

## Review Article

# Hypertensive target organ damage and its relationship with platelet indices

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## ABSTRACT

Hypertension affects vascular endothelium of retina, kidney, and heart. These are called as target organ damage (TOD). Hypertension causes endothelial damage by shear mechanical stress which leads to platelet aggregation and activation. This article is a review for prediction of TOD in hypertensives by cost effective routine indicators like platelet indices [platelet distribution width (PDW), mean platelet volume (MPV) and platelet count]. Hypertension mediated target organ damage like left ventricular hypertrophy, hypertensive retinopathy and nephropathy is associated with increased platelet indices like MPV, PDW, and PLT. The use of these cost-effective platelet indicators in newly diagnosed hypertensives may need further studies to have clinical implications.

**Keywords:** Hypertension, Organ damage, Platelet indices

## INTRODUCTION

Hypertension is one of the most common modifiable risk factors for cardiovascular events.<sup>1</sup> Hypertension being asymptomatic especially during initial days, increases the risk of target organ damage (TOD) like renal failure, retinal damage and myocardial infarction.<sup>2</sup>

Exposure of circulating platelets to the mechanical shear forces in the hypertensives results in specific cellular interactions that are responsible for the increased platelet activation which are reflected in platelet indices like mean platelet volume (MPV), platelet distribution width (PDW) and platelet count (PLT).<sup>3</sup>

An electronic internet search was used to select the English literature from 2000 to until 2020 using databases like PubMed, Google Scholar and ProQuest with hypertension, target organ damage and platelet indices as keywords. Totally 31 papers were selected excluding studies done on children and pregnant participants.

## DEFINITION OF HYPERTENSION

(a) The 2020 European guidelines define hypertension as office blood pressure  $\geq 140$  mmHg and diastolic  $\geq 90$  mmHg.<sup>4</sup> The diagnosis should not be made on a single office visit. Usually, 2-3 office visits are required to confirm the diagnosis. If the blood pressure is  $\geq 180/110$  mmHg, and if there is evidence of cardiovascular disease, hypertension can be diagnosed in a single visit.<sup>1</sup> (b) The 2019 American guidelines lower the threshold for hypertension based on a large meta-analysis SPRINT trial with systolic blood pressure  $\geq 130$  mmHg and diastolic BP  $\geq 80$  mmHg to define hypertension.<sup>5</sup>

## TARGET ORGAN DAMAGE AND PLATELET INDICES

Hypertension mediated TOD is defined as a structural or functional alteration in arterial vasculature and the organ it supply.<sup>1</sup> The most commonly involved target organs include the heart, kidney, retina, central and peripheral

arteries.<sup>1</sup> Assessment of cardiovascular (CV) risk plays an important role in the management of hypertension; TOD will provide important therapeutic guidance on the management of hypertensive patients with low or moderate CV risk. It will also help in the preferential selection of drug treatment based on the specific impact on TOD.<sup>1</sup> The effect of high blood pressure on the vital organs may be mediated by activation of the coagulation system via endothelial injury, and this might have effects on platelets.

Platelet activation plays a critical role in the pathophysiology of thrombotic events and hypertension-related target organ damages.<sup>6</sup> In order to assess cardiovascular risk and to clarify the pathogenesis of atherothrombosis, some biochemical markers are used. One of them is the platelet indices (MPV, PDW and PLT), a potential marker of platelet activity.<sup>7</sup> The effect of an over-activated sympathetic nervous system on the hemostatic system occurs in two ways; first, the platelet activation via alpha two adrenoreceptors stimulation, which causes a change in shape, thereby increases MPV. Second, larger the activated platelets, which are sequestered in the spleen, can be released into the circulatory system following the elevated levels of adrenaline that contribute to increased PDW; this might be the first mechanism for increased levels of MPV.<sup>7</sup> PLT appear to be independently associated with TOD in patients with HTN. High PDW values may indicate higher production of larger reticulated platelets. Thus, changes in platelets reflected by PDW and platelet count may reveal hypertension status and predict thrombotic risk and TOD.<sup>7</sup>

#### ***Hypertensive heart disease and platelet indices***

Hypertensive heart disease is usually asymptomatic and manifests clinically only in advance stages as angina pectoris, systolic and diastolic heart failure, and arrhythmias.<sup>8</sup> These patients have increase in left ventricular mass. Symptoms in hypertensive heart disease are due to structural and functional changes in the left ventricle, left atrium, and coronary arteries secondary to chronically elevated blood pressure.<sup>2</sup> Chronically elevated blood pressure will cause endothelial dysfunction, which predisposes the patients to develop coronary artery diseases and peripheral arterial disease and places the patient at higher risk for atherosclerotic disease.<sup>3</sup>

Active platelets contain greater MPV, PDW values and platelet count, and the coagulation of active platelets or local thrombosis would further increase the abnormality of PDW and platelet count.<sup>9</sup> Platelet indices, especially MPV, have prognostic indications with cardiovascular settings; their prognostic value is mainly linked to oxidative stress and inflammation. Large platelets are more active metabolically and enzymatically as they contain more dense granules, and they have increased thrombotic potential compared with small platelets.<sup>9</sup> Increasing platelet indices are associated with left ventricular hypertrophy as activated platelets dissipate fatty acids and activation of RAAS, causing cardiomyocyte growth and

interstitial fibrosis, which are hallmarks of LVH in hypertensive individuals.<sup>10</sup>

#### ***Hypertensive mediated kidney disease and platelet indices***

Hypertension-mediated kidney damage expresses the diffuse involvement of renal blood vessels. The HOT study showed even a mild increase in serum creatine (1.5 mg/dl) would increase the risk of cardiovascular death by three times.<sup>11</sup> The most common clinical presentation of hypertensive kidney disease is an asymptomatic rise in serum creatinine, which denote renal parenchymal damage.<sup>12</sup> Albuminuria has been regarded as a sign of hypertensive renal damage.<sup>13</sup>

A mild increase in urine albumin excretion is called microalbuminuria. It is a powerful predictor of cardiovascular mortality and is an early predictor of endothelial dysfunction in hypertensive patients.<sup>14</sup> Increased platelet indices (MPV, PDW, PCT) which leads to increased production of thromboxane which causes smooth muscle activation and proliferation which predisposes to development of microalbuminuria.<sup>10</sup> The ASCOT trial demonstrated that hypertensive patients with target organ damage, including stroke, previous MI, angina, microalbuminuria and left ventricular hypertrophy, had higher MPV levels than hypertensive patients without TOD.<sup>10</sup> Guagnano et al and Ferroni et al found a positive linear association between platelet activation and presence of microalbuminuria in their study this is attributed to high blood pressure and the endothelial dysfunction, which causes activation of platelets this will manifest as increased MPV and PDW.<sup>15</sup> Endothelial dysfunction in hypertensives with microalbuminuria are reflected by decreased levels of NO and increased plasma levels of ICAM-1 in the patients with microalbuminuria.<sup>15</sup> Cause of microalbuminuria can be traced to structural and functional transformational process in the glomeruli (endothelium, glomerular basal membrane, podocytes) that are associated with increased permeability. Interestingly, this permeability disorder is not limited to the renal vessels but can be observed in the entire vascular system. Microalbuminuria is the renal manifestation of generalized endothelial dysfunction.<sup>16</sup>

#### ***Hypertensive retinopathy and platelet indices***

Hypertension affects the eye causes choroidopathy, retinopathy and optic neuropathy.<sup>17</sup> Retinal blood vessels have characteristic features such as absence of sympathetic nerve supply and presence of blood-retinal barrier.<sup>17</sup> Coban et al found a positive relation between MPV and hypertensive retinopathy in correlation analysis. The activated platelets can aggravate the process of hypertension mediated retinal damage causing higher grades of hypertensive retinopathy.<sup>18</sup> Hypertension by means of endothelial dysfunction causes platelet activation. The activated platelets can aggravate the process of hypertension mediated retinal damage causing higher grades of hypertensive retinopathy.<sup>18</sup>

**Table 1: Comparison of variables between groups A and B.**

Variables	Group A	Group B	Significance
Platelet- PDW	14.98±0.75	15.88±0.95	<0.001
Platelet- MPV (fL)	8.44±0.23	9.19±0.47	<0.001
Platelet- Count	3.58±0.16	3.83±0.17	<0.001
LV hypertrophy- ECG platelet- PDW	16.45±0.42	15.07±0.85	<0.001
LV hypertrophy- ECG platelet- MPV (fL)	9.49±0.34	8.62±0.34	<0.001
LV hypertrophy- ECG platelet- count	3.93±0.09	3.64±0.17	<0.001
LV hypertrophy- ECHO platelet- PDW	16.01±0.83	15.01±0.87	<0.001
LV hypertrophy- ECHO platelet- MPV (fL)	9.26±0.44	8.52±0.33	<0.001
LV hypertrophy- ECHO platelet- count	3.85±0.16	3.60±0.15	<0.001
Microalbuminuria platelet- PDW	16.09±0.77	15.16±0.94	<0.001
Microalbuminuria platelet- MPV (fL)	9.33±0.44	8.62±0.38	<0.001
Microalbuminuria platelet- count	3.86±0.14	3.66±0.20	<0.001
Retinopathy (KW)- left platelet- PDW	16.18±0.73	15.00±0.76	<0.001
Retinopathy (KW)- left platelet- MPV (fL)	9.37±0.45	8.47±0.24	<0.001
Retinopathy (KW)- left platelet- count	3.87±0.14	3.58±0.15	<0.001
Retinopathy (KW)- right platelet- PDW	16.18±0.73	15.00±0.76	<0.001
Retinopathy (KW)- right platelet- MPV (fL)	9.37±0.45	8.47±0.24	<0.001
Retinopathy (KW)- right platelet- count	3.87±0.14	3.58±0.15	<0.001

Note: Group A- patients without TOD; and Group B- patients with TOD.

## CONCLUSION

Hypertension mediated target organ damage like left ventricular hypertrophy, hypertensive retinopathy and nephropathy is associated with increased platelet indices like MPV, PDW, and PLT. The use of these cost-effective platelet indicators in newly diagnosed hypertensives may need further studies to have clinical implications.

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