Risk Stratification on Systemic Target Organ Involvement Associated with Hypertensive Retinopathy

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ABSTRACT

Background: Hypertensive retinopathy is a common complication among people with hypertension. The current study assessed the risk stratification on systemic target organ involvement of people with hypertensive retinopathy.

Methods: In a hospital- based cross-sectional study conducted at a tertiary referral eye institute in Nepal, we included consecutive people ≥ 31 years with essential hypertension. Details of histories and systemic target organ involvements were documented. People with un-gradable retinal findings of hypertensive retinopathy and prior retinal surgery were excluded. All participants underwent comprehensive eye examination, including dilated fundus examination. Hypertensive retinopathy was classified by Modified Scheie classification. Multivariate analysis was performed to identify the risks for hypertensive retinopathy and target organ involvement.

Results: The study recruited 312 subjects. The mean age was 63.68 ± 12.63 years. The mean duration of hypertension was 7.0 ± 6.5 years. Hypertensive retinopathy was detected in 83.7% (n=261) people and 63.5% (n= 198) had grade 1 hypertensive retinopathy. Target organ involvement was detected in 20.5% (n =64) people. These included cardiac (12.5%; n=39), central nervous (5.1%; n= 16), and renal (4.5%; n=14) systems. In multivariate analysis, concurrent hyperlipidaemia was significantly associated with hypertensive retinopathy and target organ involvement. Target organ involvement increased with the severity of hypertensive retinopathy.

Conclusions: Over four-fifths of people with hypertension had hypertensive retinopathy and one-fifth had other systemic target organ involvements. Severity of hypertensive retinopathy and concurrent hyperlipidaemia were associated with target organ involvement. Hypertensive retinopathy can be considered for risk stratification to other target organ involvement in a clinical setting.

Keywords: Hypertension; hypertensive retinopathy; Nepal; risk stratification; target organ.

INTRODUCTION

Hypertension, a common cardiovascular problem worldwide, is responsible for coronary heart diseases, stroke, and kidney problems.[1,2] Globally, nearly one-third (31.1%) of adults suffer from hypertension.[3] The prevalence of hypertension in Nepal ranges from 24.4% to 28.4%, higher with ageing and rapidly increasing over the past 25 years.[4-6] Hypertension is responsible for hypertensive retinopathy and other vision-threatening ocular problems.[7-8]

Involvement of heart, kidney, brain, and eye by hypertension is termed as target organ involvement.[9] Retinopathy is recognized as an indicator of target organ damage, and its early recognition remains an important step for risk stratification of patients for other target organ involvements.[9-13] Target organs involvement among people with hypertensive retinopathy ranged from 12% to 30%.[9]

There is no information on target organ involvement associated with hypertensive retinopathy in our country. This study aims to assess the target organ involvement in people with hypertensive retinopathy at a hospital setting.

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METHODS

This study was a hospital- based cross-sectional study conducted in a tertiary care level hospital in the capital city of Nepal. The study was conducted from December 2020 to November 2021. It was approved by the Institutional Review Committee. Informed written consent was obtained before enrolment into the study. The study included all consecutive patients 31 years of age or older with known (taking anti-hypertensive medications) or newly diagnosed essential hypertension presenting at the vitreo-retina service of the institute. The exclusion criteria were: (1) people who did not give a written consent (2) un-gradable hypertensive retinopathy due to media haze and/or severe nystagmus (3) presence of other retinal conditions (such as branch retinal vein occlusion, central retinal vein occlusion, retinitis pigmentosa, etc), (4) those with concurrent diabetes mellitus, (5) secondary hypertension and (6) previous retinal surgeries. In calculating the sample size for the study, we referred to the outside of Nepal published report on the prevalence of target organs involvement among people with hypertensive retinopathy of 12% to 30%,[11] and used the higher side on the target organ involvement, i.e., 30%. Considering 17% relative precision at 95% confidence, the required sample size was 312.

Hypertension was defined on the following criteria: (1) Blood pressure: systolic blood pressure (SBP) > 140 mmHg, and diastolic blood pressure (DBP) > 90 mmHg, or (2) participants using antihypertensive medications.[10] Blood pressure was measured in a sitting position in the right arm with Sphygmomanometer and repeated to confirm the diagnosis. All newly diagnosed people received cardiologist/ physician workup to confirm the diagnosis. Blood pressure measurement was also taken in all subjects at the tertiary eye hospital. Detailed demographic information of the study participants included age, gender, occupation, education level, economic status, and residence (urban or rural). Economic status was categorized based on the Nepal Living Standard Survey 2010/11.[14] Patients were divided into three major groups for assessment as high, middle, and low socioeconomic status.

The detailed history of hypertension included the duration of hypertension, medications, and the control status. Specific information was collected for the target organs: Cardiac- history of angina, myocardial infarction, cardiomegaly etc; Renal- nephropathy; Neurological- transient ischemic attack, and stroke. All earlier medical records were reviewed, including blood biochemistry and other systemic problems such as depression, stress, prolonged illness, etc. Personal habits on tobacco and alcohol consumption were documented.

Both uncorrected and best- corrected visual acuity were measured using a Snellen chart at prescribed distance and illumination (6 meters and 600 lux). Detailed anterior segment and dilated fundus evaluation were done using a Slit lamp (Haag Streit, Switzerland), 90 Diopter, and 20 Diopter lens (Volk, USA). Hypertensive retinopathy was graded on clinical examination according to the Modified Scheie classification.[15] Briefly, it was grade 0: no changes; grade 1: barely detectable arterial narrowing; grade 2: obvious arterial narrowing with focal irregularities; grade 3: grade 2 plus retinal haemorrhage and/or exudates; grade 4: grade 3 plus disc swelling. Intra ocular pressure (IOP) was measured with air-puff tonometry (Pulsair Desktop Tonometer, Keeler, USA). When high in the air-puff tonometry, the IOP was also re-measured by the Goldman applanation tonometer. The pupil was dilated in all cases using tropicamide 1%. Dilated fundus photographs (Visucam 224/524, Carl Zeiss, Germany) were obtained in most patients. Macular OCT (Angioplex 6000, Carl Zeiss, Germany) was done in grades 3 and 4 hypertensive retinopathy. All information was collected in a specially designed proforma.

SPSS version 20 was used for the data analysis. Descriptive statistics such as frequencies, percentages, mean, and standard deviation (SD) were calculated. Chi Square and the Fisher exact test were applied for categorical data analysis; Student t test/ Mann Whitney U test was used for numerical data; and dependent t test/ matched pair signed rank test were used for matched continuous data, wherever applicable. Value was considered significant when it was less than 0.05.

RESULTS

The study recruited 312 subjects. Mean age of the study participants was 63.68 $\pm$ 12.63 years. There was an equal division of males (n=158) and females (n=154). One third of patients each gender were between age group 61-70 years (30.4%; n= 95) and 71 to 80 years (30.1%; n= 94). One third of participants (35.9%; n= 112) were employed (service, business, self-employed), 31.4% (n= 98) were homemakers and 23.1% (n= 72) were agriculturists. Over a quarter of the study, subjects were illiterate (28.8%; n= 118), and 18.3% (n= 57) had received higher secondary or higher education. Nearly half of the subjects (56%; n= 176) were from Kathmandu valley, 81% (n= 253) were Hindus by religion, and 98.4% (n= 307) were from middle- class family.

Table 1. Grading of hypertensive retinopathy among the study participants.			
Grading of hypertensive retinopathy	Right eye n *, (%)†	Left eye n (%)	Person n (%)
No hypertensive retinopathy	51 (16.3%)	57 (18.3%)	51 (16.3%)
Grade 1 hypertensive retinopathy	199 (63.8%)	192 (61.5%)	198 (63.5%)
Grade 2 hypertensive retinopathy	49 (15.7%)	52 (16.7%)	46 (14.7%)
Grade 3 hypertensive retinopathy	12 (3.8%)	10 (3.2%)	16 (5.1%)
Grade 4 hypertensive retinopathy	1 (0.03)	1 (0.03)	1 (0.03)

*=number, †=percent

The mean duration of hypertension was 7.0 ± 6.5 years, and the median duration was 5 years. The duration of hypertension was as follows: < 1 year- 9.9% (n=31), 1-10 years- 68.6% (n=214), 11-20 years- 17.9% (n=56), and > 21 years- 3.5% (n= 11).

Hypertensive retinopathy was detected in 261 participants (83.7%). It was grade 1 in 63.5% (n=198), grade 2 in 14.7% (n=46), grade 3 in 5.1% (n=16), and grade 4 in 0.3% (n=1). There was no preferred laterality of eye involvement in all hypertensive grading. (Table 1).

One- third of subjects (31.7%; n= 99) had hyperlipidaemia. Target organ involvement was detected in 20.5% (n=64) subjects. In descending order, it was cardiac (12.5%; n=39), CNS (5.1%; n= 16) and renal (4.5%; n=14). (Total is more than 64 because five people had multiple target organ involvement). Myocardial infarction was the most common cardiac disease (n= 15 patients, 38.5% of cardiac disorders). Stroke was the most common CNS disorder (n= 12; 75% among the CNS disorders) (Table 2).

The target organ involvement was proportionally higher with the severity of hypertensive retinopathy (22.5% in grades 1 and 2 and 29.4% in grades 3 and 4; p=0.014). (Table 3)

On the other hand, socioeconomic status (p=0.015), hyperlipidaemia (p=0.007), and overall target organ involvement (p= 0.014) were significantly associated with hypertensive retinopathy. Among the target organ involvements, cardiac diseases (p=0.043) were significantly associated with hypertensive retinopathy. The CNS problems (p=1.000) and kidney problems (p=0.137) had no significant association with hypertensive retinopathy. (Table 5)

Male gender (p=0.001), office goers (p=0.019), and hyperlipidaemia (p<0.001), were significantly associated with systemic target organ involvement. (Table 4).

In multivariate analysis, target organ involvements were significantly associated with concurrent hyperlipidaemia (p=0.002, Odds Ratio, OR: 2.586; 95% Confidence Interval, CI: 1.422-4.702). Males had two times more risk of target organ involvement than females, although the difference was not statistically significant. Similarly, in multivariate analysis, concurrent hyperlipidaemia (p=0.038, OR: 2.364, 95% CI: 1.051-5.320) was significantly associated with hypertensive retinopathy. Those with target organ involvement and uncontrolled hypertension had two times more risk of hypertensive retinopathy. For multivariate analysis, all the variables that were found statistically significant were included.

Table 2. Systemic target organ involvement and pattern of diseases among the study participants.			
Target organ disease	Category of disease	n *	Percentage (%)
Cardiac disease (12.5%; n= 39)	Angina Pectoris	1	2.6%
	Aortic Root Dilatation	1	2.6%
	Arrhythmia	2	5.1%
	Cardiomegaly	2	5.1%
	Degenerative Valvular Disease	1	2.6%
	Left Ventricle Diastolic Dysfunction	5	12.8%
	Left Ventricle Diastolic Dysfunction, sclerotic aortic valve	1	2.6%
	Left Ventricle Hypertrophy	6	15.4%
	Mitral stenosis	1	2.6%
	Myocardial Infraction	15	38.5%
	Valvular Heart disease,	1	2.6%
	Valvular Heart disease ,Left Bundle Branch Block	1	2.6%
	Valvular Heart disease, Left Ventricle Diastolic Dysfunction	1	2.6%
	Valvular Heart disease, Rheumatic Heart Disease	1	2.6%
CNS diseases (5.1%; n= 16)	Stroke	12	75.0%
	6th Cranial Nerve Palsy	1	6.3%
	7th Cranial Nerve Palsy	1	6.3%
	Cerebral Atrophy, Small Vessel Disease	1	6.3%
	Chronic Small Vessel Disease	1	6.3%
Kidney diseases (4.5%; n= 14)	Nephropathy	14	100.0%

*=number

Socio-economic status has very few sample number in each category. It was removed from the multivariate analysis since it showed the multi-collinearity problem and gave the standard error very high. (Table 6)

Table 3. Association of target organ involvement and hypertensive retinopathy.

		Hypertensive retinopathy								p value
		Total		No		Grade 1 & 2		Grade 3 & 4		
		(n) *	(%)	(n)	(%)	(n)	(%)	(n)	(%)	
Target Organ Involvement	Yes	64	20.5	4	7.8	55	22.5	5	29.4	0.014
	No	248	79.5	47	92.2	189	77.5	12	70.6	
	Total	312	100.0	51		244		17		

*=number

Table 4. Factors associated with target organ involvement among the study participants.

Parameters		Target Organ Involvement						P value
		Total		Yes		No		
		n *	% †	n	%	n	%	
Gender	Male	158	50.6	44	68.8	114	46.0	0.001
	Female	154	49.4	20	31.3	134	54.0	
Age (years)	<50	52	16.7	10	15.6	42	16.9	0.802
	>50	260	83.3	54	84.4	206	83.1	
Occupation	Agriculture	72	23.1%	12	18.8%	60	24.2%	0.019
	Office goers	95	30.4%	26	40.6%	69	27.8%	
	Homemaker	98	31.4%	12	18.8%	86	34.7%	
	Others	47	15.1%	14	21.9%	33	13.3%	
Literacy	Illiterate	118	37.8%	20	31.3%	98	39.5%	0.224
	Literate	194	62.2%	44	68.8%	150	60.5%	
Socio - economic status	Low	4	1.3%	0	0.0%	4	1.6%	0.670
	Medium	307	98.4%	64	100.0%	243	98.0%	
	High	1	0.3%	0	0.0%	1	0.4%	
Hyperlipidaemia	Yes	99	31.7%	33	51.6%	66	26.6%	<0.001
	No	213	68.3%	31	48.4%	182	73.4%	
Smoking history	Present	36	11.5%	7	10.9%	29	11.7%	0.058
	Past	103	33.0%	29	45.3%	74	29.8%	
	Never	173	55.4%	28	43.8%	145	58.5%	
Alcohol history	Present	97	31.1%	17	26.6%	80	32.3%	0.104
	Past	63	20.2%	19	29.7%	44	17.7%	
	Never	152	48.7%	28	43.8%	124	50.0%	
Duration of hypertension (years)	Less than 1 year	31	9.9%	8	12.5%	23	9.3%	0.356
	1 to 10 years	214	68.6	37	57.8%	177	71.4	
	More than 10 years	67	21.5%	19	29.7%	48	19.4%	
Duration of hypertension (years)	Median (Range)	5.0 (0.01 - 32)		6 (0.08 - 31)		5.0 (0.01 - 32)		0.280

*=number; †=percent

Table 5. Factors associated with hypertensive retinopathy among the study participants.

Parameters		Hypertensive retinopathy						p value
		Total		Yes		No		
		n	%	n	%	n	%	
Gender	Male	158	50.6%	137	52.5%	21	41.2%	0.139
	Female	154	49.4%	124	47.5%	30	58.8%	
Age (Years)	<50	52	16.7%	39	14.9%	13	25.5%	0.065
	50 and above	260	83.3%	222	85.1%	38	74.5%	
Occupation	Agriculture	72	23.1%	57	21.8%	15	29.4%	0.170
	Service	95	30.4%	86	33.0%	9	17.6%	
	Housewife/ Household work	98	31.4%	79	30.3%	19	37.3%	
	Others	47	15.1%	39	14.9%	8	15.7%	
Duration of HTN (Years)	Less than 1 year	31	9.9%	26	10%	5	9.8%	0.173
	1 to 10 years	214	68.6%	174	66.7%	40	78.4%	
	More than 10 years	67	21.5%	61	23.4%	6	11.8%	
Duration of HTN (Years)	Median (Range)	5.0 (0.01 - 32)		5.0 (0.01 - 32)		4.0 (0.01 - 28)		0.190
Literacy	Illiterate	118	37.8%	94	36.0%	24	47.1%	0.137
	Literate	194	62.2%	167	64.0%	27	52.9%	
Mental stress	Yes	97	31.1%	87	33.3%	10	19.6%	0.053
	No	215	68.9%	174	66.7%	41	80.4%	
Socio-economic status	Low	4	1.3%	1	0.4%	3	5.9%	0.015
	Medium	307	98.4%	259	99.2%	48	94.1%	
	High	1	0.3%	1	0.4%	0	0.0%	
Hyperlipidemia	Yes	99	31.7%	91	34.9%	8	15.7%	0.007
	No	213	68.3%	170	65.1%	43	84.3%	
Cardiac diseases	Yes	39	12.5%	37	14.2%	2	3.9%	0.043
	No	273	87.5%	224	85.8%	49	96.1%	
CNS problems	Yes	16	5.1%	14	5.4%	2	3.9%	1.000
	No	296	94.9%	247	94.6%	49	96.1%	
Kidney problems	Yes	14	4.5%	14	5.4%	0	0.0%	0.137
	No	298	95.5%	247	94.6%	51	100.0%	
Target Organ Involvement	Yes	64	20.5%	60	23.0%	4	7.8%	0.014
	No	248	79.5%	201	77.0%	47	92.2%	
Smoking history	Present	36	11.5%	26	10.0%	10	19.6%	0.077
	Past	103	33.0%	91	34.9%	12	23.5%	
	Never	173	55.4%	144	55.2%	29	56.9%	
Alcohol history	Present	97	31.1%	85	32.6%	12	23.5%	0.273
	Past	63	20.2%	54	20.7%	9	17.6%	
	Never	152	48.7%	122	46.7%	30	58.8%	

*=number, †=percent

Table 6. Factors associated with systemic target organ involvement and hypertensive retinopathy in multivariate analysis.

Parameters		P value	OR* (95% CI)†
Variables for target organ involvement	Gender Male vs. Female	0.106	2.068 (0.858-4.989)
	Agriculture	0.944	
	Office goers	0.602	1.253 (0.536-2.928)
	Housewife/Household work	0.987	0.991 (0.347-2.83)
	Others	0.624	1.27 (0.488-3.301)
	Hyperlipidaemia Presence vs. Absence	0.002	2.586 (1.422-4.702)
	Hypertension Uncontrolled vs. Controlled	0.242	1.473 (0.77-2.819)
Variables for hypertensive retinopathy	Hyperlipidaemia Presence vs. Absence	0.032	2.433 (1.082-5.473)
	Target Organ Involvement Presence vs. Absence	0.063	2.787 (0.948-8.198)
	Hypertension Uncontrolled vs. Controlled	0.089	2.022 (0.897-4.555)

*=Odds Ratio, †=Confidence Interval

DISCUSSION

This is the first study to assess the risk stratification on target organ involvement associated with hypertensive retinopathy in Nepal. The retina is considered a window to evaluate human circulation. Retinal arterioles can be visualized directly and noninvasively that share the common anatomical and physiological properties with cerebral and coronary microcirculation.[9,16]

In hypertension, the force of blood against the artery walls is too high, causing the arteries to stretch, reduce its calibre, and is progressively damaged over time, leading to hypertensive retinopathy. Hypertension affects precapillary arterioles and capillaries. In acute hypertension, there occurs focal intraretinal periarteriolar transudates at the precapillary level. Non-perfusion at various levels leads to cotton wool spots, which indicates ischemia of the retinal nerve fibre layer. Chronic hypertensive retinal lesions include microaneurysms, blot haemorrhage, lipid exudates, etc.[9,17,18]

In our series, hypertensive retinopathy was detected in 83.7%. It is similar to the prevalence of 83.6% in the hospital-based study by Kabedi et al.[10] In most other studies, however, the prevalence of hypertensive retinopathy was 60-80% in a hospital-based population.[19-22] In our study, all patients were examined by a fellowship-trained retina specialist. There is a possibility of underestimation of retinal findings where a general ophthalmologist conduct the examinations, and also when retinopathy was diagnosed on reading fundus photographs. Variation in other associated factors could

also be possible. In our cohort, grade one hypertensive retinopathy was most common, consistent with other studies.[10,19-22]

The extra-ocular target organ involvement was in 20.6% of our series. This was consistent with another study report of 12 to 30%.[9] After the eye, other target organs involved were the heart (12.5%), the brain (5.1%) and the kidney (4.5%). Myocardial infarction, stroke, and nephropathy were the most common systemic problems in our series. Our findings were similar to other studies.[9-11]

Our study showed that male gender, office goers, associated hyperlipidaemia, and uncontrolled hypertension had a higher risk of target organ involvement. Also, hypertensive retinopathy was more likely to occur in people with hyperlipidaemia, uncontrolled hypertension, and people with affected target organs. In multivariate analysis, hyperlipidaemia had a significant association with both hypertensive retinopathy, and for target organ involvement. Our study findings were similar to other studies.[9-13,19-22] Cardiac involvement was significantly associated with hypertensive retinopathy among the target organ involvement in our study like in many other studies.[9,11]

Hyperlipidaemia is elevated plasma cholesterol, triglycerides, and lipoproteins. The risks of developing hyperlipidaemia are positive family history, obesity, smoking, and harmful use of alcohol. In addition, hyperlipidaemia is closely linked to cardiac problems, stroke, and peripheral artery disease. In this study, one in three participants had concurrent hyperlipidaemia;

this could be linked to more sedentary work, similar to an earlier study from Nepal.[20] Hyperlipidaemia can also affect the eye and other systemic target organs. The basic pathogenesis in hyperlipidaemia is an increase in viscosity of blood, form atherosclerosis, thickening of the arterial wall leading to damage of endothelial cells, plaque formation, and embolism to target organs leading to infarction and ischemic damage. Dyslipidaemia could also aggravate rise in blood pressure leading to further increase in systemic target organ damage.[23] Also, in this series, one in five participants had another target organ involvement, including myocardial infarction. The risk of target organ involvement was higher in people with uncontrolled hypertension (OR: 1.473). Given that mortality from cardiac disorders is high in Nepal,[24] there should be provision of good control of hypertension and regular check-up.

In our study, the mean duration of hypertension was 7 years, but in contrast to other studies,[20-22] the duration of hypertension was not a risk factor for hypertensive retinopathy in our study. Delay in diagnosis and uncontrolled blood pressure could be the reason for this finding in our series. Hypertension is one of the major risk factors for many other vision- threatening retinal conditions.[7,8] So, emphasis should be given to timely diagnosis and treatment of hypertension. In our series, we found no significant association between smoking and alcohol in hypertensive retinopathy and target organ damage. However, these factors could play a role in the aggravation of systemic target organ damage.[28,29]

Furthermore, hypertensive retinopathy carries a long-term risk of stroke and cardiovascular complications.[9,12,13] Awareness on hypertensive retinopathy is low among the people with hypertension.[7,30] Awareness campaigns of target organ involvement in hypertension, regular check-up, and control of other associated factors are mandatory for all these high- risk patients.

Strength of the study: It was a prospective cross-sectional study that enrolled a large number of patients with hypertension. The fellowship-trained retina specialist examined the retina and classified hypertensive retinopathy.

Limitation of the study: It was a single and exclusive tertiary eye centre study. Hence, we presume that only people with vision problems and other eye problems reported to us. Additionally, the results can't be generalized to a wider population in Nepal with hypertension.

Further case-control and longitudinal studies are recommended for more information on risk stratification of systemic target organ involvement associated with hypertensive retinopathy.

CONCLUSIONS

Over four fifth of the patients with hypertension had hypertensive retinopathy, and one- fifth had other systemic target organ involvements in this cross-sectional study. The heart was the most commonly affected systemic target organ, followed by the brain and kidney. Target organ involvement increased with the greater severity of hypertensive retinopathy. Hyperlipidaemia was significantly associated with both hypertensive retinopathy, and systemic target organ involvement. Uncontrolled blood pressure and target organ involvement were other associated factors for hypertensive retinopathy. Emphasis should be given on advocacy for timely diagnosis and control of hypertension and hyperlipidaemia. Presence of hypertensive retinopathy can be used as a risk stratification for other target organ involvement in a clinical setting. The ophthalmologists could play a vital role in saving the sight and life of patients with hypertension by counselling on risks and precautions on major target organ involvements.

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CONFLICT OF INTEREST

None

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