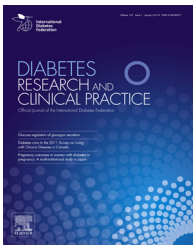
Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Development and validation of a predictive risk model for all-cause mortality in type 2 diabetes

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ARTICLE INFO

Article history:
Received 26 March 2014
Accepted 13 February 2015
Available online 16 March 2015

Keywords:
Diabetes mellitus type 2
Mortality
Risk factors
Risk assessment
Survival analysis
New Zealand

ABSTRACT

Aims: Type 2 diabetes is common and is associated with an approximate 80% increase in the rate of mortality. Management decisions may be assisted by an estimate of the patient's absolute risk of adverse outcomes, including death. This study aimed to derive a predictive risk model for all-cause mortality in type 2 diabetes.

Methods: We used primary care data from a large national multi-ethnic cohort of patients with type 2 diabetes in New Zealand and linked mortality records to develop a predictive risk model for 5-year risk of mortality. We then validated this model using information from a separate cohort of patients with type 2 diabetes.

Results: 26,864 people were included in the development cohort with a median follow up time of 9.1 years. We developed three models initially using demographic information and then progressively more clinical detail. The final model, which also included markers of renal disease, proved to give best prediction of all-cause mortality with a C-statistic of 0.80 in the development cohort and 0.79 in the validation cohort (7610 people) and was well calibrated. Ethnicity was a major factor with hazard ratios of 1.37 for indigenous Maori, 0.41 for East Asian and 0.55 for Indo Asian compared with European ($P < 0.001$).

Conclusions: We have developed a model using information usually available in primary care that provides good assessment of patient's risk of death. Results are similar to models previously published from smaller cohorts in other countries and apply to a wider range of patient ethnic groups.

1. Introduction

In 2010 about 285 million people worldwide had diabetes and this could rise to 439 million by 2030. [1] People with diabetes have been found to have a 70–80% increase in overall mortality rates and, if aged 50, will on average die 6 years earlier than those without diabetes [2,3]. About 60% of this excess mortality is due to cardiovascular disease (CVD) including stroke, with the remainder being attributable to cancers and other conditions. Many causes of these excess deaths are potentially preventable by self-care and medical management [4]. It is therefore important to identify people with diabetes who are at particularly high risk of death, so as to allow focussed and intensive intervention. Several predictive risk models have been developed to predict mortality in patients

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http://dx.doi.org/10.1016/j.diabres.2015.02.015
0168-8227/

with diabetes [5–8]. De Cosmo's study, published in 2013, was the first to be validated with an external cohort. However this involved comparatively small cohorts with only 133 and 169 deaths in the development and validation cohorts respectively.

The aim of the current study was to develop a predictive risk model for all-cause mortality in a large cohort of ethnically diverse people with type 2 diabetes in New Zealand (NZ) using information usually available in a general practice context, and to validate it in a separate cohort.

2. Subjects and methods

2.1. Settings and subjects

This study uses a prospective cohort design. It uses information from two NZ general practice-based cohorts of patients with type 2 diabetes. In New Zealand almost all patients with type 2 diabetes receive care in general practice.

2.1.1. Development cohort

Between 2000 and 2012, general practitioners were funded to provide a free annual review for their patients with diabetes ('Get Checked' programme). Data from these reviews were recorded using a standardised template and collected regionally to provide aggregated statistics about diabetes management in primary health care. The NZ Diabetes Cohort Study (NZDCS) invited 26 of the largest organisations collecting 'Get Checked' data to participate in a cohort study. Of these, 24 organisations (92%) agreed and contributed data on primary care patients collected between 2000 and 2006 [9].

2.1.2. Validation cohort

The Diabetes Care Support Service (DCSS) is an independent provider that carries out a manual systematic clinical audit of diabetes care in primary care practices in south and west Auckland, New Zealand's largest city [10]. The audit data provide a summary of diabetes care over the preceding year. Patients whose care had been audited between 1994 and 2003 were included.

In both cohorts all people with type 2 Diabetes, as determined by their primary health care physician, were included if they had complete data on the independent variables we wished to examine. The NZDCS study received ethical approval in 2004 and has on-going multi-centre approval in New Zealand (WGT/04/09/077).

2.2. Outcomes

All patients in New Zealand have a unique National Health Index (NHI) number, which is consistent across all health datasets. Patients in both cohorts were linked to New Zealand's mortality database by an encrypted NHI number to identify all deaths that occurred over the follow-up period. To develop the models, time to death was used as the outcome. To validate the models, death during the five years following baseline audit was the outcome. In both cases we assume complete attainment of outcomes was achieved, although in rare instances patients may have emigrated during the follow up period.

2.3. Risk variables

All risk variables except prior cardiovascular disease were obtained from the primary care cohort datasets. Demographic variables were age of onset and duration of diabetes, gender, ethnicity, smoking and socioeconomic status. We used primary care ethnicity records and categorised as European, Māori (the indigenous people of NZ), Pacific, Indo-Asian, East Asian, and 'Other'. Body mass index (BMI) was calculated from weight and height recordings. Other clinical variables included blood pressure, glycosylated haemoglobin (HBA1c), total cholesterol/HDL ratio and renal function. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula [11]. Clinically relevant categories were used for urine albumin creatinine ratio (UACR) because the variable was highly skewed and simple transformations did not create a useful variable. The predictive performance of the models was better using these categories than when using log-transformation. Categories were 'no albuminuria' (<2.5 mg/mmol in men or <3.5 mg/mmol in women), 'microalbuminuria' (≥2.5–<30 mg/mmol in men or ≥3.5–<30 mg/mmol in women), 'macroalbuminuria' (≥30 and <100 mg/mmol), and 'advanced albuminuria' (≥100 mg/mmol). We also tested models that included as variables whether patients were on insulin, oral hypoglycaemics, statins, antihypertensives, and angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs).

Prior cardiovascular disease was identified by the presence of any hospitalisation from myocardial infarction, angina, other ischaemic heart disease, coronary artery bypass or angioplasty, cerebrovascular accident or transient ischaemic attack, or any significant peripheral arterial disease that occurred before the baseline review date and after 1 January 1988. Details are available from previous publications [12].

2.4. Analysis

Descriptive statistics including means, medians, and proportions were used to describe the characteristics of the derivation and validation cohorts. We also examined the differences between patients with complete and missing data in both cohorts.

We developed Cox proportional hazards models for time to death to develop our predictive risk models. We first developed a model using just demographic variables and information on the onset and duration of diabetes (the 'demographic' model). We then sequentially added and tested clinical variables (smoking status, history of CVD, systolic blood pressure, BMI, HbA1c, and total cholesterol/HDL ratio) to develop a 'clinical' model. We then developed a 'renal' model by further adding eGFR and UACR. Finally, we examined the impact of adding information on whether patients were on particular drugs or combinations of drugs. For all continuous variables, we tested quadratic as well as linear relationships. We also tested a number of clinically plausible interactions such as the relationship between gender or ethnicity and age of onset or CVD history, although we did not include these in our final models.