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Navigating Hypertension: Biomarkers as Precision Tools for Diagnosis, Prognosis, and Treatment Guidance

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Hypertension, diagnosis, biomarkers, inflammation, endothelial dysfunction, C-reactive protein

ABSTRACT:

Detecting hypertension early is vital for preventing and addressing diverse health risks. It persists as a key contributor to cardiovascular diseases, neurological disorders, renal complications, and various other serious health conditions. Over a billion people worldwide suffered from hypertension in 2019, a figure that has doubled since 1990. Essential hypertension, which accounts for approximately 90% of cases of hypertension, has an unclear cause. Biomarkers are flexible diagnostic tools that can affect the decisions made by healthcare professionals and help educate patients about diagnosis, prognosis, early detection, and treatment interventions. The literature on biomarkers has been reviewed in this study. Therefore, it's becoming more and more crucial to identify reliable biomarkers and use them to forecast, diagnose, and track the effectiveness of hypertension treatments.

Hypertension is linked to heightened activity in biochemical markers indicating endothelial dysfunction and reduced nitric oxide production. It is also linked to problems with glucose metabolism and blood lipids, mainly cholesterol levels from LDL and VLDL, as well as inflammation markers such as CRP, cytokines, and adhesion molecules. Plasma cyclophilin-A (CyP-A) and frequently mentioned recurrent biomarkers such as tryptophan, pyruvate, lactic acid, and valine may serve as biomarkers for essential hypertension (EH).

Growth and differentiation factor-15, red cell distribution width, uric acid, and creatinine are prognostic biomarkers for patients with pulmonary arterial hypertension (PAH). Additionally, inflammatory biomarkers including interleukin-6, angiopoietins, and microRNAs are also considered.

The fibrosis-4 index and the improved liver fibrosis test are commonly used blood indicators to evaluate portal hypertension (PH). At the same time, vibration-controlled transient elastography is widely used as the most often used technique for elastography. Equally, significant techniques for assessing portal hypertension (PH) comprise of plasma cyclic guanosine monophosphate (cGMP),

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liver/spleen stiffness measurements (SSMs), and the hepatic venous pressure gradient (HVPG).

The measurement of uric acid, potassium, and sodium levels in the blood is essential for the identification and monitoring of hypertension in children. Copeptin also plays a significant part in this process. Likewise, the seriousness of prenatal hypertension is linked to higher amounts of interleukin-1, high levels of uric acid in the blood, and an increase in C-reactive protein in the bloodstream. Measuring the level of uric acid in the blood is an accurate and dependable diagnostic method, which demonstrates a significant association with the severity of high blood pressure in pregnant women diagnosed with pre-eclampsia.

Introduction

High blood pressure is a major risk factor for dementia, chronic kidney disease, ischemic heart disease, stroke, and other cardiovascular problems.[1] High blood pressure is defined as having a systolic pressure more than 140 and/or a diastolic pressure higher than 90.[2] A doctor's clinical toolbox includes biomarkers, a multipurpose, non-invasive instrument. They must influence expert opinions and support patient education about diagnosis, prognosis, and the course of treatment. In the last two decades, there has been a significant surge in the utilization of biomarkers for diagnosing and treating pulmonary hypertension.[3] Serum biomarkers are an essential diagnostic tool for cardiovascular disease in cancer patients receiving cardiotoxic cancer therapy because they help establish baseline risk for the condition. Elevations in cardiac biomarkers, like natriuretic peptides and cardiac troponin, can assist cancer patients in starting cardioprotective therapy, monitoring the efficacy of those treatments, and offering prognostic data.[4]

In the prognostic assessment of patients with hypertension, cardiac biomarkers may be especially important because most of them become abnormal long before overt cardiovascular events occur.[5] Studies that combine multiple omics disciplines such as genomes, epigenomics, transcriptomics, proteomics, metabolomics, and gut microbiome have provided a large number of possible biomarkers for hypertension and related cardiovascular problems, including myocardial infarction, heart failure, and stroke. These studies have been carried out throughout the past few decades.The cause of EH is complex. A number of physiological abnormalities have been observed in hypertensive individuals, including the kidneys' handling of abnormal sodium levels, increased oxidative stress (OS), endothelial dysfunction, vascular hypertrophy, systemic inflammation, and neurohormonal and adrenergic overactivity. Cross-sectional studies provide the majority of information on these abnormalities, but a number of long-term studies have demonstrated that biomarkers for crucial biological pathways, such as aldosterone (neurohormonal activity) and CRP (an inflammatory marker), are elevated prior to the onset of overt hypertension (7). Prognostic predictions are challenging due to the lack of clarity surrounding the precise molecular pathways underlying the effects of hypertension, which have been linked to thrombogenesis, altered platelet function, and modifications in the Renin-angiotensin-aldosterone system (RAAS). This non-communicable disease affects people and can have major consequences for the cardiovascular and renal systems of those who have it. In recent decades, extensive research has progressed our comprehension of the fundamental pathophysiology of hypertension (8).

Despite being rare, PAH can be fatal and has a range of underlying pathologies, including secondary causes and congenital cardiac conditions. The pulmonary artery systolic pressure is measured with transthoracic echocardiography to monitor the disease's progression. The gold standard and conclusive test is a right heart catheterization. This intrusive examination is used to predict the illness as well as diagnose it (9). PH ranks among the leading factors contributing to morbidity and death in individuals suffering from chronic liver disease. Measurement of PH is essential for liver cirrhosis staging and prognostication. The gold standard for determining the degree of PH is thought to be the measurement of the pressure gradient in the hepatic vein (10).

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Metabolic syndrome (MS) is a global public health issue that involves various cardiovascular risk factors, such as obesity, diabetes, dyslipidemia, hypertension, and impaired glucose tolerance. Oxidative stress (OS) and disruption of redox equilibrium inside cells are the common factors linking multiple sclerosis (MS) and associated diseases. These disorders arise due to the long-lasting presence of chronic inflammation, which is a defining characteristic of MS. The rise in the generation of oxidizing species in multiple sclerosis (MS) is linked to the buildup of protein and lipid oxidation byproducts, the deterioration of antioxidant mechanisms, and impairment of mitochondrial activity(11).

Epidemiology: Hypertension is the primary cause of cardiovascular disease (CVDs) and premature mortality worldwide. The use of antihypertensive medications has led to a significant decrease in global mean blood pressure or its steady decline over the past 40 years. Conversely, the occurrence of hypertension has risen, particularly in low- and middle-income countries (LMICs)(12). The Non-communicable Diseases (NCD) Risk Factor Collaboration (NCD-RisC) released research in The Lancet, there were over 1 billion hypertensive people globally in 2019—a number that had doubled since 1990 (13). Essential hypertension is the term used to describe 90% of cases of hypertension that have no known cause. Because it is so common and has a high risk of developing into cardiovascular disease and stroke, early diagnosis is crucial (14). Morbidity and mortality related to these causes may experience a sharp rise in the near future due to the aging population (15).

Material and Methods: Conducting a literature search on PubMed and Google Scholar utilizing the following search terms: essential hypertension biomarker, portal hypertension, pulmonary hypertension biomarker, cardiovascular biomarker, gestational hypertension, and others. Out of the many articles that were first screened, only 67 articles met our criteria for selection. Data from publications over the past ten years was compiled, with a focus on evaluating the original research articles relevant to the investigation. The authors of this study divided up all the necessary tasks, which included screening, selection, categorization, interpretation, analysis, tabulation, summarization, and communication, and completed them in the appropriate order.

Literature Review

The current study explores biomarkers that may provide insights into the etiology, manifestation, course, and Effectiveness of the treatment for hypertension. Both hereditary and environmental factors cause hypertension, earning it the nickname "the silent killer of the world. Diverse levels of association have been found in studies on the genetic and genomic determinants of hypertension (16). Nearly 90% of adults over 55 will eventually develop hypertension, according to data from the Framingham Heart Study. Thus, it is becoming increasingly crucial to identify and use reliable biomarkers to forecast, diagnose, and track the effectiveness of hypertension treatments (17). While some of these indicators are circulating, others are based on modern imaging technology. Among all the biomarkers, none appears trustworthy enough to replace blood pressure as a primary biomarker. The supplementary use of various biomarkers, including imaging techniques, Based on multiomics biological signatures, and carotid-femoral pulse wave velocity (PWV), could improve patient risk classification and help alleviate the burden and adverse effects of the disease (18).

Liang et al. observed the impact of varying blood pressure levels on physiological changes in the cardiovascular and circulatory systems in the hypertension classification trials with the best feature subsets. The Photoplethysmography (PPG) signal and its derivative signals more obviously showed these changes. The risk stratification model identified severe hypertension more accurately than non-severe hypertension (19). Heightened activity of biochemical indicators related to endothelial dysfunction and damage to target organs initiates prehypertension and hypertension, with their presence amplifying these effects. (20). For the purpose of accurately identifying Arterial fibrillation (AF) and risk factors for high-risk patients with hypertension, the optimal candidate is expected to include multiple atrial remodeling indices. However, the evaluated individual biomarkers may be a helpful addition to the diagnostic tools currently in use (21).

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According to a study by Palmu et al. anomalies in glucose metabolism and blood lipids, notably LDL-derived and VLDL-derived cholesterol measurements, are linked to the development of hypertension. Additionally, serum metabolite analysis may help identify people who are at a high risk of developing hypertension (22).

Tsounis et al. discovered that elevated concentrations of inflammation markers in hypertensive patients, such as adhesion molecules, cytokines, and CRP, were evidence that inflammation contributes to the etiology of hypertension. Additionally, they discovered that all of the indicators were linked to an increased likelihood of acquiring hypertension in individuals with normal blood pressure, as well as a greater chance of experiencing cardiovascular events in patients with high blood pressure (23). A meta-analysis study indicated a linear increase in the risk of hypertension as circulating inflammatory markers elevated, even within the low-risk and intermediate-risk groups. Elevated levels of CRP, hs-CRP, and Interleukin (IL-6), but not IL-1, were linked to a greater likelihood of developing hypertension (24).

Essential hypertension: Chang et al. used multiple regression analysis in their study and found that the only factors associated with significant hypertension were plasma CyP-A and body mass index (BMI). The BMI, plasma CyP-A levels, and hyperlipidemia were all higher in the hypertensive group. CyP-A and the systolic and diastolic blood pressures both exhibited positive relationships. These findings demonstrated the significance of plasma CyP-A as a molecular biomarker in the early stages of EH pathogenesis (25). According to a study by Deng et al. (26) pyruvate, lactic acid, valine, and tryptophan are among the frequently mentioned biomarkers with recurrent patterns that may function as EH biomarkers. Furthermore, arginine biosynthesis, aminoacyl-tRNA synthesis, and the metabolism of alanine, aspartate, and glutamate were found to be common metabolic pathways in both human and animal metabolomics studies. These biomarkers and pathways closely associated with insulin resistance, inflammation, and reduced nitric oxide production were observed to impact the emergence of EH. This suggests that exploring crucial metabolic biomarkers and pathways may offer opportunities for early identification or prediction of EH and for uncovering the metabolic mechanisms behind EH (26).

Cardiovascular Diseases: According to a study by Deng et al. (26) a number of frequently mentioned biomarkers with recurring patterns, including tryptophan, pyruvate, lactic acid, and valine, may function as biomarkers of EH. Furthermore, arginine biosynthesis, aminoacyl-tRNA synthesis, and the metabolism of alanine, aspartate, and glutamate were found to be common metabolic pathways in both human and animal metabolomics studies. These biomarkers and pathways, closely associated with insulin resistance, inflammation, and decreased nitric oxide production, were found to influence the development of EH. This implies that crucial metabolic biomarkers and pathways may provide opportunities for early detection or prediction of EH and identification of the metabolic mechanisms underlying EH. (27) .

Magnus et al. (28) examined biomarkers linked to major categories of cardiovascular pathology, such as heart-type fatty acid-binding protein, cardiac myosin binding protein-C, soluble CD40 ligand, P-selectin, platelet activation, plaque instability, myocardial injury, and secretoneurin) (28).

Additionally, specific drug reactions can be predicted using epigenetic data. Significantly, the scientific community is starting to recognize epigenetic biomarkers as tools for CVD prognosis and diagnosis. But because different diagnostic biomarkers differ, the current findings need to be confirmed in separate labs with different research centers and a sizable sample size. (29).

Metabolomics, a recently developed area of research, seeks to assess and anticipate the safety and effectiveness of treatments, identify biomarkers for diseases, and recognize metabolic irregularities linked to various health conditions. The use of metabolomics to characterize CVD risk factors, such as hypertension, has increased, and it appears to have a lot of potential for comprehending the intricate pathophysiology of this disease (30). While metabolomic, lipidomic, or pharmacometabolomic studies on this condition are still rare, those that have focused on hypertension have yielded further knowledge regarding the detection of biomarkers particular to the disease, the forecasting of treatment results, and the supervision of medication's

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safety and effectiveness (31)**.** In the Ruge et al. (32) study, there were few exceptions. The researchers found that endostatin levels were higher in the blood of those with hypertension, diabetes, kidney disease, CVDs, and the general population. This seemed to indicate that there was damage to the arteries and myocardium as well as a worsened prognosis for cardiovascular events or mortality (32).

Chronic Kidney Disease: One of the main indicators of hypertension, a major cause of chronic kidney disease, is peritubular capillary (PTC) loss. Circulating endothelial microparticles (EMPs) are a measure of endothelial damage in the system. Urinary PTC-EMP levels are raised in hypertension patients and may be a sign of renal microcirculation damage, even though systemic PTC-EMP levels remain constant. Sun et al. (33) suggest that urinary PTC-EMPs could be novel markers of intrarenal capillary loss (33). Impairment of kidney function and the resulting increases in tubular sodium reabsorption cause obesity-related hypertension, which often develops modestly before the onset of target organ destruction. Chronic obesity and progressive kidney damage often accompany the onset of treatment-resistant hypertension. Thus, when managing a patient, it is standard practice to treat diabetes, inflammation, dyslipidemia, insulin resistance, and various antihypertensive medications concurrently. Cardiorenal, metabolic, and other obesity-related disorders may eventually overwhelm healthcare systems if more effective obesity prevention and control strategies are not developed, according to Hall et al (34). Adolescence can be the onset of both hypertension and kidney disease. Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease (CKD) in children. Children suffering from chronic kidney disease (CKD) and exhibiting an abnormal ambulatory blood pressure monitoring (ABPM) profile showed elevated plasma concentrations of propionate and butyrate. In the study conducted by Hsu et al. (35), Researchers found that children in the early stages of chronic kidney disease (CKD) exhibit irregular blood pressure patterns associated with short-chain fatty acids (SCFAs) produced by the gut microbiota, including propionate and butyrate. In order to prevent lifetime hypertension in children with these microbial indicators, early evaluations of these indicators may help identify potential targets for early intervention CKD (35).

After accounting for BMI, MVPA-Acc showed a somewhat associated reduced risk of incident Stage 2 hypertension in both men and women, unlike self-reported moderate to vigorous physical activity (MVPA-SR), which exhibited no association in either sex. Accelerometer-derived MVPA may offer more precise risk estimates for incident diabetes compared to self-reported MVPA (36).

Nemtsova et al. (37) was discovered that when hypertension and Type 2 Diabetes Mellitus (T2DM) occur at the same time, there were no notable variations in the age-related alterations in the OS. Nonetheless, we can assume that the oxidative status has a significant impact on the state of vascular health, particularly in the older age group of individuals, based on correlations found between markers of oxidant-antioxidant systems and various indexes included in the concept of "vascular ageing" in different age groups (37). Pouvreau et al. (38) found that 8-iso-PGF2 and erythrocyte glutathione may be clinically relevant when evaluating hypertension and hypertension with T2DM as a complication. As hypertension progressed, there were also notable changes in inflammatory profile. (38)

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Table 1 : Summary of reviewed studies

Author	Year	Study design	No. of sample	Parameter	Results	Conclusion
James et al. (39)	2021	Randomized Clinical trial	140 with resistant hypertension	Lifestyle modification, C-life, dietary counselling SEPA	SBP increased in C-life relative to SEPA, and BP decreased in C-life without affecting SEPA.	Patients with resistant hypertension can reduce their blood pressure with diet and exercise.
Wei et al. (26)	2021	Original research	124	PER, PET, PFR	The volume-time curve parameters show a major link between the circumferential peak strain rate and the myocardial peak strain rate.	Individuals with essential hypertension experience an exacerbation of LV diastolic dysfunction due to T2DM. The CMR volume-time curve, which reflects alterations in the LV filling model, can provide supplementary information for early clinical intervention.
Jonathan et al. (40)	2019	Original research	44	Biomarkers from MRI and laboratory analyses	Demonstrating the existence of pulmonary hypertension, liver and spleen stiffness exhibited the most effective diagnostic capability.	Imaging outcomes in pediatric and young adult AILD patients align closely with APRI and FIB-4 scores, as well as MRI-derived measures of liver and spleen stiffness.
Chloe et al. (38)	2018	Original research	256	Blood glucose, hemoglobin A1c, eGFR and cholesterol profile	Urinary 8-iso-PGF2α and insulin-like growth factor, GSH, showed significant OS results. IL-1β and IL-10 showed a significant difference in this area.	8-iso-PGF2α and erythrocyte GSH have been shown to be clinically useful in assessing hypertension and hypertension with type 2 diabetes as a comorbidity.
Simon et al. (41)	2013	Original research	1258	CRP,, MCP-1, AA and IL-18	While IL-18 was not significantly correlated with SBP, it was with CRP, MCP-1, and AA. The combination of hypertension and DM caused the biggest rise in CRP.	When someone has MS or DM, they experience different trends of growth. There was no correlation between IL-18 and hypertension in the presence of DM or MS, while MCP-1 was most consistently elevated with hypertension; hypertension and DM also showed the largest increase

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						in CRP.
1. Ziyuan et al. (42)	2019	a comprehensive analysis and meta-analysis	994	vWF, CSPH, SPH with HVPG	The degree of correlation between vWF and HVPG was the main result. The diagnostic performance of vWF in identifying CSPH or SPH was the secondary outcome.	As a new biomarker, vWF conducts satisfactorily in the diagnosis of CSPH and SPH in cirrhosis patients and has a moderate correlation with HVPG.

Pulmonary Arterial Hypertension:

The complex interactions between immune cells and vascular stromal cells, which can happen directly or through the release of extracellular/diffusible substances like cytokines, chemokines, and growth factors, are considered to be the immune origin of pulmonary arterial hypertension (PAH). The B-cell mast-cell axis, fibroblast stimulation mediated by the endothelium that results in M2 macrophage polarization, antibodies that target endothelial cells, and the various effects of IL-6 on vascular cells are important contributors (43).

Christopher et al. (44) identified inflammatory markers, including development and proliferation factor-15, uric acid, creatinine, interleukin-6, and microRNAs, angiopoietins as predictive biomarkers in patients with PAH. It is known that several molecules are elevated in PAH that can be measured in blood or occasionally in other biological fluids. The most researched are uric acid, products produced by nitric oxide activity, and members of the natriuretic peptide family. Aubert et al. (45).

The pulmonary endothelium, circulating cells, and microparticles were the sources of biomarkers, as described in the study by Barrier et al. (46). Numerous diseases are responsible for the emergence and persistence of PAHs, which also give rise to other possible biomarkers. More specifically, pulmonary artery smooth muscle cells exhibit lactate dehydrogenase (LDH), OS, and a phenotype resembling cancer (isoprostane, uric acid). Furthermore, the elevated inflammation causes an increase in the production of biomarkers such as LIGHT, GDF-15, Englodin (Eng), Interleukin, and Endothelin (ET). It may be possible to assess these indicators using blood samples (46).

It is possible to check for PAH related to SSc by measuring the levels of PlGF, sVEGFR-1, TNF-, and VEGF-D in the blood. Plasma sVEGFR-1 is one sign that treatment may be working. Kylhammar et al. (47) found that there were no clear changes in the biomarkers in the blood between idiopathic PAH and SSc-associated PAH.The level of sVEGFR-1 in plasma dropped after PAH-targeted treatment began.(47). For the pathophysiology of PAH, noncoding RNAs are essential. The functions of CCND1, miR-942, and hsc circ 0016070 in PAH were examined by Zhou et al.(48). They used a circRNA microarray to find circRNAs linked to PAH and real-time PCR and western blot analysis to assess the expression of miR-942 and CCND1 in various groups. In conclusion, this study suggests that hsa circ 0016070 is linked to vascular remodeling in PAH by stimulating the miR-942/CCND1 pathway, which in turn stimulates the growth of pulmonary artery smooth muscle cells (PASMCs). As a result, hsc circ 0016070 can be used as a novel biomarker for PAH detection and management (48).

D'Alto et al. (49) have reported promising outcomes with triple upfront combinations of these drugs, and they are currently suggested for individuals with severe PAH. The use of ambrisentan, tadalafil, and subcutaneous treprostinil in a triple upfront combination has shown substantial enhancements in both clinical and hemodynamic results, along with notable improvements in right heart remodeling for patients with severe and nonreversible PAH. (49).

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Portal Hypertension: Chronic liver diseases (CLDs) have come a long way in the last 20 years, and it's now possible to diagnose and rate the risk of these illnesses without surgery. These methods involve assessing liver stiffness or quantifying biomarkers in serum samples using magnetic resonance or ultrasound-based elastography techniques. Widely used serum markers include the fibrosis-4 index (non-patented) and the patented enhanced liver fibrosis test. The preferred elastography method is vibration-controlled transient elastography (50).

The identification of serum biomarkers may enable the noninvasive diagnosis of PH in cirrhosis. In a study by Qi X et al. (51) subjects were prospectively recruited from six Chinese liver facilities, and the study examined the relationship between HVPG and serum biomarkers associated with immunological inflammation and endothelial dysfunction in cirrhosis. For assessing portal pressure, the gold standard measurement of HVPG is invasive and unsuitable for routine clinical practice (51). Pei-Shan et al. (52) carried out a comparable retrospective study, suggesting that elevated serum M2BPGi levels could be valuable in predicting the occurrence of bacterial infection in cirrhotic individuals with portal hypertension (PH). Furthermore, plasma M2BPGi levels showed a positive correlation with HVPG (52). Furthermore, Lukas et al. (53) found in another study that plasma cGMP is a promising biomarker of clinically significant PH in cirrhosis patients, particularly when it comes to esophageal varices screening. (53).

In a study by Christian et al. (54) For the first time, it was proposed that the liver could be the primary source of miRNA-34a. Conventional prognostic indicators are more useful in predicting long-term survival, even though there may be a correlation between higher levels of miRNA-34a and better survival in cirrhotic patients with severe portal hypertension who follow tips. (54) Christine et al. (55) state that biomarkers and liver/SSMs are promising methods for determining PH in both adults and children. (55)

Table 2: Summary of reviewed studies classified on the basis of comorbidities

Author	Year	Study design	No. of sample	Parameter	Results	Conclusion
Joonatan et al. (22)	2022	Cross-sectional	53	Blood serum	HDL particle size inversely correlated with SBP changes, while LDL cholesterol, apolipoprotein B, and acetate showed positive correlations.	Abnormal glucose metabolism and serum lipids, especially those derived from LDL- and VLDL-cholesterol observations, have been linked to the onset of hypertension..
Zeynep et al. (56)	2022	Original research	80 children with obesity	Serum copeptin	Comparing those with hypertension to those without it indicated significantly lower serum potassium levels and significantly higher serum uric acid. Blood sodium levels and copeptin levels were found to positively correlate.	There was a good link between the amount of sodium in the blood and the amountof copeptin. So, measuring copeptin, uric acid, potassium, and sodium amounts in the blood may be important for finding and keeping an eye on kids who have high blood pressure. ..
Yueting et	2021	Literature	22	Pyruvate, lactic	It was shown that these	Reviewed important

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al. (26)		review	Human & 17 Animal	acid, valine, tryptophan aspartate, glutamate metabolism, alanine, aminoacyl-tRNA and arginine biosynthesis	factors contributed to EH and were strongly associated with insulin resistance, the inflammatory state, and reduced nitric oxide production.	metabolic pathways and biomarkers that may provide chances for the early detection of EH or its metabolic processes.
Hader et al. (57)	2020	Prospective, observational, case-control study	100 pregnant women in their third trimester	Serum urate, hs-CRP, and IL-1β levels, and lipid profile	Substantially higher mean values and favorable associations were observed between serum urate levels and CRP, IR-1β, and the severity of hypertension.	Hyperuricemia and elevated serum levels of CRP and IL-1β play significant roles, correlating with the severity of pregnancy-induced hypertension. In pregnant women with pre-eclampsia, measuring serum urate serves as a sensitive and trustworthy marker, showing a strong correlation with the degree of hypertension.
Chien et al. (35)	2019	Original article	78	Gut microbial composition and SCFAs	Plasma propionate levels were reduced in children with CAKUT, and this was associated with elevated levels of Bifidobacterium bifidum, Akkermansia genus, and Verrucomicrobia phylum.	The results demonstrate the relationship between aberrant blood pressure and SCFAs derived from the gut microbiota, such as propionate and butyrate, in children with early-stage chronic kidney disease.
O Sun et al. (33)	2018	Original article	52	Urinary PTC-EMPs	In patients with hypertension, urinary PTC-EMP levels are elevated and may indicate damage to the renal microcirculation; however, systemic PTC-EMP levels remain unaltered.	As novel biomarkers of intrarenal capillary loss, urinary PTC-EMPs proved to be valuable.
Sepideh et al. (58)	2018	A systematic review and meta-analysis	451	hs-CRP	Contrasting hs-CRP levels with regular diets, there was a more significant decrease.	Compared to eating normally, adults' circulating serum inflammatory biomarkers can be improved by following the DASH diet.
Chong et al. (59)	2018	Systematic Review and	746	Shear Wave Elastography	SWE had an overall sensitivity of 85% and specificity of 85%, indicating	To be eligible to treat patients with clinically significant PH, SWE is

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		Meta-Analysis		(SWE)	that its diagnostic performance for CSPH was quite good.	regarded as a biomarker
Dimitrios et al. (23)	2014	Literature review	-	CRP, cytokines, and adhesion	Discovered to be higher in hypertensive individuals, confirming the role inflammation plays in the etiology of hypertension.	Knowing how inflammation plays a part in hypertension opens up new therapeutic options for treating the condition and its consequences by focusing on inflammation.
Chen-Shu et al. (25)	2013	Original Research	40	Vascular cytokines, total nitrite, and CyP-A	BMI as well as plasma CyP-A were discovered to be important causes of hypertension.	Demonstrated that one important molecular biomarker in the early pathogenesis of EH is plasma CyP-A.
Megan et al. (60)	2013	Literature review	-	Serum uric acid	strong evidence for the use of uric acid testing in diagnosis due to the correlation between uric acid level and essential hypertension	Serum uric acid level as a biomarker for pediatric essential hypertension diagnosis.

Coronavirus Disease (COVID-19): Due to the frequent coexistence of COVID-19 with cardiovascular issues and the virus's targeting of the angiotensin-converting enzyme (ACE)-2 cell entry receptor, there has been extensive discussion on how to manage patients with hypertension(61).. Since ACE2 is released into the bloodstream, a higher plasma level of soluble ACE2 (sACE2) may suggest a higher level of cellular expression of ACE2. Along with clinical or biomarker indicators of diabetes, cardiovascular disease, and biological aging, the masculine gender is also linked to elevated sACE2 levels. It may be possible to identify people more likely to develop a severe case of COVID-19 infection by examining GDF-15 and NT-proBNP levels. There is a higher chance of death and heart disease linked to these biomarkers, as well as a level of sACE2.(62) Patients who had elevated cardiac damage indicators over recently established cutoffs had a noticeably higher probability of dying from COVID-19. Elevated cardiac biomarkers are substantially linked to 28-day mortality in COVID-19 patients. These biomarkers may have prognostic cutoff values that are substantially lower than the current reference standards. Findings by Qin et al. (63) can help with improved COVID-19 patient care and better results. Importantly, the recently established threshold levels of cardiac biomarkers related to COVID-19 may be helpful criteria for upcoming prospective research and therapeutic trials (63).

Gestational Hypertension: Women with preeclampsia exhibited notably elevated levels of carotid intima-media thickness, pulse, augmentation index, arterial wall tension and pulse wave velocity compared to pregnant women without hypertension. While additional investigations are necessary,It is possible to figure out the chance of high blood pressure and other problems during pregnancy using Doppler and serum biomarkers. Recent research has focused on microribonucleic acids as potential biomarkers in this context (64). Sakr et al. (57) observed a notable increase in the average concentrations of serum urate, CRP, and interleukin-1 among individuals with gestational hypertension. Serum urate levels showed a significant correlation with both CRP and interleukin-1, and were positively correlated with the severity of hypertension. Elevated levels of CRP, hyperuricemia, and interleukin-1 in the bloodstream are linked to the severity of pregnancy-induced hypertension and may contribute to the pathophysiology of pre-eclampsia. Serum urate measurement is a sensitive and accurate diagnostic

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technique that is highly correlated with the degree of hypertension in pre-eclamptic pregnant women (57).

Pediatric Hypertension: Gor et al. have reported a direct association between blood salt and copeptin concentrations. In hypertensive children with obesity, lower blood potassium levels and elevated serum levels of uric acid and copeptin were observed. This implies that assessing serum uric acid, potassium, and sodium levels, alongside copeptin, is crucial for identifying and monitoring hypertension in children(56). Likewise, Yanik et al. (60) and Wei et al. (16) in separate pediatric studies, obtained analogous results, emphasizing the importance of measuring electrolyte levels.

Table 3: Study characteristics based on types of hypertension

Types of hypertension	Minor Biomarker	Major Biomarker
Pulmonary arterial hypertension (PAH)	Plasma levels of PlGF, sVEGFR-1, TNF-α, and VEGF-D,	hsc circ_0016070, Plasma sVEGFR-1,
Essential Hypertension (EH)	the level of serum uric acid, copeptin, potassium, sodium, hs-CRP, CRP, and IL-6, cytokines, MCP-1, AA, and IL-18,	Reduced nitric oxide production, CyP-A, serum urate, and 8-iso-PGF2α and erythrocyte glutathione
Portal Hypertension (PH)	miRNA-34a, SEMA6B, SFRP3, COMMD7, BMX, and VCAM1, SSM	HVPG, Plasma cGMP, SWE, serum M2BPGi, vWF antigen

Some of the crucial preventive measures are as following:

When you follow the Dietary Methods to Control Hypertension (DASH) plan, your blood pressure goes down and your risk of heart disease goes down. It is hypothesised that DASH may also lower systemic inflammatory indicators like highly sensitive hs-CRP, even though interventional studies have yielded inconsistent results. Following the DASH diet can improve circulating serum inflammatory indicators in adults more than the conventional diet can, making it a potentially helpful strategy for reducing inflammation. Serum hs-CRP levels decreased more in trials that lasted eight weeks or more. [58]

According to a 4-month trial conducted by Blumenthal et al.,[39] structured diet and exercise regimens administered as adjuvant therapy in a cardiac rehabilitation setting lead to notable reductions in both the clinic and ambulatory blood pressure, along with enhancements in multiple cardiovascular disease biomarkers.[39]

Tobacco use is a significant risk factor for CVD and hypertension. It alters mitochondrial function and induces OS and metabolic reprogramming. Dikalov et al. (65) suggest that targeting mitochondrial OS may be useful in treating pathological conditions like endothelial dysfunction, hypertension, and cardiovascular diseases that are associated with tobacco use.[65]

Hammoud et al. [66] Reviewed studies comparing water-only fasting, intermittent fasting, and Ramadan in individuals with hypertension who were fasting. The findings indicate that water-only fasting leads to reductions in body weight, blood pressure, and lipolytic activity, with no significant impact on an average heart rate. Ramadan fasting is associated with improved lipid profiles, although results for blood pressure, body weight, and heart rate variability vary across studies. Few studies have been done so far to show that fasting is good for the cardiovascular health of people with high blood pressure. More research is needed to confirm this.[66]

Hypertensive disorders of pregnancy affect about 10% of pregnancies. It is known that these women have higher rates of cardiovascular morbidity and mortality in later life when compared to parous controls with normotensive pregnancies. Melchiorre et al. [67] observed that prevention should start as soon as possible after delivery by informing the women about their

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elevated cardiovascular risk and motivating them to follow proven and reasonably priced preventive measures like controlling their weight, quitting smoking, eating a healthy diet, and exercising daily.[67]

Conclusion

High blood pressure is linked to elevated levels of biochemical indicators reflecting impaired endothelial function and reduced nitric oxide production. Irregularities in glucose metabolism and blood lipids, particularly in measurements of LDL and VLDL cholesterol, are also associated with hypertension. Adhesion molecules, cytokines, and CRP are examples of inflammation markers in hypertensive patients that attest to the involvement of inflammation in the etiology of hypertension. EH biomarkers include plasma CyP-A and many frequently reported biomarkers with recurrent patterns, like pyruvate, lactic acid, valine, and tryptophan.

Cardiac troponins, heart-type fatty acid-binding protein, and cardiac myosin binding protein-C are potential indicators of myocardial injury. Meanwhile, salivary biomarkers like salivary creatinine kinase, myocardial band, CRP, troponin-1, and myoglobin exhibit promising diagnostic value in acute cardiovascular conditions. In the evaluation of hypertension and hypertension linked to type 2 diabetes, erythrocyte GSH and 8-iso-PGF2 might hold clinical significance.

Prognostic factors for people with pulmonary arterial hypertension (PAH) include uric acid, creatinine, Growth and Differentiation Factor-15, and inflammatory markers such as interleukin-6, angiopoietins, and microRNAs.

Particularly, portal hypertension is commonly assessed using the enhanced liver fibrosis test and the fibrosis-4 index as serum markers. Vibration-controlled transient elastography is a well-received elastography technique. In individuals with cirrhosis, the gold standard for evaluating portal pressure is hepatic venous pressure gradient (HVPG), and plasma cGMP emerges as a promising biomarker for clinically significant portal hypertension. Liver/SSMs stand out as a promising diagnostic tool for portal hypertension in adults and children.

Interleukin-1, CRP, and hyperuricemia levels are correlated with the severity of pregnancy-induced hypertension. The serum urate measurement is a sensitive and accurate diagnostic technique that shows a good association with the level of hypertension in pre-eclamptic pregnant patients.Besides copeptin, it is important to keep an eye on uric acid, potassium, and salt levels in the blood to diagnose and treat high blood pressure in kids.

The management of hypertension may benefit from a DASH diet, consistent exercise, cutting back on tobacco use and other unhealthy intakes, and appropriate fasting. However, biomarkers may be the key to primordial prevention in the future, as they can reduce the morbidity and mortality rates associated with different forms of hypertension. For the improvement of medical information, a decrease in treatment costs, and better therapeutic outcomes to lessen patients' suffering and enhance their quality of life, more research and technological advancements are required.

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