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MINIREVIEWS

Clinical implication of hematological indices in the essential hypertension

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Abstract

Prognostic value of haematological indices, especially red cell distribution width, neutrophil lymphocyte ratio and mean platelet volume, was reported with numerous investigations in miscellaneous cardiovascular settings. Their major prognostic value was linked to oxidative stress and inflammation since their level was correlated with major inflammatory markers such as high sensitive C-reactive protein and interleukins. Oxidative stress and chronic inflammation are also postulated as the main pathophysiologic mechanism of essential hypertension (HT) and its vascular complication. Recently, correlation between HT and haematological parameters was searched in numerous studies, which has made the topic more popular. Herein, we reveal the correlation between haematological indices and HT and we also demonstrate the clinical implication of this correlation. Impaired haematological parameters may strongly indicate hypertensive end-organ damage.

Key words: Hypertension; Inflammation; End-organ damage; Haematological indice; Platelet activation

Core tip: We demonstrated the correlation between haematological indices, particularly red cell distribution width, neutrophil lymphocyte ratio and mean platelet volume, and hypertension and we also clarified the clinical implication of the haematological markers in hypertensive end-organ failure. Impaired haematological parameters may strongly indicate the hypertensive end-organ damage.

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INTRODUCTİON

Systemic arterial hypertension (HT) is a common health disorder with uncertain aetiology and pathophysiology.

It affects 20%-30% of the adult population and it can lead to severe end-organ damage and clinical manifestation, including coronary heart disease and stroke, which constitute the leading cause of mortality in the general population[1]. Beside genetic predisposition, several mechanisms were proposed to clarify the pathophysiology of essential HT[1-3]. Vascular reactivity and endothelial dysfunction, which result in increased peripheral vascular resistance, is one of the major hypotheses in the pathogenesis. Recently, it has become evident that the immune system and chronic inflammatory status may play a role in the pathogenesis of HT[2-5]. Many inflammatory markers, such as high sensitive c-reactive protein (hsCRP), cytokines, and adhesion molecules have been found elevated in HT, supporting the role of inflammation[2-6].

Haematological indices, particularly red cell distribution width (RDW), neutrophil lymphocyte ratio (NLR) and mean platelet volume (MPV), were established as markers of systemic inflammation and vascular pathology[7-15]. Their prognostic value was clearly demonstrated in coronary artery disease, stroke and several other vascular diseases. Correlation of such haematological indices and HT was also investigated and it was proposed that haematological indices may predict the severity of HT and end-organ damage[16-22]. With this review, we aimed to show the place of haematological indices in the essential HT and demonstrate its clinical implication.

MECHANISM OF ESSENTIAL HT

The aetiology of essential HT is not clear, however, it has been accepted as a multifactorial disease arising from the combined action of many genetic, environmental and behavioural factors. Renal sodium retention, vascular hypertrophy, endothelial cell dysfunction, sympathetic nervous system hyperactivity, upregulation of the renin-angiotensin-aldosterone system, altered T-cell function, insulin resistance and dietary and habitual factors were postulated as common mechanisms of HT[1-5]. However, oxidative stress and inflammation seem to play a major role in the pathophysiology of HT and also concomitant end-organ damage[4-6]. Excessive reactive oxygen species generation decreases nitric oxide level, which predisposes to endothelial cell dysfunction. Enhanced oxidative stress reduces antioxidant capacity in the cardiovascular, renal and nervous systems. In the cardiovascular system, reactive oxygen radicals play a pathophysiological role in inflammation, hypertrophy, proliferation, apoptosis, migration, fibrosis, angiogenesis and rarefaction, which are important processes contributing to endothelial dysfunction and cardiovascular remodelling in HT[4-6]. Recently, the synergy of haematological indices and HT was searched in many HT-associated clinical conditions after clear demonstration of the correlation between haematological indices and endothelial cell dysfunction[16-22]. Non-dipper HT had carried about three times the risk of atherosclerotic cardiovascular events compared to the dipper group. The majority of the investigations focused on this specific non-dipping group, since atherotrombosis and inflammation was more prominent in this group[23-29].

RED BLOOD CELL INDICES

Red cell distribution width

Red cell distribution width is a measure of the variability in the circulating erythrocytes' size, which is usually used for haematological disorders. It can be obtained easily from a routine complete blood count in a short period. Although the initial application of RDW was the differential diagnosis of anaemia, recent investigation revealed that RDW is also an important prognostic factor in cardiovascular diseases[7-8]. It was proposed that there is a linkage between RDW and inflammatory and neurohormonal activation and also accelerated atherosclerotic process which may enhance the impact of RDW in the was cardiovascular diseases. Several mechanisms were proposed to explain the exact role of RDW in the clinical setting[7-8]. Inflammatory and neurohormonal activation could be one of the mechanistic links between elevated RDW and increased mortality. The correlation between elevated RDW and inflammatory markers such as B-type natriuretic peptide, sedimentation and white blood cells was established. Higher RDW may result from ineffective erythropoiesis due to chronic inflammation. Inflammatory cytokines have been found to suppress the maturation of erythrocytes, which enable juvenile red cells to enter into the circulation and increases the heterogeneity in size[30-31]. Moreover, elevated RDW may reflect enhanced erythropoiesis resulting from the circulating levels of neurohormonal mediators, which lead to an increment in the heterogeneity of circulating red cells. Elevated RDW levels were also associated with carotis intima-media thickness, which reflects atherosclerotic process[32]. Finally, all these mechanisms, including chronic inflammatory state, neurohormonal activation and accelerated atherosclerotic process, may contribute to adverse clinical outcomes and bad prognosis in the variety of cardiovascular diseases. Oxidative stress was proposed as another mechanism of the prognostic value of RDW. Red blood cells have powerful antioxidant capacity and serve as a primary oxidative sink. They are prone to oxidative damage, which reduces cell survival, and enhance the release of juvenile erythrocytes into the circulation. Elevated RDW levels were associated with poorer pulmonary function and progression of pulmonary HT, which reflect oxidative stress conditions[7].

The correlation between RDW and HT was also well established. Higher RDW values are strongly correlated with higher systolic and diastolic blood pressure[19-21]. Elevated levels of RDW were also documented in non-dipping HT, which are closely related to adverse

cardiovascular outcomes and higher inflammatory status[21,23]. Elevated levels of RDW were linked to hypertensive end-organ damage. Kilicaslan *et al*[16] showed that an elevated RDW level was associated with concentric left ventricular hypertrophy. It was speculated that the development of target organ damage in HT is accompanied by the increasing impairment of erytropoiesis by the mechanism of inflammation[23]. In patients with HT, RDW levels showed a significant relationship with inflammatory markers such as hsCRP, interleukin-6 and fibrinogen[16,18,33]. Elevated RDW was also correlated with pulse wave velocity and carotid intima media thickness[32]. In the HT group, RDW levels and glomerular filtration rate seemed to be linked[30]. Erythrocyte deformability may serve as a marker of endothelial dysfunction in the kidney, which may trigger nephropathy.

Hematocrit

Haematocrit is a determinant of whole blood viscosity. Viscosity affects peripheral resistance to blood flow, and peripheral resistance affects blood pressure[34]. Most hypertensive patients exhibit increased blood viscosity compared with healthy controls[35]. Although, the details of this association is unclear, reduction of the red cell deformability and an increase in the size, numbers and aggregability of red blood cells may worsen the microcirculation and enhance the end-organ damage. Therefore, the diameter of a red cell is about 8.5 micron, and that of the smallest capillaries about 3 micron, the deformability of the red cells plays an important role in capillary flow[36]. Decreased red cell deformability could cause an increased microvascular flow resistance, which may result in target organ damage. Haematocrit in upper quartiles may indicate end-organ damage in HT.

Mean corpuscular volume

Epidemiological studies show no relation with higher mean corpuscular volume (MCV) in hypertensive, whereas, some studies suggest that hypertensive patients have lower MCV. Decreased MCV levels may reflect higher blood viscosity, since a high red cell level may lead to down-regulation of MCV as an adaptive mechanism[34].

WHITE BLOOD CELL INDICES

White blood cells play a major role in both the initiation and progression of atherosclerosis and have been implicated in acute rupture of atherosclerotic plaques[37]. In addition, neutrophils aggregate with platelets to exacerbate vascular plugging in the microcirculation. Neutrophils also prompt the secretion of inflammatory mediators[38].

Neutrophil-lymphocyte ratio

The neutrophil-lymphocyte ratio is associated with a worse outcome in various diseases and is defined as an emerging potent marker of inflammation[38]. It was reported that NLR is an independent factor of mortality and major adverse cardiac events in acute and chronic ischaemic heart diseases[13]. The NLR was also found to be significantly higher in non-dipping HT[27,28]. Increased NRL may indicate hypertensive end-organ damage. The neutrophil-lymphocyte ratio is not static, and varies with the of critical illness. Thus, NLR may give prognostic clues about the activity of disease and response to therapy. In addition, the protective effect of some anti-hypertensive drugs correlated with NLR decrement, which suggests the role of NLR in the severity of HT[39,40].

White blood cell count

White blood cell (WBC) count constitutes an inflammatory marker and it tends to increase in HT. The WBC count was higher in non-dipping HT and WBC counts in the highest quartile may reflect enhanced inflammatory response and end-organ damage[41]. Hypertensive men with a high Framingham 10-year cardiovascular risk score showed higher levels of WBC[42].

PLATELET INDICES

Mean platelet volume

Mean platelet volume has known to be an indicator of platelet activation and, its correlation with cardiovascular disease is well established[9,11-12]. Platelets play a pivotal role in the development of atherosclerotic lesions, plaque destabilization, and atherothrombosis. It has been clearly demonstrated that MPV is an unfavourable prognostic factor in ischaemic coronary heart disease[11,12]. A few studies have also proposed that MPV may predict microvascular injury in coronary vessels and diabetic microvascular complications, including nephropathy and hypertensive microvascular end-organ damage[17,43-45]. Gunebakmaz *et al*[17] reported that higher MPV quartile values were more common in left ventricular concentric hypertrophy compared to normal cases. High MPV levels were also linked to non-dipping HT[24-26]. Platelet activation and inflammatory response is the probable mechanism of MPV prognostic value. Hence, an increased MPV value usually accompanies high hsCRP value. Mean platelet volume levels were associated with severity of end end-organ damage, including carotid atherosclerosis, left ventricular hypertrophy and renal damage[43-45]. There is a stepwise increase between MPV and the severity of hypertensive disease. Mean platelet volume was also found higher in ophthalmologic complications[46]. Moreover, its level was increased in masked HT[47].

Platelet distribution width

Platelet distribution width reflects the platelets' reactivity. The platelet distribution width (PDW) is a more specific marker of platelet activation, since it does not increase during simple platelet swelling[10]. Spencer *et al*[48] reported that there is a strong correlation between PDW and the severity of hypertensive disease.

P-selectin (CD62P)

P-selectin also shows platelet activation. It is a direct mediator of vascular inflammation and injury[49]. Preston *et al*[49] showed that platelet activation and p-selectin may participate in the accelerated target organ injury in high-risk hypertensive patients[50].

Anti-hypertensive therapy results in a reversal of platelet morphology abnormalities and indices of platelet activation. This may contribute to a reduction in thrombosis-related complications seen in those whose blood pressure lowering is effective[51].

CONCLUSION

Haematological indices, predominantly RDW, NLR and MPV, reflect oxidative stress and inflammatory state, which also postulate as major mechanisms of HT and its vascular complication. There is a stepwise relation between the severity of HT, hypertensive end-organ damage and haematological indices. However, it is still not clear whether these parameters are responsible in the pathogenesis of HT or they increase as a result of the progression of hypertensive disease. There is a need of further investigations to clarify definitive pathophysiologic mechanism of HT regarding the role of hematological indices. Nevertheless, there is a clear consensus that these haematological parameters have a prognostic value in the essential HT and their abnormality may strongly suggest hypertensive end-organ damage.

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