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Pathogenesis of hematological parameters in hypertension

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Abstract

Hypertension is a significant risk factor for cardiovascular disease and is often assessed in clinical settings using reference ranges for various hematological and immunological parameters. This review article specifically focuses on red blood cells, hematocrit, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, neutrophil-to--lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio in hypertension. It also highlights the pathophysiological aspects of hematological parameters in the pathogenesis of hypertension.

Key words: hematological parameters, hypertension, pathogenesis, red blood cells, white blood cells, platelets

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Introduction

Hypertension poses a significant danger for cardiovascular disorders. If left untreated, it can lead to severe consequences such as sudden cardiac death, atherosclerosis, heart failure, brain hemorrhagic stroke, and renal failure. The occurrence of hypertension is on the increase in both developed and developing countries. The implementation of new guidelines is expected to result in a substantial increase in the number of individuals with hypertension [1]. In clinical settings, reference ranges are commonly employed to assess the state of health and disease by analysing hematological and immunological parameters. These reference ranges can also serve as vital indicators for monitoring the progression of a disease or the effectiveness of treatment. It should be noted that these criteria can vary based on factors such as age, gender, race, environment, and genetic background [2, 3].

The study conducted by Göbel et al. [4] revealed statistically significant associations between mean arterial blood pressure and various measurements such as hemoglobin concentration, hematocrit, and red blood cell count. It has been suggested that whole blood viscosity may act as a mediator in the connection between blood pressure and red cell measurements [5]. Also, Emamian et al. [6] reported that the hematological parameters in individuals with hypertension were higher compared to a control group. This review article specifically only focuses on red blood cells (RBC), hematocrit (Hct), platelet count, white blood cells (WBC), lymphocytes, neutrophils, monocytes, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) in hypertension. These parameters and their involvement in hypertension are elaborated in Figure 1. Additionally, Figure 2 illustrates the pathophysiological aspects of hematological parameters in hypertension.

To conduct this literature review, multiple databases such as Google Scholar, PubMed, and Science Direct were searched. The search process was concluded on 10 March, 2023. Various key words, including 'hematological parameters', 'hypertension', 'pathogenesis', 'red blood cells', 'white blood cells', and 'platelets' were employed. It should be

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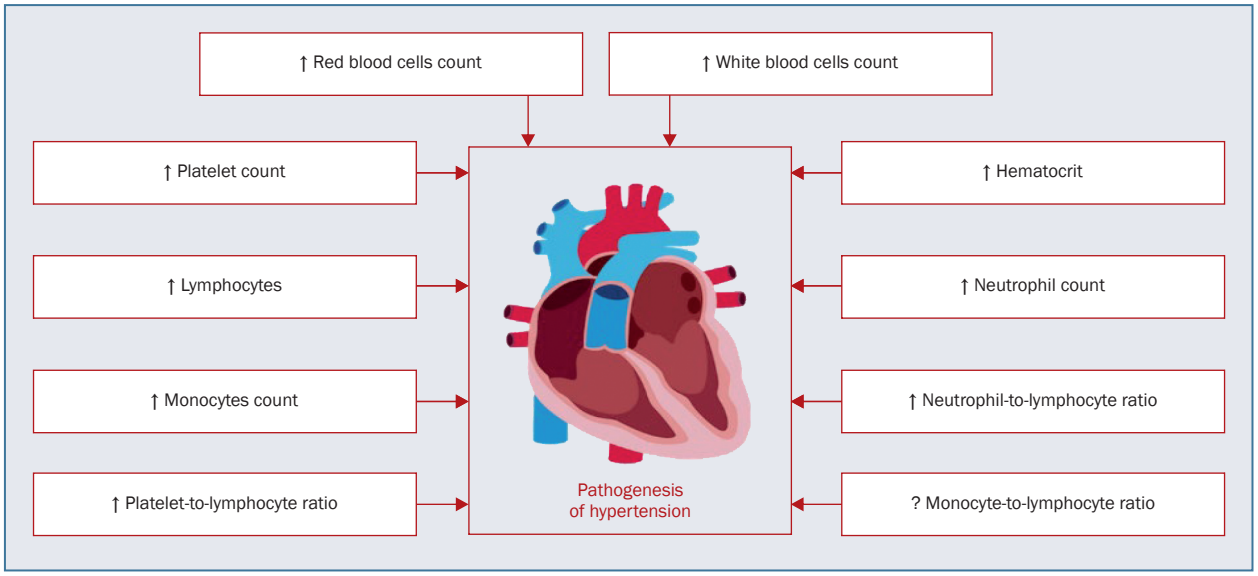

Figure 1. Circulating levels of hematological parameters in hypertensive patients (designed by authors with help of articles); ↑ — increased levels; ? — no study is reported yet on hypertension

noted that the clinical investigations were limited to articles published in English. While the focus was on more recent studies, no specific time limit was set. Furthermore, the reference lists of relevant articles were examined, leading to the discovery of additional related articles for comparison.

Role of major hematological parameters in pathogenesis of hypertension

Red blood cells

Hypertensive men have been shown to exhibit elevated plasma levels of the amino acid asymmetric dimethylarginine (ADMA), which is associated with a reduction in the flexibility of red blood cell membranes [7]. Hypertensive individuals experienced impaired deformability of red blood cells, and this impairment was dependent on their current blood pressure control rather than damage to target organs [8].

The findings from an electron paramagnetic resonance (EPR) study indicated a potentially strong correlation between abnormalities in RBC membranes in hypertension and two factors: hyperresistinemia and heightened oxidative stress. It was observed that reduced fluidity of RBC membranes was associated with elevated levels of plasma resistin and 8-iso-prostaglandin F2, indicating the presence of oxidative stress. Hyperresistinemia was found to be closely linked to abnormal rheological behavior and microcirculation of RBCs, and it appears to contribute to circulatory disorders in hypertensive men, partly through a mechanism dependent on oxidative stress [9].

Hypertension is associated with significant changes in the rheological, mechanical, and biochemical properties of erythrocytes, as well as alterations in blood flow. Several important factors have been observed, including the formation of RBC 'rouleaux' and RBC aggregates, increased blood viscosity, and changes in red blood cell deformability. These hemorheological factors can contribute to the elevation of peripheral resistance and arterial blood pressure, potentially causing or worsening hypertension. Moreover, they might lead to reduced oxygen delivery to tissues, impaired peripheral perfusion, and a decrease in the active exchange surface area in the microvasculature, particularly in complicated cases of hypertension. Studies have shown various abnormalities in hypertensive individuals, such as decreased erythrocyte deformability (measured by Elongation Index), elevated fibrinogen levels, an increased shear rate required to disaggregate erythrocytes, reduced cellular oxygen supply, compromised tissue oxygenation, and impaired microcirculation. These changes could play a role in the pathophysiology and development of arterial hypertension (AH) [10].

When compared to their effects on the aortas of normotensive Wistar-Kyoto (WKY) rats, red blood cells were found to increase tension in isolated aortas of spontaneously hypertensive (SHR) rats during the pre-hypertensive stage. This ability of red blood cells to elevate blood pressure was observed in both WKY and SHR rats at 16 weeks of age. Furthermore, the contraction caused by red blood cells was augmented by removing the endothelium, particularly in SHR rats compared to WKY rats [11].

Hematocrit

To determine hematocrit (HCT), the length of the packed layer of RBCs is divided by the total length of both the cells and plasma. HCT is expressed as a ratio and does not have

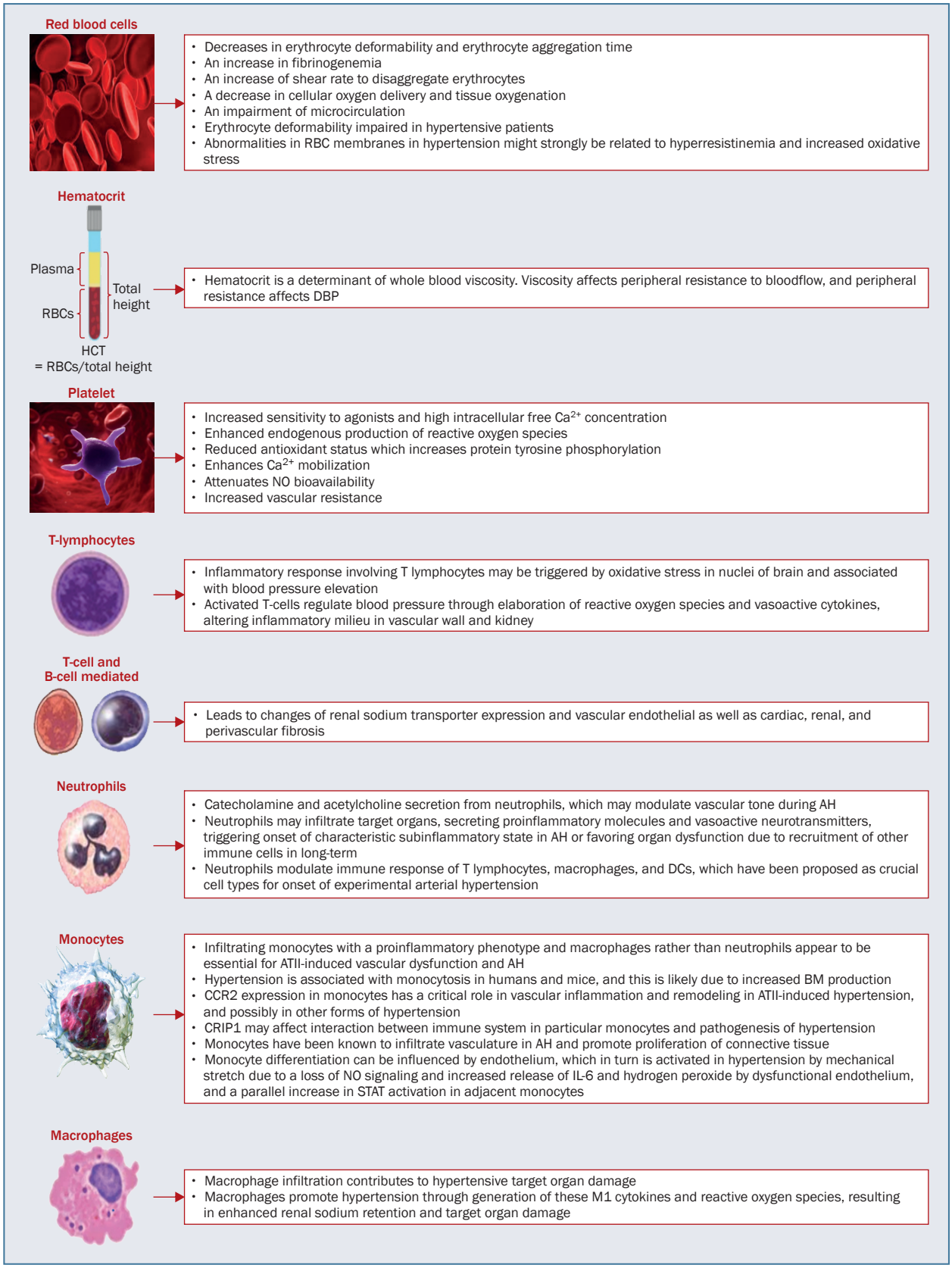

Figure 2. Pathophysiological aspects of hematological parameters in hypertension (designed by authors with help of articles); RBC — red blood cell; HCT — hematocrit; DBP — diastolic blood pressure; Ca — calcium; NO — nitric oxide; AH — arterial hypertension; DCs — dendritic cells; ATII — angiotensin II; CRIP1 — cysteine-rich protein 1; BM — bone marrow; IL-6 — interleukin-6; STAT — signal transducers and activators of transcription

a unit [12]. The significant correlation between blood pressure and hematocrit, a major determinant of blood viscosity, suggests that considerations related to bloodflow characteristics play a role in the long-term regulation of blood pressure [10]. Another study strongly indicated that among these markers, hematocrit independently contributed to the risk of hypertension [6]. Additionally, the exponentiation of multiple logistic coefficients revealed that individuals with hematocrit levels higher by 10 units had a prevalence of hypertension at least twice as high as those with lower levels [13]. Similarly, hemoglobin (Hb) count and HCT were positively correlated with systolic and diastolic blood pressure. In children and adolescents between the ages of 10 and 18, Hb count and HCT showed a positive correlation with both systolic and diastolic blood pressure [14].

Furthermore, Vázquez et al. [15] concluded that acute anemic conditions, although limited, lead to an increase in mean arterial blood pressure during the initial two-hour period. Interestingly, this effect was quantitatively similar to, but opposite to, the acute increase in hematocrit during the same period. In addition, it was discovered that individuals with hypertension who had unilateral renal atrophy due to ischemia were more likely to have a higher hematocrit level compared to those with parenchymal disease caused by pyelonephritis [16].

Platelet count

Platelet activity can play a role in the development of hypertension, as an elevated mean platelet volume (MPV) has been associated with an increased incidence of hypertension, independent of other risk factors [17]. The relationship between homocysteine and blood pressure was found to be stronger in individuals with low platelet counts compared to those with high platelet counts, with platelet counts partially attenuating this relationship [18].

Platelets in individuals with hypertension demonstrate elevated intracellular free calcium (Ca^{2+}) levels and heightened sensitivity to agonists. Furthermore, these platelets show the increased generation of endogenous reactive oxygen species (ROS) and decreased antioxidant capacity, which collectively contribute to enhanced protein tyrosine phosphorylation, augmented mobilization of Ca^{2+}, and reduced availability of nitric oxide (NO). Anomalies in platelet function observed in hypertensive individuals have the potential to guide the development of novel pharmacological strategies for preventing and treating hypertension-related complications associated with platelet hyperactivity [19]. According to Mehta et al., there appears to be a correlation between higher vascular resistance and increased platelet activation in primary hypertension [20].

In cases of prolonged hypertension, there has been shown to be no correlation between MPV levels, the non-dipping pattern of blood pressure (lack of night-time blood pressure decline), and the left ventricular mass index (LVMI) [21]. Compared to the normotensive group, the hypertensive group in a study exhibited a significant increase in both platelet volume and count. Notably, hypertensive individuals who were smokers showed an even greater platelet count compared to non-smokers with normal blood pressure, despite low doses of nicotine not inducing platelet release reaction. This suggests that smoking might contribute to higher platelet counts in hypertensive males [22].

Notably, increased morning blood pressure surge (MBPS) and higher MPV levels have been associated with atherothrombotic cardiovascular events [23]. Similarly, a study conducted by Zhao et al. [24] suggested that certain platelet indices might be utilized for early detection of high blood pressure in adults who have been exposed to prolonged severe platelet index values.

Furthermore, elevated MPV and C-reactive protein (CRP) levels have been implicated as potential reasons for the increased cardiovascular risk observed in individuals with masked hypertension [25]. In a study conducted by Surgit et al. [26], it was observed that patients with resistant hypertension (RHTN) had significantly higher MPV levels compared to controlled hypertensive individuals and normotensive participants. A higher platelet count was causally associated with an increased risk of hypertension. However, further investigations are required to elucidate the underlying biological pathways and pathogenic processes involved [27].

Essential hypertension has been associated with an increased risk of arterial thrombosis. The use of antiplatelet medication has been shown to improve prognosis in hypertensive patients with high cardiovascular risk or established atherosclerotic disease, as platelet activation plays a significant role in the development of thrombotic events. However, the use of antiplatelet therapy in hypertensive patients with modest cardiovascular risk is less certain [28]. Similarly, alpha-blocker or angiotensin-converting enzyme inhibitor (ACEI) monotherapy has been shown to reverse platelet activation observed in patients with essential hypertension. These medications have the potential to prevent platelet activation in individuals with essential hypertension, thereby reducing the occurrence of hypertensive vascular complications [29].

White blood cells

Even after accounting for average 24-hour blood pressure, established risk factors, and target organ damage, a high WBC count remains an independent predictor of cardiovascular morbidity in hypertensive patients [30]. Observational and genetic analysis has revealed a consistent and positive association between lymphocyte count and both systolic and diastolic blood pressure, indicating a potential causal link [31].

In a Japanese population, there was shown a general association between WBC count and the development of

hypertension. Utilizing a high-risk approach based on WBC count may provide enhanced prevention strategies for hypertension in the future [32]. In a predominantly white population, elevated WBC count was found to be associated with the incidence of hypertension in both men and women, regardless of smoking and most traditional cardiovascular risk factors [33]. Correlations between WBC count, neutrophils, and blood pressure readings were only observed in the later stages of hypertension.

Another study was unable to differentiate between individuals with optimal blood pressure (OBP) and high normal blood pressure (HNBP) based on WBC count, suggesting that inflammation may not be a factor in prehypertension. It is also possible that WBC count is not a sufficiently sensitive biomarker [34]. However, the NHANES I Epidemiological Follow-up Study (NHEFS) reported an association between higher WBC count and increased incidence of hypertension in white men, and possibly in older white and black women [35]. In a study conducted by Shi et al. [36], it was found that certain types of circulating leukocytes in hypertensive patients using antihypertensive medications might be linked to left ventricular hypertrophy (LVH).

Lymphocytes

In hypertension, T lymphocytes infiltrate various organs involved in cardiovascular control, including the kidneys and vasculature. Notably, T cell accumulation occurs in the adventitia of the aorta during hypertension. This infiltration of T lymphocytes has been associated with increased collagen deposition, exacerbated stiffness of the aorta, and dysfunction of the endothelium [37]. The contribution of T lymphocytes to hypertension is influenced by their level of activation. Activated T cells produce reactive oxygen species and vasoactive cytokines, which regulate blood pressure by modulating the inflammatory environment in the kidneys and vascular walls. Recent genome-wide association studies (GWAS) have also provided evidence suggesting the involvement of T cells in human hypertension [38].

Additionally, Schiffrin et al. [39] have proposed that oxidative stress in brain nuclei could trigger an inflammatory response involving T cells, ultimately leading to an increase in blood pressure. The initiation of hypertension and the development of target organ damage are both influenced by adaptive immune responses, specifically T-cell and B-cell mediated responses. In the early stages of the disease, activation of adaptive immunity triggers the involvement of both T cells and B cells, leading to the release of pro-inflammatory cytokines and antibodies. These immune-mediated processes contribute significantly to pathological changes. These alterations include modifications in the expression of renal sodium transporters and vascular endothelial cells, as well as the development of cardiac, renal, and perivascular fibrosis. While these pathways have been well studied in animal models, there is still limited information available for humans. Nevertheless, the evidence strongly supports the development of innovative anti-hypertensive strategies that target the processes of adaptive immunity in hypertension [40].

Neutrophils

The current understanding suggests that the involvement of neutrophils in AH is most likely related to vascular injury caused by reactive oxygen species (ROS). However, it is important to consider not only the production of catecholamine and acetylcholine by neutrophils, which can affect vascular tone during AH, but also the adrenergic control of neutrophils. In AH, the presence of neutrophils infiltrating target organs and releasing proinflammatory substances and vasoactive neurotransmitters might contribute to the development of a sub-inflammatory state. This infiltration can lead to prolonged organ dysfunction or the recruitment of other immune cells. Neutrophils can modulate the immune response, affecting T lymphocytes, macrophages, and dendritic cells, which are crucial for the development of experimental AH. However, it is important to note that the exact causal role of neutrophils in AH has not been definitively established. Further research is needed to validate this hypothesis and explore the potential mechanisms underlying the interaction between neutrophils and AH [41]. Also, Krishnan et al.'s study [42] showed that isoLGs (isolevuglandins) play a crucial role in neutrophil migration and NET formation (NETosis) in hypertension, and offer a potential treatment for disorders linked to neutrophil extracellular traps (NET) such as hypertension and its accompanying end-organ damage.

Monocytes

Monocytes play a critical role in the development of hypertension, and there are different types of circulating monocytes in humans, namely classical, intermediate, and non-classical monocytes. The endothelium, which is subjected to mechanical stretch in hypertension, can influence the differentiation of monocytes. This activation is probably influenced by various factors, including the increased release of interleukin-6 (IL-6) and hydrogen peroxide from the dysfunctional endothelium, impaired NO signaling, and signal transducers and activators of transcription (STAT) activation in the nearby monocytes. Interventions aimed at increasing bioavailable NO, reducing IL-6 or hydrogen peroxide production, or inhibiting STAT3 might have anti-inflammatory effects in hypertension and related diseases [43].

Monocytes play a significant role in the immunological activation associated with the development of hypertension. Deletion of monocytes has been shown to prevent experimental hypertension, while macrophages and dendritic cells derived from monocytes promote T cell activation and tissue damage. Carmo et al. [44] revealed that hypertension in both humans and mice is associated with

an increase in monocytosis, possibly due to enhanced production in the bone marrow. This elevation in monocyte levels could lead to immune system activation and increased tissue inflammation. The number of circulating monocytes may serve as a valuable biomarker for inflammation in hypertension [44].

Both animal models and humans with hypertension exhibit activated monocytes within the walls of their arteries. The presence of monocyte chemoattractant protein-1 (MCP-1) regulates monocyte activity through the CCR2 receptor, and has been associated with inflammatory changes in the arterial wall during hypertension. However, the impact of monocyte CCR2 expression on vascular remodeling in hypertension has not been extensively studied. In a study conducted by Ishibashi et al. [45], the role of CCR2 expression in monocytes was investigated in vascular remodeling and inflammation in angiotensin II-induced hypertension, as well as in other types of hypertension. Their findings indicated that CCR2 expression in monocytes significantly influenced vascular remodeling and inflammation in hypertension [45].

The contribution of underlying immune system dysregulation to the development of hypertension is not yet fully understood. However, emerging evidence suggests that macrophage infiltration plays a role in hypertensive target organ damage. The release of chemokines and adhesion molecules by the vascular wall due to vasoactive hormones and high blood pressure promotes the infiltration of macrophages. Furthermore, these factors might directly activate macrophages [46].

The involvement of tissue macrophages and circulating monocytes in the development of hypertension is also not fully understood. A protein called cysteine-rich protein 1 (CRIP1), produced abundantly in immune cells, may play a role in blood pressure regulation through its association with monocytes. CRIP1 mRNA expression in monocytes has been found to be related to blood pressure and to be influenced by proinflammatory changes.

Schweigert et al. [47] found that endogenous hormones, such as angiotensin II, might contribute to the inflammatory processes associated with hypertension, which involve CRIP1-positive circulating and splenic monocytes. These findings indicate that CRIP1 could potentially influence the interaction between the immune system, specifically monocytes, and the pathophysiology of hypertension [47]. These results indicate that hypertensive left ventricular hypertrophy (LVH) patients exhibit inflammation and a proinflammatory monocyte phenotype, characterized by increased expression of pro-inflammatory factors, and decreased expression of anti-inflammatory factors. Irbesartan appears to modulate the inflammatory state and monocyte phenotype in hypertensive LVH patients, which could contribute to its ability to reduce LVH through this previously unknown mechanism [48].

Recent research suggests that infiltrating macrophages, rather than neutrophils and proinflammatory monocytes, play a crucial role in angiotensin II-induced vascular dysfunction and the development of AH. This finding aligns with previous knowledge that monocytes infiltrate the vascular system in AH and contribute to the proliferation of connective tissue [49, 50].

Monocytes play a critical role in the inflammatory process of AH and offer potential targets for the development of antihypertensive medications. These targets include cytokines such as IL-1, IL-6, IL-12, and interferons (IFNs), which are either produced by, or act upon, myelomonocytic cells. Additionally, the MCP/CCR2 axis involved in chemokine signaling presents a promising target to prevent monocyte recruitment, adhesion, and infiltration into the vasculature. Modulating the activity of phagocyte-type NADPH oxidase or antioxidant enzymes is another potential approach. Excitingly, the pleiotropic effects of thrombin inhibition and other advanced anti-thrombotic therapies may also support the anti-inflammatory treatment of hypertension. By reducing the inflammatory burden imposed by myelomonocytic cells, it is possible to alleviate the global disease burden associated with AH [51].

Macrophages and their proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and IL-1, play a crucial role in the development of hypertension. These macrophages contribute to target organ damage and increased renal sodium retention by producing these M1 cytokines and reactive oxygen species, leading to hypertension. Human studies have supported this finding, showing higher levels of these cytokines in monocytes and serum of individuals with hypertension. Modifying macrophage function could potentially serve as a therapeutic approach for patients with resistant hypertension and end-organ damage. It has been observed that broad immune suppression can lead to a decrease in blood pressure in patients with rheumatological diseases, suggesting the potential efficacy of targeting macrophages as a class of therapy for hypertension [52].

Hence, additional research is being conducted to explore the blocking of macrophage functions or cytokines, particularly in patients with hypertension who exhibit M1 macrophage activation and indicators of cardiac or renal damage. Immunomodulation holds potential long-term benefits for these patients, outweighing any short-term risks. To develop more effective immunomodulatory treatments for this widespread disease, pre-clinical investigations should accurately identify the specific subpopulations of myeloid cells involved in hypertension development and its associated consequences. Furthermore, increased expression of transient receptor potential canonical type 3 (TRPC3) channels has been associated with enhanced monocyte migration in individuals with essential hypertension [53, 54].

Neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio

Liu et al.'s study [55] was the first to establish a strong association between higher levels of neutrophil-to-lymphocyte ratio and an increased risk of developing hypertension, providing insight into the underlying mechanisms of hypertension onset. Collectively, these findings indicate that NLR can serve as a useful indicator of organ damage, such as kidney dysfunction, in the hypertensive population undergoing normal health assessments. Moreover, an increase in MLR has been shown to probably be associated with declines in liver or kidney function, particularly in healthy populations [56].

Hou et al. [57] revealed elevated NLR levels in children with hypertension, which exhibited a positive correlation with office blood pressure measurements. Moreover, NLR showed potential as an indicator for evaluating left ventricular diastolic function in children with hypertension [57]. Also, a study by Sun et al. [58] showed that NLR may be useful in identifying the risk groups of older individuals with hypertension and informing treatment plans. When the participants were categorized, another study observed that older males in the higher NLR group tended to have higher blood pressure compared to those in the lower NLR group. However, there were no statistically significant differences observed among the female, younger, and BMI-specific groups [59]. Non-dipper status refers to individuals whose blood pressure does not significantly decrease during night-time sleep compared to daytime levels. It has been found that NLR and PLR can serve as cost-effective and easily accessible indicators of non-dipper status, particularly in individuals with hypertension [60].

Belen et al. [61] stated that compared to controlled hypertension and normotension (NT) patients, NLR and neutrophil count were considerably greater in resistant hypertension (RHT) patients. Increasing drug use and invasive procedures are the current standards of care for treating uncontrolled HT. More research is therefore required to ascertain the importance of the NLR in defining cardiovascular risk, particularly in individuals with uncontrolled HT and those who require intensive treatment and thorough monitoring. Additionally, larger-scale studies should be used to clarify how antihypertensive medication types affect NLRs [61]. Likewise, higher NLR hypertensives have been shown to be more susceptible to atherothrombotic and atherosclerotic events [62].

Platelet-to-lymphocyte ratio

Although the platelet-to-lymphocyte ratio (PLR) was found to be higher in a study group of hypertensive patients, the difference was not statistically significant [62]. A study conducted by Bayrakci et al. [63] indicated that a high PLR in individuals with hypertension might suggest an increased risk of atherosclerosis, and this could potentially have predictive value in the future. In contrast to other findings, patients with non-dipper hypertension exhibit significantly higher levels of NLR and PLR compared to those with dipper hypertension. Furthermore, a PLR above 107, but not NLR, has been found to be a reliable indicator of non-dipper status [64]. Another study also observed that non-dipper hypertensive individuals had significantly higher levels of PLR compared to dippers, suggesting that PLR could serve as a cost-effective and easily accessible biomarker [65].

Conclusions

Red blood cells, hematocrit, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio all play significant roles in the pathogenesis of hypertension, as explained in Figure 2. There are many other hematological parameters which have not been reported yet, a fact which underscores the need for additional research to elucidate the precise mechanism through which such parameters influence hypertension.

Article information and declarations

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Author contributions

All authors have read and agreed to the published version of the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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Supplementary material

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