Validation and extension of a multivariable prediction model of perioperative mortality in a national perioperative dataset: NZRISK

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Background
There is no widely used multivariable clinical tool for predicting perioperative mortality that has been validated in New Zealand patients. We aim to validate the SORT, a parsimonious, 6 risk factor multivariate model in a New Zealand cohort. We also aim to extend the model to include gender and ethnicity to tailor the model to New Zealand conditions. We will also aim to derive extended models incorporating one and two year mortality as well as 30 day mortality.
Methods
Data of approximately 300,000 patients from the PeriOperative Review Committee (POMRC) dataset will be combined with data from the National Cancer Registry and the National Mortality Registry. The dataset will be split for derivation and validation. We will use multivariable logistic regression with backward stepwise regression to derive the models
Results
A parsimonious multivariable mortality risk model including ethnicity should be produced tailored for New Zealand patients. Models will be produced with longer term outcomes and validation will help determine their utility. The models will be disseminated by publication and a freely available web calculator.

Rationale
Prior to surgery, patients and clinicians are faced with decisions based on the balance of risks and benefits. In aged, comorbid patients facing major or emergency surgery the risk of mortality is significant. Multivariate risk models or risk tools are more accurate than clinician estimate of risk [1-2]. However, clinicians often have to use data or models that are historic, based on geographically distinct populations or different health care settings. They are not widely for these reasons, complexity or use risk factors that require further investigation or may not be available in every patient.

In comparison, cardiovascular risk calculators are parsimonious, easy to use, accurate and have been incorporated into established treatment algorithms [3-4]. The United Kingdom National Health Service is a healthcare system fairly similar to the New Zealand system. In this setting, the Surgical Outcome Risk Tool (SORT) has recently been described that uses six freely available preoperative characteristics and exhibits as high accuracy and discrimination as any of the other 34 risk tools that have been described previously [5]. This suggests that a risk tool could be developed that is quick and simple to use yet exhibits high accuracy and discrimination. The advantages of basing a model on SORT rather than any other are its combination of parsimony, accuracy and derivation in a similar healthcare system. Most perioperative risk calculators have not been validated in multiple settings [1]. The important risk factors have been described so, rather than searching for new risk factors, we should be making best use of existing knowledge.

Most existing risk tools were validated in datasets of less than 10,000 patients [1] and often had insufficient endpoints to provide reliable estimation of model parameters in the validation study. New Zealand has an advantage in that we have a National Minimum Dataset that could be reconciled with national mortality data and the national cancer database to obtain a very large, unbiased dataset to validate or derive a New Zealand model. One year of data would give over 300,000 subjects' data to derive and validate a model. Risk factors for mortality are well described and the initial proposal would be to use those risk factors that incorporate the interaction of medical and surgical risk eg age, acuity, ASA physical status, speciality, grade of surgery, cancer. In our model, we would include ethnicity and gender as exploratory variables in the expectation that Maori ethnicity would be an important independent risk that could be incorporated into the model. Any other exploratory variables that markedly improve performance can be included but parsimony and ease of use is an overriding principle for this model.

Nearly all existing risk tools use one-month mortality. In addition, this risk tool will model longer term outcomes based on the findings of Campbell et al that surgery is associated with excess mortality for over two years in many cases. Separate models based on one-month, one and two year mortality would be useful as it will demonstrate the nonlinear, time dependent effects and identify patients with high medium term mortality (up to two years). Apart from this, the plan is to model known risk factors rather than explore for new risk factors. The large, national dataset, readily available parsimonious covariates should produce an accurate and discriminatory model that is simple to use that could be made available to all New Zealanders (patients and clinicians) to improve informed consent, shared decision making and with longer-term outcomes will give a more realistic estimate of the risks associated with surgery. In the future, risk tools could be embedded in clinical guidelines prior to therapeutic surgical management and included in the electronic health record.

Aims

- To externally validate the SORT in a large New Zealand dataset.
- To extend SORT with ethnicity and gender to tailor the model to New Zealand conditions.
- To develop a parsimonious, easy to use, non-cardiac surgical risk calculator freely available for patients and clinicians in New Zealand.
- To extend the one-month mortality risk calculator to include one and two year mortality.

Methods

Sources of data

A one-year sample from the National Minimum Dataset from Jan 1st 20013 to December 31st 2013 will be reconciled with the relevant mortality dataset allowing at least two years of follow-up. In addition, data from the National Cancer database will be reconciled with codes for neoplasms that confer significant mortality and exclude those that do not eg some skin cancers, carcinoma in situ etc

Participants

There is no active recruitment or involvement of participants. No additional testing, assessments, or evaluations will be conducted. The information gathered is purely ascertained from scrutiny of the existing health information under robust ethical and regulatory requirements for data protection and safety. Data will be analysed for all patients aged 18 or over who underwent a surgical procedure of any acuity (elective, expedited, urgent or emergency). Cardiac surgery was excluded. Surgery was defined by (insert POMRC definition). If a patient multiple procedures during the study period the most complex procedure was analysed.

Outcome

The outcome in the SORT external validation study is 30-day mortality. The outcomes in the extended derivation and internal validation study are 30-day, one year and two year mortality. Mortality is defined as a date of death recorded on the New Zealand Births and Deaths Registry.

Predictors

The candidate predictors for the SORT validation study are grade of surgery, age, ASA, cancer, acuity and high-risk surgery. The additional predictors for the extension study are gender and ethnicity.

Sample size

A derivation model requires 10 events per candidate variable and 100 events for a validation study. As we have 8 candidate variables we require a minimum of 800 events to achieve stable estimates from the regression model (TRIPOD2). We estimate that over 300,000 will be available in each annual dataset with a mean 30-day mortality of 0.6% producing 1800 endpoints. A full one year dataset will be used to adjust for any seasonal mortality effects.

Missing data

As date of death is a mandatory report in New Zealand we assume all mortality outcomes will be reported. We assume missing data occurs randomly. Multiple imputation will be used to handle missing data in non-outcome data.

Statistical analysis and methods

ASA was handled as a categorical predictor with 5 categories. Operation type was mapped onto surgical grade in 4 categories of minor, intermediate, major and major-complex. Cancer was a bivariate variable for presence or absence of a cancer with potential to affect mortality. Acuity was categorical elective or acute. Age was handled as a continuous predictor.

We will use multivariable logistic regression with backward stepwise regression. Univariate analysis will be performed initially using chi-squared testing to test the relationship between each independent variable and 30-day mortality. All analyses will performed to validate a predictive model of 30-day mortality and then repeated to derive predictive models of 30-day, one-year and two-year mortality respectively. Variables that had more than 10% missing values were excluded from the analysis. Incremental improvements in the extended models by incorporating gender and ethnicity will be assessed by change in AUC and integrated discrimination improvement.

The predictive model will be derived from the full dataset and was then resampled using bootstrapping (or cross-validation?) to evaluate performance. Reporting the results will be according to the TRIPOD statement.

Amendments to protocol

There are plans to extend this work to validate NZRISK in high risk subsets such as the neurosurgical, vascular, paediatric, thoracic and gastrointestinal populations. In order to do this we will do the following

1. Use an extended NMDS dataset from 2007 to 2019
2. Utilise extra exploratory covariates from the NMDS dataset including diabetes status, socioeconomic status, renal failure and ICD-9 and ICD-10 diagnostic codes

In addition, we will explore mortality patterns such as the Gompertz-Makeham law to provide improved modelling methods using mortality, statistical interactions, and incorporating days alive out of hospital as a modelling endpoint.

References

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