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Predicting long-term survival after coronary artery bypass graft surgery

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Abstract

OBJECTIVES: To develop a model for predicting long-term survival following coronary artery bypass graft surgery.

METHODS: This study included 46 573 patients from the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZCTS) registry, who underwent isolated coronary artery bypass graft surgery between 2001 and 2014. Data were randomly split into development (23 282) and validation (23 291) samples. Cox regression models were fitted separately, using the important preoperative variables, for 4 'time intervals' (31–90 days, 91–365 days, 1–3 years and >3 years), with optimal predictors selected using the bootstrap bagging technique. Model performance was assessed both in validation data and in combined data (development and validation samples). Coefficients of all 4 final models were estimated on the combined data adjusting for hospital-level clustering.

RESULTS: The Kaplan–Meier mortality rates estimated in the sample were 1.7% at 90 days, 2.8% at 1 year, 4.4% at 2 years and 6.1% at 3 years. Age, peripheral vascular disease, respiratory disease, reduced ejection fraction, renal dysfunction, arrhythmia, diabetes, hypercholesterolaemia, cerebrovascular disease, hypertension, congestive heart failure, steroid use and smoking were included in all 4 models. However, their magnitude of effect varied across the time intervals. Harrell's C-statistics was 0.83, 0.78, 0.75 and 0.74 for 31–90 days, 91–365 days, 1–3 years and >3 years models, respectively. Models showed excellent discrimination and calibration in validation data.

CONCLUSIONS: Models were developed for predicting long-term survival at 4 time intervals after isolated coronary artery bypass graft surgery. These models can be used in conjunction with the existing 30-day mortality prediction model.

Keywords: Coronary artery bypass graft • Long-term survival • Risk prediction model • Risk stratification • Cardiac surgery • Coronary revascularization

INTRODUCTION

The prediction of 30-day or in-hospital mortality is popularly used to evaluate operative risk in cardiac surgery [1–4]. However, this short-term mortality does not provide adequate information to guide long-term post-surgery patient management [5]. Because of advancements in surgical technologies and perioperative care, operative and 30-day mortality rates have declined over the last few decades, and consequently, more attention is now required towards improving long-term survival following cardiac surgery, which is becoming increasingly important in informing management strategies for patients following coronary artery bypass graft (CABG) surgery [6, 7]. Prediction of long-term survival can be used to determine the most appropriate

post-discharge care strategies. This would essentially help patients and their doctors to implement behavioural and therapeutic modifications to optimize benefit from surgery [6]. In addition, these models can be used for various scientific purposes and to facilitate research.

EuroSCORE, a short-term mortality risk prediction model, has been shown to predict intermediate- to long-term survival following cardiac surgery [8]. It is expected that the short-term models may to some extent predict long-term mortality risk as most predictors are similar. However, this does not justify the use of short-term risk model for the prediction of the long-term survival. AusSCORE, EuroSCORE, etc. were not intended for predicting long-term survival, and their development process was not based on survival analysis, which allows the time-varying nature

of the risk (i.e. hazard) of the event. Shahian *et al.* [7] showed that the impact of predictor variables on mortality fluctuates as time following surgery increases. Hence, separate models for predicting long-term survival may be needed. Two such models have been developed in the USA in the Cardiac Surgery Reporting System (CSRS) [9] and the Society of Thoracic Surgeons (STS) [10] databases. No model is currently available for predicting long-term survival following CABG surgery in Australian patients. It is widely recognized that a risk prediction model will generally predict outcomes more accurately in the population setting where it was originally developed [11, 12]. Therefore, the aim of this study was to develop a risk prediction model for predicting long-term survival following CABG surgery using an Australian patient cohort.

MATERIALS AND METHODS

Data set

The study used data from 46 573 patients, included in the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZCTS) registry, who underwent isolated CABG surgery between 2001 and 2014. The ANZCTS registry collects preoperative, intraoperative and postoperative variables using internationally standardized data definitions, on adult patients undergoing cardiac surgery in 28 hospitals across Australia. The data collection and its audit methods have been discussed elsewhere [13]. In-hospital and 30-day mortality data were collected by the registry. Outcome of the model was long-term survival following cardiac surgery. Mortality data outside 30 days postsurgery were collected through linkage with the National Death Index (NDI) database. The data were divided, at a ratio of 1:1, into development set (23 282) and validation (23 291) set. The analysis in this study involved 30 plausible preoperative variables identified through a variety of methods, including literature review, clinical acumen or their use in other models developed using the same database. Current models are intended for the preoperative prediction of survival after CABG surgery. Hence, all the predictors are collected prior to surgery. None of them are time-varying covariates.

Statistical analysis

Missing data. The variable 'family history of heart disease' (10.8%) had the highest percentage of missing data, followed by 'New York Heart Association (NYHA) classification' (3.8%), 'reduced ejection fraction (EF)' (2.2%) and 'renal dysfunction' (1.3%). The remaining predictors each had < 1% missing observations (Supplementary Material, Table S1). Missing data were imputed using the multiple imputation by chained equations (MICE) method. Ten imputations were generated. The analysis was performed separately on each imputed data set, and then final parameter estimates were obtained by aggregating across the imputed data sets [14].

Model development. Univariable associations between preoperative patient characteristics and mortality were assessed using univariable Cox regression. Previous studies have shown that the effects of some variables on mortality depend on the time since CABG surgery [7]. To accommodate the fact that the effect of

each of the risk factors on mortality differs across time (non-proportional hazards in a single Cox model), 4 separate Cox regression models were fitted, to generate piecewise hazard, forcing same set of variables into these models. Selection of the 4 time intervals was done using the technique adopted by Shahian *et al.* [7] while developing STS survival model. The first time interval started at 31 days to maintain continuum with the existing AusSCORE II model that predicts 30-day mortality following CABG surgery [15]. The first interval included a range up to 90 days since recent advancements in modern critical care leads to the potential for an extension of early postoperative period; some already consider 90-day mortality as a new convention or benchmark [1, 7]. The second, third and fourth time intervals were decided based on a preliminary analysis that involved fitting Cox regression models with several relatively narrow intervals (each spanning 90 days), then collapsing adjacent intervals into larger intervals (1 year, 3 years and > 3 years), while retaining sufficient events in each merged interval to ensure precise estimation of interval-specific hazard ratio (HR) [7].

Bootstrap bagging techniques were used to select predictors for the multivariable models [16]. A bootstrap sample of the same size as the development sample was drawn from each of the imputed data sets. For each bootstrap sample, all plausible risk factors were entered into a multivariable Cox regression model. A predictor with a *P*-value ≤0.05 was considered as significant. For each imputed data set, 1000 bootstrap samples were taken, and the percentage of times that each predictor appeared as significant across the 1000 bootstraps was recorded (bootstrap coverage). Bootstrap coverage of each predictor was averaged across 10 imputed data sets to generate an overall coverage for each predictor [17]. The predictors were then ranked per their overall bootstrap coverage (Supplementary Material, Table S2).

Fourteen multivariable Cox regression models were then fitted with the predictors that achieved at least 50% overall bootstrap coverage [18]. The first model comprised 6 predictors which each achieved 100% overall bootstrap coverage. Thirteen subsequent models were generated through adding 1 variable at a time to the model, based on decreasing rank per the overall bootstrap coverage (Supplementary Material, Table S2). The area under the receiver operating characteristic curve (AUC) was calculated for each of these 14 models to provide an estimate of model discrimination. The model with the highest AUC value was selected as the final model.

For the final model, non-linearity of continuous predictors (age) was considered by fitting fractional polynomials in the Cox regression model [19] and using a sensitivity analysis to assess whether the inclusion of a non-linear term changes the model fit. However, there was little improvement in discrimination or calibration with the inclusion of non-linear terms, and, hence, the final model retained linear terms for each of the continuous variables. The first-order interaction effects between clinically relevant risk factors were also investigated. Interaction effects between some pairs of predictor variables appeared significant (*P* < 0.05); however, their inclusion did not improve model performance, and therefore, only the main effects were retained in the final model.

Model performance and validation. Model performance was assessed first in the validation data set. Subsequently multifold (*k* = 100) cross-validation was done in combined data sets (development set plus validation set) to avoid optimistic prediction.

Finally, Harrell's C-statistics, a global measure for the assessment of a fitted survival model for the continuous event time [7, 20], was generated in the combined data set. Calibration of the final model was assessed using the Regression Modelling Strategies package version 4.4-2 in the R statistical software [21]. Bootstrap resampling was used to get overfitting-corrected estimates of predicted survival probabilities.

Final model estimation. Coefficients of all 4 final models were estimated on the combined data (development and validation samples) including a shared frailty term in the model to account for hospital-level clustering [22]. Frailty effects were assumed to have gamma distribution. Coefficients (and standard errors) for the smoothed baseline hazard were generated using the approach proposed by Royston *et al.* [23].

Statistical software. Statistical software packages Stata version 14 (StataCorp. Release 14, 2015) and R version 3.3.2 were (R core team version 3.3.2, 2013) used for the analyses.

Ethical approval

The institutional review board of each participating hospital had approved the use of their data for research purposes (Alfred HREC: 262/09). The ANZCTS registry has approved collection of patient data using an 'opt-out consent approach' (MUHREC: CF08/0322-2008000065). This study received ethics approval from the Monash University Standing Committee on Ethics in Research Involving Humans (SCERH) (MUHREC: CF14/1117-2014000476).

RESULTS

Preoperative characteristics of the 46 573 patients were analysed. The mean ± standard deviation age of the patients at surgery was 65.9 ± 10.4 years, and 79.4% of them were male. Median follow-up time was 4.2 (interquartile range 1.8–7.0) years since surgery. Distribution of preoperative patient characteristics is presented in the Supplementary Material, Table S3. Figure 1 presents the
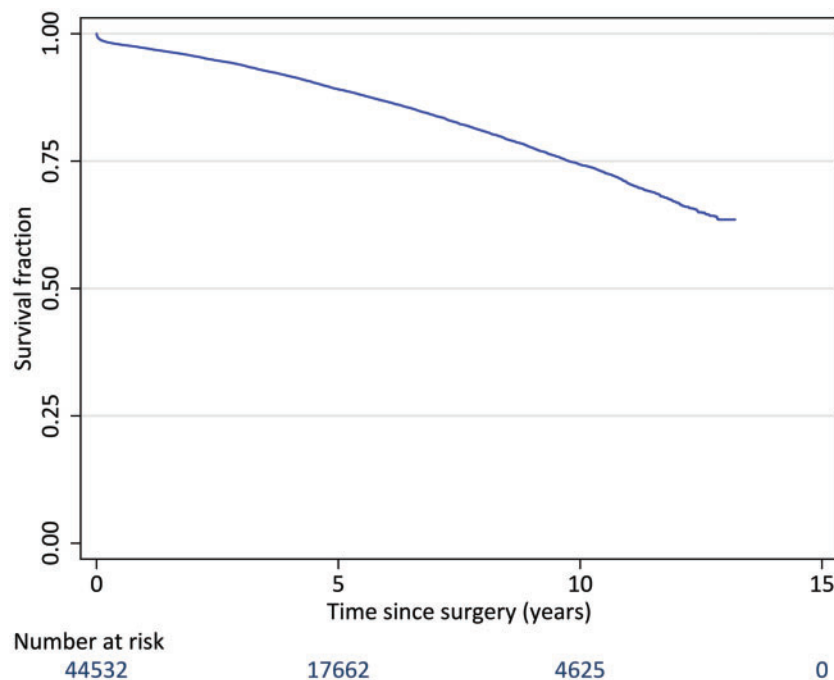
Figure 1: The Kaplan–Meier estimates of mortality in the study sample.

Table 1: The Kaplan–Meier mortality rate estimates for the study sample

Time interval	Development		Validation		Overall sample		
	Total patients	Death	Total patients	Death	Total patients	Death	Kaplan Meier estimates (%)
30 days	21 822	272	21 851	250	43 673	522	1.17 (1.08–1.28)
90 days	21 258	114	21 294	123	42 552	237	1.72 (1.60–1.84)
1 year	19 088	221	19 081	231	38 169	452	2.81 (2.66–2.97)
2 years	16 190	300	16 338	268	32 527	568	4.36 (4.17–457)
3 years	13 705	297	13 813	265	27 518	562	6.14 (5.69–6.39)
4 years	11 167	291	11 309	304	22 476	595	8.35 (8.06–8.65)

Values in parentheses denote 95% confidence interval.

Table 2: Cox proportional hazards models for long-term survival following CABG surgery

| Predictors	31 days–90 days HR (95% CI)	91 days–1 year HR (95% CI)	>1 year–3 years HR (95% CI)	>3 years HR (95% CI)
Age (years)	1.05 (1.03–1.07)	1.06 (1.05–1.08)	1.05 (1.04–1.06)	1.07 (1.06–1.08)
Peripheral vascular disease	1.24 (0.91–1.67)	1.76 (1.42–2.18)	1.64 (1.42–1.89)	1.48 (1.36–1.61)
Respiratory disease	2.03 (1.53–2.70)	1.25 (0.99–1.58)	1.40 (1.21–1.63)	1.39 (1.27–1.52)
Ejection fraction (%)				
46–60	1.34 (0.95–1.90)	1.55 (1.21–1.98)	1.49 (1.29–1.73)	1.23 (1.13–1.34)
30–45	2.10 (1.47–3.01)	2.42 (1.87–3.13)	1.96 (1.67–2.31)	1.48 (1.34–1.63)
<30	4.11 (2.65–6.36)	3.12 (2.18–4.46)	2.47 (1.94–3.15)	1.78 (1.54–2.07)
Renal dysfunction				
Mild	1.44 (0.81–2.55)	0.88 (0.62–1.25)	1.04 (0.85–1.28)	1.01 (0.89–1.15)
Moderate	2.21 (1.23–3.99)	1.43 (0.98–2.07)	1.23 (0.98–1.54)	1.28 (1.11–1.47)
Severe	5.99 (3.05–11.78)	2.14 (1.29–3.52)	2.21 (1.61–3.04)	1.90 (1.55–2.34)
On dialysis	9.23 (4.67–18.26)	4.80 (2.96–7.77)	4.17 (3.05–5.71)	3.55 (2.76–4.52)
Smoking	1.36 (1.02–1.81)	1.59 (1.28–1.98)	1.28 (1.12–1.47)	1.37 (1.27–1.48)
Arrhythmia	2.39 (1.80–3.18)	1.68 (1.33–2.11)	1.34 (1.14–1.57)	1.30 (1.17–1.44)
Diabetes				
No treatment	0.86 (0.46–1.48)	1.18 (0.80–1.73)	0.88 (0.66–1.16)	1.08 (0.94–1.25)
On drug	1.31 (0.96–1.79)	1.29 (1.03–1.62)	1.20 (1.03–1.39)	1.23 (1.12–1.35)
On insulin	1.49 (1.03–2.14)	1.21 (0.90–1.62)	1.38 (1.15–1.65)	1.60 (1.43–1.79)
Hypercholesterolaemia	1.03 (0.73–1.46)	0.86 (0.67–1.08)	0.81 (0.70–0.94)	0.77 (0.71–0.84)
Cerebrovascular disease	1.77 (1.32–2.37)	1.03 (0.80–1.33)	1.45 (1.25–1.69)	1.24 (1.13–1.37)
Hypertension	1.35 (0.89–2.03)	1.16 (0.88–1.54)	1.10 (0.92–1.30)	1.14 (1.04–1.25)
CHF				
Past	1.15 (0.78–1.69)	1.69 (1.30–2.20)	1.15 (0.95–1.39)	1.26 (1.14–1.39)
Current	1.43 (0.99–2.05)	1.45 (1.09–1.94)	1.30 (1.07–1.59)	1.27 (1.12–1.44)
Steroid use at surgery	1.89 (1.06–3.37)	1.49 (0.87–2.57)	2.48 (1.87–3.28)	1.53 (1.21–1.93)
AUC ROC	0.833	0.791	0.753	0.739
Harrell's C-statistics	0.8308	0.7813	0.7448	0.7403

All the covariates are measured at baseline.

AUC: area under curve; CABG: coronary artery bypass graft; CHF: coronary heart failure; CI: confidence interval; HR: hazard ratio; ROC: receiver operating characteristics.

Kaplan–Meier estimates of mortality in the study sample. The Kaplan–Meier mortality rate estimates for the study sample were 1.72% at 90 days, 2.81% at 1 year, 4.36% at 2 years and 6.14% at 3 years (Table 1).

Supplementary Material, Table S4 presents the univariable associations between preoperative characteristics and mortality using univariable Cox regression for each of the time intervals (31–90 days, 91–365 days, 1–3 years and >3 years). EF <30 was strongly associated with mortality at the '31–90-day' interval [HR 7.82, 95% confidence intervals (CIs) 5.24–11.67]; however, the magnitude of its association with mortality diminished steadily over time (91–365 days: HR 5.18, 95% CI 3.70–7.24; 1–3 years: HR 3.55, 95% CI 2.82–4.47; >3 years: HR 2.52, 95% CI 2.18–2.89). Severe renal dysfunction was strongly associated with mortality at the '31–90-day' interval (HR 21.4, 95% CI 11.45–39.84), whereas its association with mortality diminished over time (91–365 days: HR 7.31, 95% CI 4.59–11.67; 1–3 years: HR 6.31, 95% CI 4.71–8.45; >3 years: HR 6.08, 95% CI 5.02–7.36). Similar associations were evident for respiratory disease, congestive heart failure, steroid use and NYHA class. Each of body mass index >25 kg/m^2, inotrope use, previous cardiac surgery, cardiogenic shock, intravenous nitrite use, resuscitation and urgency of operation showed strong associations with mortality at the earlier time intervals, namely 31–90 days and 91–365 days; however, their associations with mortality were less evident during later time intervals.

Table 2 presents the HR and 95% CI from the multivariable Cox regression models estimated at each of the 4 time intervals. Thirteen predictors including age, peripheral vascular disease, respiratory disease, reduced EF, renal dysfunction, smoking history, arrhythmia, diabetes, hypercholesterolaemia, cerebrovascular disease, hypertension, congestive heart failure and steroid use appeared in all 4 models. However, the magnitude of their association with mortality varies over time. Peripheral vascular disease (HR 1.24, 95% CI 0.91–1.07) and congestive heart failure at current admission (HR 1.43, 95% CI 0.99–2.05) were not significantly associated with mortality at 31–90 days, but they were associated with mortality at later periods. Hypertension was associated with mortality only at 3 years post-surgery (HR 1.16, 95% CI 1.05–1.27). Diabetes on insulin, steroid use and cerebrovascular disease appeared as significant predictors in the models for 1–3 years and >3 years. Older age and smoking were strongly associated with mortality, with similar magnitudes of HRs across time periods. Respiratory disease, reduced EF, severe renal dysfunction and arrhythmia were significantly associated with mortality, with decreasing magnitude of HRs over time. Hypercholesterolaemia was not significant in the first of the 2 time intervals but appeared as protective factor after 1 year onwards (HR 0.81 at 1–3 years and HR 0.77 at >3 years). Supplementary Material, Table S5 presents baseline hazard coefficients and standard error of 4 models [22].
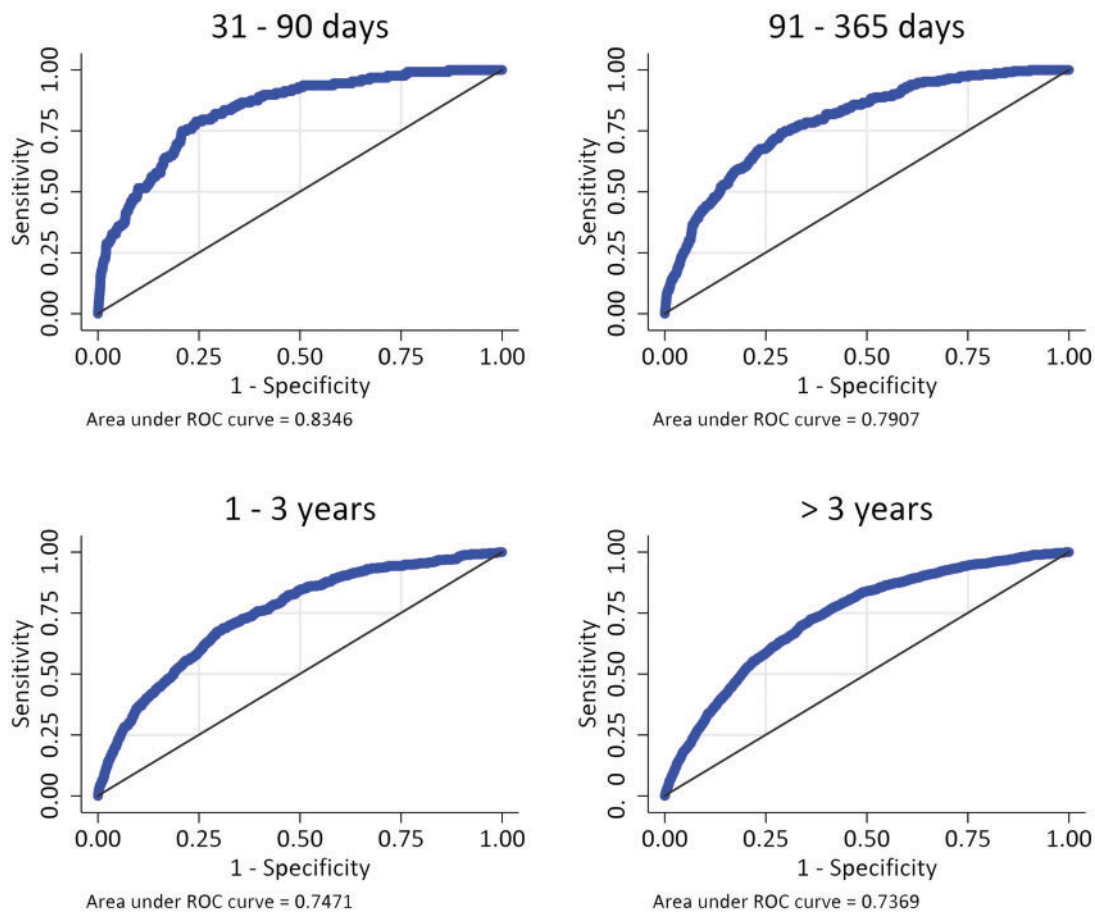
Figure 2: Model discrimination curves for the 4 time intervals in the validation data set. ROC: receiver operating characteristics.

Model discrimination (AUC) in the validation set was 0.84 (95% CI 0.80–0.87) for predicting 31–90-day survival, 0.79 (95% CI 0.76–0.82) for predicting 91–365-day survival, 0.75 (95% CI 0.73–0.77) for predicting 1–3-year survival and 0.74 (95% CI 0.73–0.75) for predicting >3-year survival. Receiver operating characteristic curves for model discrimination in validation data set (Fig. 2) and in combined data set (Supplementary Material, Fig. S1) show excellent discrimination. Model discrimination (AUC) in the multifold cross-validation was 0.833 (95% CI 0.83–0.84) within the 31–90-day interval, 0.79 (95% CI 0.79–0.80) within the 91–365-day interval, 0.75 (95% CI 0.75–0.76) within the 1–3-year interval and 0.74 (95% CI 0.74–0.742) after 3 years. The Harrell's C-statistics for the 4 period-specific Cox regression models were 0.83, 0.78, 0.75 and 0.74 at 31–90 days, 91–365 days, 1–3 years and >3 years, respectively.

DISCUSSION

In this study, a set of models have been developed for predicting long-term mortality risk at 4 distinct time intervals (31–90 days, 91–365 days, 1–3 years and >3 years), recognizing the fact that the effect of various risk factors on mortality may differ depending on the time since CABG surgery.

The models developed in this study are expected to complement the previously published AusSCORE II [15] model that predicts 30-day mortality following CABG surgery. The rationale for

keeping 90 days as the upper bound of the interval for the first time period was the potential expansion of the early postoperative period due to improvements in surgical techniques, postoperative care and, most importantly, the critical care system [7]. The increased capacity of the medical system for resuscitating critical postoperative patients, as well as the use of advanced mechanical and pharmacological support, has increasingly delayed the death of many seriously ailing postoperative patients. Given that these patients are now more likely to die outside of 30 days post-surgery, 30-day mortality alone is likely to underestimate the true rate of operative deaths [1, 7]. Accordingly, a 31–90-day mortality risk model should be used to supplement 30-day mortality risk information obtained from a short-term mortality risk prediction model such as the AusSCORE II. The remaining 3 time intervals provide an opportunity to estimate survival probabilities beyond the period of operative death.

Many of the significant predictors of short-term mortality reported in AusSCORE II [15] did not appear in the long-term models developed in this study and *vice versa*. This finding supports the post-surgery mortality risk pattern that long-term outcomes of surgery are less affected by conventional predictors of early mortality, such as emergency status and cardiogenic shock [24], whereas late mortality is more strongly related to comorbidities and chronic conditions, such as diabetes and renal impairment, as well as behavioural characteristics such as smoking [7]. Gardner *et al.* [25] also reported a similar pattern, most of their short-term mortality predictors were cardiac-related variables,

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whereas most of their long-term mortality predictors were non-cardiac-related variables.

The findings in this study underpin the importance of behavioural characteristics, functional status and comorbidities in predicting long-term survival following CABG surgery. Smoking history—history of any tobacco consumption—which did not appear in the AusSCORE II model, did appear as a significant predictor in all the models developed in this study. Herlitz *et al.* [26] also showed an association between smoking and 5-year mortality following CABG. A study by Saxena *et al.* [27] using an Australian CABG cohort reported an increased risk of pulmonary complications and reduced long-term survival among smoking patients. This may be because of a permanent preoperative injury due to smoking or may be because previous smokers are much more likely to restart smoking at some point after surgery than pre-existing non-smokers. Respiratory problems also showed a similar association with mortality in this study, confirming that respiratory complications may be an intermediate pathway to mortality.

Among the preoperative cardiac conditions, only reduced EF appeared as an independent predictor in all long-term models developed in this study and in the 30-day mortality model reported in AusSCORE II. Among the comorbid conditions, renal impairment, peripheral vascular disease and cerebrovascular disease appeared as independent predictors in all survival models and in AusSCORE II. Because preoperative reduced EF and the aforementioned preoperative comorbidities were associated with both short-term mortality and long-term mortality following CABG, these probably form the core set of predictors that contribute to mortality risk after CABG at all times following surgery. Hence, caution should be taken with patients who present with these comorbid conditions prior to CABG surgery.

In this study, several of the risk factors showed a temporal pattern similar to that reported by Shahian *et al.* [7]. For example, the magnitude of the effects of a reduced EF, severe renal impairment, preoperative dialysis, respiratory disease and arrhythmia on mortality risk decreased over time. A possible explanation of such trends might be that these predictors are linked to a patient's recovery from surgery during the early postoperative period, and if a patient survives that early postoperative period, then the effect of these risk factors on survival diminishes. The opposite trend was seen in some of the other risk factors. The magnitude of the effects of smoking, diabetes, hypertension and congestive heart failure on mortality risk all increased over time, suggesting an accumulation of risk from these debilitating chronic behaviours and diseases [7]. The risk with high cholesterol was seen to be progressively falling. A possible explanation for such a paradox may be the use of statins. Published evidence also demonstrated similar evidence that perioperative statin therapy improves outcomes in patients undergoing coronary artery bypass grafting [28]. Further research is needed to explore the precise dynamics of the time-varying effects of risk factors across time.

In general, the prediction models for all 4 time intervals performed well. However, models for later time intervals showed lower discrimination compared with those for earlier time intervals. This is likely because, as more time passes since the surgery, the relative influence of factors unrelated to surgery increases and thus compromises the discriminatory power of the model.

This is the first study to predict long-term survival after isolated CABG surgery in an Australian patient cohort. One of the major strengths of this study is the use of data from a nationwide cardiac surgery registry and the NDI. Moreover, the use of a bootstrap model selection technique [29], multiple imputation of missing values and model adjustment for hospital-level variation are major strengths of the model development process used in this study.

Limitations

The long-term survival model presented in this article was developed based on preoperative patient characteristics. Intraoperative predictors such as the use of cardiopulmonary bypass use might improve the prediction. However, as interoperative data are not available prior to surgery, surgeons can only rely on preoperative patient characteristics to foresee long-term prognosis for patient counselling and surgical decision making. This study used data from patients who underwent isolated CABG surgery during 2001–14, and this includes many patients who were operated on a decade ago. Advancements in technology, surgical procedures and post-surgical care may have decreased mortality risks over time and prolonged survival times among newer patients who have undergone CABG surgery more recently. However, this study used the latest available ANZSCTS registry and NDI data. The authors also acknowledge that there is inherent scope for bias due to voluntary data collection and the fact that some risk factors (e.g. body mass index) may change over time (but only baseline values were used in developing our prediction model). As the mortality data were collected through linkage with the NDI, the cause of death was not available, and therefore, there is the potential for an overestimation of cardiac-specific mortality risks due to contamination by all-cause mortality in long-term outcome analyses. Considering the complexity and the mathematical understanding required by the clinician to obtain predicted survival probabilities from our regression model, we considered a Web-based survival probability calculator would be most appropriate. The authors are currently working towards developing this tool.

CONCLUSION

Prediction models were developed in an Australian cohort for predicting mortality risk at 31–90 days, 91–365 days, 1–3 years and >3 years after isolated CABG surgery. These risk prediction models can be used in continuum with the AusSCORE II 30-day mortality risk model to get a complete prognosis and thus facilitate evidenced-based surgical decision making.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Conflict of interest: none declared.

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