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Hypertensive Retinopathy and Risk of Serious Cardiovascular Events: Five Years Prospective Cohort Study in Primary Care

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Abstract: Introduction: Poorly controlled hypertension causes damage to the retinal microcirculation, which is predictive and associated to risk of stroke. Studies have shown that retinal microvascular changes can be reliably documented by retinal photographs. This study aims at examine the associative risk and incident of hypertensive retinopathy related serious cardiovascular events in primary care. Methodology: This is a prospective cohort study involving hypertensive patients in one regional primary care clinic of Hong Kong. Eligible digital retinal photographs of hypertensive patients done in the period Jan 1, 2011 to Dec 31, 2012 were graded based on Wong & Mitchell criteria. Consecutive subjects with hypertensive retinopathy (HTR) and without HTR (Non-HTR) were allocated to cohort and control group respectively until ceiling of 138. All patients will be followed prospectively for five years to exam the incidence of serious cardiovascular events. The relative risk of hypertensive retinopathy related serious cardiovascular events were investigated. Results: The cohort group patients are younger (mean age 57.3 versus 61.0, P<0.01), and have higher proportion of comorbid hyperlipidaemia (P=0.02). There are no statistical difference in sex, smoking status, duration of hypertension (HT), number of anti-hypertensive medication taking and mean blood pressure. At five year, both groups have no cardiovascular related mortality. Cohort group has 13 events of cardiovascular disease (incidence rate 9.42%), while control group has 5 events (incidence rate 3.62%). The five year realative risk (RR) of HTR for serious cardiovascular events is 2.77 (95% CI: 0.96-7.98, P=0.051), while five year RR of HTR for stroke is 9.56 (95% CI 1.19-76.5, P=0.010). With logistic regression analysis, HTR is independent risk factor for stroke, with RR 8.55 (p=0.047). Conclusion: Hypertensive retinopathy is the independent predictive risk factor for stroke. The sensitivity and specificity of HT patients with HTR in predicting stroke in 5 years is 90.0% and 51.5% respectively.

Keywords: Hypertensive Retinopathy, Cardiovascular Disease, Stroke

1. Introduction

Hypertension (HT) is a key risk factor for cardiovascular disease, the largest cause of morbidity and mortality worldwide. [1] Elevated blood pressure (BP) causes damage to the retinal microcirculation, which are termed as hypertensive retinopathy (HTR). [2] Studies had shown that retinopathy signs were predictive and associated to risk of stroke, including incident clinical stroke, ischaemic stroke, and lacunar infarct. [3-8] Both prevalence and incidence of between 2 to 51% have been reported for various retinal microvascular lesions. [4, 9-12] Recognition of HTR may be important in cardiovascular risk stratification of hypertensive patients. [3] Several studies have shown that retinal microvascular changes can be reliably documented by retinal photograph (RP). [13-16]

The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) indicates generically retinopathy as target organ damage. [17] The WHO International Society of Hypertension (WHO-ISH),

[18] the British Hypertension Society Guideline (BHS IV) [19] and the European Society of Hypertension – European Society of Cardiology Guideline (ESH-ESC 2007) [20] indicate that hypertensive retinopathy grades III and IV as target organ damage. There is no standardized management guideline for HTR in primary care setting of Hong Kong. In addition, there is lacking research in progression of HTR in Hong Kong.

We hypothesize that HTR associates with higher incident of serious cardiovascular events among hypertensive patients; and secondly, presence of HTR is predictive risk factor for serious cardiovascular events. This study aims to investigate the five year incidence of hypertensive retinopathy related cardiovascular events; and to examine the predictive correlation between hypertensive retinopathy and cardiovascular events.

2. Methodology

2.1. Study Design

Prospective cohort study in public primary care clinic.

2.2. Study Population

All Chinese hypertensive patients who had eligible and gradable retinal photography done during the period from January 1, 2011 to December 31, 2012 in one regional primary care clinic of Hong Kong were included. There were around 8,000 Chinese hypertensive patients cared under the clinic during the study period, and they were arranged for HT complication screening at triennial cycle. Hypertension retinopathy was examined by direct ophthalmoscope by clinician or retinal photographs (RPs). Indicated patients were referred to Diabetes Mellitus Centre of Kwong Wah Hospital for retinal photography. Retinal photograph was taken for both eyes by retinal photo camera (Model: Topcon TRC-NW8) at resolution of 3,216 x 2,136 pixels after pupil dilatation. Both of the hard copy retinal photos and digital photos in computer can be accessed by primary care physicians.

Those HT patients with the comorbidity of diabetes mellitus (DM), and had previous diagnosis of transient ischaemic attack (TIA), cerebrovascular accident (CVA)/stroke, ischaemic heart disease/coronary heart disease/coronary artery disease (IHD/CHD/CAD), peripheral vascular disease (PVD), atrial fibrillation (AF), or congestive heart failure (CHF) were excluded from current study. In addition, those RPs with poor quality and difficulty in interpretation were also excluded.

Hypertensive patients with RPs documented HTR were cohort group while hypertensive patients without HTR were control group. Consecutive patients were allocated to relevant group until ceiling of 138 on both groups. Both groups were followed prospectively to examine the incidence of serious cardiovascular events. The incidence and predictive risk factors for cardiovascular events between cohort and control groups were compared and analyzed.

2.3. Definition of Serious Cardiovascular Events (SCE)

Incident event of cardiovascular related mortality;

Incident event of cerebrovascular disease, including diagnosis of stroke (cerebral infarction or haemorrhagic stroke), CVA or TIA;

Incident event of coronary artery disease (CAD), including diagnosis of acute coronary syndrome (ACS), IHD/CHD, acute myocardial infraction (AMI), coronary artery bypass surgery (CABG), or percutaneous angioplasty (PTCA).

2.4. Outcome Measures

The incident rate of serious cardiovascular events;

The relative risk of HTR related serious cardiovascular events;

The predictive risk of HTR associate with serious cardiovascular events.

All relevant data, namely smoking status, years of diagnosis of hypertension, number of antihypertensive drugs, co-morbidities, and summary of complications screening were retrieved from the computerized Clinical Management System (CMS) of Hospital Authority (HA), Hong Kong. All RPs were reviewed firstly by attending physician and secondly by research team member. All research team members and primary care doctors among the clinic had completed training course in HTR interpretation. HTR interpretation and documentation were standardized. Retinal findings were recorded as exact description based on visual impression of clinic physicians and researchers, and then graded according to classification proposed by Wong and Mitchell (Table 1). [21] Simplified Wong and Mitchell classification of HTR is both reliable and repeatable, and has advantage over the traditional Keith-Wagener-Barker classification in correlating retinal microvascular signs to incident cardiovascular risk. [22] If discrepancy of grading existed, a consensus would be made after a group discussion of 3 researchers. All RPs (both available right and left eye) were included for grading. The eye with higher severity of grading would be accounted as the grade of HTR for the patient.

2.5. Definition of Wong and Mitchell Hypertensive Retinopathy [21]

Table 1. *Wong and Mitchell Hypertensive Retinopathy.*

Grade of Retinopathy	Retinal signs	Systemic Associations
Non	No detectable signs	None
Mild	Generalized arteriolar narrowing; Focal arteriolar narrowing; Arteriovenous nicking; Opacity ("copper wiring or silver wiring") of arteriolar wall; or A combination of these signs	Modest association with risk of clinical stroke, subclinical stroke, coronary heart disease and death

Grade of Retinopathy	Retinal signs	Systemic Associations
Moderate	Hemorrhage (blot, dot, or flame-shaped); Microaneurysm; Cotton-wool spot; Hard exudate; or A combination of these signs	Strong association with risk of clinical stroke, subclinical stroke, cognitive decline, and death from cardiovascular causes
Malignant	Signs of moderate retinopathy plus swelling of the optic disk	Strong association with death

2.6. Sample Size Calculation

According to Ong TY study [4] the 5 years cumulative prevalence of stroke in hypertensive patients with HTR was 7.5%. Sample size was calculated on estimated prevalence HTR related cardiovascular complication in the primary care setting of 8% with 5% margins of error and 95% confidence level. Using computer generated sample size calculator, the calculated sample size was 110. [23]

An attrition rate of 20% was assumed, then 138 patients with HTR were recruited to cohort group, while another 138 hypertensive patients without HTR were allocated to control group. On total, the sample size was 276.

2.7. Case Recruitment and Follow up

All RPs done for hypertensive patients during the period from Jan 1, 2011 to Dec 31, 2012 were retrieved. Research team assessed the quality of RPs and eligibility of subjects, and then allocated the cases to cohort and control group according to inclusion and exclusion criteria. All cases were following progressively up to 5 years to assess the stated outcomes. At five years, there was no drop out cases and all 276 cases were traceable in the CMS of Hospital Authority.

2.8. Statistical Analysis

Descriptive statistics including mean, standard deviation, frequency and percentage will be used to summarize the characteristics of the variables. Descriptive information for each of the explanatory variables will be derived. Univariate association of the variables with cardiovascular complication will be assessed using Mann-Whitney test for continuous variables while Chi-Square test for categorical variable. If applicable, logistic regression will be applied to adjust for confounding factors. Risk ratio and 95% confidence interval (95%CI) for HTR specific mortality and cardiovascular complications were calculated according to HTR severity. In addition, RP was presumed as a clinical test, where HTR was test positive while non-HTR was test negative. Stroke was the outcome measurement. The sensitivity and specificity of HTR in predicting of stroke in 5 years were calculated. A p-value of less than 0.05 is considered as significant. Data analysis will be performed with the Statistical Package for the Social Sciences (SPSS, version 21.0, SPSS Inc, United States).

2.9. Ethical Approval

This study was approved by Hong Kong Hospital Authority Research Ethics Committee (Kowloon Central / Kowloon East, KC/KE-17-0095/ER-3).

3. Results

Figure 1 summarized the case recruitment flow of the cohort group and the control group. All of the 138 cohort and 138 control group patients had followed for 5 years and completed evaluation. Table 2 illustrated their demographics. The cohort group was younger than the control group (mean age 57.3 versus 61.0, P<0.01), and they had higher proportion of concomitant hyperlipidaemia (63.0% versus 49.3%, P=0.021). Other demographics or clinical parameters did not show statistical difference among two groups, including sex, smoking status, duration of HT, number of anti-hypertensive drugs, mean systolic and diastolic BP, mean fasting sugar and low density lipoprotein (LDL) cholesterol level.

Table 2. *Patient demographics of the cohort group and the control group.*

	Cohort		Control		P value
	n	%	n	%	
Male, Female	4494	31.968.1	3999	28.371.7	0.58-
Mean Age (SD), years	57.3 (8.0)	-	61.0 (8.2)	-	<0.01
Current or Ex-smoker	23	16.7	18	13.0	0.40
Hyperlipidaemia	87	63.0	68	49.3	0.02
Chronic kidney disease	11	7.8	9	6.5	0.64
Obesity, BMI>25 kg/m^2	66	47.8	62	44.9	0.63
No of antihypertensive drug	-	-	-	-	-
1	65	47.1	74	53.6	0.28
2	63	45.7	50	36.2	0.11
3 or above	10	7.2	14	10.2	0.39
Duration of HT, years	6.6 (5.4)	-	6.8 (4.8)	-	0.71
Mean SBP (SD), mmHg	128.9 (11.9)	-	127.6 (11.5)	-	0.47
Mean DBP (SD), mmHg	75.9 (7.8)	-	74.4 (7.4)	-	0.11
Mean FBS (SD), mmol/L	5.2 (0.4)	-	5.2 (0.4)	-	0.56
Mean LDL-C (SD), mmol/L	3.3 (0.8)	-	3.5 (0.8)	-	0.66
Severity of HTR	-	-	-	-	-

	Cohort		Control		P value
	n	%	n	%	
Mild	109	79.0	-	-	-
Moderate	29	21.0	-	-	-
Severe	0	0	-	-	-

SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; LDL-C: low density lipoprotein cholesterol.

Table 3. *Five years cardiovascular events outcome.*

	Cohort	Incidence rate	Control	Incidence rate	RR	P value	95% CI
Number of patients	138	-	138	-	-	-	-
CVD related mortality	0	-	0	-	-	-	-
Cardiovascular events	13	9.42	5	3.62	2.77	0.051	0.96-7.98
Stroke/CVA/TIA	9	6.52	1	0.72	9.56	0.010	1.19-76.5
CHD/IHD/AMI	4	2.90	4	2.90	1	-	-

CVD: cardiovascular disease; CVA: cerebrovascular accident; TIA: transient ischaemic attack; CHD: coronary heart disease; IHD: ischaemic heart disease; AMI: acute myocardial infarction.

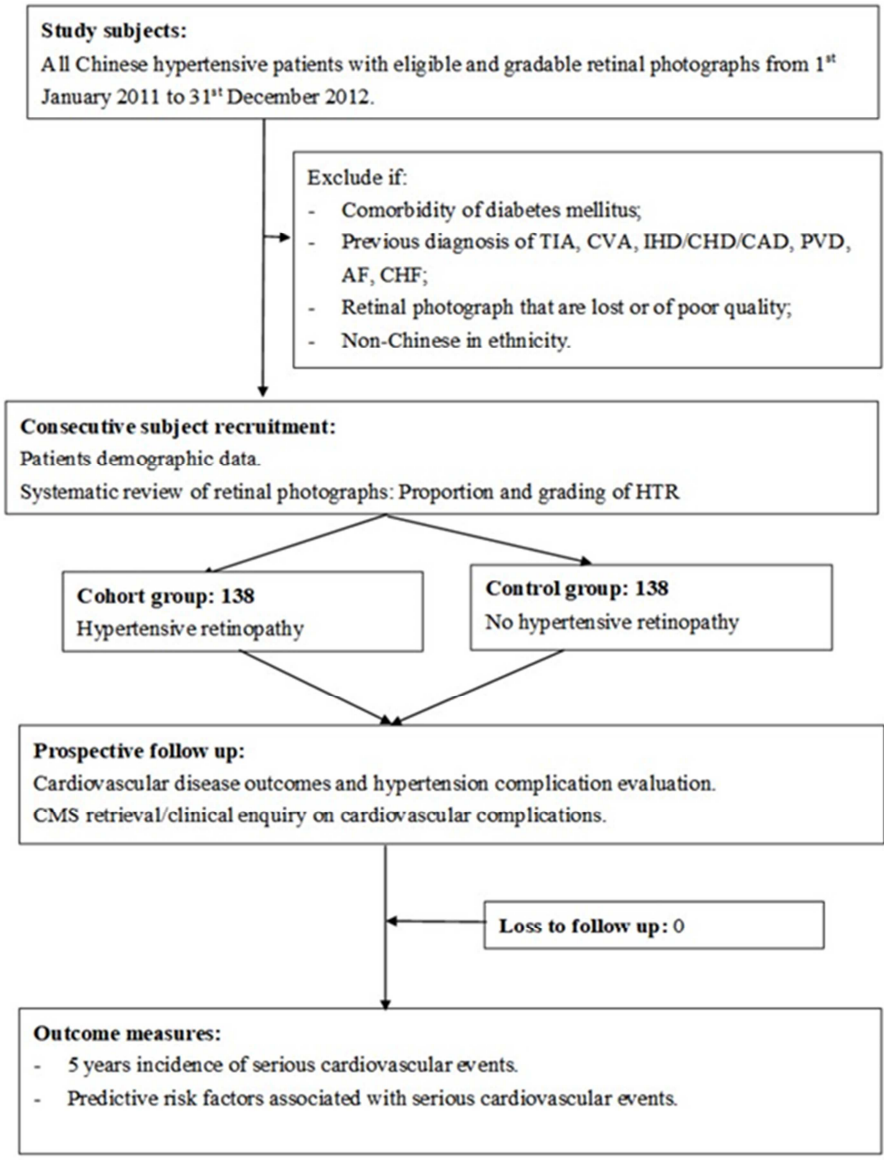

Figure 1. *Study flow chart.*

Serious cardiovascular events at five years were summarized in Table 3. At five year, there was no occurrence of HTR related mortality among two groups. There were 13 events of serious cardiovascular events in cohort group (incidence rate 9.42%), including 9 cases of stroke and 4 cases of CHD. One case of stroke and 4 cases of CHD (incidence rate 3.62%) occurred in

control group. The risk ratio (RR) of HTR versus non-HTR related serious cardiovascular disease was 2.77 (95% CI 0.96-7.98, p=0.051). There were 9 cases of stroke in cohort group while only 1 case in control group, the RR was 9.56 (95% CI 1.19-76.5, p=0.01). The incidence of cardiovascular events among mild and moderate HTR were 9.2% and 10.3% respectively (Table 4). Moderate HTR did not show significant higher incidence rate of cardiovascular events.

Table 4. *Stratification of cardiovascular events outcome and severity of HTR.*

Hypertensive retinopathy	Frequency	%	CVD events	Incidence rate	p-value
Mild	109	79.0	10	9.2%	0.801
Moderate	29	21.0	3	10.3%	-
Severe	0	0	0	0	-

Univariate analysis reveals that HTR was the associated risk factor for stroke, with RR 9.56 (95% CI: 1.19-76.5, P=0.01) (Table 5). Logistic regression model had applied for the risk factors associated with stroke, including HTR, age, sex, smoking status, duration of HT, number of antihypertensive agents, concomitant chronic diseases and systolic BP. Final fitted model showed that HTR was an independent predictive factor for stroke, RR is 8.55 (95%CI: 1.03-70.98, p=0.047).

Table 5. *Predictive factors associated with stroke.*

	Number	Stroke	%	RR	P-value	95% CI
HTR	138	9	6.52	9.56	0.010	1.19-76.50
Non-HTR	138	1	0.72	1	-	-
Hyperlipidaemia	155	7	4.52	1.86	0.369	0.47-7.35
Non-Hyperlipidaemia	121	3	2.48	-	-	-
CKD	20	1	5.00	1.44	0.732	0.17-12.0
Non-CKD	256	9	3.52	-	-	-
Obese	128	6	4.69	1.77	0.379	0.49-6.42
Non-Obese	148	4	2.70	-	-	-
Ex-/Smoker	41	2	4.88	1.46	0.641	0.30-7.11
Non-Smoker	235	8	3.40	-	-	-
Female	193	6	3.11	0.63	0.486	0.17-2.31
Male	83	4	4.82	-	-	-

HTR: hypertensive retinopathy; CKD: chronic kidney disease.

Sensitivity and Specificity of HTR in Predicting Stroke

There were 9 cases of stroke (incidence rate 6.5%) in cohort group while only 1 case in control group (incidence rate 0.7%) in 5 years follow up. Confirmation of HTR among HT patients associated with higher risk in development of stroke. Assuming HTR was test positive while non-HTR was test negative for the stroke. The sensitivity and specificity of HT patients with HTR in predicting stroke in 5 years is 90.0% and 51.5% respectively, while the positive likelihood radio is 1.86 (95% CI: 1.46 – 2.36) and positive predictive value is 6.52% (Table 6).

Table 6. *Prediction performance of HTR in predicting stroke in 5 years.*

Parameters	Performance	95% CI
Sensitivity	90.0%	55.5 to 99.8%
Specificity	51.5%	45.3 to 57.7%
Positive Likelihood Ratio	1.86	1.46 to 2.36
Negative Likelihood Ratio	0.19	0.03 to 1.25
Positive predictive value	6.5%	5.2 to 8.2%
Negative predictive value	99.3%	95.5 to 99.9%

4. Discussion

In this five years cohort study, we find that in patients with HT but without DM, HTR is associated with higher risk for stroke.

Histopathologic studies suggest that hypertensive retinopathy lesions result from small vessel arteriosclerosis, retinal ischemia and breakdown of the blood-retina barrier. [24] HTR parallel hypertensive microvascular changes described in the brain, suggesting that retinal photography is a potential clinical tool to indirectly assess potential microvascular damage in the cerebral vasculature. [4, 25] More recent population-based studies have adopted retinal photography and standardized protocols for the assessment of retinopathy signs. It has been suggested that retinal photography, widely available in primary clinics, hospitals, and even in the community may be a more precise means to document reginal signs. [8, 9] Several studies have shown that retinal microvascular changes, including retinopathy signs, are related to subclinical and clinical cerebrovascular pathology. (4, 26) Our study have confirmed that HTR is associated with higher risk for stroke among Chinese hypertensive patients in Hong Kong.

Hypertension is prevalent in Hong Kong. The Population Health Survey 2014-15 of the Department of Health revealed that around 17.8% of the population aged 15 or above had increased blood pressure. [27] Among those ever diagnosed with hypertension, 70% were prescribed blood pressure lowering medication, but only about 40% of those receiving treatment group attained control of their blood pressure. [28] Worldwide, hypertension awareness, treatment and control remain less than optimal. [29] Hypertensive retinopathy are at an increased risk of stroke, retinal assessment may be useful especially in those with good control of hypertension. In our

study, the blood pressure among cohort group patients is as good as control group, with mean BP 128.9/75.9 mmHg. However, they have higher risk to develop stroke. Recognition of hypertensive retinopathy is important in cardiovascular risk stratification and in prediction of long term cardiovascular complication of hypertensive patients. [3, 4] The physician should undertake more vigilant monitoring of the cardiovascular risk in patients with mild retinopathy, or adopt an aggressive approach to risk reduction in patients with moderate retinopathy. Urgent antihypertensive treatment and ophthalmologist care should be initiated for patients who have severe retinopathy. [21] Clinical guidelines strongly recommend that lowering blood pressure can lead to significant reduction of stroke risk. [30, 31]

There is no clear consensus regarding the classification of hypertensive retinopathy or whether a retinal examination is useful to stratify risk. The usefulness of the traditional hypertensive retinopathy classification, Keith-Wagener-Baker classification is frequently questioned. It is difficult for the clinician to distinguish between low grades of retinopathy. i.e. grade 1 and grade 2. Secondly, the retinopathy grade does not correlated to the severity of the hypertension. [21, 22] In our study, Wong and Mitchell classification is used, which is relatively simpler for the clinician to differentiate between mild and moderate grades.

Information of current study will promote additional prospective studies that aim to demonstrate independent association of hypertensive retinopathy with various cardiovascular complications. This information should be important while formulating clinical protocol, planning screening services or projecting cost, especially in the fact of an escalating awareness of hypertension care in our local community.

4.1. Strength and Limitation

This study is the first research in HTR in primary care of Hong Kong. The study also recommends the clinical usage of new classification of HTR, i.e. Wong and Michell classification. In addition, all clinical data and comorbidities were retrieved from the computerized CMS of HA, therefore recall bias is minimized. All recruited 276 subjects had completed follow up and outcome measurement in five years, which also geared a strength in our study.

On the other hand, there are some limitations of the study. Firstly, all study patients were recruited from one public primary care clinic of Hong Kong, therefore findings of our study may not be generalized to private settings or secondary care settings. Secondly, the grading of the RPs are done by primary care physicians, although they had completed training in RP interpretation, interpersonal bias may be one potential risk. Thirdly, there are statistical difference in age and proportion of hyperlipidaemia between cohort and control group, which may be one confounding factors in the development of cardiovascular complications.

4.2. Future Research Directions

HT patients with moderate grade HTR do not show statistical significantly higher risk for serious cardiovascular complication. Time to cardiovascular events and dose effect of HTR severity should be further studies to consolidate the predictive associative risk between HTR and cardiovascular complications.

4.3. Implications to Primary Care

This study has showed higher risk of stroke among HT patients with HTR in primary care setting. Primary care profession should consider to formulate a standardized protocol in identification, management on HTR among hypertensive patients cared under primary care setting.

5. Conclusion

This five years cohort study shows that hypertensive retinopathy is an independent risk factor for stroke, RR is 8.55 (95%CI: 1.03-70.98). The sensitivity and specificity of HT patients with HTR in predicting stroke in 5 years is 90.0% and 51.5% respectively. Well-structured management of cardiovascular risk prevention should be formulated for hypertensive patients with hypertensive retinopathy.

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