ORIGINAL ARTICLE

Hypertensive Retinopathy: A Prognostic Factor for Morbidity and Mortality after Acute ST Elevation Myocardial Infarction

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ABSTRACT

Objective: To determine the association between hypertensive retinopathy (HR) and post ST elevation myocardial infarction (STEMI) complications among successfully thrombolysed patients.

Study Design: A cohort study.

Place and Duration of Study: Cardiology Unit, Lady Reading Hospital, Peshawar, from June 2016 to December 2017.

Methodology: Patients with history of hypertension for at least 5 years who presented with STEMI and were successfully thrombolysed, were included. On the basis of fundoscopy, patients were grouped into no, mild, moderate, and severe hypertensive retinopathy. Primary and secondary endpoints included a composite of death, re-MI, stroke, re-hospitalisation secondary to left ventricular failure, cardiogenic shock, arrhythmia, heart block, and ventricular septal rupture at 30 days and 4 months, respectively. Association between hypertensive retinopathy and post STEMI complications was determined by Chi-square test. Regression model was used to calculate relative risk of complications with hypertensive retinopathy. P $\leq$0.05 was taken as significant.

Results: A total of 118 patients with a mean age of 54.83 ±8.6 years were included in the study. Of these, 49.2% (n=58) were males. Moreover, 38.1% (n=45) of patients were grouped under no HR, 22.8% (n=27) under mild HR, 21.1% (n=25) and 17.7% (n=21) under moderate and severe HR, respectively. Primary endpoints achieved were 0% in no HR group and 19% in severe HR group (χ^2 = 18.1, p <0.001). Secondary endpoints were achieved in 2.2% in no HR group and 40.7%, 56% and 100% in mild, moderate and severe HR group, respectively, (χ^2 = 81.1, p <0.001). HR also increased the relative risk of complications by 3.17 times (p <0.001) and death by 1.75 times (p <0.001).

Conclusion: Hypertensive retinopathy is an independent risk factor for post-acute STEMI complications in successfully thrombolysed patients and increased the relative risk for complications by 3.17 times.

Key Words: *Hypertensive retinopathy (HR), ST elevation myocardial infarction (STEMI), Left ventricular failure (LVF), Cardiogenic shock (CS), Heart block (HB), Ventricular septal rupture (VSR).*

INTRODUCTION

Hypertension has emerged as a major health problem in recent years worldwide.[1,2] It is a top ranked cause of morbidity and mortality in developing countries with a projected prevalence to reach 30% of entire population by 2025.[3] Sub-optimal blood pressure control results in a number of cardiovascular, cerebrovascular, renal, and retinal complications, often referred to as target organ damage.[1] Elevated blood pressure opens a cascade of pathophysiological changes in retinal vasculature.[4] These changes then manifest as hypertensive retinopathy (HR). Signs of HR can be grouped into vascular changes including focal segmental arteriolar narrowing, diffuse arteriolar narrowing, artetiovenous (AV) nipping and opacification; and advanced changes including micro aneurysms, dot and blot hemorrhages, cotton wool spots, hard and soft exudates, and papilloedema. These signs can even be easily seen among persons without known history of hypertension.[5]

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Microvascular subclinical damage in the form of retinopathy, or microalbuminuria with glomerular dysfunction precedes the major adverse complications like cerebrovascular accidents, myocardial infarction etc.[6,7] HR has been advocated as a predictor of mortality and morbidity since long.[8] Even the international guidelines of JNC and British Hypertension Society recommend the routine screening for signs of HR to risk stratify the patients.[8] Data from recent studies demonstrate a 3-14% prevalence of signs of HR among patients above 40 years of age.[9] Wisconsin *et al*. showed the 5-year incidence of HR in a range of 6-16%.[10]

This study was aimed to determine the association between HR and post STEMI complication rates among successfully thrombolysed patients to predict high risk patients requiring aggressive interventions.

METHODOLOGY

This prospective cohort study was conducted in Cardiology Unit, Lady Reading Hospital (LRH), Peshawar, from June 2016 to December 2017, after approval from the Hospital Ethical Review Board. All patients admitted to Cardiology Unit with acute STEMI and positive highly sensitive-Troponin T, who were successfully thrombolysed and had history of hypertension for at least five years, were included in the study. After taking written informed

consent detailed history was taken and records reviewed followed by physical examination to fulfill the exclusion criteria. Patients with a history of previous STEMI, percutaneous intervention or coronary artery bypass graft surgery, congenital heart disease, cardiac failure, cardiomyopathy, chronic liver or kidney disease, malignancy, diabetic retinopathy, cataracts, retinitis pigmentosa, pan retinitis, maculopathies, conjunctivitis, and other conjunctival diseases like pterygium and history of retinal photocoagulation were excluded from the study.

Patients were enrolled in this cohort study from June 2016 to December 2017 on the basis of successful thrombolysis after acute STEMI. These patients were observed for one month after inclusion in the cohort for primary endpoints, *i.e.* a composite of re-myocardial infarction, stroke, death and re-hospitalisation secondary to cardiogenic shock (CS), left ventricular failure (LVF), heart block, arrhythmia and ventricular septal rupture (VSR) or any of the above complications alone. Secondary endpoints were defined as a composite of the above complications or alone, occurring after one month till four months.

Data regarding baseline variables including age, gender, comorbid conditions, type of MI, systolic blood pressure (SBP), diastolic blood pressure (DBP), highly sensitive-Troponin T, lipid profile at the time of admission, and medicines used for hypertension, were recorded. Fundoscopy was performed by two residents of cardiology for all the included patients under the supervision of a consultant ophthalmologist. The patients were categorised into 4 groups: no HR, mild HR (mild focal narrowing of vessels), moderate HR (diffuse narrowing of vessels with AV nipping, cotton wool spots and hemorrhages), and severe HR (papilloedema), on the basis of classification proposed by Keith *et al*.[11] Successful thrombolysis was defined as at least 50% resolution of ST elevations in ECG at 90 minutes of initiating the streptokinase infusion. Patients were followed on monthly basis for four months in outpatient department with review of records and a thorough examination followed by appropriate investigations, if needed, including ECG, echocardiography, chest X-ray, and CT brain to look for any complications.

Data regarding re-hospitalisation was obtained by interview and reviewing records. All the above mentioned information were recorded in a pre-designed proforma. All data were analysed with SPSS version 20.0. Mean ±SD was calculated for continuous variables. Frequencies and percentages were calculated for categorical variables. Association between hyper-tensive retinopathy and different complications was calculated by using Chi-Square test. Relative risk was calculated by using regression model. Kaplan-Meier survival curve was drawn for overall incidence of complications over four months and for death. A p-value of $\leq$0.05 was taken as significant.

RESULTS

A total of 118 patients were recruited in the study with mean age of 54.83 ±8.6 years, of which 49.2% (n=58) were males. The mean duration of hypertension was 8.2 ±2.7 years. Mean SBP and DBP were 132.7 ±36.2 and 90.1 ±18.7 mmHg, respectively. Fifty-eight (49.2%) patients were on calcium channel blockers, 33.1% (n=39) on angiotensin converting enzyme inhibitors/ angiotensin receptor blockers, 9.3% (n=11) on beta blockers, and 8.4% (n=10) were using a combination therapy for BP control. Baseline characteristics of the included patients are given in Table I.

Primary composite endpoints at one month were achieved in 3.7% (n=1) of patients in mild HR group, 8% (n=2) of patients in moderate HR group, and 19% (n=4)

Table I: Baseline characteristics.

Variables	Mean ± SD / Freq: (%)	Variables	Mean ± SD / Freq: (%)
Age	54.83 ±8.6	STEMI category	
Male	58 (49.2%)	Anterior MI	19 (16.1%)
Female	60 (50.8%)	Anterolateral MI	36 (30.5%)
Duration of hypertension	8.2 ±2.7 years	Anterior + Inferior MI	3 (2.5%)
Diabetes mellitus	49 (41.5%)	Inferior MI	13 (11%)
Smoking	46 (39%)	Lateral MI	12 (10.2%)
Family history of CAD	39 (33.1%)	Inferoposterior MI	12 (10.2%)
Family history of hypertension	40 (33.1%)	avR↑+ Widespread ST↓	10 (8.5%)
Calcium channel blockers	58 (49.2%)	Posterior MI	3 (2.5%)
ACEIs / ARBs	39 (33.1%)	Inferior ± RV MI	10 (8.5%)
Beta blockers	11 (9.3%)	TGs	185.58 ±54.8 (mg/dl)
Combination	10 (8.4%)	LDL	123.6 ±28.8 (mg/dl)
Systolic BP	132.7 ±36.2	HDL	40.3 ±4.5 (mg/dl)
Diastolic BP	90.1 ±18.7	Cholesterol	199.1 ±25.0 (mg/dl)
Fractional shortening	26.7 ±2.3		
LV ejection fraction	53.7 ±5.1		

Table II: Association of hypertensive retinopathy with complications.

Variable	No HR	Mild HR	Mod HR	Severe HR	X^2 value	p-value
No. of patients	45 (38.1%)	27 (22.8%)	25 (21.1%)	21 (17.7%)		
Primary endpoints	0 (0%)	1 (3.7%)	2 (8%)	4 (19%)	18.1	0.001
Left ventricle failure	1 (2.2%)	9 (33.3%)	18 (72%)	18 (85.7%)	56.6	<0.001
Cardiogenic shock	0	3 (11.1%)	4 (16%)	8 (38%)	15.8	0.001
Arrhythmia	0	3 (11.1%)	7 (28%)	7 (33.3%)	17.6	0.001
AV block 2nd degree	0	0	1(4%)	0	16.1	0.001
CHB	0	2 (7.4%)	2 (8%)	3 (14.2%)		
Ventricular Septal rupture	0	0	1 (4%)	2 (9.5%)	11.1	0.041
Stroke	0	0	2 (8%)	0	7.5	0.056
Death	0	1 (3.7%)	5 (20%)	11 (52.3%)	35.2	<0.001
Secondary Endpoints	1 (2.2%)	11 (40.7%)	14 (56%)	21 (100%)	81.1	<0.001

of patients in severe HR group. No adverse event was observed in no HR group.

Secondary endpoints at four months were achieved in 2.2% (n=1) of patients in no HR group, 40.7% (n=11) in mild HR group, 56% (n=14) in moderate HR group, and 100% (n=21) in severe HR group. The details are given in Table II.

Table III: Relative risk of complications with hypertensive retinopathy.

Complication	RR	Exp (RR)	CI Exp	p-value
Complications overall	3.17	23.81	7.4-75.8	<0.001
Left ventricular failure	1.75	5.78	3.2-10.3	<0.001
Arrhythmia	1.05	2.88	1.63-5.07	<0.001
Cardiogenic shock	0.73	2.09	1.2-3.5	0.007
AV Block	1.36	1.81	0.32-3.87	0.019
Stroke	0.64	1.91	0.51-3.91	0.334
Ventricular septal rupture	1.58	4.87	2.18-7.36	0.086
Death	1.75	5.8	2.57-9.12	<0.001

Table IV: Multivariate analysis for association of hypertensive retinopathy and complication rates post-STEMI.

Variable	X^2 value	p-value
Diabetes mellitus		
Yes	36.7	<0.001
No	43.5	<0.001
Sex		
Male	39.47	<0.001
Female	44.44	<0.001
Smoking		
Yes	44.49	<0.001
No	48.20	<0.001
Family history		
Yes	49.81	<0.001
No	54.66	<0.001

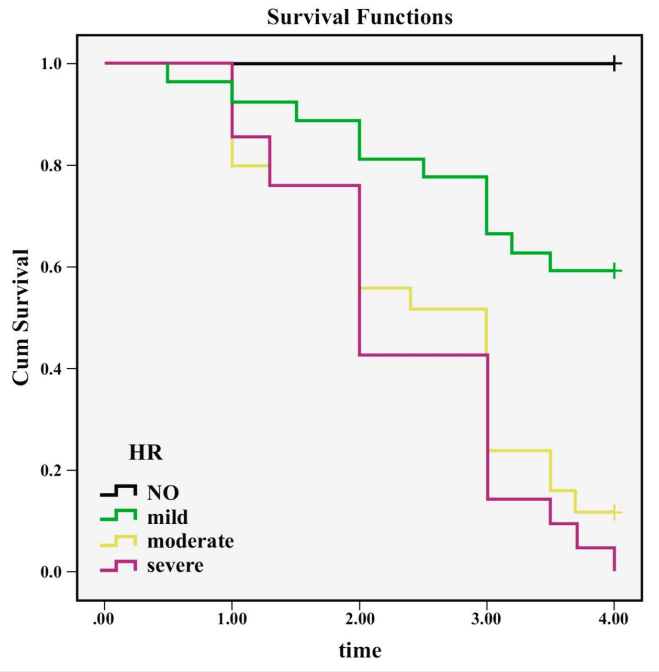

Figure 1: Kaplan-Meier curve for survival against hypertensive retinopathy and complications.

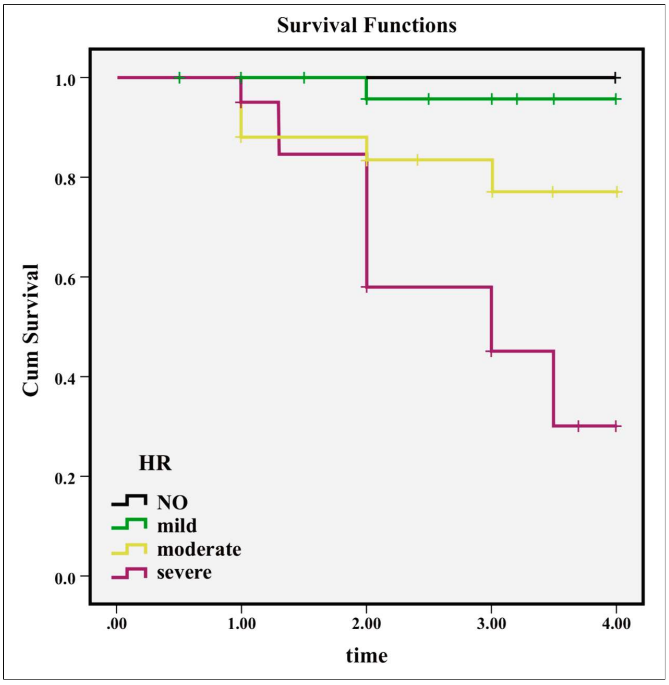

Figure 2: Kaplan-Meier curve for survival against hypertensive retinopathy and death.

The relative risk for overall complications and individual components of primary and secondary endpoints were calculated with severe HR by using regression model. The relative risk for complications increased by 3.17 times {CI-Exp: (RR) 7.4-75.8} with p <0.001 with severe HR. The calculated relative risk for various other complications are shown in Table III. Multivariate analysis for association between HR and post STEMI complication rates in successfully thrombolysed patients with multiple comorbid conditions is shown in Table IV. It showed that HR was associated with post STEMI complication rates (p<0.001) independent of gender, diabetes and smoking, and family history.

Kaplan-Meier curve was plotted for survival of patients with HR for death as well as for complications. Death and complications increased while the survival decreased with the increase in stage of HR (Figures 1 and 2).

DISCUSSION

Hypertension has become the leading risk factor for cardiovascular disease worldwide.[12] Despite the rising trend towards hypertension awareness ranging from 72% in US to 62% in Australia, the BP control rates remained discouraging at 35% and 24%, respectively. In South Asian countries like China and India, the reported control rates were 8% and 6%, respectively.[2] Control rates vary according to geographic region.[13,14] National Health Survey of Pakistan reported an overall 18% of adults and 33% of adults above 45 years of age are hypertensive. It also stated that only 50% of hypertensive individuals were diagnosed and only half of those hypertensive individuals were on treatment.[14]

Previous studies have demonstrated the relationship between HR and cardiovascular disease.[7,15,16] Retinal artery thickening had been associated with fibrous nodules formation and fibrinous degeneration in cerebral vessels.[17] Association between retinal arteriolar-venular ratio and carotid intimal thickness had also been established in a study.[18] Duncan *et al*. reported a two-fold increase in cardiovascular disease with HR.[19] Wong *et al*. in his case control study reported 1.8 times increased odds of coronary artery disease with HR.[20] Atherosclerosis risk in communities (ARIC) documented 2.6 times increased risk of stroke with HR.[21]

The present study is unique in a sense that the association between HR and post-STEMI complications in successfully thrombolysed patients is documented. So far, the studies available were regarding new incidence of cardio-vascular disease and its relationship with HR or association of HR with angiographic severity of coronary artery disease. The present results were quite promising and demonstrated a very strong association between HR and post STEMI complications in successfully thrombolysed patients. Moreover, the incidence of post STEMI complications progressively increased from no HR to severe HR group. The overall death rate also increased while moving from no to severe HR. Relative risk of various complications with severe HR demonstrated that the relative risk of composite endpoints increased by 3.17 times {CI of Exp(RR) 7.4-75.8} with severe HR. Relative risk of death also increased by 1.75 times {CI of Exp(RR) 2.57-9.12 ($p \leq 0.001$)} with severe HR. Multi-factorial analysis also proved an independent association between HR and post STEMI complications in this cohort study. Kaplan-Meier curve plotted for this study results showed an overall decreased survival with increasing grades of HR.

The strengths of the study were its prospective cohort design, appropriate follow-up, and adequate sample size. However, the main limitation of this study was that fundoscopy was performed with a hand-held ophthalmoscope, which is not the gold standard.

So far, limited data was available regarding reversal of HR changes. However, studies are needed to be done to see whether reversal of HR reduces the risk of coronary artery disease and complications after acute coronary events or not.

CONCLUSION

HR was an independent risk factor for complications after successful thrombolysis of acute STEMI. HR also increased the relative risk of primary and secondary endpoints. Patients with acute STEMI should be routinely screened for HR to identify high risk individuals for early aggressive interventional management.

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