Screening interval for diabetic retinopathy: a personalised approach (abridged secondary publication)

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KEY MESSAGES

1. A Hong Kong–specific algorithm with good discriminatory and calibration powers was developed to identify individuals with diabetes who have a high risk of sight-threatening diabetic retinopathy (STDR), compared with individuals with diabetes who have a lower risk of STDR.
2. Overall, the use of a risk-based interval is safe; it can prevent blindness, increase the preservation of sight years relative to annual screening, and reduce the frequency of screening among individuals with diabetes who have a lower risk of STDR.

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Introduction

Diabetic retinopathy (DR) is among the most common microvascular complications of diabetes mellitus (DM) and the leading cause of new cases of blindness in developed countries. DR screening is a cost-effective approach to prevent blindness. However, the optimal screening interval remains controversial. In 2010, Hong Kong began systematic DR screening as a component of the multi-disciplinary risk assessment and management programme for diabetes (RAMP-DM). The Iceland model was used to determine screening intervals according to individualised risk of sight-threatening diabetic retinopathy (STDR).[1] However, the Iceland model significantly underestimated the risk of STDR in our pilot DR screening study, although it has an acceptable discrimination level. Risk factors for DR were mainly based on western diabetic populations. Using data collected during the screening programme in Hong Kong, we sought to identify the most important risk factors and improve risk stratification for Hong Kong populations. In this study, we aimed to (1) develop an STDR prediction model based on the diabetic population in Hong Kong, using data from the systematic DR screening programme; (2) test the internal validity of the resulting model; (3) investigate the safety, feasibility, and cost-effectiveness of the prediction model; and (4) build a cost-effectiveness model that could estimate the cost-effectiveness of the new prediction model.

Methods

This retrospective cohort study was conducted to develop an algorithm to predict the risk of STDR in Hong Kong populations. Individuals who participated in RAMP-DM on or before 31 December 2016 and had at least one DR screening assessment using the standardised grading were eligible for inclusion. DR was graded as no DR (R0), background DR (R1), pre-proliferative DR (R2), or proliferative DR (R3) / maculopathy (M1) according to the UK national DR screening programme procedures. The DR grading R2 and R3/M1 were regarded as STDR. The risk algorithm was developed using data from individuals without STDR (ie, individuals with a DR grading of R0 or R1) at baseline who had at least one follow-up record. Eligible individuals were randomly allocated into derivation and validation datasets at a ratio of 2:1.

Parametric survival analysis using the Weibull distribution provided the best fit for the risk algorithm after stratification according to sex and DR grading of R1 at baseline (ie, R0 male, R0 female, R1 male, and R1 female groups). Time from baseline screening was used as the time scale (t), and the first occurrence of STDR after baseline screening was regarded as the outcome event. Both right censoring and interval censoring were considered in the model.

Potential predictors were identified through literature review; they were at least 80% complete

in the RAMP-DM data. Best-fitting predictors were selected using a recommended procedure for prognostic survival modelling. Univariate analysis was conducted to select significant variables, which were then entered into a multivariate model; subsequently, the Wald test was used to reduce the number of covariates. Selections were confirmed using the Akaike information criterion. Previously excluded variables were re-entered into the model to ensure that none would improve prediction results. A separate risk algorithm was derived for each of the four groups: R0 male, R0 female, R1 male, and R1 female.

Coefficients from the survival model were transformed into a mathematical algorithm and applied to the validation cohort. Algorithm performance was assessed by comparing the total number of STDR events over 2 years (ie, 2-year observed risk) with the 2-year predicted risk, then examining discriminatory power using receiver operating characteristic curves and calibration power using the Hosmer-Lemeshow Chi-squared test.

The algorithm was then used to estimate the time for an individual to reach a pre-determined STDR risk margin. The time was converted to screening intervals of 6 months (for predictions of ≤9 months), 12 months (for predictions between 10 and 21 months), or 24 months (for predictions of ≥22 months), based on current practice. To assess the safety of the risk-based intervals, we compared the observed time for detection of new STDR cases with the assigned intervals.

An individual-based Markov state-transition model was constructed to simulate the long-term effect on cost and the consequences of using risk-based screening intervals established by the Hong Kong algorithm, compared with a fixed annual screening strategy. The model simulated transitions among health states based on the natural progression of DR (R0, R1, R2, or R3) and maculopathy, blindness, and death over an individual's lifetime. Values for model parameters (eg, transition probabilities and costs) were based on data from Hong Kong when possible. If no data from Hong Kong were available, international data were used, with adjustment to fit local circumstances. If no international or local data were available, expert opinions were used as a basis for model parameters. In total, 100 000 individuals, with profiles randomly selected from the RAMP-DM cohort, were modelled for each screening strategy. The mean lifetime cost and consequences in term of blindness incidence, number of sight years preserved, and quality-adjusted life-years (QALYs) were summarised and compared. The procedure was repeated 10 times; the mean costs and effectiveness results were used to generate incremental cost-effectiveness ratios. The provider perspective was adopted for the base case analysis.

Results

Six predictors were selected in the final best-fit model: duration of diabetes, HbA1c level, systolic blood pressure, presence of chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 or urinary albumin to creatinine ratio ≥3 mg/mmol),[3] use of DM medication, and age. Prediction performance validation revealed that the respective 2-year predicted and observed risks were 5.6% and 5.1% (P=0.724) for men and 4.8% and 4.6% (P=0.099) for women. The discriminatory powers of the prediction models were moderate to good, with a receiver operating characteristic curve of 0.797 (95% confidence interval=0.780-0.814) for men and 0.810 (95% confidence interval=0.793-0.827) for women.

Using a risk margin of 2.5% for both R0 and R1 (ie, 2.5%/2.5%), which was approximately equivalent to the overall annual incidence of STDR, 96.6% (1107/1146) of STDR cases would have been assigned to a safe screening interval near the time of STDR development, whereas 3.0% (34/1146) of STDR cases would have had a screening date 12 months beyond the time of STDR development. None of these 34 cases were R3 requiring urgent referral, and 70% were due to M1. Using this risk margin, 36.6%, 8.5%, and 54.8% of subjects would have been assigned to 6-month, 12-month, and 24-month screening intervals, respectively, leading to a 9.2% increase in the total number of screening visits over a 2-year period. Using risk margins of 2.5% for R0 and 5.0% for R1 (approximately equivalent to the annual incidence in the R1 group), 93.5% of STDR cases would have been assigned to a safe screening interval, but 4.1% of STDR cases would have had a 12-month delay in detection; notably, none of these cases were R3. Approximately 26.7%, 14.5%, and 58.8% of subjects would have been assigned to 6-month, 12-month, and 24-month screening intervals, leading to a 2.7% decrease in the total number of screening visits.

The use of a risk-based screening with a risk margin of 2.5% for both R0 and R1 led to a mean decrease of -0.32% in the cumulative incidence of blindness, which would preserve approximately 0.015 sight years per individual according to the model; however, it would have a limited effect on the number of QALYs (approximately 0.0003 QALYs gained per person), compared with annual screening. This approach also carried an additional lifetime cost of HK$316 per individual, compared with annual screening. Overall, the risk-based screening strategy would cost HK$99 990 per additional case of blindness prevented and HK$20 752 per additional sight year preserved, compared with annual screening. Because the number of QALYs did not substantially differ between risk-based screening

and annual screening, the calculation of incremental cost-effectiveness ratio according to QALYs had limited use. Risk margins of 2.5% for R0 and 5.0% for R1 led to a mean decrease of -0.20% in the cumulative incidence of blindness, 0.006 sight years preserved per person, 0.001 QALYs gained per person, and an increased lifetime cost of HK$162 per individual, compared with annual screening.

Discussion

Our prediction model generally demonstrated good discriminatory and calibration powers when the predicted and observed risks of STDR were compared. Most STDR cases would be assigned to a safe screening interval around the time of STDR development. The use of a higher risk margin would reduce safety but would require fewer screening visits.

Risk-based screening using a risk margin of 2.5% for both R0 and R1 prevented blindness and preserved sight years. The proportion of blindness prevention was 0.32%, which represented vision preservation in an additional 320 of every 100 000 individuals with diabetes. Annual screening is already an effective screening strategy; the additional benefit of the risk-based screening mainly arises from assigning high-risk individuals to semi-annual screening, rather than annual screening.

There is no benchmark for an acceptable threshold value for prevention of a case of blindness or saving of a sight year. Vision loss can lead to comorbidities including falls and depression.[4] These comorbidities can result in further use of public healthcare resources, primarily by older people with chronic diseases such as diabetes. The benefit of avoiding blindness was not considered in the current cost-effectiveness analysis. In this study, we used a conservative approach from a government perspective when estimating the cost per case of blindness prevented or sight year preserved.

A risk-based approach with individualised screening intervals improves vertical equity, which is defined as subjects with different levels of needs (ill health) have appropriately different access to healthcare services. In contrast, fixed annual screening provides the same screening interval for the entire population, regardless of risk. The use of different risk margins involve trade-off between screening interval safety and resource utilisation during screening. If there are sufficient resources to accommodate additional screening visits, an approach involving a risk margin of 2.5% for both R0 and R1 is the safest strategy.

Conclusion

A Hong Kong–specific algorithm with good discriminatory and calibration powers was developed to identify individuals with diabetes who have a high risk of STDR. Overall, the use of a risk-based interval is safe and reduces the need for more frequent screening of low-risk individuals. However, more research is needed to refine the risk for the higher risk people so that fewer of these cases need to be allocated to a 6-monthly screening interval.

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