Heliyon 9 (2023) e16830

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Associations between blood pressure levels and diabetic retinopathy in patients with diabetes mellitus: A population-based study

Min Zhang [a,1], Jinye Wu [a,1], Yimin Wang [a,b,c,d,e], Jiali Wu [a,b,c,d,e], Weiting Hu [f], Huixun Jia [a,b,c,d,**], Xiaodong Sun [a,b,c,d,e,*]

[a] Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] National Clinical Research Center for Eye Diseases, Shanghai, China
[c] Shanghai Key Laboratory of Ocular Fundus Diseases, Shanghai, China
[d] Shanghai Engineering Center for Visual Science and Photomedicine, Shanghai, China
[e] Shanghai Engineering Center for Precise Diagnosis and Treatment of Eye Diseases, Shanghai, China
[f] Shanghai Phoebus Medical Co. Ltd., Shanghai, China

ARTICLE INFO

Keywords:
Diabetic retinopathy
Proliferative diabetic retinopathy
Blood pressure
Hypertension
Nomogram

ABSTRACT

Purpose: To evaluate the associations of blood pressure levels with diabetic retinopathy (DR), proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) in patients with diabetes mellitus.

Design: A cross-sectional, population-based study.

Subjects: A total of 152,844 patients with diabetes from 90 major cities in 19 provincial regions of mainland China during 2018–2021 were finally recruited.

Methods: Blood pressure was graded into 5 levels: normal (without hypertension and <120/80 mmHg), normal high (without hypertension and ≥120/80 mmHg), HT-intensive (hypertension and <120/80 mmHg), HT-moderate (hypertension and blood pressure between 120/80 mmHg and 140/90 mmHg) and HT-high (hypertension and ≥140/90 mmHg). Logistic regression was employed to verify the associations of hypertension and blood pressure levels with DR, PDR and DME. The impacts of blood pressure levels on the outcomes were qualified with nomogram models.

Main outcome measures: The main outcome was DR.

Results: There were 16,685 (10.92%) participants having DR, 2841 (1.86%) having PDR, and 1566 (1.02%) having DME. There were 8126 (5.32%) patients without hypertension and 1350 (0.88%) patients with hypertension having blood pressure <120/80 mmHg. When compared to the normal group with covariates adjusted, an increased prevalence of DR was observed in normal

Abbreviations: DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; DME, diabetic macularedema; HT, hypertension; OR, odds ratio; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; RRSPD, Real-world Retinopathy Screening Project for Diabetic Population; FBG, fasting blood glucose; ICC, interclass correlation coefficient; BMI, body mass index; SD, standard deviation.

* Corresponding author. Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, 100 Haining Rd, Shanghai, 200080, China.

** Corresponding author. Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, 100 Haining Rd, Shanghai, 200080, China.

E-mail addresses: jiahuixun@163.com (H. Jia), xdsun@sjtu.edu.cn (X. Sun).

[1] These two authors contributed equally to this manuscript.

https://doi.org/10.1016/j.heliyon.2023.e16830
Received 24 July 2022; Received in revised form 28 May 2023; Accepted 30 May 2023
Available online 1 June 2023

high (adjusted odds ratio [OR] = 1.114, 95% confidence interval [CI] = 1.033–1.202), HT-moderate (adjusted OR = 1.163, 95% CI = 1.065–1.271), and HT-high (adjusted OR = 1.203, 95% CI = 1.114–1.300).

Conclusions: There were associations between hypertension and DR, PDR, and DME in the diabetic population. Increased prevalence of DR was found with blood pressure >120/80 mmHg in both patients with and without hypertension. A nomogram was developed for DR prediction based on blood pressure levels.

1. Introduction

Diabetic retinopathy (DR), defined as a microvascular complication of diabetes, is the leading cause of preventable vision loss in working-aged population [1]. Approximately one in five people with diabetes have DR worldwide, and the global number of adults with DR in 2020 was estimated to be 103.12 million [2]. More importantly, the rapid economic growth and urbanization of the diabetic population are projected to increase by 51% by 2045 [3]. Therefore, strategies to reduce DR in diabetic patients are needed.

Hypertension is a well-known risk factor for DR [4,5]. A beneficial effect of blood pressure control was shown to prevent DR incidence and progression [6,7]. However, this effect has not been fully quantified with different blood pressure targets. For patients with diabetes and hypertension, the Appropriate Blood Pressure Control in Diabetes (ABCD) trail [8] reported no differential effect on DR between the intensive (diastolic blood pressure [DBP] goal of 75 mmHg) and moderate (DBP goal of 80–89 mmHg) antihypertensive medication groups. The robustness of the findings may be limited because the intensive group did not achieve the target blood pressure. In addition, for patients with diabetes but without hypertension, the results of the ABCD trial showed that intensive blood pressure control (10 mmHg below the baseline DBP) could decrease the progression of DR [9]. As the cardiovascular benefits of systolic blood pressure (SBP) <120 mmHg have been recently realized [10], the blood pressure control has become increasingly intensive over the past decades. In 2017, the American College of Cardiology (ACC)/American Heart Association (AHA) guideline reduced "normal blood pressure" from SBP/DBP <140/90 mmHg to <120/80 mmHg for the sake of cardiovascular risks [11]. Furthermore, in 2021, an intensive target of SBP <120 mmHg was first proposed in clinical practice guidelines for chronic kidney disease (CKD) [12]. Considering that patients with diabetes and CKD both gain cardiovascular benefits from intensive blood pressure control [13–15], we hypothesized that in the diabetic population, the blood pressure target of 120/80 mmHg also has advanced beneficial effects on DR prevention compared with the blood pressure target of 140/90 mmHg.

In this nationwide study, we investigated the prevalence of DR in diabetic patients with different blood pressure levels and explored the appropriate target blood pressure to reduce DR. We further quantified the DR probability based on blood pressure levels using nomograms.

2. Methods

2.1. Study population

The Real-world Retinopathy Screening Project for Diabetic Population (RRSPD) is a large-scale, nationwide, ongoing hospital-based cohort study guided by the National Clinical Research Center for Ophthalmic Diseases of China. It started in December 2018. By November 2021, this cohort had a total of 570,978 registered patients with diabetes from 1010 hospitals at different levels (i.e., 300 tertiary hospitals, 215 secondary hospitals, and 595 primary hospitals or healthcare institutions) from 140 major cities in 28 provincial regions of mainland China. This study was approved by the Institutional Review Board of National Clinical Research Center for Ophthalmic Diseases (2022KY-120) and adhered to the tenets of the Declaration of Helsinki. All the participants provided written informed consent.

All participants had diagnosed diabetes at the registration, meeting at least one of the following criteria: fasting plasma sugar ≥7.0 mmol/L (no caloric intake for at least 8 h), 2-h plasma glucose ≥11.1 mmol/L during oral glucose tolerance test. In addition, HbA1c ≥6.5%, random plasma glucose ≥11.1 mmol/L, according to the Classification and Diagnosis of Diabetes (revised 2018) [16]. The types of diabetes were generally classified according to patients' symptoms: type 1 diabetes with absolute insulin deficiency and type 2 on the background of insulin resistance [16]. These data were first collected from medical history. Other collected information included age at the diagnosis of diabetes, with or without a diagnosis of hypertension/taking anti-hypertensive medication, and demographic information (date of birth and sex). Participants were required to complete ocular screening, physical examination, and a standardized questionnaire on personal information, such as residential address, socioeconomic status, lifestyle, and medical history. A fasting blood glucose (FBG) test was also performed. Detailed biocular data were documented at the individual level. Ocular examinations were conducted by local licensed ophthalmologists, including, but not limited to, slip-lamp and ophthalmoscopic examinations. One-field color fundus images were acquired by local professional technicians using non-mydriatic handle-held cameras (Smartscope PRO, Optomed Oy, Oulu, Finland) [17], according to RRSPD standard operation protocols for fundus image acquisition. Deidentified fundoscopy images were uploaded to an online image interpretation center. For each eye, fundus images were assessed by two blinded, licensed, and well-trained ophthalmologists from the center. The consistency of the assessment was evaluated by the interclass correlation coefficient (ICC), and it is generally believed that an ICC >0.75 indicates good consistency. Images with controversial reports were submitted to a review panel of senior ophthalmologists to determine the final decision.

The exclusion criteria were as follows: (1) invalid images of fundoscopy in either eye (n = 45,722); (2) missing data on any important covariates, including blood pressure status, FBG value, diabetic duration, height, and weight (n = 372,412). The reasons for invalid images included incorrect positions not centered on the fovea, defocusing, overexposure/underexposure, no images/wrong images/broken images due to uploading errors, and invisible fundus due to cataract/corneal scars/vitreous opacity (vitreous hemorrhage not included). Finally, 152,844 participants from 90 cities in 19 provincial regions of mainland China were included in the final analysis (Fig. 1).

2.2. Diabetic retinopathy and diabetic macular edema

The primary outcome of this study was DR. The lesions listed below were documented for DR diagnosis and grading: microaneurysm, intraretinal hemorrhage, venous beading, hard exudates, cotton wool spots, intraretinal microvascular abnormalities, neovascularization, preretinal hemorrhage, vitreous hemorrhage, preretinal proliferative membrane, and macular edema. DR is defined according to the well-accepted International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scale [18].

The secondary outcomes were the proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). PDR is the advanced stage of DR. It was defined as cases with neovascularization, vitreous/preretinal hemorrhage, or preretinal proliferative membrane. DME was defined as the presence of a serous exudate in the macula.

2.3. Blood pressure and blood pressure levels

Blood pressure was measured using a manual mercury sphygmomanometer applied to the right upper arm of a seated patient. The patient should have an arm supported at the heart level, with all clothing covering the location of cuff placement removed [19]. Two measurements were taken 10 min apart, and if the two measurements differed by more than 10 mm systolic and 5 mm diastolic, a third measurement was taken, and the average of the two closest readings was documented.

Blood pressure levels were evaluated based on the medical history of hypertension: non-hypertension and hypertension. Prevalent hypertension was defined by a previous diagnosis of hypertension by physicians (SBP/DBP $\geq$140/90 mmHg, according to the Guidelines for Prevention and Treatment of Hypertension in China [revised 2018] [20]) or the use of antihypertensive medication in this study.

Blood pressure in patients without hypertension was graded as follows: (1) normal blood pressure with SBP $<$120 mmHg and DBP $<$80 mmHg[11], and (2) normal high blood pressure with SBP $\geq$120 mmHg or DBP $\geq$80 mmHg. The blood pressure in patients with hypertension was further graded as follows: (1) hypertension (HT)-moderate with 120 mmHg $\leq$ SBP $<$140 mmHg and 80 mmHg $\leq$ DBP $<$90 mmHg [10,21–23], (2) HT-intensive with SBP $<$120 mmHg and DBP $<$80 mmHg[10], (3) HT-high with SBP $\geq$140 mmHg or DBP $\geq$90 mmHg [21,22]. Therefore, this study had five blood pressure levels: normal, normal high, HT-intensive, HT-moderate, and HT-high.

3. Covariates

Covariates included sex (male, female), age at diabetes diagnosis ($<$50, $\geq$50 years), diabetic duration ($<$3, $\geq$3 years), FBG ($<$6.1, $\geq$6.1 mmol/L), body mass index (BMI, defined as weight/height [2]), and diabetic type (type 1, type 2).

Fig. 1. Geographical distribution of enrolled diabetic population.
A total of 152,844 patients registered in the Real-world Retinopathy Screening Project for Diabetic Population (RRSPD) study were included in the final analysis, from 90 cities in 19 provincial regions of mainland China. Each red dot represented one city. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.1. Statistical analyses

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as counts and percentages. Demographics of patients with and without DR or PDR were compared using independent samples *t*-tests for continuous variables and chi-square tests or Fisher's exact test for categorical values.

Multiple logistic regression was used to compute odds ratios (ORs) with 95% confidence intervals (CIs) to (1) confirm the association between hypertension and the outcomes and (2) assess the association of blood pressure levels with DR, PDR and DME, adjusting for sex, age at diabetes diagnosis, diabetes duration, blood pressure status, BMI, diabetic type, and FBG as independent variables. Nomograms for blood pressure levels and other possible contributing factors associated with DR and PDR were also established according to multiple logistic regression. They can be interpreted by summing the points assigned to blood pressure control and other variables, which are indicated by the top scale. The total points can be converted into the predicted probability of the overall DR or PDR for a patient on the bottom scale.

The model performance for prediction was evaluated using a calibration curve that compared the observed risks with the predicted risks. X-axes indicate nomogram-predicted probability, and Y-axes indicate actual observations. The two lines represent the logistic calibration and ideal model. The general alignment of the ideal 45-degree line and logistic model line demonstrated good calibration of the prediction.

The potential clinical impact was evaluated using decision curves and clinical impact curves. One decision curve included two perfect prediction models: screen none and screen based on the nomogram. This demonstrated the benefit of using the nomogram to predict the probability of developing DR or PDR rather than treating either all or no patients with diabetes who would have DR or PDR in the threshold. Clinical impact curves plot the number of patients with diabetes classified into DR or PDR and the number of cases classified as DR or PDR at each high-risk threshold. When evaluating the models, small differences between the two classifications and quick unification of the two lines indicated the reliability of the risk prediction.

All analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC) and R 3.5.2 (R Foundation, Vienna, Austria) software, and a $P < 0.05$ was considered statistically significant.

4. Results

Of the 152,844 patients with diabetes, 16,685 (10.92%) had DR, 2841 (1.86%) had PDR, and 1566 (1.02%) had DME. The ICC was 99.31% for DR diagnosis and grading (including non-DR, non-proliferative DR, or PDR) and 97.47% for DME diagnosis. These patients aged 64.02 ± 10.43 years, with the diabetes duration of 4.71 ± 5.07 years (Table 1). Their diabetes was not well controlled, as the mean FBG was 7.80 ± 2.26 mmol/L. Compared to patients without DR, PDR or DME, patients with DR, PDR or DME were more likely to have younger ages at both diabetes diagnosis and trial registrations, longer diabetes duration, higher FBG levels, and higher percentage of type 1 diabetes (Table 1, Table S1 and Table S2 in the Supplementary Materials). The distribution of patients with different blood pressure levels did not significantly differ between patients with and without DR ($P = 0.250$) but was significantly different between patients with and without PDR ($P < 0.001$) or DME ($P < 0.001$). As DR, PDR, and DME can be affected by various systematic factors, multivariable regression analysis was performed to explore the role of blood pressure levels with covariate adjustment.

A total of 70,743 (46.28%) patients had hypertension. When divided by blood pressure levels, only 8,126 (5.32%) patients without hypertension and 1,350 (0.88%) patients with hypertension had SBP/DBP <120/80 mmHg (Table 1). Instead, 54,301 (35.53%)

Table 1
Diabetic patient demographics and breakdown of the database by diabetic retinopathy (DR).

Mean ± SD or n (%)		*All (N = 152,844)*	*Non-DR (n = 136,159)*	*DR (n = 16,685)*	P *value*
Sex	Male	64,142 (41.97)	57,058 (41.91)	7084 (42.46)	0.175
	Female	88,702 (58.03)	79,101 (58.09)	9601 (57.54)	
Age, years old		64.02 ± 10.43	64.08 ± 10.51	63.49 ± 9.72	<0.001
Age at diabetes diagnosis, years old		59.30 ± 11.09	59.70 ± 11.01	56.06 ± 11.16	<0.001
Diabetes duration, years		4.71 ± 5.07	4.38 ± 4.77	7.43 ± 6.41	<0.001
DM type	Type 1	1275 (0.83)	1081 (0.79)	194 (1.16)	<0.001
	Type 2	151,564 (99.17)	135,078 (99.21)	16,491 (98.84)	
Height, m		1.62 ± 0.08	1.62 ± 0.08	1.62 ± 0.08	0.133
Weight, kg		64.79 ± 10.63	64.80 ± 10.65	64.75 ± 10.43	0.570
BMI, kg/m^2		24.58 ± 3.33	24.59 ± 3.33	24.54 ± 3.29	0.120
SBP, mmHg		136.03 ± 16.91	136.09 ± 16.80	135.57 ± 17.74	<0.001
DBP, mmHg		81.46 ± 9.77	81.46 ± 9.76	81.40 ± 9.87	0.404
FBG, mmol/L		7.80 ± 2.26	7.71 ± 2.15	8.59 ± 2.87	<0.001
Blood pressure level	Normal	8126 (5.32)	7259 (5.33)	867 (5.20)	0.250
	Normal high	73,975 (48.40)	65,968 (48.45)	8007 (47.99)	
	HT-intensive	1350 (0.88)	1211 (0.89)	139 (0.83)	
	HT-moderate	15,092 (9.87)	13,372 (9.82)	1720 (10.31)	
	HT-high	54,301 (35.53)	48,349 (35.51)	5952 (35.67)	

SD = standard deviation.
DM = diabetes mellitus, BMI = body mass index, HT = hypertension, SBP = systolic blood pressure, DBP = diastolic blood pressure, FBG = fasting blood sugar.

patients with hypertension had SBP/DBP ≥140/90 mmHg. Logistic regression showed that a medical history of hypertension had increased ORs for DR (adjusted OR = 1.081, 95% CI = 1.045–1.117), PDR (adjusted OR = 1.381, 95% CI = 1.280–1.491), and DME (adjusted OR = 1.235, 95% CI = 1.115–1.367; Table 2). Compared to patients with normal blood pressure, the prevalence of DR increased by 11.4%, 16.3%, and 20.3% in normal high, HT-moderate, and HT-high blood pressure groups, respectively (Table 3). In addition, an increased prevalence of DR was not detected in the HT-intensive group (adjusted OR = 1.081, 95% CI = 0.893–1.310).

Regarding secondary outcomes, compared to the normal pressure group, an increased prevalence of PDR or DME was observed in the HT-moderate group, but not in the HT-intensive group (Table 3), indicating the beneficial effect of lower blood pressure levels in patients with hypertension. However, a comparable prevalence of PDR or DME was also detected between normal and normal high blood pressure patients, suggesting no additional ophthalmic gains in low blood pressure levels in patients without hypertension. Therefore, the beneficial effects of blood pressure <120/80 mmHg on PDR and DME were only suggested in patients with hypertension.

Nomogram models were constructed for DR (Fig. 2) and PDR (Fig. S1 in the Supplementary Materials) according to multiple logistic models. As the incidence of PDR was quite low (<1%) in this study, its prediction range was relatively narrow, only 1%–10%, much smaller than the prediction range for DR (5%–20%). In the DR model, the point of blood pressure levels increased from normal, HT-intensive, normal high, HT-moderate to HT-high levels. However, the HT-moderate level had the highest blood pressure level point in the PDR model.

In the calibration curves, both models had generally aligned ideal 45-degree line and the logistic model line, demonstrating good calibration of DR and PDR prediction (Fig. 3A and Fig. S2A in the Supplementary Materials). In addition, the decision curves showed that if the threshold probability was between 5% and 20% for DR prediction or between 1% and 10% for PDR prediction, then using the nomogram to predict the probability of developing DR or PDR added more benefit than treating either all or no patients with diabetes who would have DR or PDR (Fig. 3B and Fig. S2B in the Supplementary Materials). For both models, the clinical impact curves plotted small differences between the two classifications and quick unification of the two lines, indicating their reliability in risk prediction (Fig. 3C and Fig. S2C in the Supplementary Materials).

5. Discussion

This nationwide study confirmed the association between hypertension and DR, PDR, and DME in the diabetic population. We found that patients with and without hypertension benefited from a blood pressure <120/80 mmHg for reducing DR. Nomogram models were provided to quantify the DR probability and to assist ophthalmic screening in diabetes care.

First, patients with hypertension had an 8.1%, 38.1%, and 23.5% increased risk of DR, PDR, and DME, respectively. This finding is consistent with previous observations regarding hypertension as a risk factor for DR [5,24]. However, most studies have only explored the detrimental effects of hypertension (or blood pressure >140/90 mmHg) on DR, rather than the effects of different blood pressure levels [4]. The ACC/AHA guidelines [25,26] have tightened the definition of hypertension, and the 2021 KDIGO guidelines first reduced the target systolic blood pressure to <120 mmHg, based on the SPRINT findings [10,13]. To test if these recommendations could be applied in a diabetic population for DR prevention, the additional effects of a lower blood pressure level were studied.

Furthermore, even if the blood pressure was reduced to <140/90 mmHg but ≥120/80 mmHg, patients with hypertension still had a 16.3% increased risk of DR and a 55.2% increased risk of PDR. This can be systematically explained by the chronic subclinical inflammation and residual cardiovascular risk in patients with moderately controlled hypertension [27–31]. The ocular accumulation of harmful advanced glycation end products may also contribute to local pathologies in moderately controlled hypertension [32]. Moreover, the poor companions of diabetes and hypertension [33,34], including insulin resistance in the nitric oxide (NO) pathway, sodium-fluid retention, and activation of the renin-angiotensin-aldosterone system, call for additional blood pressure care in patients with diabetes compared to patients without diabetes. For the sake of cardiovascular risks, the reduction is usually 10–20 mmHg, corresponding to a blood pressure target of 120–130/80–90 mmHg in diabetes [11,26,35]. However, an appropriate blood pressure target to reduce DR in diabetes is still lacking.

Additionally, we found that patients in the HT-intensive group did not have an increased prevalence of DR or PDR. Meanwhile, patients in the normal high blood pressure group had an 11.4% increased risk of DR, indicating additional benefits of blood pressure <120/80 mmHg on DR. These results were also reflected by the nomogram model of DR, as patients with blood pressure <120/80 mmHg had the lowest “blood pressure level” point (<0.5), followed by patients with blood pressure between 120/80 mmHg and 140/

Table 2
Odds ratio (OR) for the associations between hypertension and outcomes.

Outcomes	Blood pressure control	No. of cases	Rate (%)	OR (95% CI)	*P* value
DR	non-HT	8874	10.81	1.000 (Reference)	–
	HT	7811	11.04	1.081 (1.045–1.117)	<0.001
PDR	non-HT	1387	1.69	1.000 (Reference)	–
	HT	1454	2.06	1.381 (1.280–1.491)	<0.001
DME	non-HT	759	0.92	1.000 (Reference)	–
	HT	807	1.14	1.235 (1.115–1.367)	<0.001

Model: logistic model, controlled by sex, age at diabetes diagnosis, diabetes duration, body mass index, diabetes types, and fasting blood sugar.
CI = confident interval.
DR = diabetic retinopathy, PDR = proliferative diabetic retinopathy, DME = diabetic macular edema, HT = hypertension.

Table 3
Odds ratio (OR) for the associations between blood pressure levels and outcomes.

Outcomes	*Blood pressure control*	*No. of cases*	*Rate (%)*	*OR (95% CI)*	P *value*
DR	Normal	867	10.67	1.000 (Reference)	–
	Normal high	8007	10.82	1.114 (1.033–1.202)	0.005
	HT-intensive	139	10.30	1.081 (0.893–1.310)	0.424
	HT-moderate	1720	11.40	1.163 (1.065–1.271)	<0.001
	HT-high	5952	10.96	1.203 (1.114–1.300)	<0.001
PDR	Normal	152	1.87	1.000 (Reference)	–
	Normal high	1235	1.67	1.082 (0.911–1.285)	0.370
	HT-intensive	24	1.78	1.227 (0.792–1.901)	0.359
	HT-moderate	349	2.31	1.552 (1.276–1.889)	<0.001
	HT-high	1081	1.99	1.468 (1.232–1.750)	<0.001
DME	Normal	89	1.10	1.000 (Reference)	–
	Normal high	670	0.91	0.918 (0.738–1.156)	0.455
	HT-intensive	14	1.04	0.999 (0.541–1.709)	0.997
	HT-moderate	216	1.43	1.338 (1.043–1.730)	0.024
	HT-high	577	1.06	1.091 (0.874–1.378)	0.455

Model: logistic model, controlled by sex, age at diabetes diagnosis, diabetes duration, body mass index, diabetes types, and fasting blood sugar.
CI = confident interval.
DR = diabetic retinopathy, PDR = proliferative diabetic retinopathy, DME = diabetic macular edema, HT = hypertension.

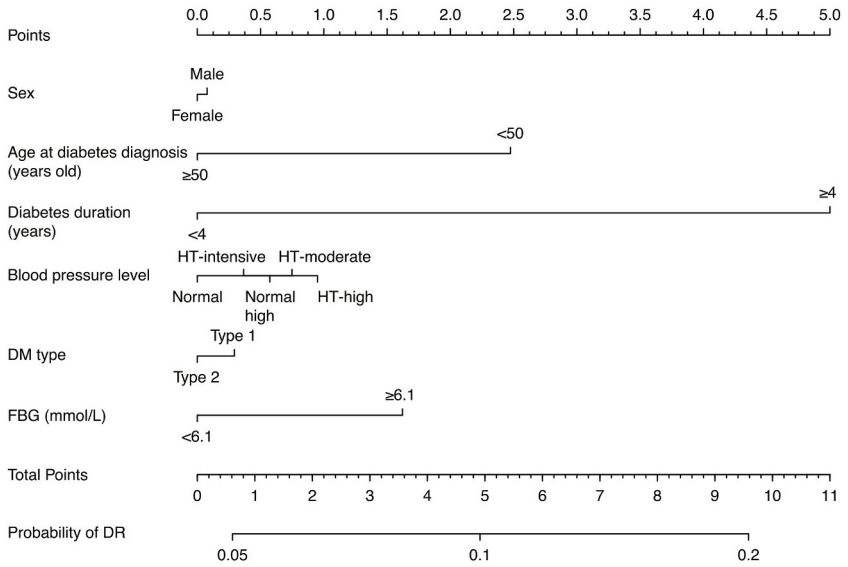

Fig. 2. A constructed nomogram for prediction of DR in the diabetic population. Nomograms can be interpreted by summing up the points assigned to blood pressure levels and other variables, which are indicated by the top scale. The total points can be converted to the predicted probability of DR for a patient on the bottom scale. HT = hypertension, FBG = fasting blood sugar.

90 mmHg, and patients with blood pressure ≥140/90 mmHg had the highest point (approximately 1) (Fig. 2). Possible explanations for this can be complex and unspecified. One is endothelial dysfunction induced by hyperglycemia, as a given systolic blood pressure drop from 160 mmHg to 120 mmHg, was reported to have three times more cardiovascular benefits for patients with diabetes versus without diabetes [36]. Intensive blood pressure control also reduces oxidative stress in patients, improves NO bioavailability, and improves endothelial function in patients without hypertension [37]. Based on these systematic changes, the benefits of blood pressure <120/80 mmHg on DR in patients with and without hypertension reported in this study can be quite reliable and assertive.

We recommend that patients with diabetes should have blood pressure <120/80 mmHg to reduce the risk of DR, similar to the 2021 KDIGO guidelines for cardiovascular protection in the CKD population. Besides pharmacological treatment, the DASH diet [38] characterized by low sodium but high potassium consumption, can be a good antihypertensive choice. Regular physical activities [39], weight loss strategies [40], limited alcohol intake [41], and comprehensive lifestyle modification [42] are also recommended for blood pressure control. Furthermore, DR and its high blood pressure risk must be considered before taking action. Our nomogram models for DR and PDR prediction can be useful tools for patient education. They involved multiple contributing factors of DR, not limited to blood pressure, and could have quantified the probabilities of DR and PDR. As only scale alignment and point addition are needed for nomogram prediction, these two models are user-friendly and can be used both in clinics and at home.

This study has several strengths. First, this population-based study covered almost all types of rural and urban areas in mainland

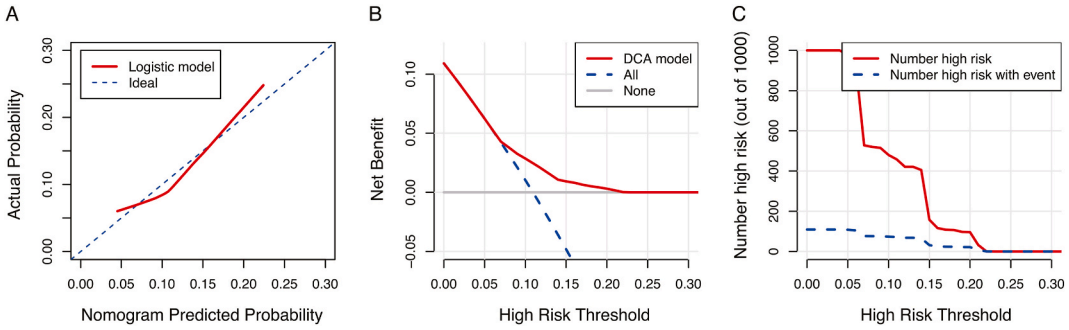

Fig. 3. Evaluations of the nomogram model for DR prediction in the diabetic population.
(A) Calibration curves for DR prediction. X-axes indicated nomograms predicted DR probability, and Y-axes indicated actual observations. (B) Decision curves compared the net clinical benefits in predicting the probability of DR: a perfect prediction model (blue dash line), screen none (horizontal gray line), and screen based on the nomogram (red line). DCA = decision curve analyses. (C) Clinical impact curves plot the number of diabetic patients classified as high risk (blue dash line), and the number of cases classified as high risk with DR at each high-risk threshold (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

China, thus minimizing the potential influence of selection bias. Second, the distributions of the DR and PDR were evaluated at different blood pressure levels. In the ACCORD Eye study [43,44], only insignificant increases in the risk of DR progression were found between intensive (SBP <120 mmHg) and standard (SBP <140 mmHg) blood pressure control in hypertensive patients. With a relatively high rate of loss of follow-up (31.8%), the trials could be underpowered, and the benefit of intensive blood pressure control was not observed. As blood pressure is higher and more resistant to treatment in patients with diabetes than without diabetes [45], and an SBP target of <120 mmHg in diabetes has not yet been recommended in current guidelines, very few patients have a blood pressure <120/80 mmHg, let alone those with DR, in real-world settings. Therefore, it was difficult for observational studies [24,46] to recruit enough patients to explore the effects of blood pressure <120/80 mmHg on DR. However, in our study, 9,476 patients with blood pressure <120/80 mmHg were recruited, of which 1,006 had DR. Our results added substantial evidence to the benefits of intensive blood pressure control. Third, blind assessment of all fundus images by a professional reading center largely reduced the bias of DR misdiagnosis. Finally, the DR/PDR prediction tools were developed. Nomogram models can be a good visualization tool for quantitative DR prediction and evaluation in clinical and public health practices.

This study had several limitations. First, possible underestimation of DR due to the non-mydriatic one-field fundus images. In addition, although we adjusted for a wide range of potential confounders, we cannot entirely exclude uncontrolled confounding by unmeasured genetic, environmental, or behavioral factors. The observed exposure-outcome associations could change if these factors were considered. Further research encompassing a broad range of socioeconomic and lifestyle factors is warranted. Finally, the cross-sectional nature of this study and the relatively short duration of diabetes in the study population. Follow-ups of this cohort may produce more useful and solid evidence for diabetes care to further validate our points.

6. Conclusions

There were associations between hypertension and DR, PDR, and DME in the diabetic population. Increased prevalence of DR was found with blood pressure >120/80 mmHg in both patients with and without hypertension. A nomogram was developed for DR prediction based on blood pressure levels. This study provides important evidence for blood pressure control in diabetes care.

Financial Support

Supported by the National Natural Science Foundation of China (81970845, 82171076, 82003554), the Science and Technology Commission of Shanghai Municipality (20Z11900400), the Shanghai Hospital Development Center (SHDC2020CR2040B), the Shanghai Collaborative Innovation Center for Translational Medicine (TM202115PT), Scientific Project of Shanghai Municipal Health Commission (201940151), Shanghai Sailing Program (22YF1435500).

Author contribution statement

Min Zhang, MD; Huixun Jia, MPH: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Jinye Wu, BS: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Yimin Wang, MD; Jiali Wu, MD; Weiting Hu, MD: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Xiaodong Sun: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

The authors do not have permission to share data.

Financial disclosures

No financial disclosures.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16830.

References

[1] N. Cheung, P. Mitchell, T.Y. Wong, Diabetic retinopathy, Lancet 376 (9735) (2010) 124–136.
[2] Z.L. Teo, Y.C. Tham, M. Yu, et al., Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis, Ophthalmology 128 (11) (2021) 1580–1591.
[3] P. Saeedi, I. Petersohn, P. Salpea, et al., Global and Regional Diabetes Prevalence Estimates for 2019 and Projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th, edition, Diabetes Res Clin Pract, 2019, 107843, 157.
[4] J.W. Yau, S.L. Rogers, R. Kawasaki, et al., Global prevalence and major risk factors of diabetic retinopathy, Diabetes Care 35 (3) (2012) 556–564.
[5] L. Liu, N.D. Quang, R. Banu, et al., Hypertension, blood pressure control and diabetic retinopathy in a large population-based study, PLoS One 15 (3) (2020), e0229665.
[6] D.V. Do, X. Wang, S.S. Vedula, et al., Blood pressure control for diabetic retinopathy, Cochrane Database Syst. Rev. 1 (2015) CD006127.
[7] Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group, BMJ 317 (7160) (1998) 703–713.
[8] R.O. Estacio, B.W. Jeffers, N. Gifford, R.W. Schrier, Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes, Diabetes Care 23 (2) (2000) B54–B64.
[9] R.W. Schrier, R.O. Estacio, A. Esler, P. Mehler, Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes, Kidney Int. 61 (3) (2002) 1086–1097.
[10] S.R. Group, C.E. Lewis, L.J. Fine, et al., Final report of a trial of intensive versus standard blood-pressure control, N. Engl. J. Med. 384 (20) (2021) 1921–1930.
[11] P.K. Whelton, R.M. Carey, W.S. Aronow, et al., ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines, 2017, Hypertension 71 (6) (2018) e13–e115.
[12] A.K. Cheung, T.I. Chang, W.C. Cushman, et al., Executive summary of the KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease, Kidney Int. 99 (3) (2021) 559–569.
[13] S.R. Group, J.T. Wright Jr., J.D. Williamson, et al., A randomized trial of intensive versus standard blood-pressure control, N. Engl. J. Med. 373 (22) (2015) 2103–2116.
[14] B. Zinman, C. Wanner, J.M. Lachin, et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, N. Engl. J. Med. 373 (22) (2015) 2117–2128.
[15] H.H. Parving, Impact of blood pressure and antihypertensive treatment on incipient and overt nephropathy, retinopathy, and endothelial permeability in diabetes mellitus, Diabetes Care 14 (3) (1991) 260–269.
[16] A. American Diabetes, 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018, Diabetes Care 41 (Suppl 1) (2018) S13–S27.
[17] S. Ruan, Y. Liu, W.T. Hu, et al., A new handheld fundus camera combined with visual artificial intelligence facilitates diabetic retinopathy screening, Int. J. Ophthalmol. 15 (4) (2022) 620–627.
[18] C.P. Wilkinson, F.L. Ferris 3rd, R.E. Klein, et al., Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales, Ophthalmology 110 (9) (2003) 1677–1682.
[19] T.G. Pickering, J.E. Hall, L.J. Appel, et al., Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research, Circulation 111 (5) (2005) 697–716.
[20] Joint Committee for Guideline R, Chinese guidelines for prevention and treatment of hypertension-A report of the revision committee of Chinese guidelines for prevention and treatment of hypertension, 2018, J. Geriatr. Cardiol. 16 (3) (2019) 182–241.
[21] P.A. James, S. Oparil, B.L. Carter, et al., evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8), 2014, JAMA 311 (5) (2014) 507–520.
[22] C. Cuspidi, M. Tadic, G. Grassi, G. Mancia, Treatment of hypertension: the ESH/ESC guidelines recommendations, Pharmacol. Res. 128 (2018) 315–321.
[23] A. American Diabetes, Cardiovascular disease and risk management: standards of medical care in diabetes-2019, Diabetes Care 42 (Suppl 1) (2019) S103–S123, 10.
[24] P. Jin, J. Peng, H. Zou, et al., The 5-year onset and regression of diabetic retinopathy in Chinese type 2 diabetes patients, PLoS One 9 (11) (2014), e113359.
[25] P. Muntner, R.M. Carey, S. Gidding, et al., Potential US population impact of the 2017 ACC/AHA high blood pressure guideline, Circulation 137 (2) (2018) 109–118.
[26] D.K. Arnett, R.S. Blumenthal, M.A. Albert, et al., ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines, 2019, Circulation 140 (11) (2019) e596–e646.
[27] R. Prijic, V. Premuzic, M. Brinar, et al., Increased arterial stiffness - similar findings in patients with inflammatory bowel disease without prior hypertension or diabetes and in patients with well-controlled hypertension, Blood Pres. 27 (4) (2018) 240–246.
[28] Y. Tsukihashi, Y. Shiga, Y. Suematsu, et al., Presence and severity of coronary artery disease in patients who achieved intensive blood pressure reduction at the time of coronary computed tomography angiography, Hypertens. Res. 44 (2) (2021) 206–214.
[29] M. Tadic, C. Cuspidi, B. Pencic, et al., Association between myocardial work and functional capacity in patients with arterial hypertension: an echocardiographic study, Blood Pres. 30 (3) (2021) 188–195.

[30] N. Onishi, M. Kawasaki, R. Tanaka, et al., Comparison between left atrial features in well-controlled hypertensive patients and normal subjects assessed by three-dimensional speckle tracking echocardiography, J. Cardiol. 63 (4) (2014) 291–295.
[31] T. Maruhashi, J. Soga, N. Fujimura, et al., Endothelial function is impaired in patients receiving antihypertensive drug treatment regardless of blood pressure level: FMD-J study (Flow-Mediated dilation Japan), Hypertension 70 (4) (2017) 790–797.
[32] S. Pehlivanoglu, Z. Bayraktar, M. Karakaya, et al., Assessment of lens autofluorescence in patients with well-controlled essential hypertension and those with renal failure secondary to hypertension undergoing hemodialysis, Photodiagnosis Photodyn. Ther. 34 (2021), 102268.
[33] E. Ferrannini, W.C. Cushman, Diabetes and hypertension: the bad companions, Lancet 380 (9841) (2012) 601–610.
[34] S.S. Roscioni, H.J. Heerspink, D. de Zeeuw, The effect of RAAS blockade on the progression of diabetic nephropathy, Nat. Rev. Nephrol. 10 (2) (2014) 77–87.
[35] G. Bakris, W. Ali, G. Parati, ACC/AHA versus ESC/ESH on hypertension guidelines: JACC guideline comparison, J. Am. Coll. Cardiol. 73 (23) (2019) 3018–3026.
[36] J. Stamler, O. Vaccaro, J.D. Neaton, D. Wentworth, Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial, Diabetes Care 16 (2) (1993) 434–444.
[37] D.H. Craighead, T.C. Heinbockel, K.A. Freeberg, et al., Time-efficient inspiratory muscle strength training lowers blood pressure and improves endothelial function, NO bioavailability, and oxidative stress in midlife/older adults with above-normal blood pressure, J. Am. Heart Assoc. 10 (13) (2021), e020980.
[38] F.M. Sacks, L.P. Svetkey, W.M. Vollmer, et al., Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. DASH-sodium collaborative research group, N. Engl. J. Med. 344 (1) (2001) 3–10.
[39] S.R. Colberg, R.J. Sigal, B. Fernhall, et al., Exercise and type 2 diabetes: the American College of sports medicine and the American diabetes association: joint position statement, Diabetes Care 33 (12) (2010) e147–e167.
[40] M.E. Hall, J.B. Cohen, J.D. Ard, et al., Weight-loss strategies for prevention and treatment of hypertension: a scientific statement from the American heart association, Hypertension 78 (5) (2021) e38–e50.
[41] M. Roerecke, J. Kaczorowski, S.W. Tobe, et al., The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis, Lancet Public Health 2 (2) (2017) e108–e120.
[42] L.J. Appel, C.M. Champagne, D.W. Harsha, et al., Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial, JAMA 289 (16) (2003) 2083–2093.
[43] A.S. Group, A.E.S. Group, E.Y. Chew, et al., Effects of medical therapies on retinopathy progression in type 2 diabetes, N. Engl. J. Med. 363 (3) (2010) 233–244.
[44] Action to control cardiovascular risk in diabetes follow-on eye study G, the action to control cardiovascular risk in diabetes follow-on study G. Persistent effects of intensive glycemic control on retinopathy in type 2 diabetes in the action to control cardiovascular risk in diabetes (ACCORD) follow-on study, Diabetes Care 39 (7) (2016) 1089–1100.
[45] A. Grossman, E. Grossman, Blood pressure control in type 2 diabetic patients, Cardiovasc. Diabetol. 16 (1) (2017) 3.
[46] G.S. Tan, A. Gan, C. Sabanayagam, et al., Ethnic differences in the prevalence and risk factors of diabetic retinopathy: the Singapore epidemiology of eye diseases study, Ophthalmology 125 (4) (2018) 529–536.