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ORIGINAL ARTICLE

Missing Value Imputation Improves Mortality Risk Prediction Following Cardiac Surgery: An Investigation of an Australian Patient Cohort

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Background The aim of this study was to evaluate the impact of missing values on the prediction performance of the model predicting 30-day mortality following cardiac surgery as an example.

Methods Information from 83,309 eligible patients, who underwent cardiac surgery, recorded in the Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) database registry between 2001 and 2014, was used. An existing 30-day mortality risk prediction model developed from ANZSCTS database was re-estimated using the complete cases (CC) analysis and using multiple imputation (MI) analysis. Agreement between the risks generated by the CC and MI analysis approaches was assessed by the Bland-Altman method. Performances of the two models were compared.

Results One or more missing predictor variables were present in 15.8% of the patients in the dataset. The Bland-Altman plot demonstrated significant disagreement between the risk scores ($p<0.0001$) generated by MI and CC analysis approaches and showed a trend of increasing disagreement for patients with higher risk of mortality. Compared to CC analysis, MI analysis resulted in an average of 8.5% decrease in standard error, a measure of uncertainty. The MI model provided better prediction of mortality risk (observed: 2.69%; MI: 2.63% versus CC: 2.37%, $P<0.001$).

Conclusion 'Multiple imputation' of missing values improved the 30-day mortality risk prediction following cardiac surgery.

Keywords Cardiac surgery • Risk prediction model • Missing data • Multiple imputation

Background

Risk prediction models for postoperative outcome have become an integral part of cardiac surgical risk assessment and are used for benchmarking quality of care and outcomes. They can also be used to educate and counsel patients as to the preoperative risk associated with the surgery [1]. Risk prediction allows comparison between risks and benefits of the surgery and facilitates evidenced based surgical decision-making [2,3]. Risk prediction models should be precise. To achieve a high level of precision, the model development process should ensure that the predictors are reliably and

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completely measured. However, irrespective of the design and diligence of those involved in the data collection process, missing data is common in medical research [4].

Missing data compromise the quality of data, and subsequently affect the accuracy of the models derived from the data. Their potential to dent the soundness of research finding has often been disregarded in the medical literature [5]. The issue of missing data is usually addressed by keeping only those individuals who have no missing data in any of the variables required for that analysis (complete cases analysis). In statistical modelling, which typically concerns associations of outcome with several predictors simultaneously, the cumulative effect of missing data in several variables leads to the exclusion of a sizeable proportion of the original sample, which in turn causes a loss of power in risk models [6,7]. Besides, while deleting the incomplete cases, available information of other predictors is lost. Apart from wastage of valuable information, collected with cost and effort, complete case analysis (CC analysis) may lead to biased results [8,9] which subsequently may give rise to an inaccurate prediction of outcome. Hence, missing values should be treated with appropriate method. The need for adequate handling of missing data in medical research is increasingly recognised in recent literature [5].

Filling the gap (imputation) with values (ie, mean, median etc.) generated from the observed data of the same variable [10]′ is a popular concept for handling missing values. These single imputation approaches may lead to bias, since they do not account for the uncertainty of the missing values. Multiple imputation (MI) is an advanced and robust method of handling missing values. Rubin and colleagues [11] proposed the method several decades ago, however its use remained limited to the field of statistics only because of the lack of computational tools for generating multiple imputations. A notable variety of simulation methods reported in the recent statistical literature has paved the way for its use in medical and other fields.

Multiple imputation accounts for the uncertainty in predicting the missing values. Imputation more than once ensures the randomness of the estimation technique [12]. This technique generates multiple complete datasets, with the missing values replaced by imputed values. These values are the best estimates of missing predictor values generated, based on existing associations between the variables under consideration in the observed data [13]. Each imputed dataset is analysed separately. The parameter estimates of all the imputed datasets are averaged to give an overall estimate [11].

In the area of cardiac surgery, none of the currently used risk prediction models addressed the impact of missing data adequately. The Parsonnet score [14] and modified Parsonnet score [15] dropped predictors which have the potential to generate missing data. The Amphiascore [16] replaced missing values with the most prevalent values. The Pons score [17], Toronto score [18] and UK national score [19] like most prediction models, didn't address the missing value issue. Whilst developing the EuroSCORE I [20] & II [21], cases with incomplete information were excluded from the analysis, assuming it was missing completely at random (MCAR). The Society of Thoracic Surgeons (STS) risk models [22,23] estimated missing values using single imputation. Development of the ANZSCTS risk prediction scores also excluded cases due to missing observations [24–26]. Although the AusSCORE II [27] model incorporated multiple imputation, it didn't assess the impact of imputation on prediction performance of risk models.

The aim of this study was to evaluate the impact of missing values on preoperative risk prediction following cardiac surgery using 30-day mortality as an example. In this study an existing 30-day mortality risk prediction model [25], developed from ANZSCTS database registry using only the complete cases, was re-estimated employing both complete case and multiple imputation approaches to find whether there is any difference in prediction performance.

Methods

The ANZSCTS database registry collects information on adult patients undergoing cardiac surgery in 28 hospitals across Australia. The database collects preoperative, intraoperative and postoperative variables from each patient undergoing cardiac surgery. Between 2001 and 2014 the database recorded the information of 84,233 patients. Patients with missing information on procedure type were exempted from imputation, as imputation of this particular variable is clinically implausible. Exclusion of the cases with incomplete procedure type information led to a final dataset of 83,309 patient records. A total of 62,737 patients' records between 2001 and 2012 was used for estimation of the model and 20,572 patients' records between 2013 and 2014 were used for external validation of the models. The split resulted in comprising roughly 75% of the records in the estimation set and 25% of the records in the validation set.

Descriptive statistics were generated to assess the pattern and extent of missing-ness. A missing indicator variable was created, where patients with missing information in one or more predictors were categorised as missing. The association of each independent predictor with a missing indicator variable was evaluated using the chi-square test. Multiple imputation of missing values was done using the Imputation by Chained Equations (ICE) method along with multivariable logistic regression. The imputation was repeated five times as suggested by Rubin [11], Schafer and Olsen [28]. The analysis was performed separately on each imputation. The results were then combined into an aggregated MI result.

The regression coefficients of an existing model [25] for predicting the 30-day mortality were estimated on 62,737 patients of the ANZSCTS dataset (a) without (CC: complete cases analysis) and (b) with imputation (MI: multiple imputation analysis). Predicted risk of 30-day mortality was generated for the two risk prediction models (CC model and MI model). The agreement between the predicted risk of MI and CC models was assessed using the Bland-Altman plot which is a graphical method commonly used in medical research to compare two measurement techniques.

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