Prediction of 90-day mortality after Total Hip Arthroplasty: a simplified and externally validated model based on Swedish and English register data

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# Abstract

**OBJECTIVE:** Early mortality after total hip arthroplasty (THA) is associated with comorbidity. Diagnosis-based tools such as the Charlson or Elixhauser comorbidity indices have been used to quantify this. Those instruments are however complex and requires extensive data sets not routinely available in most doctor-patient settings. We searched for a simplified model to substitute those complex indices in predicting early mortality after THA.

**PATIENTS AND METHODS:** We studied 53,099 patients with THA due to primary osteoarthritis 2008 - 2015 from the Swedish Hip Arthroplasty Register, linked to the national population register, the National Patient Register and the longitudinal integration database for health insurance and labor market studies from Statistics Sweden. We used a bootstrap ranking procedure with logistic regression and a LASSO-type penalty to develop a prediction model for patient deaths within 90 days after surgery. Predictive power was assessed by the area under the receiver operating characteristic curve (AUC). The final model was applied to British data for external validation.

**RESLUTS:** The unadjusted cumulative 90-day survival was 99.7 % (95 % CI: 99.6 - 99.7). Best predictive performance for 90-day mortality was found for a model combining age, sex, ASA, cancer, CNS, kidney disease, obesity, anemia and heart condition (AUC = 0.78 (0.75-0.82)). This model was superior to the established but complex Charlson comorbidity index (AUC = 0.66 (0.62-0.70)), and the Elixhauser comorbidity score (AUC = 0.64 (0.59-0.68)). A web calculator to aid clinical usage was published at <https://erikbulow.shinyapps.io/thamortpred/>.

**CONCLUSION:** We found a relatively simple prediction model of 90 day mortality after total hip arthroplasty. This model requires less data and is easier to calculate compared to previously well-known comorbidity indices.

# Introduction

The presence of pre-surgery comorbidity is associated with poorer outcome after the insertion of total hip arthroplasty (THA) (Inacio et al. 2015), as well as inferior patient-reported outcomes (Gordon et al. 2013; Hofstede et al. 2016). In research settings, comorbidity is commonly measured using multi-faceted diagnosis- or prescription-based coding algorithms (Bozic et al. 2013). Inacio et al. (2016) studied the ability of the Charlson (CCI) and Elixhauser (ECI) Comorbidity indices to to predict mortality after THA and total knee arthroplasty. These comorbidity measures are quite complex to estimate and are based on the availability of extensive data sets including in- and outpatient data on ICD-codes. Oftentimes, such data sets can only be created by linking several population-based registries, raising both ethical and practical concerns. Also, each of the comorbidity indices exist in numerous versions (Sundararajan et al. 2004; Deyo, Cherkin, and Ciol 1992; Quan et al. 2011; Cleves, Sanchez, and Draheim 1997; Walraven et al. 2009). Interpretation and comparison between different studies is therefore difficult.

Comorbidity data have also been used in several universal and arthroplasty-specific risk prediction tools to make risk profiles for individual patients. In the context of trauma, prediction tools are common, and it has been possible to reduce the number of variables without losing predictive power (Gerdin et al. 2016). No model has so far been broadly accepted for elective THA however (Manning, Edelstein, and Alvi 2016; Bülow et al. 2017). An easily applicable tool with few dimensions is thus needed, both in research and in clinical practice. We aimed to find such a model to predict the risk of 90-day postoperative mortality after elective THA.

# Patients and Methods

Patients recorded in the Swedish Hip Arthroplasty Register (SHAR) with cemented primary hip osteoarthritis 2008 - 2015 were included in the development phase of the study (Figure 1). Only the last operated hip was accounted for in patients with bilateral THA (Bülow 2019).

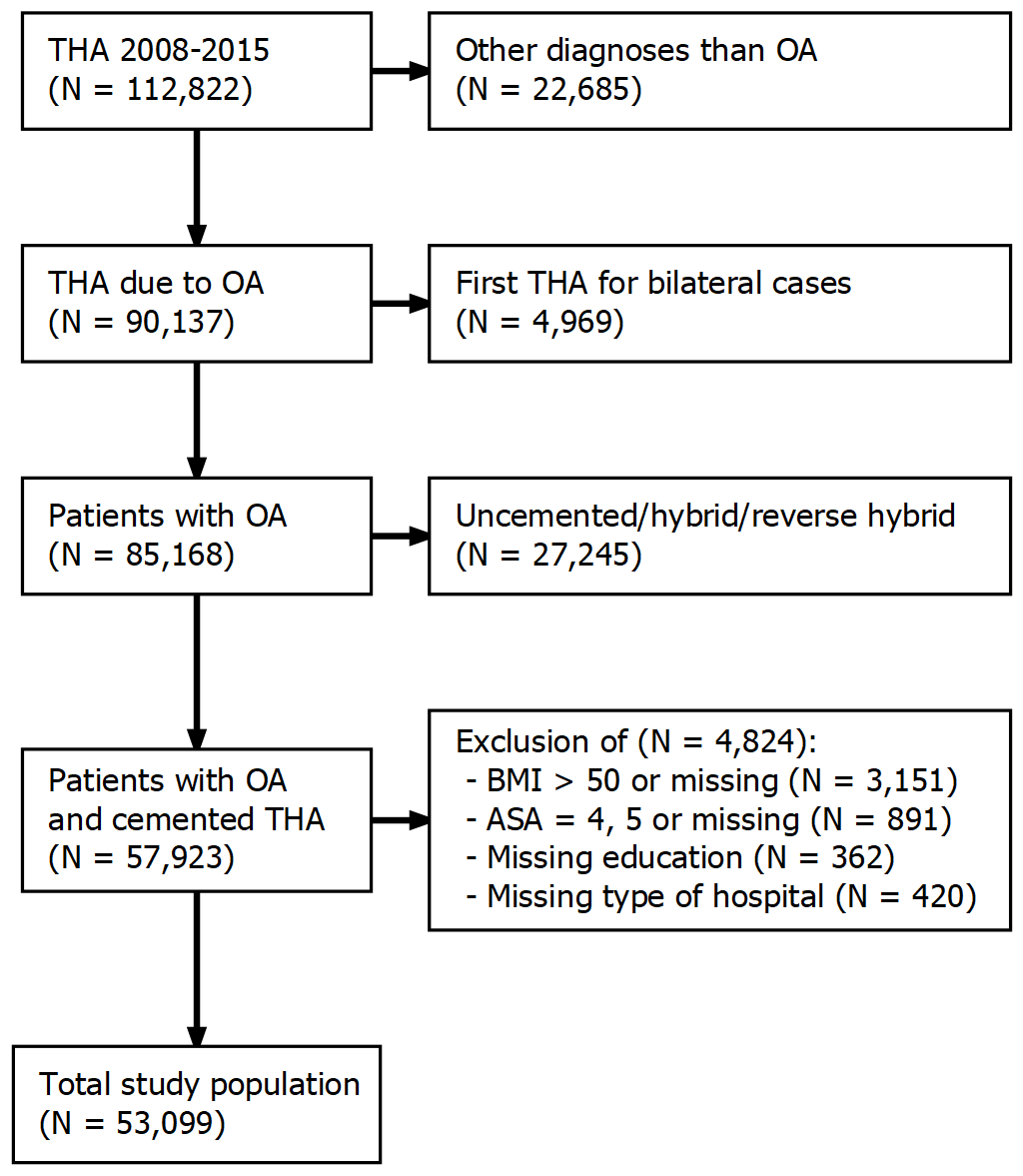


Figure 1: Flowchart depicting inclusion criteria and number of patients included in the development phase of the model.

Data linkage, based on the unique identity numbers assigned to all Swedish residents (Ludvigsson et al. 2009), were used to collect data from a variety of sources, as previously described by Cnudde et al. (2016).

Age, sex, body mass index (BMI), ASA class, type of hospital (university/county/rural/private) and year of surgery were collected from SHAR, with a completeness of 96-98 % (Kärrholm et al. 2019). Data on education level (low/middle/high) and civil status (married/un-married/divorced/widow[er]), were collected from the longitudinal integration database for health insurance and labor market studies from Statistics Sweden (Ludvigsson et al. 2019). The Swedish National Patient Register was used for comorbidity data during one year before surgery. The register contains all relevant diagnoses coded by ICD-10, as well as admissions and discharge dates for in- and outpatient visits in all private and public hospitals (Ludvigsson et al. 2011). Death dates were linked from the national population register.

Comorbidity was recognized by individual ICD-10 grouped into 17 categories according to CCI (Charlson et al. 1987; Deyo, Cherkin, and Ciol 1992; Quan et al. 2005) and 31 categories according to ECI (Elixhauser et al. 1998; Quan et al. 2005). Patients with no recorded hospital visits during one year before surgery, were assumed to have no comorbidity.

Table 1: Categorization of individual Charlson (CCI) and Elixhauser (ECI) comorbidities into broader comorbidities.

|  |  |  |
| --- | --- | --- |
| new | CCI | ECI |
| AIDS/HIV | AIDS/HIV | AIDS/HIV |
| Anemia |  | blood loss anemia, deficiency anemia |
| Arrhythmia |  | cardiac arrhythmias |
| Cancer | malignancy, metastatic solid tumor | lymphoma, metastatic cancer, solid tumor |
| CNS | dementia, hemiplegia or paraplegia | depression, paralysis, other neurological disorders, psychoses |
| Diabetes | diabetes without complication, diabetes complication | diabetes uncomplicated, diabetes complicated |
| Drug alcohol abuse |  | alcohol abuse, drug abuse |
| Heart condition | congestive heart failure | congestive heart failure, valvular disease |
| Heart infarct | myocardial infarction |  |
| Hypertoni |  | hypertension uncomplicated, hypertension complicated |
| Kidney disease | renal disease | renal failure |
| Liver disease | mild liver disease, moderate or severe liver disease | liver disease |
| Lung airways disease | chronic pulmonary disease | chronic pulmonary disease, pulmonary circulation disorder |
| Peptic ulcer | peptic ulcer disease | peptic ulcer disease |
| Reuma | rheumatic disease | rheumatoid arthritis |
| Vascular disease | peripheral vascular disease, cerebrovascular disease | peripheral vascular disorder |

Some comorbidities were identified by both CCI and ECI, and some distinct comorbidities were closely related (such as hypertension with and without complications, or abuse of either drugs or alcohol). We used those categories to establish 16 broader categories (Table 1) in addition to 5 standalone ECI classes that were kept unchanged (hypothyroidism, coagulopathy, obesity, weight loss and fluid electrolyte disorders). Groups were merged according to clinical relevance as to be recognized in a patient-doctor meeting without access to external register data. Comorbidities recorded for at least one patient who died within 90 days, and one who did not, were included in the modelling process described below. The final model was also altered to not include cancer as a predictor. Patients with cancer are sometimes treated differently in the clinical setting, introducing difficulties in interpretation of this variable.

## Statistics

We used the Kaplan-Meier estimator to assess unadjusted cumulative survival.

Further analysis were based on logistic regression since no censoring occurred within the 90 day study period. We used a modelling procedure described by Guo et al. (2015) as a bootstrap ranking procedure with a logistic least absolute shrinkage and selection operator (LASSO) model. Numeric variables (age and BMI) were normalized before modelling to have mean = 0 and standard deviation = 1. 1,000 bootstrap samples were drawn from the initial data set (Austin and Tu 2004). We used 10-fold cross validation for every bootstrap sample with a broad range of potential penalty values (:s) in a logistic LASSO model. We then only kept :s minimizing the mean cross-validated deviances in each sample. Those :s were used to estimate model coefficients for each potential predictor. Absolute values from those estimates were used as a measure of variable importance. Piece-wise linear regression was then used to detect a break point where a significant drop in variable importance were observed. Potential predictors with variable importance above this break point were considered important and kept as model candidates. The whole process was repeated ten times.

Covariates that were selected each of the ten times were used in a main effects model of multivariable logistic regression without penalty, and without pre-normalization of numeric variables. We will call this model “BRL all”, where BRL stands for bootstrap ranking LASSO. A similar model, including any variable selected at least one out of ten times will be called “BRL any”. Univariable models with the ASA score, CCI and ECI were used for comparison, as well as a multivariable model with age and sex. Each model including age where fitted three times, once with age as a main effect and twice with restricted cubic splines, either by two or three knots.

Each of those models were used to predict the probability of death within 90 days for each patient. Sensitivity and specificity were estimated to form receiver operating characteristic (ROC) curves and the area under those curves (AUC) were used as a measure of predicitve power. Models with a lower 95 % confidence limit (Delong and Carolina 1988) above 0.7, were considered good.

Odds ratios for the model with highest AUC were estimated with 95 % confidence intervals based on interpolations of profile traces (Venables and Ripley 2002).

We used R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) with significant packages tidyverse, tidymodels, furrr and pROC. We build an online web calculator using the shiny package. All R-scripts and necessary software (but no personal data) is available as a live Binder environment (<https://mybinder.org/v2/gh/eribul/thamortpred/master?urlpath=rstudio>). A static archived version is also available at zenodo.org/XXX. **Prepared but non-public until paper is accepted/published!**

## Ethical approval

Ethical approval for this study was obtained from the Regional Ethical Review Board in Gothenburg (271-14 and 360-13).

# Results

We found 53, 099 patients (Figure 1), 35 - 99 years old, whereof 61 % were female. 175 (0.33 %) patients died within 90 days and no one was censored before that. The unadjusted cumulative 90-day survival was 99.7 % (95 % CI: 99.6 - 99.7).

Some characteristics of the study population are presented in Table 2. 26 % of all patients had at least one pre-surgery comorbidity according to CCI, and 48 % according to ECI. The proportion of patients with ASA class 3 was 18 %. Most individual comorbidities were more common among patients who died.

Table 2: Baseline demographics. CCI/ECI = Charlson/Elixhauser comorbidity indices. Comorbidities prefixed with ECI are defined by the Elixhauser classification. Remaining comorbidities are based on the previously described combination of CCI and ECI. Comorbidities recorded for at least one patient who survived 90 days, and one who did not, were modeled as potential predictors.

|  |  |  |  |
| --- | --- | --- | --- |
| what | level | alive | dead |
| n |  | 52924 | 175 |
| Age (mean (SD)) |  | 72.66 (7.76) | 77.99 (7.89) |
| Sex = Female (%) |  | 32363 (61.1) | 77 (44.0) |
| BMI (mean (SD)) |  | 27.19 (4.39) | 26.81 (5.18) |
| ASA (%) |  |  |  |
|  | 1 | 9582 (18.1) | 7 ( 4.0) |
|  | 2 | 33795 (63.9) | 86 (49.1) |
|  | 3 | 9547 (18.0) | 82 (46.9) |
| Hospital (%) |  |  |  |
|  | University | 24386 (46.1) | 74 (42.3) |
|  | County | 16441 (31.1) | 66 (37.7) |
|  | Rural | 9921 (18.7) | 19 (10.9) |
|  | Private | 2176 ( 4.1) | 16 ( 9.1) |
| education (%) |  |  |  |
|  | low | 11615 (21.9) | 30 (17.1) |
|  | middle | 20522 (38.8) | 82 (46.9) |
|  | high | 20787 (39.3) | 63 (36.0) |
| civil status (%) |  |  |  |
|  | married | 29353 (55.5) | 83 (47.4) |
|  | single | 12850 (24.3) | 38 (21.7) |
|  | widow/widower | 10721 (20.3) | 54 (30.9) |
| CCI (%) |  |  |  |
|  | 0 | 39178 (74.0) | 78 (44.6) |
|  | 1 | 8076 (15.3) | 41 (23.4) |
|  | 2 | 3737 ( 7.1) | 25 (14.3) |
|  | 3 | 1164 ( 2.2) | 12 ( 6.9) |
|  | 4+ | 769 ( 1.5) | 19 (10.9) |
| ECI (%) |  |  |  |
|  | 0 | 27717 (52.4) | 56 (32.0) |
|  | 1 | 13720 (25.9) | 46 (26.3) |
|  | 2 | 7208 (13.6) | 31 (17.7) |
|  | 3+ | 4279 ( 8.1) | 42 (24.0) |
| heart condition (%) |  | 2608 ( 4.9) | 31 (17.7) |
| heart infarct (%) |  | 2163 ( 4.1) | 23 (13.1) |
| arrythmia (%) |  | 4473 ( 8.5) | 32 (18.3) |
| hypertoni (%) |  | 16607 (31.4) | 70 (40.0) |
| kidney disease (%) |  | 537 ( 1.0) | 14 ( 8.0) |
| diabetes (%) |  | 4051 ( 7.7) | 26 (14.9) |
| vascular disease (%) |  | 1671 ( 3.2) | 15 ( 8.6) |
| cancer (%) |  | 2689 ( 5.1) | 26 (14.9) |
| aids hiv (%) |  | 5 ( 0.0) | 0 ( 0.0) |
| liver disease (%) |  | 207 ( 0.4) | 0 ( 0.0) |
| lung airways disease (%) |  | 2860 ( 5.4) | 18 (10.3) |
| drug alcohol abuse (%) |  | 222 ( 0.4) | 1 ( 0.6) |
| cns (%) |  | 1668 ( 3.2) | 14 ( 8.0) |
| reuma (%) |  | 1912 ( 3.6) | 10 ( 5.7) |
| anemia (%) |  | 412 ( 0.8) | 4 ( 2.3) |
| peptiulcer (%) |  | 339 ( 0.6) | 2 ( 1.1) |
| ECI hypothyroidism (%) |  | 1784 ( 3.4) | 7 ( 4.0) |
| ECI coagulopathy (%) |  | 192 ( 0.4) | 0 ( 0.0) |
| ECI obesity (%) |  | 993 ( 1.9) | 7 ( 4.0) |
| ECI weight loss (%) |  | 35 ( 0.1) | 0 ( 0.0) |
| ECI fluid electrolyte disorders (%) |  | 304 ( 0.6) | 0 ( 0.0) |

There were 5 comorbidities that were not recorded for any patient who died: AIDS/HIV, liver disease, ECI coagulopathy, ECI weight loss and ECI fluid electrolyte disorders. Corresponding variables were excluded from the modelling process.

The “BRL any” model included age, sex, ASA, cancer, CNS, kidney disease, obesity, anemia and heart condition. The "BRL all model only included ASA, cancer, CNS and kidney disease.

There were no observed differences for two versus three knots in models with age modeled by restricted cubic splines. We will therefore only present results for three knots. No use of splines however improved the observed AUCs compared to simpler main effect models. The “BRL any” model had an estimated AUC (95 % CI) of 0.78 (0.75-0.82). The altered version without cancer performed equally good. The “BRL any” model was significantly better than the “BRL all” model with AUC 0.70 (0.66-0.74). Univariable models with ASA, CCI or ECI performed poorly with AUC lower than, or at least not distinguishable from 0.7. The model with age and sex performed better but still with AUC not significantly higher than 0.7 (Table 3).

Table 3: Area Under the Curve (AUC) as a measure of predictive power for the ‘BRL any’ model compared to ‘BRL all’, a simpler model with age and sex, as well as univariable models with ASA score and the Charlson (CCI) or Elixhauser (ECI) comorbidity indices. Age was included as either a main effect, or in the form of restricted cubic splines (RCS) with three knots.

|  |  |
| --- | --- |
| Model | AUC |
| BRL any (RCS) | 0.79 (0.76-0.82) |
| BRL any | 0.78 (0.75-0.82) |
| BRL any-cancer | 0.78 (0.74-0.81) |
| Age and sex (RCS) | 0.72 (0.68-0.76) |
| Age and sex | 0.72 (0.68-0.76) |
| BRL all | 0.70 (0.66-0.74) |
| ASA | 0.68 (0.64-0.71) |
| CCI | 0.66 (0.62-0.70) |
| ECI | 0.64 (0.59-0.68) |

ROC curves for some of the models are displayed in Figure 2. The “BRL any” model is superior to all other models.

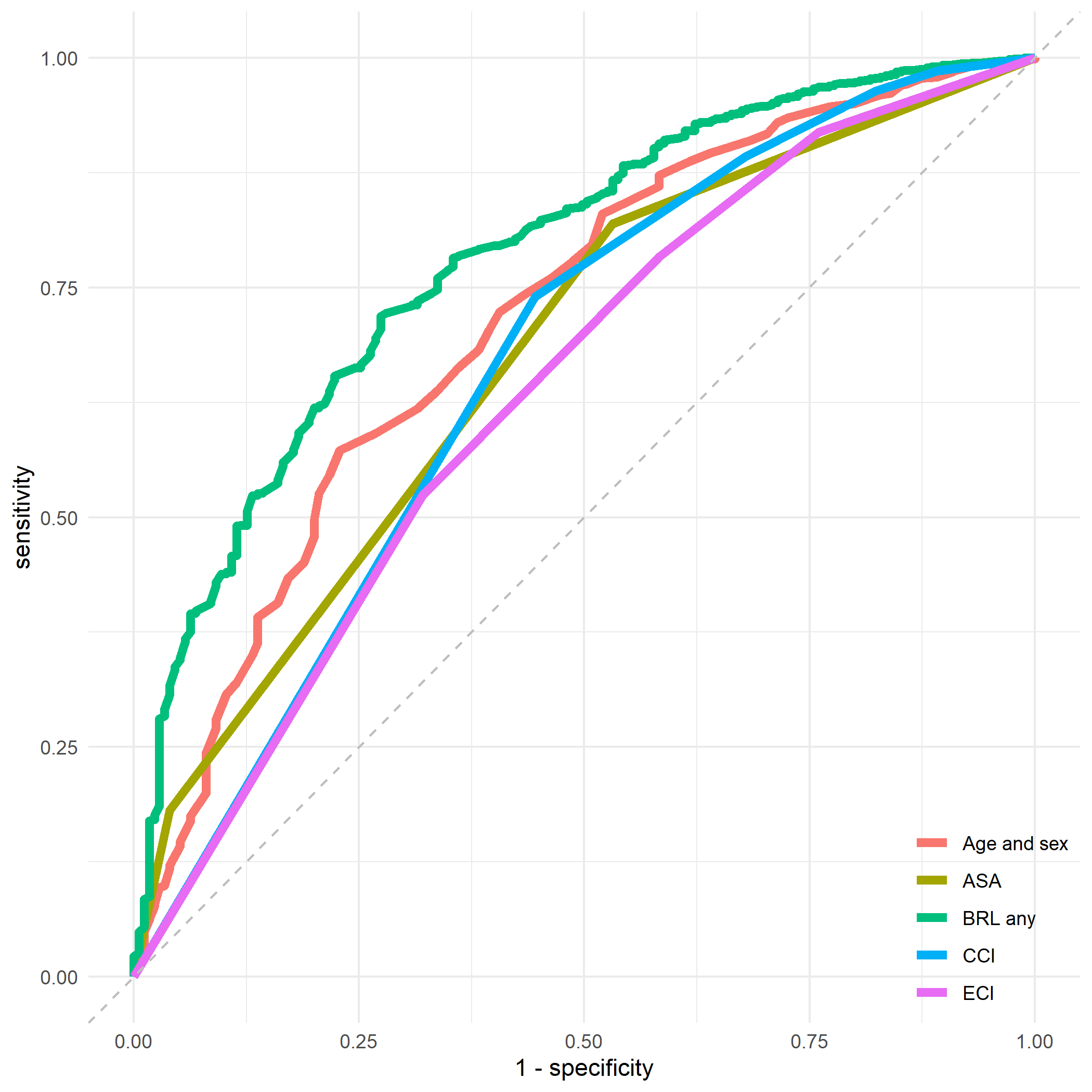


Figure 2: ROC curves for some of the models. The ‘BRL any’ model is distinguished from other models, which are partially over-lapping.

AUCs and 95 % confidence intervals are illustrated for the same models in Figure 3).

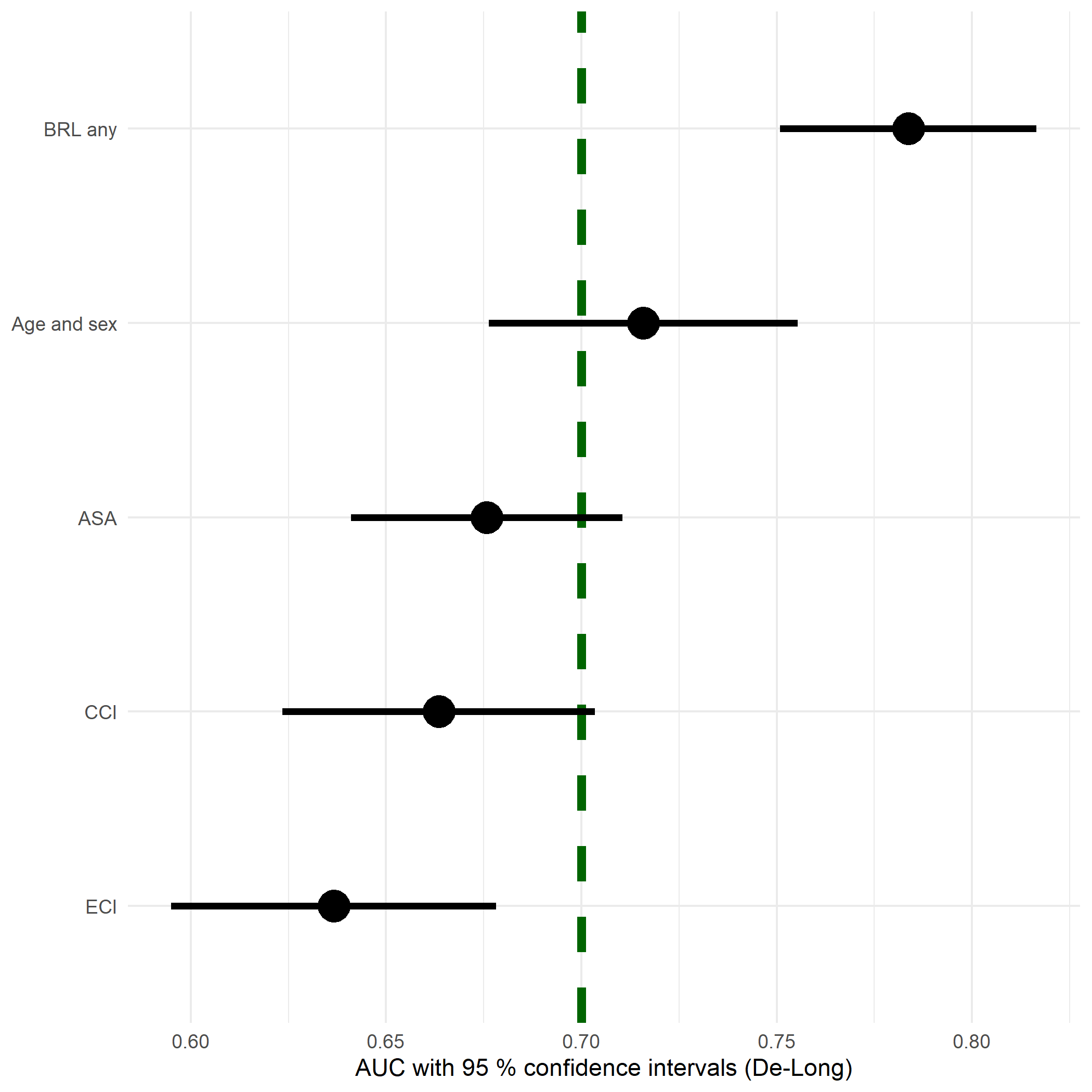


Figure 3: Area Under the Curve (AUC) as a measure of predictive power for the ‘BRL any’ model compared to a simpler model with age and sex, as well as univariable models with ASA score and the Charlson (CCI) or Elixhauser (ECI) comorbidity indices.

The ability of model “BRL any” to estimate probabilities of death within 90 days is illustrated in Figure 4. Patients who died had, on average, higher predicted probabilities to do so.

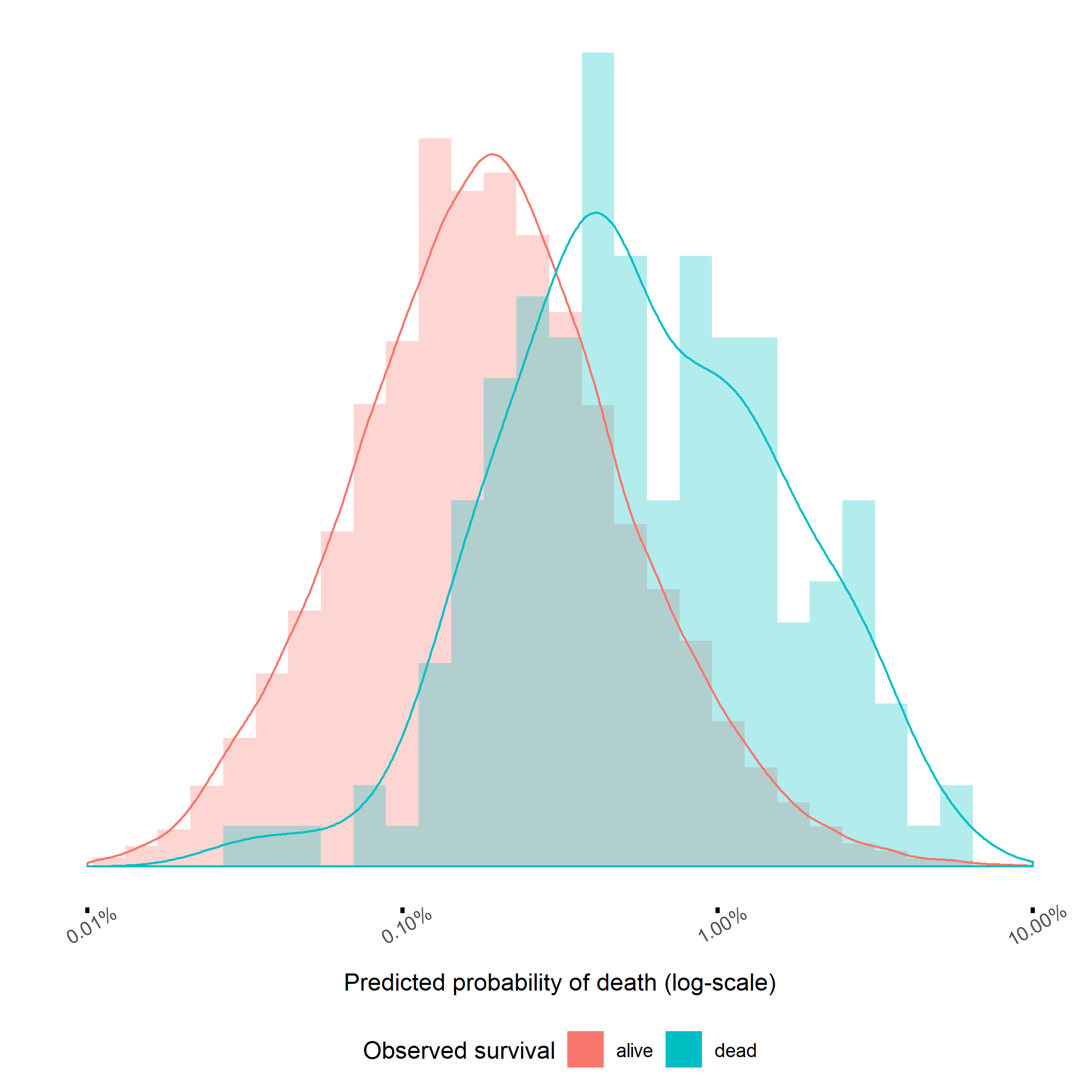


Figure 4: Patients who died within 90 days (blue) were, on average, estimated to have a higher probability to do so.

Estimated coefficients and corresponding odds ratios for the “BRL any” model is presented in Table 4.

Table 4: Estimated coefficients and odds ratios with 95 % confidence intervals for the “BRL any” model. Notations from the X-column is used in the formula in the disussion section.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| term | X | beta | OR | p |
| (Intercept) |  | -13 |  |  |
| cancer |  | 1 | 2.05 (1.31-3.11) | 0.001 |
| cns |  | 1 | 2.46 (1.35-4.13) | 0.001 |
| kidney disease |  | 1 | 3.46 (1.86-5.98) | <0.001 |
| ASA2 |  | 1 | 2.37 (1.17-5.67) | 0.029 |
| ASA3 |  | 2 | 4.73 (2.28-11.51) | <0.001 |
| ECI obesity |  | 1 | 2.09 (0.87-4.21) | 0.063 |
| GenderMan |  | 1 | 1.83 (1.34-2.49) | <0.001 |
| Age |  | 0 | 1.08 (1.06-1.10) | <0.001 |
| anemia |  | 1 | 1.83 (0.56-4.42) | 0.238 |
| heart condition |  | 1 | 1.73 (1.12-2.59) | 0.010 |

We have provided a web calculator to aid clinical model usage in practice (<https://erikbulow.shinyapps.io/thamortpred/>).

# Discussion

In this nationwide cohort study we intended to compare the performance of a set of easily accessible data that are routinely collected in daily clinical practice with the complex comorbidity coding algorithms suggested by Charlson and Elixhauser. We found that a multivariable main effects logistic regression model with age, sex, ASA, cancer, CNS, kidney disease, obesity, anemia and heart condition was able to make better predictions than either CCI or ECI.

The resulting “BRL any” model can predict the probability of death () within 90 days for new patients as:

where indicate independent variables as notated in table 4. This formula is valid for patients within the observed age range (35 - 99 years).

For example a 35 yer old woman with ASA = 1 and none of the important comorbidities would only have a 0.0032 % risk to die within 90 days after elective THA surgery. Another woman, 67 years old (the first age quantile), have a higher risk of 0.038 %. A man, 78 years old (the third age quantile) with ASA = 3 and a previous heart condition would have a risk of 1.3 % risk. The perhaps unrealistic case of a 99 year old man with ASA = 3 and all listed comorbidities would have a theoretical risk as high as 82 %. Note however that this extreme case relies on extrapolation which is highly unreliable, since no such person was actually observed.

Some covariates in the “BRL any” model were not statistically significant by themselves but were still relevant due to unobserved heterogeneity (Mood 2010). Obesity for example is known to be associated with a higher risk of morbidity and all-cause mortality (Must and McKeown 2000). However, previous studies on primary THA cohorts have not indicated a higher risk of mortality in obese patients (Wallace et al. 2014). An explanation could be that obese patients selected for THA are comparably healthy and often younger.

Cancer could also be dropped as a predictor without any loss of predictive power. It was also encouraging that socio-demographic factors such as education and civil status, or organizational factors such as type of hospital, did not have a strong enough influence of death to be included in the final model.

It is known that male sex is associated with earlier deaths and that the remaining life span will decrease with increased age. It is less obvious that this relation must be linear. We used restricted cubic splines to allow a more flexible relation, but found that a linear relationship was equally good. Our model includes ASA class which is routinely assessed pre-operatively in most developed countries. It is however known to have a high degree of internal variability (Haynes and Lawler 1995). It has previously been compared to the CCI, but not with respect to mortality after THA (Whitmore et al. 2014; Kork et al. 2015). Patients with ASA 4-6 were excluded since those categories describe severe disease, moribund and brain-dead individuals. It can be questioned whether such classification is correct for our cohort. Comorbidities are also known to influence the outcome after THA (Inacio et al. 2015; Gordon et al. 2013; Hofstede et al. 2016). Coding algorithms on the other hand are complex and not used in clinical settings since the administrative burden is too high. CCI comprise 1,178 ICD-10 codes and ECI 1,516. Therefore, such indices are only used by researchers.

Risk prediction may be useful in the process of patient selection prior to surgery, in the preoperative risk management including a review of current medications, and in perioperative anesthesia management. A number of risk prediction tools of various complexity for adverse outcomes after total joint replacements have been introduced but none has been broadly accepted (Manning, Edelstein, and Alvi 2016). In the context of trauma surgery outcome prediction tools are common, and it seems possible to reduce the number of items without losing predictive power (Gerdin et al. 2016). Our results indicate that the risk of early postoperative mortality after THA could be assessed by a relatively simple prediction model.

A strength of this study is the nationwide design with a large cohort of primary THA patients. We were able to use exact data linkage by the Swedish unique identity numbers and had no censoring. Our data sources are valid with low proportions of missing data (Söderman et al. 2000, 2001; Kärrholm et al. 2019; Ludvigsson et al. 2011).

The risk of coding errors might be a limitation to the study, especially so if coding routines might change over time. It should also be remembered that the risk model does not study THA as an observed intervention. We merely followed the cohort who did already have THA. Hence, deaths within 90 days might occur for the patients regardless if THA is inserted or not. The proximity in dates however, the maximum of 90 days from THA to death, is an indication that the operation might have influenced the deaths observed. The insertion of an elective THA is always preceded by a clinical judgement. Hence, no patient with a foreseen death near-by is given THA to begin with. We therefore believe that at least a non-significant proportion of deaths within 90 days are related to the THA surgery, or with complications thereafter.

We hope that the supplied web calculator and the transparent reporting of this model might lead to clinical usage that can be part of a pre-surgery discussion between doctors and patients in need of THA.

# Contribution of authors

AG and NH initiated the study and managed the ethical review board application. EB, EL and SN performed the statistical analyses. AG and EB drafted the manuscript. All authors edited and finalized the manuscript.

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