCI, prior CABG.
* Model 3: Model 2 + PCI, CA, thrombolysis, CABG, IABP.
* Model 4: Model 3 + categorical CCI.
* Model 5: Model 3 + continuous CCI.
* Model 6: Model 3 + categorical ECS.
* Model 7: Model 3 + continuous ECS.

We also examined simple non-linear forms of the continuous ECS and continuous CCI as a sensitivity analysis, which included:

* Model 8: Model 5 + continuous $CCI^{2}$.
* Model 9: Model 5 + continuous $CCI^{2}$ + continuous $CCI^{3}$.
* Model 10: Model 7 + continuous $ECS^{2}$
* Model 11: Model 7 + continuous $ECS^{2}$ + continuous $ECS^{3}$

To evaluate the prognostic value of the comorbidity measures, for each of the eleven models, for all outcomes, we calculated the C-statistic,24 Akaike information criterion (AIC)25,26 and Bayesian information criterion (BIC)26,27. We calculated the pooled C-statistic for each model-outcome combination from the imputed datasets. Given the dataset was extremely large (> 7 million records), we refrained from testing for a difference in C-statistics, as any p-value would be an unreliable indicator. Hence, we examined point estimates and 95% confidence intervals (CI) for each C-statistic using the bootstrap procedure to compare model discrimination. We broadly considered 95% CIs that crossed each other to indicate that there was not a statistically significant difference between the discrimination of the models being compared, but emphasize the width of the interval.28,29 AIC and BIC provide a means to assess a model’s goodness of fit, while penalising models with greater complexity.25,27 The AIC and BIC can be compared as a difference relative to the lowest value, among models having the same dependent variable but with different numbers of independent variables. Unlike the likelihood ratio test, comparing AIC or BIC does not require models be nested.30,31 Models with the lowest AIC or BIC were preferred. A difference in AIC or BIC between models of < 2, 4-7, and >10 was interpreted as no, weak, and strong evidence of improved model fit, respectively.32

All analyses were conducted using survey estimation commands to obtain a national estimate, which is the recommendation from AHRQ. Model analyses using C-statistics were performed using STATA version 14.0, analyses using AIC and BIC were performed using “survey” packages33 using R language version 3.6.2.

# Results

From 2004 to 2014, a total of 7,201,900 weighted records ≥18 years of age with a principal diagnosis with ACS were included in the analysis, with at most 20% missing data in a single variable.Descriptive statistics of baseline characteristics, treatments, outcomes, and comorbidities before multiple imputations are listed in **Table 1**. 33.1% of patients had a ST-segment elevation myocardial infarction (STEMI), the median age of the whole dataset was 67 (56-79) years old, and women accounted for 40.3% of the population. The prevalence of diabetes was 33.9%, with 10.2% of the population with a previous history of MI. 62% of the population received CA and 40.7% of the population received revascularisation with PCI.

**Table 2** presents the C-statistics from the seven different logistic regression models predicting the risk of each of the in-hospital outcomes of interest; mortality, MACCE and major bleeding. For every outcome, compared to the baseline models, adding risk factors, interventions or comorbidity measures consistently improved the model’s performance as evidenced by an increase in C-statistic. For example, when predicting mortality, the C-statistic of the model including interventions (Model 3) was 0.818 (95% CI: 0.817, 0.819), which was substantially higher than the baseline model (Model 1: 0.692 (95% CI: 0.690, 0.693)) and the model with risk factors added (Model 2: 0.752 (95% CI: 0.750, 0.753)). For all outcomes in this study, models using the ECS as a measure of comorbidity, showed higher C-statistics compared to models using the CCI, irrespective of whether the score was defined as a categorical or continuous variable. Models with the highest discrimination for mortality and MACCE were those incorporating the ECS as a continuous score (Model 7: 0.837 (95% CI: 0.836, 0.839) and 0.776 (95% CI: 0.774, 0.777), respectively), and as a categorical score (Model 6: 0.837 (95% CI: 0.836, 0.838) and 0.775 (95% CI: 0.773, 0.776), respectively). However, differences in discrimination between model 6 (where ECS was used as a categorical score) and model 7 (where ECS was used as a continuous score) for in hospital mortality and MACCE were not significantly different **(Fig.1)**. We observed that the best model for the prediction of bleeding was using ECS as a categorical score (Model 6: 0.668 (95% CI: 0.666, 0.670)), closely followed by the model using ECS as a continuous score (Model 7: 0.659 (95% CI: 0.657, 0.661)).

**Table 3** and **Fig.2** provide an overview of AIC and BIC values for model goodness-of-fit. Similar to the C-statistics results, model goodness-of-fit was incrementally improved by adding risk factors, interventions, and comorbidities into the baseline model. For all outcomes studied, AIC or BIC values of models using ECS as a measure of comorbidity were much lower than (difference > 10) those of models using CCI as a measure of comorbidity, which implies ECS consistently outperformed CCI on model goodness-of-fit. Continuous ECS score resulted in superior model fit to categorical ECS for mortality and MACCE but not for bleeding (where ECS categorical was superior): findings which were again consistent with the pattern of C-statistic results.

The linearity assumption for the continuous CCI model or continuous ECS model was explored in the sensitivity analysis. Adding non-linear terms of ECS or CCI into the model of in-hospital mortality did not improve the model discrimination (95%CI of C-statistics crossed) while this improved the discriminated ability of the model of in-hospital bleeding. For all outcomes, there were improvements in model goodness of fit when included non-linear terms into models with continuous CCI or continuous ECS. In addition, odds ratios (ORs) of almost all non-linear terms were close to 1 or their 95%CI included 1 (e.g., $ECS^{3}$for mortality: OR:1.00001 95%CI: 0.99999-1.00003). Detailed results were provided in **Supplementary Table 3**. As another sensitivity analysis, we also re-ran models without the inclusion of interventions such as cardiac catheterization or receipt of PCI, and our findings remained consistent, in that the Elixhauser score outperformed the Charlson score (**Supplementary Table 4**).

# Discussion

This study extends and updates previous comparative studies of the predictive performance of Charlson and Elixhauser comorbidities indexes, by applying both methods’ scoring systems to a nationwide database of hospitalization of ACS patients with multiple adverse outcomes from 2004-2014. Our findings suggest that the ECS method significantly outperforms the CCI method in predicting important in-hospital adverse outcomes studied in terms of model discrimination and goodness of fit, irrespective of whether the comorbidity measures were defined as categorical or continuous variables. In summary from two different performance measures, models using the ECS measure as a continuous variable might provide better goodness of fit (and hence risk adjustment) although the improvement in model discrimination over the models using it as a categorised score is minor and, for predicting bleeding, may even be inferior.

There are several studies that have been conducted to compare the predictive performance of the CCI and ECS measures,16,17,34 which support our findings, albeit in different clinical settings. A study using data between 2008-2009 from five European countries indicated that the ECS had better performance than the CCI in predicting 30-day mortality in acute MI patients.16 Southern et al. also reported that models based on the ECS method discriminated better than the CCI using Canadian administrative data on 4,833 patients with MI.34 However, all the studies that included ECS measure applied its comorbidities as separate binary variables in the model rather than using its scoring system due to the lack of the weighting algorithm of the original ECS method at that time. Nevertheless, even though the CCI score is widely used in clinical practice, previous studies still used Charlson comorbidities as individual binary variables instead of using Charlson weights to compare with ECS. It is possible that modelling the ECS and CCI in this way could lead to the models using Elixhauser comorbidities having a higher C-statistic or being ​overfitted compared to the ones using Charlson comorbidities as Elixhauser contains nearly twice the number of conditions,35 potentially leading to bias. Our study utilised both the Charlson and Elixhauser's weighting systems for a direct comparison of their predictive performance across three important in-hospital outcomes. In addition, our analysis included over 7 million ACS admissions that gives our analysis the statistical power to detect even small differences in comparative performance.

Our findings on in-hospital mortality contribute further evidence to the findings of three earlier studies16,17,34 that also demonstrated that the ECS more optimally predicted in-hospital mortality compared to the CCI score. For example, Stukenborg et al. found the ECS outperformed the CCI in predicting in-hospital mortality in 5 clinical categories of California hospital patients from 1994 to 1997 (acute MI, congestive heart failure, chronic obstructive pulmonary disease, hypertension with complications, and acute cerebrovascular disease).34 In addition, our study not only investigated in-hospital mortality but also included other adverse outcomes such as in-hospital MACCE and bleeding, which built upon prior comparative studies of the ECS and CCI that only considered mortality, and might contribute to a greater general understanding of the performance of comorbidity measures, particularly when considering outcomes other than mortality. We report that the ECS displayed better performance than the CCI score for all adverse outcomes studied irrespective of whether the comorbidity score was treated as a categorical or continuous variable in the model. Not only that, but our results also showed models using the ECS as a continuous variable were a little better in terms of model goodness of fit, than ones using it as a categorical variable, when predicting mortality and MACCE. This observation may be due to underestimation of variation caused by categorising a continuous variable. When categorising a continuous variable at several cut points, we are treating individuals either side of a cut-point as distinctly different, when they may in fact be very similar, and individuals within a group as similar, when there may in fact be large variation in outcome risks within the group.36

European Society of Cardiology (ESC) clinical practice guidelines in patients with ACS suggests clinicians should take comorbidity into account for risk-adjustment in predicting patient prognosis or developing treatment strategies as comorbidity can have a substantial impact on patient outcomes and decision-making of the intervention.37 However, there is so far no explicit definition in what comorbidity indices should be used to measure the comorbid burden in ACS patients. Our study reports that risk-adjustment models using the ECS to define comorbid burden had better performance in predicting in-hospital outcomes than the ones using the CCI. Clinicians are advised to focus efforts in using ECS to define the comorbid burden and consider integrating the ECS into the existing ACS prognosis scores such as the global registry of acute coronary events (GRACE) risk prediction index.38

This study has some limitations, that are common to all research using administrative datasets. The NIS dataset has potential selection bias due to coding errors,39 as many administrative databases do not have external validation. Furthermore, our analysis was limited to clinical outcomes during the hospital stay because data for post discharge outcomes are not captured in the NIS database, which limits our ability to conduct comparisons of comorbidity measures when investigating longer term outcomes. Nevertheless, our findings are still clinically relevant, particularly when related to in-hospital outcomes, for example when risk adjusting and benchmarking of in-hospital clinical outcomes. However, we cannot speculate whether ECS still outperforms CCI in long-term ACS outcomes. However, a previous study 18 reported that the performance of ECS was better than CCI in predicting long-term (1-year) mortality in patients with acute MI, which was consistent with our findings in the in-hospital outcomes. Even so, this previous study still had the limitations highlighted previously (did not use scores), therefore, our findings should drive further research into the performance of ECS and CCI relating to post discharge outcomes. Moreover, we found that the performance of the Elixhauser score in a continuous form was better than the performance of it in a categorical form for in-hospital mortality and MACCE. However, this conclusion is based on assuming that the continuous form of the ECS (and CCI) variable has a linear relationship with the outcome.40 We explored this assumption by adding simple non-linear terms (i.e., ECS/CCI score squared and cubed) to the models that used the ECS/CCI as a continuous score. Although the model fit was improved when including non-linear terms, the size of the effects (ORs) of the non-linear terms we observed was extremely close to 1 or at least half of their 95%CIs crossed 1, which implied no strong evidence of a non-linear relationship between the continuous form of ECS/CCI and clinical outcomes. Given the complexity of our analyses, which included using multiple imputation and survey weightings, we were unable to explore more complex non-linear functions such a fractional polynomials or splines due to computational limitations. Further research may look to explore more complex non-linear relationships between patient outcomes and comorbidity measures such as the ECI and CCI in simpler examples.

# Conclusion

In conclusion, based on analyses of nationally representative US data from 2004-2014, the Elixhauser measure outperforms the Charlson method in predicting several important in-hospital outcomes and should therefore be preferred for risk adjustment in future work to investigate whether their performance improves and whether they optimise patient centred approaches in ACS management.

# Author Contributions

**FZ-** Data curation, Formal Analysis, Writing-Original Draft, **YC-** Software, Reviewing & Editing, **MOM-** Reviewing & Editing, Supervision, **JE-** Methodology, Reviewing & Editing, Supervision, **GP-** Writing-Reviewing & Editing, Supervision, **MAM-** Conceptualization, Writing-Reviewing & Editing, Supervision.

# Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

# Reference

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: A report from the american heart association. *Circulation*. 2020;141(9):e139-e596. doi: 10.1161/CIR.0000000000000757 [doi].

2. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002;162(20):2269-2276.

3. Sanchis J, Bonanad C, Ruiz V, et al. Frailty and other geriatric conditions for risk stratification of older patients with acute coronary syndrome. *Am Heart J*. 2014;168(5):784-791. e2.

4. Graham MM, Galbraith PD, O'Neill D, Rolfson DB, Dando C, Norris CM. Frailty and outcome in elderly patients with acute coronary syndrome. *Can J Cardiol*. 2013;29(12):1610-1615.

5. Klykylo WM. Comorbidity. In: Hersen M, Sledge W, eds. *Encyclopedia of psychotherapy.* New York: Academic Press; 2002:475-479.

6. Potts J, Nagaraja V, Al Suwaidi J, et al. The influence of elixhauser comorbidity index on percutaneous coronary intervention outcomes. *Catheterization and Cardiovascular Interventions*. 2019;94(2):195-203.

7. Zhang F, Bharadwaj A, Mohamed MO, Ensor J, Peat G, Mamas MA. Impact of charlson co-morbidity index score on management and outcomes after acute coronary syndrome. *Am J Cardiol*. 2020;130:15-23.

8. Zhang F, Mohamed MO, Ensor J, Peat G, Mamas MA. Temporal trends in comorbidity burden and impact on prognosis in patients with acute coronary syndrome using the elixhauser comorbidity index score. *Am J Cardiol*. 2020.

9. Canivell S, Muller O, Gencer B, et al. Prognosis of cardiovascular and non-cardiovascular multimorbidity after acute coronary syndrome. *PloS one*. 2018;13(4):e0195174.

10. Chen H, Saczynski JS, McManus DD, et al. The impact of cardiac and noncardiac comorbidities on the short-term outcomes of patients hospitalized with acute myocardial infarction: A population-based perspective. *Clinical epidemiology*. 2013;5:439.

11. Erickson SR, Cole E, Kline-Rogers E, Eagle KA. The addition of the charlson comorbidity index to the GRACE risk prediction index improves prediction of outcomes in acute coronary syndrome. *Population health management*. 2014;17(1):54-59.

12. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of clinical epidemiology.* 1992;45(6):613-619. doi: 10.1016/0895-4356(92)90133-8.

13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Clin Epidemiol*. 1987;40(5):373-383.

14. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care*. 2009:626-633.

15. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8-27. doi: 10.1097/00005650-199801000-00004 [doi].

16. Gutacker N, Bloor K, Cookson R. Comparing the performance of the charlson/deyo and elixhauser comorbidity measures across five european countries and three conditions. *The European Journal of Public Health*. 2015;25(suppl\_1):15-20.

17. Southern DA, Quan H, Ghali WA. Comparison of the elixhauser and charlson/deyo methods of comorbidity measurement in administrative data. *Med Care*. 2004:355-360.

18. Chu Y, Ng Y, Wu S. Comparison of different comorbidity measures for use with administrative data in predicting short-and long-term mortality. *BMC health services research*. 2010;10(1):1-7.

19. NIS, HCUP Nationwide Inpatient Sample. Healthcare cost and utilization project (HCUP). 2002-20012. . 2012.

20. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: What is it and how does it work? *International journal of methods in psychiatric research*. 2011;20(1):40-49.

21. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-399. doi: 10.1002/sim.4067 [doi].

22. Rubin DB. Multiple imputation for survey nonresponse. 1987.

23. Kontopantelis E, White IR, Sperrin M, Buchan I. Outcome-sensitive multiple imputation: A simulation study. *BMC Medical Research Methodology*. 2017;17(1):2. doi: 10.1186/s12874-016-0281-5.

24. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine. *Clin Chem*. 1993;39(4):561-577.

25. H. Akaike. A new look at the statistical model identification. *IEEE Transactions on Automatic Control*. 1974;19(6):716-723. doi: 10.1109/TAC.1974.1100705.

26. Lumley T, Scott A. AIC and BIC for modeling with complex survey data. *Journal of Survey Statistics and Methodology*. 2015;3(1):1-18.

27. Schwarz G. Estimating the dimension of a model. *Annals of Statistics*. 1978;6:461-464.

28. Bland JM, Peacock JL. Interpreting statistics with confidence. *The Obstetrician & Gynaecologist*. 2002;4(3):176-180. doi: 10.1576/toag.2002.4.3.176.

29. Using confidence intervals to compare means.2019. <https://statisticsbyjim.com/hypothesis-testing/confidence-intervals-compare-means/>. Accessed Oct 4, 2020.

30. Anderson D, Burnham K. Aic myths and misunderstandings. *Website, April*. 2006.

31. Kuha J. AIC and BIC: Comparisons of assumptions and performance. *Sociological Methods & Research*. 2004;33(2):188-229. doi: 10.1177/0049124103262065.

32. Burnham KP, Anderson DR. Multimodel inference: Understanding AIC and BIC in model selection. *Sociological methods & research*. 2004;33(2):261-304.

33. Lumley T. Survey: Analysis of complex survey samples. R package version 4.0. 2020.

34. Stukenborg GJ, Wagner DP, Connors AFJ. Comparison of the performance of two comorbidity measures, with and without information from prior hospitalizations. *Med Care*. 2001;39(7):727-739.

35. Zhang Z. Too much covariates in a multivariable model may cause the problem of overfitting. *J Thorac Dis*. 2014;6(9):E196-E197. doi: 10.3978/j.issn.2072-1439.2014.08.33.

36. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ*. 2006;332(7549):1080. doi: 10.1136/bmj.332.7549.1080.

37. Corrigendum to: 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation [eur heart J 2020;doi: 10.1093/eurheartj/ehaa575]. *Eur Heart J*. 2020:ehaa895. doi: 10.1093/eurheartj/ehaa895.

38. Tang EW, Wong CK, Herbison P. Global registry of acute coronary events (GRACE) hospital discharge risk score accurately predicts long-term mortality post-acute coronary syndrome. *Am Heart J*. 2007;153(1):29-35. doi: S0002-8703(06)00896-9 [pii].

39. van Walraven C, Austin P. Administrative database research has unique characteristics that can risk biased results. *J Clin Epidemiol*. 2012;65(2):126-131. doi: 10.1016/j.jclinepi.2011.08.002 [doi].

40. Hosmer DW, David W. Stanley lemeshow, rodney X. sturdivant. *Applied logistic regression*. 2013.

stylefix