科技部補助專題研究計畫報告

建立與驗證不同性別第二型糖尿病患者發生心血管疾病之風險預測模式(L03)

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本研究具有政策應用參考價值：■否 □是，建議提供機關
（勾選「是」者，請列舉建議可提供施政參考之業務主管機關）
本研究具影響公共利益之重大發現：□否 □是

中 華 民 國 110 年 10 月 21 日

中 文 摘 要 ： 目的： 女性罹患第二型糖尿病後所增加心血管疾病的發生率與死亡率幅度均超過男性所增加的幅度。為此，本計畫擬分別針對男、女性第二型糖尿病人建立並驗證全死因死亡之風險預測模式，提供治療預後評估之參考。
方法： 本計畫總共納入2012與2015年2年參加美兆健康檢查之4,798名成年（>=20歲）第二型糖尿病患者，其中男性2,965人，女性1,833人。這些第二型糖尿病人隨機區分為70%（n=3,358）樣本為訓練資料集（男性2,070人，女性1,288人）以及30%樣本為驗證資料集(n=1,440，男性895人，女性545人)。本研究利用世代研究設計將訓練資料及樣本比對2012/1/1至2020/10/31期間之全國死因統計資料，獲得樣本於追蹤期間可能發生的全因死亡事件訊息，並利用Cox比例危害模式分別針對男、女性訓練資料集樣本分析其社會人口學變項、生活習慣、個人與家人疾病史、以及實驗室生化檢查數據等潛在風險因子與全因死亡之間的相關性。在界定出顯著影響全因死亡的風險因子後，本研究使用Sullivan等人方法根據風險因子的迴歸係數大小加權計算全因死亡的預測分數，並將此計分系統帶入驗證資料集，也比對死因統計資料，並依據最適切點計算預測模式的敏感度、特異度、以及接受者操作曲線線下面積。最後也將驗證資料集樣本之風險分數按4分位數區分，計算4組風險等級驗證資料集樣本之實際全因死亡率作為校準的依據。
結果： 經過最多8年的追蹤後，訓練資料集中有117名男性與60名女性發生全因死亡，累積死亡率分別為5.65%與4.66%。Cox複迴歸模型指出男女性第二型糖尿病人有不同的風險因子組合，在男性樣本中，包括年齡、腦血管疾病、收縮壓、高密度膽固醇、白蛋白、C-反應蛋白、與身體質量指數等7個變項；女性樣本中則是有年齡、規律運動、以及身體質量指數等3個變項，在複迴歸分析中顯示與全因死亡有顯著的相關性。依據計分系統，計算驗證資料集樣本之風險分數，並以最適切點區分（男生為9分、女生為0分），男性預測模式的敏感度分別為0.70與0.71，接受者操作曲線線下面積為0.751；女生相對應的區辨指標數據則是0.56、0.73、及0.715。進一步將風險分數按四位分數區分進行校準，男性4組風險分數從低到高的實際全因死亡率為1.12%、3.11%、4.31%、以及14.29%；女性則是1.15%、0.68%、5.26%、以及6.36%。
結論：影響男女性第二型糖尿病人全因死亡的因子不完全相同，除了年齡與身體質量指數外，男性的死亡風險因子較多為實驗室生化檢查數值，女性則是運動習慣。本研究針對男女性第二型糖尿病人分別所建立的全因死亡風險預測模式具有不錯的區辨與校準能力，但此等能力距離臨床應用尚有改善的空間。

中 文 關 鍵 詞 ： 第二型糖尿病、全因死亡、世代研究、迴歸模式、預測模式

英 文 摘 要 ： OBJECTIVE: Thus, this study aimed to develop and validate sex-specific mortality risk prediction models, and this information may be used by clinicians for prognosis evaluation.
RESEARCH DESIGN AND METHODS: All 4,798 adults (>=20 years) including 2,965 men and 1,833 women who received health check-up at MJ Health Management Institution in 2012 or/and

2015 were enrolled. These participants were randomly split into a training dataset (n=3,358; men: n=2,070, women: n=1,288) and a validation dataset (n=1,440; men: n=895, women: n=545), which accounted for 70% and 30%, respectively of the original study sample. A cohort study design was used to link between study participants from the training dataset and Taiwan Death Registry (TDR) for identification of possible all-cause mortality from 2012/1/1 to 2020/10/31. We used Cox proportional hazard model to determine the risk factors significantly associated with all-cause mortality. The potential significant risk factors were in the categories of socio-demographic characteristics, lifestyle, disease history, and laboratory data. The risk score was calculated by using the regression coefficient weighing method proposed by Sullivan et al. based on the significant risk factors identified. Based on the point system of risk scores, study participant from the validation dataset were assigned risk scores, and linked to TDR to find out the optimal cut-off point. The corresponding sensitivity, specificity, and area under the curve (AUC) estimated from receiver operation curves (ROC) were calculated accordingly.
RESULTS: Over up to 8 years of follow-up, 117 male and 60 female participants from the training dataset encountered all-cause mortality, representing a cumulative mortality risk of 5.65% and 4.66%, respectively. Multiple Cox proportional hazard regression models suggested different sets of risk factors for all-cause mortality between men and women patients with type 2 diabetes. In male participants, age, a history of cerebrovascular disease, systolic blood pressure, high density lipoprotein cholesterol, albumin, c-reactive protein, and body mass index (BMI) were found to be significantly associated with all-cause mortality. On the other hand, age, physical activity, and BMI were significant risk factors for all-cause mortality in female participants. Based on the cohort analysis of study participants from the validation dataset, the optimal cut-off point of risk score (men: 9 points; women: 0 point) was associated with a sensitivity, specificity, and AUC of 0.70, 0.71, and 0.751, respectively. The corresponding figures for women patients were 0.56, 0.73, and 0.715. The calibration analysis revealed an actual risk of mortality of 1.12%, 3.11%, 4.31%, and 14.29% from the lowest to the highest risk score quartile in male patients. The corresponding figures for the female patients were 1.15%, 0.68%, 5.26%, and 6.36%.
CONCLUSIONS: Male and female patients with type 2 diabetes shared different sets of risk factors for all-cause

mortality. While age and BMI were significant risk factors for all-cause mortality in both men and women patients, male patients had more risk factors related to laboratory data, but female patients' risk factor was related to physical activity. The two sex-specific all-cause prediction models developed in our study showed satisfactory levels of discrimination and calibration capability.

英文關鍵詞：Type 2 diabetes mellitus, All-cause mortality, Cohort studies, Regression models , Prediction models

題目

第二型糖尿病人全因死亡與相關因子的性別差異

Title

Sex differences in all-cause mortality and its covariates in patients with type 2 diabetes.

摘要

目的： 女性罹患第二型糖尿病後所增加心血管疾病的發生率與死亡率幅度均超過男性所增加的幅度。為此，本計畫擬分別針對男、女性第二型糖尿病人建立並驗證全死因死亡之風險預測模式，提供治療預後評估之參考。

方法： 本計畫總共納入 2012 與 2015 年 2 年參加美兆健康檢查之 4,798 名成年（>=20 歲）第二型糖尿病患者，其中男性 2,965 人，女性 1,833 人。這些第二型糖尿病人隨機區分為 70%（*n*=3,358）樣本為訓練資料集（男性 2,070 人，女性 1,288 人）以及 30%樣本為驗證資料集(*n*=1,440，男性 895 人，女性 545 人)。本研究利用世代研究設計將訓練資料及樣本比對 2012/1/1 至 2020/10/31 期間之全國死因統計資料，獲得樣本於追蹤期間可能發生的全因死亡事件訊息，並利用 Cox 比例危害模式分別針對男、女性訓練資料集樣本分析其社會人口學變項、生活習慣、個人與家人疾病史、以及實驗室生化檢查數據等潛在風險因子與全因死亡之間的相關性。在界定出顯著影響全因死亡的風險因子後，本研究使用 Sullivan 等人方法根據風險因子的迴歸係數大小加權計算全因死亡的預測分數，並將此計分系統帶入驗證資料集，也比對死因統計資料，並依據最適切點計算預測模式的敏感度、特異度、以及接受者操作曲線線下面積。最後也將驗證資料集樣本之風險分數按 4 分位數區分，計算 4 組風險等級驗證資料集樣本之實際全因死亡率作為校準的依據。

結果： 經過最多 8 年的追蹤後，訓練資料集中有 117 名男性與 60 名女性發生全因死亡，累積死亡率分別為 5.65%與 4.66%。Cox 複迴歸模型指出男女性第二型糖尿病人有不同的風險因子組合，在男性樣本中，包括年齡、腦血管疾病、收縮壓、高密度膽固醇、白蛋白、C-反應蛋白、與身體質量指數等 7 個變項；女性樣本中則是有年齡、規律運動、以及身體質量指數等 3 個變項，在複迴歸分析中顯示與全因死亡有顯著的相關性。依據計分系統，計算驗證資料集樣本之風險分數，並以最適切點區分（男生為 9 分、女生為 0 分），男性預測模式的敏感度分別為 0.70 與 0.71，接受者操作曲線線下面積為 0.751；女生相對應的區辨指標數據則是 0.56、0.73、及 0.715。進一步將風險分數按四位分數區分進行校準，男性 4 組風險分數從低到高的實際全因死亡率為 1.12%、3.11%、4.31%、以及 14.29%；女性則是 1.15%、0.68%、5.26%、以及 6.36%。

結論：影響男女性第二型糖尿病人全因死亡的因子不完全相同，除了年齡與身體質量指數外，男性的死亡風險因子較多為實驗室生化檢查數值，女性則是運動習慣。本研究針對男女性第二型糖尿病人分別所建立的全因死亡風險預測模式具有不錯的區辨與校準能力，但此等能力距離臨床應用尚有改善的空間。

關鍵字：第二型糖尿病、全因死亡、世代研究、迴歸模式、預測模式

ABSTRACT

OBJECTIVE: Thus, this study aimed to develop and validate sex-specific mortality risk prediction models, and this information may be used by clinicians for prognosis evaluation.

RESEARCH DESIGN AND METHODS: All 4,798 adults (>=20 years) including 2,965 men and 1,833 women who received health check-up at MJ Health Management Institution in 2012 or/and 2015 were enrolled. These participants were randomly split into a training dataset (*n*=3,358; men: *n*=2,070, women: *n*=1,288) and a validation dataset (*n*=1,440; men: *n*=895, women: *n*=545), which accounted for 70% and 30%, respectively of the original study sample. A cohort study design was used to link between study participants from the training dataset and Taiwan Death Registry (TDR) for identification of possible all-cause mortality from 2012/1/1 to 2020/10/31. We used Cox proportional hazard model to determine the risk factors significantly associated with all-cause mortality. The potential significant risk factors were in the categories of socio-demographic characteristics, lifestyle, disease history, and laboratory data. The risk score was calculated by using the regression coefficient weighing method proposed by Sullivan *et al*. based on the significant risk factors identified. Based on the point system of risk scores, study participant from the validation dataset were assigned risk scores, and linked to TDR to find out the optimal cut-off point. The corresponding sensitivity, specificity, and area under the curve (AUC) estimated from receiver operation curves (ROC) were calculated accordingly.

RESULTS: Over up to 8 years of follow-up, 117 male and 60 female participants from the training dataset encountered all-cause mortality, representing a cumulative mortality risk of 5.65% and 4.66%, respectively. Multiple Cox proportional hazard regression models suggested different sets of risk factors for all-cause mortality between men and women patients with type 2 diabetes. In male participants, age, a history of cerebrovascular disease, systolic blood pressure, high density lipoprotein cholesterol, albumin, c-reactive protein, and body mass index (BMI) were found to be significantly associated with all-cause mortality. On the other hand, age, physical activity, and BMI were significant risk factors for all-cause mortality in female participants. Based on the cohort analysis of study participants from the validation dataset, the optimal cut-off point of risk score (men: 9 points; women: 0 point) was associated with a sensitivity, specificity, and AUC of 0.70, 0.71, and 0.751, respectively. The corresponding figures for women patients were 0.56, 0.73, and 0.715. The calibration analysis revealed an actual risk of mortality of 1.12%, 3.11%, 4.31%, and 14.29% from the lowest to the highest risk score quartile in male patients. The corresponding figures for the female patients were 1.15%, 0.68%, 5.26%, and 6.36%.

CONCLUSIONS: Male and female patients with type 2 diabetes shared different sets of

risk factors for all-cause mortality. While age and BMI were significant risk factors for all-cause mortality in both men and women patients, male patients had more risk factors related to laboratory data, but female patients' risk factor was related to physical activity. The two sex-specific all-cause prediction models developed in our study showed satisfactory levels of discrimination and calibration capability.

Keywords: Type 2 diabetes mellitus, All-cause mortality, Cohort studies, Regression models , Prediction models

INTRODUCTION

Compared to men, women have a much lower risk of cardiovascular disease (CVD) through the entire lifespan. However, women were found to experience a greater increased risk for cardiovascular complications than men after diabetes (Peters et al., 2014a; Peters et al., 2014b; Huxley et al., 2015; Ohkuma et al., 2019). Peters et al. (2014a) conducted a meta-analysis examining the relationship between diabetes and incident coronary heart disease (CHD) in men and women, respectively and found that the relative risk (RR) for incident CHD associated with diabetes was significantly elevated at 2.82 for women and 2.16 for men. The multiple-adjusted RR ratio for incident CHD was 44% greater in women with diabetes than in diabetes men. In another meta-analysis, Peters et al. (2014b) noted that RR of stroke associated with diabetes was significantly increased at 2.28 in women and 1.83 in men. Again, pooled data indicated that compared with men with diabetes, women with diabetes therefore had a greater RR for incident stroke, with a magnitude of 27%.

Although not fully illustrated, several reasons have been proposed to explain such "catch-up" effect by women after diabetes, including contribution of sex hormones and sex-specific risk factors (Ding et al., 2006; Kim et al., 2015; Woodward et al., 2015). Meanwhile, some non-biological reasons, including physician and patient characteristics and behaviors, have also been suspected to be associated with such sex-difference in RR of CVD. Previous studies showed that women with diabetes encountered more barriers than male diabetes to have access to appropriate and cardio-protective medical care (Eapen et al., 2014; NHS Digital, 2014; Zhao et al., 2017; Zhao et al., 2020). The UK National Diabetes Audit reported that compared to male patients, female diabetes were 15% less likely to receive medical care recommended by the treatment guidelines or to meet diabetes care targets (NHS Digital, 2014).

Additionally, a previous US study noted that women with diabetes were 25% less likely to achieve target cholesterol levels than men suspected due to inadequate medication for women patients (Eapen et al., 2014). Moreover, Kirkman et al. (2015) conducted a large-scale study in the US and its territories and found that adherence to antidiabetic medication was slightly lower among women. The authors commented that it is very likely that physicians have undoubtedly been liable to treat cardiovascular disease as predominantly a '*man's disease*', which was traditionally an opinion, and some physicians maybe still think this way (Woodward et al., 2015).

In addition to differential increase in cardiovascular disease incidence between male and female diabetes patients, studies also noted sex-specific associations between diabetes and complications and mortality (Wang et al., 2019; Xu et al., 2019). This points to an urgent need to develop sex- and gender-specific risk assessment strategies and therapeutic interventions that target diabetes management in the context of premature mortality prevention among patients with type 2 diabetes. We therefore carried out this study to explore the sex-specific prognostic factors for all-cause mortality in people after diabetes.

Based on the information of sex-specific risk profile, we also aimed to create sex-specific scoring algorithm in predicting all-cause mortality in male and female patients with type 2 diabetes, respectively.

RESEARCH DESIGN AND METHODS

The study proposal was approved by the Institutional Review Board of National Cheng Kung University Hospital (HREC No. 109-091).

Data Source

Health data were obtained from the MJ Health Management Institution, a membership-oriented private institute in Taiwan with four health check-up clinics located in Taipei, Taoyuan, Taichung, and Kaohsiung. A health questionnaire was completed by each participant, and clinical evaluation including anthropometric measurements, biochemical tests, and pulmonary function tests were performed. The health questionnaire included socio-demographic characteristics, personal and family medical history, and lifestyle such as tobacco exposure, alcohol consumption, physical activity (PA), and food habits. This standard health examination program is run by a private firm (MJ Health Management Institution, Taiwan), and all the procedures (http://www.mjhrf.org/file/en/report/MJHRF-TR-01MJ%20Health%20Database.pdf) were approved per ISO 9001 standards.

This study included all MJ health check-up participants who either self-reported a history of diagnosed type 2 diabetes or had a fasting plasma glucose level of 126 mg/dL (7 mmol/L) or higher on two separate tests (American Diabetes Association , 2021) at time of health check-up visits in 2012 and/or 2015. All study participants aged 20 years or older. The flowchart of study participants is shown in Figure 1. A total of 4,798 participants (male 2,965; female 1,833) were included in the analysis. The covariates in 2012 were considered as baseline covariates for those study participants who attended health check-up in both years.

In Taiwan, all live births and deaths should be registered within 10 days after birth or death as a legal requirement. Death certificates included in the Taiwan Death Registry (TDR) include various information, including socio-demographic variables, underlying cause of death (UCOD), place of death, and marital status. Data quality for TDR have been evaluated and are considered valid and complete (Lu et al., 2000). Information of all-cause mortality was retrieved from TDR.

Study Design and Sample

This was a retrospective cohort study design with all study participants were randomly split into either “training dataset” or “validation dataset”. The training and validation

dataset accounts for 70% (*n*=3358) and 30% (*n*=1440) of all study participants, respectively. Th cohort studies based on the training dataset were used to identify risk factors (i.e., exposure variables) significantly associated with all-cause mortality for male and female patients with type 2 diabetes, respectively. These identified risk factors were further used to calculate the risk scores for the prediction of all-cause mortality. On the other hand, the cohort studies based on the validation dataset were used to link the risk score (i.e., exposure variable) calculated from the training dataset to all-cause mortality. It aimed to assess the generalizability of risk score derived from the training dataset.

Follow-up and Study Outcome

The study participants were followed from the date of baseline check-up in either 2012 or 2015 to the occurrence of all-cause mortality or end-of-follow-up (i.e., October, 2020). Information of date of mortality was obtained from linkage between study cohort and TDR.

Covariates

The potential risk factors for all-cause mortality were divided into four categories, namely, socio-demographic variables, lifestyle, medical history, and laboratory data. Information of the above covariates was retrieved from MJ health check-up data. Socio-demographic variables included age at cohort enrollment, family annual income, and educational years. Lifestyle included smoking status, alcohol consumption, and regular physical activity in the past 2 years. Medical histories included cerebrovascular disease, cardiovascular disease, and hypertension of participants themselves and their family.

Laboratory data included the following information: body mass index (BMI), systolic blood pressure (SBP), HbA1c, homocysteine, triglycerides (TG), cholesterol, high density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC), white blood cell (WBC), hemoglobin, albumin, creatinine, uric acid, and c-reactive protein (CRP).

Statistical Analysis

Descriptive statistics and identification of predictors for all-cause mortality

We firstly compared socio-demographic and lifestyle characteristics as well as laboratory data between male and female patients with type 2 diabetes in the training and validation dataset, respectively. A Cox proportional hazard regression model with all selected socio-demographic, lifestyle, and laboratory simultaneously being included in the model was separately performed for male and female patients in the training dataset to identify significant predictors for all-cause mortality. A potential violation of proportional

hazards assumption was examined by plots of *log(−log(survival function))* vs. *log(time),* and no violations were detected for both models. Covariates significantly associated with all-cause mortality at a significance level of α-level of 0.05 were considered as risk factors for all-cause mortality and were included in the subsequent procedure of prediction model development.

Model development

We developed a categorization point system according to the methods suggested by Sullivan et al. (2004). First, all risk factors included in the prediction model were selected based on the abovementioned multiple Cox proportional hazard models. Second, to make our prediction model more practical, we chose hazard ratio (HR) from subgroups. For example, in considering age as a factor, we selected the HR of age at 10-year increments. Beta-coefficients of each risk factor and their corresponding 95% confidence interval (CI) were retrieved from Cox proportional hazard models. Then, scores were calculated by multiplying the beat-coefficients by 10 and rounding off one decimal place. Finally, all risk factors in the prediction model were categorized based on the clinical practice guidelines, and each category was assigned a score. The gross score was calculated by summing the scores of all components in the prediction model. The all-cause mortality risk prediction model was developed for male and female patients with type 2 diabetes, respectively.

Model validation

Validation data from the study cohort described above were used to examine the generalizability of the risk prediction model, identifying the best implementation strategy. Baseline variables were used to calculate the total score according to the risk prediction model. However, follow-up all-cause mortality was used to calculate the area under the receiver operating characteristic curve, which was used as an indicator for discrimination capability. Sensitivity, specificity, and the area under the curve (AUC) were calculated at different cutoff values, and the calculations were used to identify the optimal cutoff point (Cook et al., 2007; Jiang et al., 2020). According to the optimal cutoff point, patients were categorized into 2 risk levels (i.e., low vs high risk). We also manually categorized the score onto 4 risk levels, including relatively low, moderate, high, and very high risk. To calibrate the predictive power of the prediction model, the actual incidence of all-cause mortality was calculated and a Kaplan-Meier curve was generated for different risk levels. All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Table 1 shows comparisons of socio-demographic variables, lifestyle, and medical histories between male and female type 2 diabetes in the training (*n*=3358) and validation dataset (*n*=1440), respectively. In the sample of training dataset, participants aged <50 years accounted for the majority of male sample (39.66%), while those aged 60-69 years dominated in the female sample (30.59%). Family annual income was higher in male than in female participants. Male participants also had more educational years than females. Fifty-two point seventy-five percent of male participants had more than 18 years of education, whereas only 26.09% of female participants had similar education level. While male participants had much greater prevalence of smoking and alcohol consumption than females, the prevalence of regular physical activity was similar between two sexes (men: 68.70%, women: 65.99%). The prevalence of cerebrovascular disease, cardiovascular disease, and hypertension was similar between male and female participants, as well as between their families. Similar distributions of socio-demographic variables, lifestyle, and medical histories were observed in the sample of validation dataset.

Among various laboratory data, compared to their female counterparts, male participants tended to have higher BMI but lower SBP. Additionally, male participants had higher prevalence of increased HbA1c (≥6.5%), abnormal homocysteine (<5 or >15 μmol/L), higher TG (≥150 mg/dl), lower HDLC (<40 mg/dl), abnormal hemoglobin (<12 or >16 g/dl), abnormal creatinine (<0.6 or >1.3 mg/dl), and abnormal uric acid (<3 or >7 mg/dl); but lower prevalence of higher cholesterol (≥200 mg/dl) and higher CRP (>0.5 mg/dl). On the other hand, male and female participants had similar prevalence of higher LDLC (≥130 mg/dl) and abnormal WBC level (<4000 or >10000 count/ml). Again, similar distributions of laboratory data were observed in the sample of validation dataset (Table 2).

Over up to 8 years of follow-up, 117 male and 60 female participants from the training dataset encountered all-cause mortality, representing a cumulative mortality risk of 5.65% and 4.66%, respectively. In males, higher cumulative mortality risks were observed in those with an abnormal albumin level (54.55%), with a BMI <18.5 kg/m^2 (27.27%), aged 70+ years (28.02%), and had a history of cerebrovascular disease (21.05%). In females on the other hand, the highest cumulative mortality was also noted for those with an abnormal albumin level (16.67%), followed by those with an abnormal homocysteine level (15.79%), aged 70+ years (15.14%), and with a history of cerebrovascular disease (15.00%) (Table 3).

Multiple Cox proportional hazard regression models suggested different sets of risk factors for all-cause mortality between men and women patients with type 2 diabetes (Table 4). In male participants, older age at cohort enrollment, a history of cerebrovascular disease,

higher SBP, abnormal HDLC, abnormal albumin, and abnormal CRP were significantly associated with an increased all-cause mortality. But a higher BMI (>=24 kg/m^2) was associated with a significantly decreased all-cause mortality. In female participants, only three covariates were found to be significantly associated with an increased all-cause mortality including older age, lack of regular physical activity, and lower BMI (<18.5 kg/m^2). The score points corresponding top the abovementioned significantly risk factors for all-cause mortality were presented in Table 5.

The optimal cut-off point of the risk score for male and female participants was estimated at 9 and 0 points, respectively. Based on the optimal cut-off point, the sensitivity and specificity of the prediction model was 0.79 and 0.71, respectively in the male sample of the training dataset. The corresponding figures for the validation dataset were 0.70 and 0.71 (Table 6). Additionally, the AUC for the training and validation dataset was 0.817 and 0.751, respectively for the male sample (Figure 2). In female sample, the sensitivity and specificity of the prediction model based on the optimal cut-off point was 0.70 and 0.74 for the training dataset; and the corresponding figures for the validation dataset were 0.56 and 0.73 (Table 7). The AUC for the training and validation dataset was 0.770 and 0.715, respectively for the female sample (Figure 2)

In the calibration analysis with risk scores being categorized into quartiles, the actual all-cause mortality rate for the risk score in Q1 (Min.-25th) (1.29%), Q2 (25th-50th) (2.07%), Q3 (50th-75th) (4.60%), and Q4 (75th-Max.) (13.04%) gradually increased in male participants. The corresponding figures for the validation dataset were 1.15%, 0.68%, 5.26%, and 6.36% (Table 6). In female participants, the actual all-cause mortality rate for the risk score in Q1 (Min.-25th) (1.29%), Q2 (25th-50th) (2.07%), Q3 (50th-75th) (4.60%), and Q4 (75th-Max.) (13.04%) gradually increased in female participants. The corresponding figures for the validation dataset were 1.15%, 0.68%, 5.26%, and 6.36% (Table 7). Figure 3 shows a satisfactory level of calibration by demonstrating significant differences in Kaplan-Meier survival curves no matter risk scores were categorized into 2 or 4 ordinal levels. Such a satisfactory level of calibration was observed for male and female patients with type 2 diabetes.

DISCUSSION

Main Findings

The current study developed two sex-specific prediction models with different combination of risk factors for all-cause mortality based on the health check-up and mortality registry data from Taiwan. Both predictions showed satisfactory levels of discrimination and calibration capability. The AUC was estimated at 0.751 and 0.715 for male and female patients, respectively.

Interpretations

Both clinical and animal studies demonstrate significant sex differences in prevalence, pathophysiology, and outcomes of CVDs, including those associated with diabetes. The increased risk of CVDs with diabetes is higher in women compared to men with 50% higher risk of coronary artery diseases and increased mortality when exposed to acute myocardial infarction. Endothelial dysfunction, atherosclerosis, coagulation, and fibrosis are mechanisms found to be sex-differentially modulated in the diabetic cardiovascular system, which ultimately leads to mortality (Fourny et al., 2021). Not only CVD incidence, the consequences of diabetes on associated end-organ complications, including diabetic kidney disease appear to be more sex-specific. Particularly, women with diabetes have higher mortality rates for diabetes-related deaths, and higher prevalence of diabetic kidney disease risk factors such as hypertension, hyperglycemia, obesity, and dyslipidemia (Maric-Bilkan, 2020.

Wang et al. (2019) conducted a meta-analysis of 49 studies and found that the pooled women-to-men relative risk ratio (RRR) showed a 13% greater risk of all-cause mortality associated with diabetes in women than in men (RRR 1.13, 95% CI 1.07 to 1.19; P < 0.001). The pooled multiple-adjusted RRR indicated a 30%, 58%, and 8% increase in mortality from CVD, CHD, and stroke.. However, no sex differences were observed in pooled results of individuals with or without diabetes for all-cancer (RRR 1.02, 95% CI 0.98 to 1.06; P = 0.21), infectious (RRR 1.13, 95% CI 0.90 to 1.38; P = 0.33), and respiratory mortality (RRR 1.08, 95% CI 0.95 to 1.23; P = 0.26). The 35 analyzed prospective cohort studies included 2 314 292 individuals, among whom 254 038 all-cause deaths occurred. Similar results were noted by Xu et al.'s study (2019) who found that the pooled women vs men ratio of the HRs for all-cause and CHD mortality were 1.17 (95% CI: 1.12-1.23, I2 = 81.6%) and 1.97 (95% CI: 1.49-2.61, I2 = 86.4%), respectively. On the other hand, Ohkuma et al. (2018) found that diabetes is a risk factor for all-site cancer for both women and men, but the excess risk of cancer associated with diabetes is slightly greater for women than men.

Our study showed a difference in sex-specific risk sets associated with all-cause mortality. Risk factors including SBP, HDLC, albumin, and CRP were found to be significantly associated with all-cause mortality in men but not in women patients. Biological age contributes to sexual dimorphism, as premenopausal women experience a higher degree of cardioprotection than men of similar age. Furthermore, sex hormones such as oestrogen and testosterone as well as sex chromosome complement likely contribute to sex differences in BP and CVD) (Colafella et al., 2018). Although evidence suggests that cardioprotection in women is lost under conditions of obesity and type 2 diabetes mellitus, our sample comprised a quarter of women patients aged <50 years. Furthermore, sex hormones have a great impact on energy metabolism, body composition, vascular function, and inflammatory responses (Kautzky-Willer et al., 2016).

In SHIP-0 and MONICA/KORA S3 investigations, Markus et al. (2021) found that in participants with type 2 diabetes mellitus, the risk for cardiovascular mortality was not different between men and women in the unadjusted model and after adjustment for age, body mass index, low-density lipoprotein-cholesterol, fasting status and study sample (SHIP-0, MONICA/KORA S3). In individuals with type 2 diabetes mellitus, however, further adjustment for lipoprotein(a) led to an increased risk for cardiovascular mortality in men and a decreased risk in women resulting in a statistically significant difference between men and women (HR: 1.53; 95% CI 1.04 to 2.24; p = 0.029), suggesting Higher lipoprotein(a) concentrations in women with type 2 diabetes mellitus than in men with type 2 diabetes mellitus might partially explain this finding (Markus et al., 2021).

In both male and female patients, higher BMI was found to be associated with a reduced risk of all-cause mortality, which is consistent with an argument that in type 2 diabetes, BMI is nonlinearly associated with all-cause mortality with lowest risk in the overweight group in both men and women (Zaccardi et al., 2017). In a meta-analysis, Zaccardi et al. (2017) included 21 studies including 24 cohorts, 414,587 participants, 61,889 all-cause and 4470 cardiovascular incident deaths; follow-up ranged from 2.7 to 15.9 years, and found a strong nonlinear relationship between BMI and all-cause mortality in both men and women, with the lowest estimated risk from 31-35 kg/m^2 and 28-31 kg/m^2 (p value for nonlinearity <0.001) respectively. The risk of mortality at higher BMI values increased significantly only in women, whilst lower values were associated with higher mortality in both sexes.

Regular physical exercise In addition to biological reasons, previous studies also reported diversities in culture, lifestyle, environment, and socioeconomic status that may have impacted differences between males and females in predisposition, development, and clinical presentation after type 2 diabetes (Kautzky-Willer et al., 2016). A local Taiwanese

study also reported that lower urbanization of residency was also significantly associated with an increased risk of mortality with a dose-gradient pattern (Lin et al., 2015). It is believed that both biological and psychosocial factors are responsible for sex and gender differences in diabetes risk and outcome. Besides, psychosocial stress appears to have greater impact on women rather than on men (Kautzky-Willer et al., 2016).

While some progress has been made toward understanding the underlying mechanisms of sex differences in the pathophysiology of diabetic vascular complications, many questions and controversies remain. Future research leading to understanding of these mechanisms may contribute to personalized- and sex-specific treatment for diabetic micro- and macro-vascular disease (Maric-Bilkan, 2017).

Strengths and limitations

This is the first local study using the same health check-up data and mortality registry data to develop sex-specific prediction model for mortality in patients with type 2 diabetes. Through the linkage between the two datasets, the chance of loss to follow-up is low, which minimized the potential for selection bias. Second, the follow-up period in our cohort study ranged from 5 to 8 years, which is considered long enough to etiologically link type 2 diabetes and mortality. Third, our study considered a comprehensive list of potential risk factors for mortality, including socio-demographic characteristics, lifestyle, history of chronic disease, and laboratory data, which largely reflected the outcomes of treatment (Laposata and Dighe, 2007).

Despite the above strengths, a number of limitations should also be noted. First, although we enrolled thousands of male and female patients with type 2 diabetes, the number of deceased individuals were not considered enough for various stratified analyses, which might have underpowered some sub-group analyses. Second, the questionnaires administered to the health check-up participants did not collect a comprehensive list of prior history of diseases. For example, in addition to cardiovascular disease, patients with type 2 diabetes also at increased mortality from other causes of death. A Taiwanese study found that the leading causes of death in type 2 diabetes included neoplasm (22.68%), cardiovascular diseases (21.46%), and endocrine diseases (20.78%) (Lin et al., 2015). Third, glycated hemoglobin (HbA1c) has been one of the important risk factors for mortality in patients with diabetes. A recent meta-analysis a total of five studies, comprising 22,035 patients with type 2 diabetes mellitus. The median follow-up duration was 5.0 years. After adjusted for multiple conventional cardiovascular risk factors, an increased level of hemoglobin glycation index (HGI) was associated with a higher risk of composite cardiovascular disease (CVD) (per 1 standard deviation (SD) increment: HR =

1.14, 95% CI = 1.04-1.26) and all-cause mortality (per 1 SD increment: HR = 1.18, 95% CI = 1.05-1.32). However, when further adjusted for HbA1c, the association between HGI and risk of composite CVD (per 1 SD increment of HGI: HR = 1.01, 95% CI = 0.93-1.10) and all cause mortality (per 1 SD increment of HGI: HR = 1.03, 95% CI = 0.96-1.10) became insignificant (Wu et al., 2021). The information of HbA1c was not available in our study.

Conclusion

In summary, male and female patients with type 2 diabetes shared different sets of risk factors for all-cause mortality. While age and BMI were significant risk factors for all-cause mortality in both men and women patients, male patients had more risk factors related to laboratory data, but female patients' risk factor was related to physical activity. The two sex-specific all-cause prediction models developed in our study showed satisfactory levels of discrimination and calibration capability. Nonetheless, there is still room for improvement when considering administration of these developed prediction models in clinical settings.

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Table 1. Comparisons of socio-demographic and lifestyle characteristics between male and female diabetes in the training (*n*=3358) and validation dataset (*n*=1440), respectively.

	Training data				Total	Validation data				Total
	Male		Female			Male		Female		
	n	%	*n*	%		*n*	%	n	%	
Total	2070	100.00	1288	100.00	3358	895	100.00	545	100.00	1440
Age at enrollment (years)										
<50	821	39.66	309	23.99	1130	353	39.44	134	24.59	487
50-59	591	28.55	367	28.49	958	250	27.93	146	26.79	396
60-69	451	21.79	394	30.59	845	191	21.34	174	31.93	365
70+	207	10.00	218	16.93	425	101	11.28	91	16.70	192
Family yearly income (NTD)										
0	425	20.53	441	34.24	866	188	21.01	192	35.23	380
<=800,000	619	29.90	454	35.25	1073	267	29.83	193	35.41	460
810,000-1,200,000	483	23.33	206	15.99	689	193	21.56	86	15.78	279
>=1210,000	543	26.23	187	14.52	730	247	27.60	74	13.58	321
Educational years										
<=6	394	19.03	568	44.10	962	170	18.99	253	46.42	423
7-18	584	28.21	384	29.81	968	258	28.83	151	27.71	409
>18	1092	52.75	336	26.09	1428	467	52.18	141	25.87	608
Smoking status										
No	1484	71.69	1249	96.97	2733	647	72.29	530	97.25	1177
Yes	586	28.31	39	3.03	625	248	27.71	15	2.75	263
Drinking status										
No	1535	74.15	1249	96.97	2784	680	75.98	519	95.23	1199
Yes	535	25.85	39	3.03	574	215	24.02	26	4.77	241
Regular physical activity										

No	648	31.30	438	34.01	1086	266	29.72	172	31.56	438
Yes	1422	68.70	850	65.99	2272	629	70.28	373	68.44	1002
Participant's disease history										
Cerebrovascular disease	38	1.84	20	1.55	58	12	1.34	8	1.47	20
Cardiovascular disease	207	10.00	155	12.03	362	93	10.39	60	11.01	153
Hypertension	699	33.77	515	39.98	1214	317	35.42	231	42.39	548
Disease history of family										
Cerebrovascular disease	288	13.91	180	13.98	468	141	15.75	85	15.60	226
Cardiovascular disease	297	14.35	163	12.66	460	112	12.51	69	12.66	181
Hypertension	837	40.43	540	41.93	1377	385	43.02	253	46.42	638

NTD: New Taiwan Dollars

Table 2. Comparisons of laboratory date between male and female diabetes in the training (*n*=3358) and validation dataset (*n*=1440), respectively.

	Training data				Total	Validation data				Total
	Male		Female			Male		Female		
	n	%	*n*	%		*n*	%	*n*	%	
Total	2070	100.00	1288	100.00	3358	895	100.00	545	100.00	1440
Body mass index (kg/m²)										
<18.5	11	0.53	30	2.33	41	5	0.56	10	1.83	15
18.5-24	486	23.48	384	29.81	870	200	22.35	178	32.66	378
>=24	1573	75.99	874	67.86	2447	690	77.09	357	65.50	1047
Systolic blood pressure (mmHg)										
<120	650	31.40	391	30.36	1041	275	30.73	173	31.74	448
120-129	450	21.74	244	18.94	694	207	23.13	104	19.08	311
130-139	455	21.98	242	18.79	697	201	22.46	112	20.55	313
140-149	266	12.85	185	14.36	451	107	11.96	71	13.03	178
>=150	249	12.03	226	17.55	475	105	11.73	85	15.60	190
HbA1c (%)										
<6.5	149	7.20	91	7.07	240	67	7.49	38	6.97	105
≥6.5	1921	92.80	1197	92.93	3118	828	92.51	507	93.03	1335
Homocysteine (μmol/L)										
5-15	2022	97.68	1269	98.52	3291	880	98.32	539	98.90	1419
<5 or >15	48	2.32	19	1.48	67	15	1.68	6	1.10	21
TG (mg/dl)										
<150	1048	50.63	770	59.78	1818	453	50.61	320	58.72	773
≥150	1022	49.37	518	40.22	1540	442	49.39	225	41.28	667
Cholesterol (mg/dl)										
<200	1163	56.18	652	50.62	1815	513	57.32	272	49.91	785

	≥200	907	43.82	636	49.38	1543	382	42.68	273	50.09	655
HDLC (mg/dl)											
	<40	386	18.65	60	4.66	446	176	19.66	27	4.95	203
	≥40	1684	81.35	1228	95.34	2912	719	80.34	518	95.05	1237
LDLC (mg/dl)											
	<130	1301	62.85	819	63.59	2120	593	66.26	353	64.77	946
	≥130	769	37.15	469	36.41	1238	302	33.74	192	35.23	494
WBC (count/ml)											
	4000-10000	1924	92.95	1179	91.54	3103	832	92.96	500	91.74	1332
	<4000 or >10000	146	7.05	109	8.46	255	63	7.04	45	8.26	108
Hemoglobin (g/dl)											
	12-16	1590	76.81	1157	89.83	2747	683	76.31	489	89.72	1172
	<12 or >16	480	23.19	131	10.17	611	212	23.69	56	10.28	268
Albumin (g/dl)											
	3.8-5.3	2059	99.47	1282	99.53	3341	892	99.66	542	99.45	1434
	<3.8 or >5.3	11	0.53	6	0.47	17	3	0.34	3	0.55	6
Creatinine (mg/dl)											
	0.6-1.3	1860	89.86	1238	96.12	3098	805	89.94	528	96.88	1333
	<0.6 or >1.3	210	10.14	50	3.88	260	90	10.06	17	3.12	107
Uric acid (mg/dl)											
	3-7	1415	68.36	1097	85.17	2512	612	68.38	477	87.52	1089
	<3 or >7	655	31.64	191	14.83	846	283	31.62	68	12.48	351
CRP (mg/dl)											
	≤0.5	1889	91.26	1104	85.71	2993	821	91.73	477	87.52	1298
	>0.5	181	8.74	184	14.29	365	74	8.27	68	12.48	142

TG: Triglycerides; HDLC: High Density Lipoprotein Cholesterol; LDLC: Low Density Lipoprotein Cholesterol; WBC: White Blood Cell; CRP: c-reactive protein

Table 3. Overall and cause-specific numbers of all-cause mortality up to the end of study (i.e., Oct. 2020) in the ***training dataset*** (*n*=3358)

	Male				Total	Female				Total
	Survivor		All-cause death			Survivor		All-cause death		
	n	%	n	%		n	%	n	%	
Total	1953	94.35	117	5.65	2070	1228	95.34	60	4.66	1288
Age at enrollment (years)										
<50	808	98.42	13	1.58	821	303	98.06	6	1.94	309
50-59	572	96.79	19	3.21	591	360	98.09	7	1.91	367
60-69	424	94.01	27	5.99	451	380	96.45	14	3.55	394
70+	149	71.98	58	**28.02**	207	185	84.86	33	**15.14**	218
Family yearly income (NTD)										
0	382	89.88	43	10.12	425	416	94.33	25	5.67	441
<=800,000	578	93.38	41	6.62	619	433	95.37	21	4.63	454
810,000-1,200,000	467	96.69	16	3.31	483	198	96.12	8	3.88	206
>=1210,000	526	96.87	17	3.13	543	181	96.79	6	3.21	187
Educational years										
<=6	350	88.83	44	11.17	394	531	93.49	37	6.51	568
7-18	549	94.01	35	5.99	584	370	96.35	14	3.65	384
>18	1054	96.52	38	3.48	1092	327	97.32	9	2.68	336
Smoking status										
No	1396	94.07	88	5.93	1484	1191	95.36	58	4.64	1249
Yes	557	95.05	29	4.95	586	37	94.87	2	5.13	39
Drinking status										
No	1441	93.88	94	6.12	1535	1190	95.28	59	4.72	1249
Yes	512	95.70	23	4.30	535	38	97.44	1	2.56	39

Regular physical activity										
No	611	94.29	37	5.71	648	415	94.75	23	5.25	438
Yes	1342	94.37	80	5.63	1422	813	95.65	37	4.35	850
Participant's disease history										
Cerebrovascular disease	30	78.95	8	**21.05**	38	17	85.00	3	**15.00**	20
Cardiovascular disease	179	86.47	28	13.53	207	137	88.39	18	11.61	155
Hypertension	644	92.13	55	7.87	699	477	92.62	38	7.38	515
Disease history of family										
Cerebrovascular disease	276	95.83	12	4.17	288	172	95.56	8	4.44	180
Cardiovascular disease	278	93.60	19	6.40	297	157	96.32	6	3.68	163
Hypertension	798	95.34	39	4.66	837	518	95.93	22	4.07	540
Body mass index (kg/m^2)										
<18.5	8	72.73	3	**27.27**	11	26	86.67	4	13.33	30
18.5-24	443	91.15	43	8.85	486	362	94.27	22	5.73	384
>=24	1502	95.49	71	4.51	1573	840	96.11	34	3.89	874
Systolic blood pressure (mmHg)										
<120	626	96.31	24	3.69	650	381	97.44	10	2.56	391
120-129	416	92.44	34	7.56	450	235	96.31	9	3.69	244
130-139	441	96.92	14	3.08	455	227	93.80	15	6.20	242
140-149	247	92.86	19	7.14	266	175	94.59	10	5.41	185
>=150	223	89.56	26	10.44	249	210	92.92	16	7.08	226
HbA1c (%)										
<6.5	147	98.66	2	1.34	149	87	95.60	4	4.40	91
≥6.5	1806	94.01	115	5.99	1921	1141	95.32	56	4.68	1197
Homocysteine (μmol/L)										
5-15	1909	94.41	113	5.59	2022	1212	95.51	57	4.49	1269
<5 or >15	44	91.67	4	8.33	48	16	84.21	3	**15.79**	19
TG (mg/dl)										

<150	979	93.42	69	6.58	1048	737	95.71	33	4.29	770
≥150	974	95.30	48	4.70	1022	491	94.79	27	5.21	518
Cholesterol (mg/dl)										
<200	1091	93.81	72	6.19	1163	618	94.79	34	5.21	652
≥200	862	95.04	45	4.96	907	610	95.91	26	4.09	636
HDLC (mg/dl)										
<40	357	92.49	29	7.51	386	57	95.00	3	5.00	60
≥40	1596	94.77	88	5.23	1684	1171	95.36	57	4.64	1228
LDLC (mg/dl)										
<130	1225	94.16	76	5.84	1301	777	94.87	42	5.13	819
≥130	728	94.67	41	5.33	769	451	96.16	18	3.84	469
WBC (count/ml)										
4000-10000	1817	94.44	107	5.56	1924	1128	95.67	51	4.33	1179
<4000 or >10000	136	93.15	10	6.85	146	100	91.74	9	8.26	109
Hemoglobin (g/dl)										
12-16	1501	94.40	89	5.60	1590	1113	96.20	44	3.80	1157
<12 or >16	452	94.17	28	5.83	480	115	87.79	16	12.21	131
Albumin (g/dl)										
3.8-5.3	1948	94.61	111	5.39	2059	1223	95.40	59	4.60	1282
<3.8 or >5.3	5	45.45	6	**54.55**	11	5	83.33	1	**16.67**	6
Creatinine (mg/dl)										
0.6-1.3	1770	95.16	90	4.84	1860	1186	95.80	52	4.20	1238
<0.6 or >1.3	183	87.14	27	12.86	210	42	84.00	8	16.00	50
Uric acid (mg/dl)										
3-7	1338	94.56	77	5.44	1415	1053	95.99	44	4.01	1097
<3 or >7	615	93.89	40	6.11	655	175	91.62	16	8.38	191
CRP (mg/dl)										
≤0.5	1797	95.13	92	4.87	1889	1055	95.56	49	4.44	1104

>0.5	156	86.19	25	13.81	181	173	94.02	11	5.98	184

NTD: New Taiwan Dollars; TG: Triglycerides; HDLC: High Density Lipoprotein Cholesterol; LDLC: Low Density Lipoprotein Cholesterol; WBC: White Blood Cell; CRP: c-reactive protein

Table 4. Covariate adjusted hazard ratio and 95% CI of all-cause mortality in association with potential risk factors according to sex in the ***training dataset*** (*n*=3358).

	Male (*n*=2070)		Female (*n*=1288)	
	AHR	95%CI	AHR	95%CI
Total				
Age at enrollment (years)				
<50				
50-59	2.12	1.02-4.39	1.02	0.32-3.29
60-69	3.28	1.58-6.77	1.87	0.59-5.95
70+	13.24	6.28-27.90	6.92	2.22-21.59
Family yearly income (NTD)				
0				
<=800,000	1.09	0.68-1.74	1.72	0.89-3.32
810,000-1,200,000	0.81	0.42-1.54	1.55	0.62-3.87
>=1210,000	1.09	0.55-2.15	1.56	0.57-4.25
Educational years				
<=6				
7-18	0.75	0.46-1.22	0.79	0.38-1.65
>18	0.72	0.42-1.22	0.93	0.37-2.37
Smoking status				
No				
Yes	1.40	0.88-2.23	2.60	0.58-11.64
Drinking status				
No				
Yes	0.95	0.58-1.56	0.64	0.08-4.88
Regular physical activity				
No				
Yes	0.84	0.55-1.27	0.53	0.30-0.96
Participant's disease history				
Cerebrovascular disease	2.53	1.16-5.52	1.20	0.33-4.39
Cardiovascular disease	1.42	0.87-2.31	1.58	0.83-2.99
Hypertension	1.08	0.69-1.67	1.61	0.84-3.08
Disease history of family				
Cerebrovascular disease	0.90	0.49-1.67	0.94	0.42-2.09
Cardiovascular disease	1.37	0.80-2.35	0.88	0.35-2.17
Hypertension	0.86	0.55-1.34	0.78	0.42-1.42
Body mass index (kg/m^2)				
<18.5	1.79	0.50-6.45	3.55	1.08-11.74
18.5-24	1.00		1.00	
>=24	0.45	0.29-0.70	0.59	0.33-1.07
Systolic blood pressure (mmHg)				

<120	1.00		1.00	
120-129	2.10	1.22-3.61	1.11	0.42-2.96
130-139	0.76	0.38-1.53	1.69	0.69-4.15
140-149	2.07	1.09-3.93	1.03	0.38-2.81
>=150	2.00	1.08-3.69	1.26	0.49-3.23
HbA1c (%)				
Abnormal: ≥6.5	3.19	0.77-13.20	1.45	0.41-5.08
Homocysteine (μmol/L)				
Abnormal: <5 or >15	1.63	0.56-4.73	3.02	0.65-14.06
TG (mg/dl)				
Abnormal: ≥150	0.94	0.62-1.43	1.34	0.76-2.38
Cholesterol (mg/dl)				
Abnormal: ≥200	0.86	0.48-1.55	0.74	0.34-1.58
HDLC (mg/dl)				
Abnormal: <40	1.71	1.07-2.74	1.08	0.31-3.77
LDLC (mg/dl)				
Abnormal: ≥130	1.53	0.86-2.74	1.22	0.54-2.75
WBC (count/ml)				
Abnormal: <4000 or >10000	0.97	0.48-1.95	1.69	0.75-3.81
Hemoglobin (g/dl)				
Abnormal: <12 or >16	1.27	0.80-2.01	1.67	0.83-3.34
Albumin (g/dl)				
Abnormal: <3.8 or >5.3	12.95	4.98-33.66	3.05	0.31-30.35
Creatinine (mg/dl)				
Abnormal: <0.6 or >1.3	0.95	0.55-1.62	1.64	0.66-4.08
Uric acid (mg/dl)				
Abnormal: <3 or >7	1.22	0.79-1.89	1.72	0.93-3.17
CRP (mg/dl)				
Abnormal: >0.5	2.14	1.30-3.51	1.19	0.56-2.52

NTD: New Taiwan Dollars; TG: Triglycerides; HDLC: High Density Lipoprotein Cholesterol; LDLC: Low Density Lipoprotein Cholesterol; WBC: White Blood Cell; CRP: c-reactive protein

Table 5. Sex-specific risk scores of all-cause mortality in diabetes patients

	Male (*n*=2070)		Female (*n*=1288)	
	Beta-coef.	Score	Beta-coef.	Score
Age at enrollment (years)				
<50	Reference	0	Reference	0
50-59	0.75	8	0.02	0
60-69	1.19	12	0.63	6
70+	2.58	26	1.94	19
Body mass index (kg/m^2)				
<18.5	0.58	6	1.27	13
18.5-24	Reference	0	Reference	0
>=24	-0.80	-8	-0.52	-5
Systolic blood pressure (mmHg)				
<120	Reference	0		
120-129	0.74	7		
130-139	-0.27	-3		
140-149	0.73	7		
>=150	0.69	7		
HDLC (mg/dl)				
<40	0.54	5		
40>=	Reference	0		
Albumin (g/dl)				
3.8-5.3	Reference	0		
<3.8 or >5.3	2.56	26		
CRP (mg/dl)				
<=0.5	Reference	0		
>0.5	0.76	8		
Medical history				
Cerebrovascular disease (no)	Reference	0		
Cerebrovascular disease (yes)	0.93	9		
Physical activity in their past 2 weeks				
No			Reference	0
Yes			-0.63	-6

HDLC: High Density Lipoprotein Cholesterol; CRP: c-reactive protein

Table 6. Calibration capability among ***male*** diabetes patients.

	Training dataset (*n*=2070)						Training dataset (*n*=2070)				
Score	Total	Alive	Death	Death rate (%)	*p*-value	Score [a]	Total	Alive	Death	Death rate (%)	*p*-value
<=9	1415	1390	25	1.77	<0.0001	Min-25th	670	6	676	0.89	<0.0001
>9	655	563	92	14.05		25th-50th	390	10	400	2.50	
Total	2070	1953	117			50th-75th	460	19	479	3.97	
	Sensitivity= 92/117=0.79					75th-Max	433	82	515	15.92	
	Specificity= 1390/1953=0.71					Total	1953	117	2070		

	Validation dataset (*n*=895)						Validation dataset (*n*=895)				
Score	Total	Alive	Death	Death rate (%)	*p*-value	Score [b]	Total	Alive	Death	Death rate (%)	*p*-value
<=9	613	598	15	2.45	<0.0001	Min-25th	266	3	269	1.12	<0.0001
>9	282	247	35	12.41		25th-50th	187	6	193	3.11	
Total	895	845	50			50th-75th	200	9	209	4.31	
	Sensitivity= 35/50=0.70					75th-Max	192	32	224	14.29	
	Specificity= 598/845=0.71					Total	845	50	895		

[a.] min, -11; 25th, -1; 50th, 5; 75th, 11; max, 59.

[b.] min, -11; 25th, -1; 50th, 5; 75th, 11; max, 52.

Table 7. Calibration capability among ***female*** diabetes patients.

	Training dataset (*n*=1288)						Training dataset (*n*=1288)				
Score	Total	Alive	Death	Death rate (%)	*p*-value	Score [a]	Total	Alive	Death	Death rate (%)	*p*-value
<=0	931	913	18	1.93	<0.0001	Min-25th	387	382	5	1.29	<0.0001
>0	357	315	42	11.76		25th-50th	386	378	8	2.07	
Total	1288	1228	60			50th-75th	239	228	11	4.60	
	Sensitivity= 42/60=0.70					75th-Max	276	240	36	13.04	
	Specificity= 913/1228=0.74					Total	1288	1228	60	18.77	

	Validation dataset (*n*=545)						Validation dataset (*n*=545)				
Score	Total	Alive	Death	Death rate (%)	*p*-value	Score [b]	Total	Alive	Death	Death rate (%)	*p*-value
<=0	394	387	7	1.78	0.01898 [c]	Min-25th	174	172	2	1.15	0.00775 [c]
>0	151	142	9	5.96		25th-50th	147	146	1	0.68	
Total	545	529	16			50th-75th	114	108	6	5.26	
	Sensitivity= 9/16=0.56					75th-Max	110	103	7	6.36	
	Specificity= 387/529=0.73					Total	545	529	16	16.48	

[a.] min, -11; 25th, -6; 50th, -5; 75th, 1; max, 32.

[b.] min, -11; 25th, -6; 50th, -5; 75th, 1; max, 32.

[c.] based on Fisher's exact test

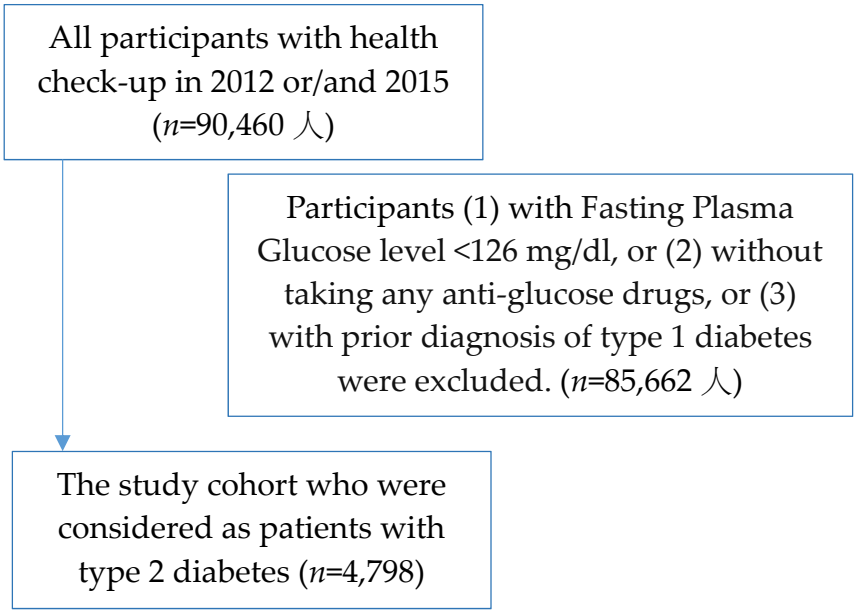


Figure 1. Flow chart of study participants selection

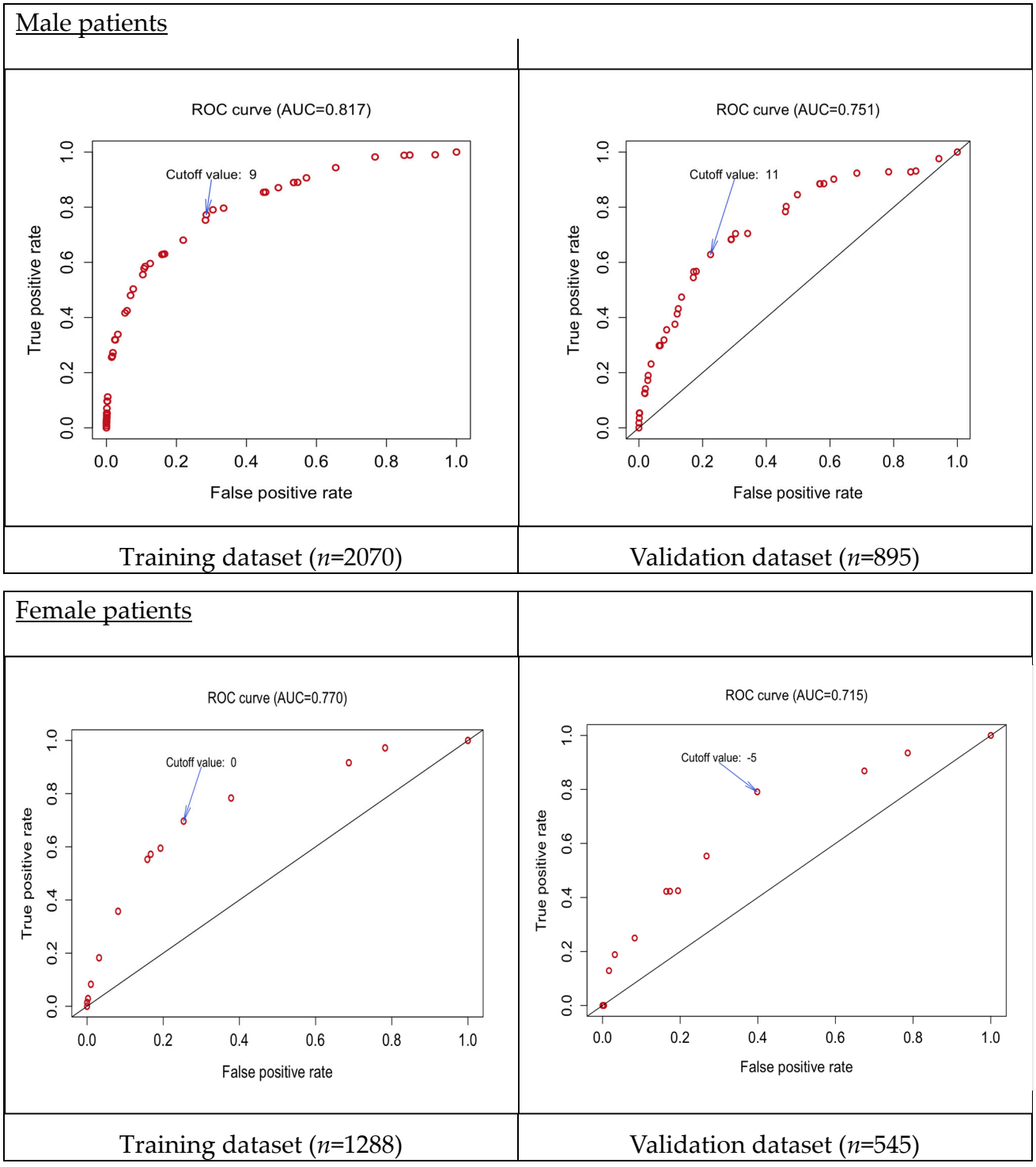
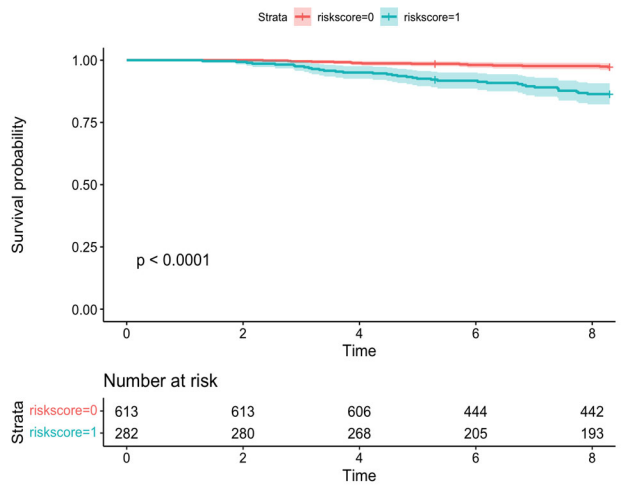
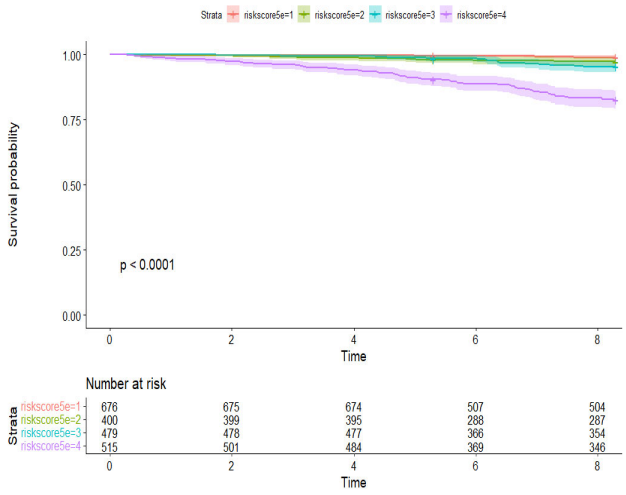


Figure 2. Discrimination capability indicated by Receiver Operator Curves (ROC) among male (***upper***) and female (***lower***) patients with type 2 diabetes.

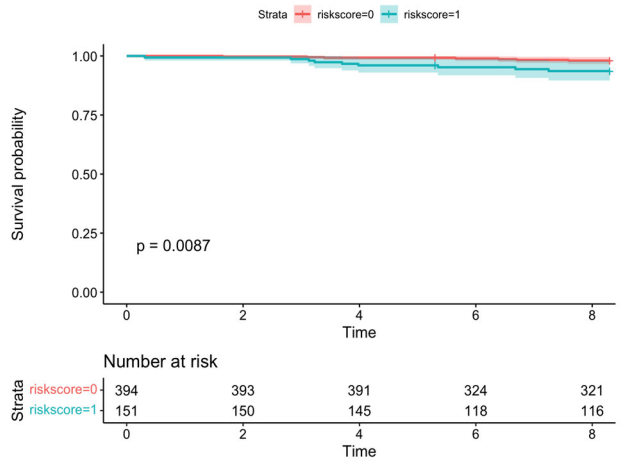
Male patients (Validation dataset, *n*=895)

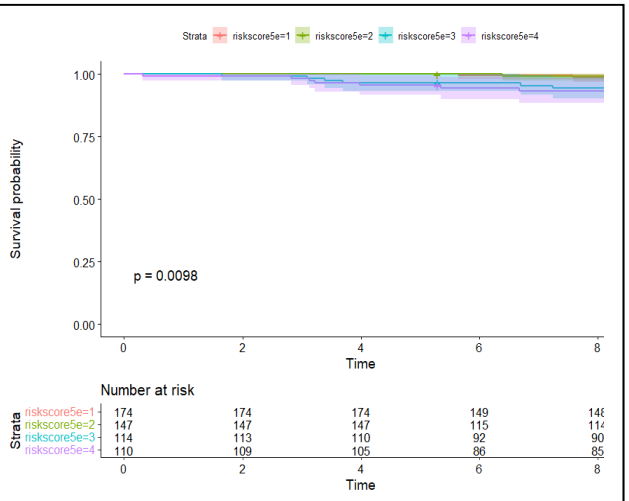




Riskscore=0 (score<=9); Riskscore=1 (score>9)	Riskscore=1 (-11~ <-1); Riskscore=2 (-1~ <-5); Riskscore=3 (5~ <11); Riskscore=4 (11~52)

Female patients (Validation dataset, *n*=545)





Riskscore=0 (score<=0); Riskscore=1 (score>0)	Riskscore=1 (-11~ <-6); Riskscore=2 (-6~ <-5); Riskscore=3 (-5~ <1); Riskscore=4 (1~32)

Figure 3. Calibration capability indicated by Kaplan-Meier curves among male (***upper***) and female (***lower***) patients with type 2 diabetes.

109年度專題研究計畫成果彙整表

計畫主持人：李中一	**計畫編號：**109-2629-B-006-001-
計畫名稱：建立與驗證不同性別第二型糖尿病患者發生心血管疾病之風險預測模式(L03)	

成果項目			量化	單位	質化 （說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文	0	篇	
		研討會論文	0		
		專書	0	本	
		專書論文	0	章	
		技術報告	0	篇	
		其他	0	篇	
國外	學術性論文	期刊論文	0	篇	
		研討會論文	0		
		專書	0	本	
		專書論文	0	章	
		技術報告	0	篇	
		其他	0	篇	
參與計畫人力	本國籍	大專生	0	人次	
		碩士生	3		3位碩士班研究生參與，其中2位研究生完成論文畢業
		博士生	1		1位博士班研究生參與
		博士級研究人員	0		
		專任人員	0		
	非本國籍	大專生	0		
		碩士生	0		
		博士生	0		
		博士級研究人員	0		
		專任人員	0		
其他成果 （無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。）					