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Diagnosis and management of hypertension understanding imperative role of various biomarkers

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ABSTRACT

As hypertension,almost 90% of cases of hypertension with an unknown origin called as essential hypertension, continues to be one of the most important risk factors for various fatal health conditions, its early diagnosis using trustworthy biomarkers to predict, diagnose, and monitor the therapeutic progress of hypertension is proving to be of utmost importance for the preventive as well as curative purpose of various health hazards. A rise in the activity of biochemical markers of endothelial dysfunction and blood lipids, notablyLow-density lipoprotein (LDL) andverylow-density lipoprotein(VLDL)measurements, and inflammation markers including C-reactive protein(CRP), cytokines, and adhesion molecules are linked to the development of hypertension. Growth and differentiation factor-15, red cell distribution width, uric acid, creatinine, inflammatory markers including interleukin-6, angiopoietins, and microRNAs are prognostic indicators in individuals with pulmonary arterial hypertension (PAH).The most extensively used blood markers for portal hypertension (PH) are the fibrosis-4 index and the improved liver fibrosis test. Likewise, Hepatic venous pressure gradient (HVPG), liver/SSMs and Plasma cyclic guanosine monophosphate (cGMP) being clinically significant tools to assess for PH. Along with Copeptin, serum levels of uric acid, potassium, and sodium may be crucial for the identification and monitoring of hypertension in pediatrics.Similarly, the severity of gestational hypertension correlates with hyperuricemia, elevated CRP, and interleukin-1 serum levels. Here, in this study, literature on biomarkers has been reviewed which are versatile diagnostic tools posing the influence in healthcare professional's judgement and assist in patient education regarding diagnosis, prognosis, early detection and treatment intervention.

Keywords: Hypertension, Diagnosis, Biomarkers, Inflammation, Endothelial dysfunction, C-reactive protein.

INTRODUCTION

High blood pressure is one of the most dominant risk factors for dementia, chronic renal failure, ischemic heart disease, stroke, and other cardiovascular diseases [1]. Systolic pressure >140 mm of Hg and/or diastolic pressure >90 mm of Hg is considered to be high blood pressure [2]. Biomarkers are a versatile, non-invasive tool in a doctor's clinical toolbox. Their responsibility is to influence professional judgment and assist in patient education regarding diagnosis, prognosis, and treatment intervention. Utilization and integration of biomarkers into the diagnosis and management of pulmonary hypertension have skyrocketed over the past 20 years [3]. In cancer patients receiving cardiotoxic cancer therapy, serum biomarkers are a crucial tool for determining baseline cardiovascular disease risk and making a diagnosis of the condition. Increases in cardiac biomarkers, such as cardiac troponin and natriuretic peptides, can help cancer patients initiate cardioprotective therapy, track how well those treatments are working, and provide prognostic information [4].As most cardiac biomarker levels become aberrant a long time before the start of overt cardiovascular events, cardiac

biomarkers may play an important role in the prognostic evaluation of patients diagnosed with hypertension [5]. Numerous potential biomarkers for hypertension and its associated cardiovascular complications, such as myocardial infarction, heart failure, and stroke, have been discovered in recent decades thanks to the development of multi-omics studies, which include genomics, epigenomics, transcriptomics, proteomics, metabolomics, and gut microbiome [6].

The handling of sodium abnormalities by the kidneys, neurohormonal and adrenergic overactivity, endothelial dysfunction, vascular hypertrophy, systemic inflammation, decreased fibrinolytic potential, and increased Oxidative stress (OS) are just a few of the physiological changes that have been noted in hypertensive people. The majority of the information on these abnormalities comes from cross-sectional studies, but several long-term studies have shown that biomarkers for important biological pathways, like CRP (a marker of inflammation) and aldosterone (neuro hormonal activity), are elevated before the onset of overt hypertension [7]. Hypertension has been linked to thrombogenesis, altered platelet function, and alterations in the Renin-angiotensin-aldosterone system (RAAS), however, the precise molecular pathways behind these effects have not been pinpointed, making prognostic predictions difficult. Humans are affected by this non-communicable illness, which poses serious hazards to sufferers' kidney and cardiovascular systems. Extensive research over the last few decades has improved our comprehension of the underlying pathophysiology of hypertension [8].

Although uncommon, PAH can be fatal and has a variety of underlying pathologies, including congenital heart conditions, as well as secondary causes. Using transthoracic echocardiography, the pulmonary artery systolic pressure is measured to track the progression of the condition. Right heart catheterization is the definitive test and the gold standard. This invasive test is used to both diagnose and forecast the disease [9]. In emerging regions, where inadequate hypertension treatment and management contribute to the burgeoning cardiovascular disease epidemic, the prevalence of hypertension is rising quickly. In the current era, ischemic heart disease accounts for 50% of instances and strokes for 2/3 of cases, respectively. Due to this, high blood pressure remains one of the main global public health problems and the leading cause of death worldwide [10].

Hypertension, diabetes, dyslipidemia, obesity, and impaired glucose tolerance are some of the major cardiovascular risk factors that make up Metabolic syndrome (MS), a global public health concern. OS and intracellular redox imbalance, both brought on by the persistence of the chronic inflammatory conditions that characterize MS, serve as a link between MS and related illnesses. The accumulation of protein and lipid oxidation products, degradation of the antioxidant systems, and mitochondrial dysfunction are all associated with the rise in oxidizing species production in MS [11].

Epidemiology

Hypertension is the main factor in CVDs and early mortality on a global scale. Due to the widespread use of antihypertensive medications during the past forty years, the average blood pressure around the world has either remained stable or dramatically decreased. On the other hand, hypertension has become increasingly prevalent, particularly in LMICs (low- and middle-income countries) [12]. The Non-communicable diseases (NCD) Risk factor collaboration (NCD-RisC) revealed in The Lancet that there were over 1 billion hypertensives worldwide in 2019 - a figure that has increased by twofold since 1990 [13]. 90% of cases of hypertension have an unknown origin and are referred to be essential hypertension. Early diagnosis is essential due to its high prevalence and dangers of developing into CVDs and stroke [14]. The aging population may cause difficulties with morbidity and death connected to these causes to significantly increase shortly [15].

MATERIALS AND METHODS

The terms “essential hypertension biomarker, “portal hypertension”, "pulmonary hypertension biomarker”, “cardiovascular biomarker, “gestational hypertension” and other terms were used to search the literature on PubMed and Google Scholar. Numerous numbers of articles were screened initially, out of which only 67 articles were selected as per our requirement. Data was taken from last 10 years publications focusing the search to review and original research articles and were relevant to our study. All the tasks needed to get done were divided among the authors involved in this present study and done accordingly, i.e., screening, selection, categorization, interpretation, analysis, tabulation, summarization and communication eventually

Literature Review

Here, in this present study, literature on biomarkers has been reviewed that may help in clarifying the pathogenesis, development, progression, and therapy effectiveness of hypertension. Hypertension which is known as the silent killer of the globe is brought on by both genetic and environmental factors. Studies on the genetic and genomic determinants of hypertension have reported varying degrees of connection [16]. According to statistics from the Framingham Heart Study, nearly 90% of adults over the age of 55 will eventually acquire hypertension. So, finding and using trustworthy biomarkers to predict, diagnose, and monitor the therapeutic progress of hypertension is proving to be of utmost importance [17]. Some of these indicators are based on contemporary imaging technology, while others are circulatory. No biomarker in

the sea of others appears to be reliable enough to take the place of blood pressure as a biomarker. Ancillary use of various biomarkers, including carotid-femoral Pulse wave velocity (PWV), imaging methods, and multi-omics-based biological signatures, may improve patient risk classification and help to lessen the burden of the disease and its negative effects [18].

In the hypertension classification trials with the best feature subsets, Liang *et.al*, in 2019 noticed the effects of varying blood pressure levels on physiological changes in the cardiovascular and circulatory systems. These changes were more clearly reflected in the Photoplethysmography (PPG) signal and its derivative signals. When compared to non-severe hypertension, the risk stratification model performed better in identifying severe hypertension [19]. An increase in the activity of biochemical markers of endothelial dysfunction and harm to target organs, which are more expressed in the presence of hypertension, characterizes the course of prehypertension and hypertension [20]. The evaluated individual biomarkers might be a useful supplement to current diagnostic tools, but the ideal candidate is anticipated to include several atrial remodeling indices to accurately identify Arterial fibrillation (AF) and risk factors for high-risk patients with hypertension [21].

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. found that numerous heightened inflammation markers in hypertensive patients, including CRP, cytokines, and adhesion molecules, were evidence that inflammation plays an important role in the etiology of hypertension and discovered that all of the markers were linked to the risk of acquiring hypertension in normotensive people and also linked to the risk of future cardiovascular events in hypertensive patients [23]. Even in the low-risk and intermediate-risk groups, a meta-analysis study showed that the risk of hypertension increased linearly with rising levels of circulating inflammatory markers. Higher circulating levels of CRP, hs-CRP, Interleukin (IL-6), but not IL-1, were linked to an increased risk of hypertension [24].

Essential hypertension

A study conducted by Chang et al. used multiple regression analysis and concluded that only Body mass index (BMI) and plasma CyP-A were significant causes of hypertension. The hypertensive group had higher BMI, hyperlipidemia, and plasma CyP-A levels. Both the systolic and diastolic blood pressures and CyP-A showed favorable correlations. These results showed that plasma CyP-A is an important molecular biomarker in the early pathogenesis of EH [25]. A study by Deng *et.al* has numerous often-reported biomarkers with recurrent patterns, such as pyruvate, lactic acid, valine, and tryptophan, which had the potential to serve as biomarkers of EH. Additionally, other common metabolic pathways were discovered in human and animal metabolomics investigations, including alanine, aspartate, and glutamate metabolism, aminoacyl-tRNA production, and arginine biosynthesis. It was established that these biomarkers and pathways, which are intimately connected to insulin resistance, the inflammatory state, and reduced nitric oxide generation, play a role in the development of EH summarizing that significant metabolic biomarkers and pathways that may provide chances for the early detection or prediction of EH and the identification of the metabolic mechanisms underlying EH [26].

Cardiovascular Diseases

Worldwide, CVDs constitute the leading cause of death. Time has a critical role in how the disease is managed in acute cardiovascular diseases. Salivary biomarkers may offer a quick and accurate diagnosis of CVDs due to how simple and non-invasive it is to acquire saliva. Eshak *et.al* demonstrated that many biomarkers, including salivary creatinine kinase, myocardial band, CRP, troponin-1, and myoglobin, had potential diagnostic qualities that were on par with those of their blood equivalents. Other molecules, such as myeloperoxidase, brain natriuretic peptide, and certain OS markers, were also examined and provided contentious results [27].

In 2019, Magnus *et.al*, analyzed the biomarkers concerning the major cardiovascular pathology groups: Inflammation (CRP, interleukin 6, galectin-3, growth differentiation factor 15 and soluble suppressor of tumorigenicity 2), platelet activation (soluble CD40 ligand and P-selectin), plaque instability (matrix m, lipoprotein-associated phospholipase A2), myocardial injury (cardiac myosin binding protein-C, cardiac troponins, heart-type fatty acid-binding protein), and myocardial (secretoneurin) [28].

Epigenetic data can also be used to forecast specific medication reactions. Importantly, epigenetic biomarkers are becoming more widely accepted in the scientific community as diagnostic and prognostic tools for CVDs. However, the current findings must be replicated in independent laboratories, with various research centers, and a large sample size, due to differences in specific diagnostic biomarkers [29].

In a relatively recent area of study called metabolomics, metabolic abnormalities linked to the disease have been assessed, disease biomarkers have been found, and treatment safety and efficacy have been assessed and predicted. Metabolomics has been utilized more frequently to describe CVD risk factors, such as hypertension, and it looks to hold great promise for understanding the pathophysiology of this complicated illness [30]. Even though there haven't been many metabolomic, lipidomic, or pharmacometabolomic studies on this condition to date, those that have focused on hypertension have revealed more information about

the identification of disease-specific biomarkers, prognosticating treatment outcomes, and monitoring the safety and effectiveness of medications [31].

But few exceptions were found in the study by Ruge et al., who discovered that people with hypertension, diabetes, kidney disease, CVDs, and the general population all had higher circulating levels of endostatin, which appeared to reflect vascular and myocardial damage and a worsened prognosis for cardiovascular events or mortality [32].

Chronic Kidney Disease

Peritubular capillary (PTC) loss is one of the key symptoms of hypertension, a major contributor to chronic kidney disease. Endothelial microparticle (EMP) levels in circulation represent systemic endothelial damage. While systemic PTC-EMPs levels are constant, urinary PTC-EMPs levels are elevated in hypertension patients and may indicate renal microcirculation damage. According to Sun *et.al*, Urinary PTC-EMPs may serve as new indicators of intrarenal capillary loss [33].

Table 1: Summary of the reviewed studies

Author	Year	Study design	No. of sample	Parameter	Results	Conclusion
James *e.t al*,[39]	2021	Randomized Clinical Trial	140 with resistant hypertension	Lifestyle modification, C-LIFE, dietary counseling, SEPA	BP was decreased in C-LIFE with no change in SEPA and SBP was higher in C-LIFE compared with SEPA.	Diet and exercise can lower BP in patients with resistant hypertension
Wei*et .al*,[26]	2021	Original research	124	PER, PET, PFR	Significant association between cardiac peak strain rate, notably circumferential peak strain, and volume-time curve parameters	When individuals already have essential hypertension, T2DM makes their LV diastolic dysfunction worse. The CMR volume-time curve's reflection of changes in the LV filling model may offer more details for early therapeutic intervention.
Jonathan*et.al.*[40]	2019	Original research	44	MRI- and laboratory-based biomarker	Liver and spleen stiffness demonstrated the highest diagnostic performance for indicating the presence of PH.	Imaging findings of PH in children and young adults with AILD are strongly correlated with laboratory-based APRI and FIB-4 scores, as well as MRI-derived markers of liver and spleen stiffness.
Chloe *et.al*,[38]	2018	Original research	256	Blood glucose, hemoglobin A1c, eGFR and cholesterol profile	Significant results for OS were seen for urinary 8-iso-$PGF_2\alpha$ and insulin-like growth factor,GSH. Where, IL-1β and IL-10 were significantly different	Demonstrated that 8-iso-$PGF_2\alpha$ and erythrocyte GSH may be clinically evidence for assessing Hypertension and Hypertension with T2DM as a comorbidity
Simon*et.al*,[41]	2013	Original research	1258	CRP, MCP-1, AA and IL-18	SBP was significantly correlated with CRP, MCP-1 and AA but not IL-18. The greatest increase in CRP was with HYPERTENSION plus DM.	The related circumstances Different patterns of increases are induced by DM or MS, with MCP-1 continuously increasing with hypertension, CRP significantly increasing with hypertension and DM, and IL-18 not increasing with hypertension in the presence of DM or MS.
Ziyuan*et.al*,[42]	2019	a systematic review and meta-analysis	994	vWF, CSPH, SPH with HVPG	The correlation coefficient between vWF and HVPG was the main finding. The ability of vWF to diagnose CSPH or SPH was the secondary result.	As a novel biomarker, vWF exhibits a reasonable level of performance for the detection of CSPH and SPH in patients with cirrhosis and has a moderate connection with HVPG.

The development of hypertension in obesity, which is frequently modest before the onset of target organ destruction, is brought on by impaired kidney function and the resulting increases in tubular sodium reabsorption. The emergence of hypertension that is resistant to treatment is frequently accompanied by chronic obesity and gradual kidney damage. Therefore, it is common practice to treat diabetes, inflammation, dyslipidemia, insulin resistance, and various antihypertensive medications at the same time when managing a patient. If more effective measures for the prevention and control of obesity are not created, cardiorenal, metabolic, and other disorders connected with obesity may eventually overtake healthcare systems, according to Hall *et.al*, kidney disease, and hypertension can both start in adolescence. The most common cause of Chronic kidney disease (CKD) in children is Congenital abnormalities of the kidney and urinary tract (CAKUT) [34]. Children with CKD with an abnormal ambulatory blood pressure monitoring (ABPM) profile had higher plasma levels of propionate and butyrate. Short-chain fatty acids (SCFAs) produced by the gut microbiota, such as propionate and butyrate, are linked to BP abnormalities in children with early-stage CKD, according to research by Hsu *et.al*, Early analyses of these microbial markers may aid in identifying potential targets for early intervention to stop lifelong hypertension in kids with CKD [35].

In comparison to Moderate to vigorous physical activity self-reported (MVPA-SR), which was not linked in either sex,

MVPA-Acc was modestly associated in both men and women with lower risk of incident Stage 2 and increased hypertension, but only after adjusting for BMI. In comparison to self-reported MVPA, accelerometer-derived MVPA may offer more reliable risk estimates for incident diabetes [36].

Nemtsova *et.al,* in 2018 reported that there were no appreciable variations in the age-associated changes in the OS in the concomitant course of hypertension and Type 2 Diabetic Meletus (T2DM). However, we can assume that oxidative status has a significant impact on the status of vascular age, especially in the older age group of people, based on correlations between various indexes included in the concept of "vascular aging" and markers of oxidant-antioxidant systems in different age groups [37]. When evaluating hypertension and hypertension with T2DM as a complication, 8-iso-PGF2 and erythrocyte glutathione could be clinically relevant, significant changes in the inflammatory profile were also seen as hypertension progressed observed in a study conducted by Pouvreau *et.al,* in 2018[38].

Pulmonary Arterial Hypertension

The complex interaction between immune cells and vascular stromal cells, which can happen directly or by producing extracellular/diffusible compounds including cytokines, chemokines, and growth factors, is assumed to be the immunological cause of PAH. Anti-endothelial cell antibodies, the B-cell—mast-cell axis, fibroblast stimulation mediated by endothelium and subsequent M2 macrophage polarization, and the various effects of IL-6 on vascular cells are a few of these[43].

Christopher *et.al*, suggest that inflammatory indicators including interleukin-6, angiopoietins, growth and differentiation factor-15, red cell distribution width, uric acid, creatinine, microRNAs, and all of these have all been thought of as prognostic biomarkers in patients with PAH [44]. It is known that PAH has higher levels of several compounds that can be detected in the blood and occasionally in other bodily fluids. The most thoroughly investigated include natriuretic peptide family members and uric acid by Aubert *et.al*, also, they additionally included nitric oxide activity products [45].

Barrier *et.al* has outlined how biomarkers were produced from the pulmonary endothelium, circulating cells, and microparticles. The emergence and persistence of PAHs, which also give rise to other potential biomarkers, are caused by a wide variety of illnesses. In particular, Lactate dehydrogenase (LDH), OS, and a cancer-like phenotype in pulmonary artery smooth muscle cells are present (isoprostane, uric acid). Additionally, the production of biomarkers such as Endothelin (ET), Interleukin, Englodin (Eng), GDF-15, and LIGHT is increased as a result of the increased inflammation. Blood samples could be used to evaluate these indicators [46].

PlGF, sVEGFR-1, TNF-, and VEGF-D plasma levels may be used to screen for SSc-associated PAH. One potential indicator of therapy response is plasma sVEGFR-1. According to Kylhammar *et.al,* in 2018 found no appreciable variations in the circulating biomarkers between idiopathic and SSc-associated PAH. sVEGFR-1 in plasma decreased following the start of PAH-targeted therapies [47]. Noncoding RNAs play a crucial role in the pathogenesis of PAH. Zhou *et.al,* in 2019 looked at the functions of CCND1, miR-942, and circ 0016070 in PAH. While real-time PCR and western blot analysis were utilized to find miR-942 and CCND1 expression in various groups, circRNA microarray was employed to look for circRNAs involved in PAH. In conclusion, this finding indicates that circ 0016070 promoted the growth of pulmonary artery smooth muscle cells (PASMCs) via the miR-942/CCND1 and hence was connected to vascular remodeling in PAH. Thus, the use of circ 0016070 as a new biomarker for the detection and management of PAH is possible [48].

According to D'Alto *et.al,* triple upfront combinations of these medications have had outstanding outcomes and are currently advised for patients with severe PAH. In patients with severe nonreversible PAH, triple upfront combination therapy with ambrisentan, tadalafil, and subcutaneous treprostinil is linked to significant clinical and hemodynamic improvement as well as right-sided heart reversal remodeling [49].

Portal Hypertension

Significant progress has been made in the non-invasive diagnosis and risk classification of chronic liver disorders (CLDs) over the past 20 years. Non-invasive methods are based on the detection of liver stiffness using either ultrasound- or magnetic resonance-based elastography techniques, or on the quantification of biomarkers in serum samples. The most extensively used serum markers are the fibrosis-4 index and the improved liver fibrosis test, whereas the most popular elastography method is vibration-controlled transient elastography [50].

The noninvasive diagnosis of PH in cirrhosis may be possible by the identification of serum biomarkers. In 2021, Qi X *et.al* conducted a study in which participants were prospectively enrolled in 6 liver facilities in China and studied the connection between HVPG and serum biomarkers linked to immunological inflammation and endothelial dysfunction in cirrhosis. The measurement of HVPG, the gold standard for determining portal pressure, is intrusive and not appropriate for everyday clinical practice[51].

Table 2: Summary of the 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	LDL cholesterol, remnant cholesterol, apolipoprotein B, and acetate were positively, and HDL particle size was negatively, associated with SBP change over time	Serum lipids, and particularly LDL-derived and VLDL-derived cholesterol measures, and glucose metabolism abnormalities are associated with hypertension onset.
Zeynep *et .al*,[56]	2022	Original research	80 children with obesity	Serum copeptin	While serum potassium levels were substantially lower than in those without hypertension, serum uric acid levels were significantly greater. Blood salt and copeptin levels were found to be positively correlated.	Blood salt levels and copeptin levels showed a favorable correlation. Therefore, in the diagnosis and follow-up of children with hypertension, copeptin, serum uric acid, potassium, and sodium levels may be significant.
Yueting*et.al*,[26]	2021	Literature review	22 Human & 17 Animal	Pyruvate, lactic acid, valine, tryptophan alanine, aspartate, glutamate metabolism, aminoacyl-tRNA and arginine biosynthesis	EH was found to be strongly correlated with insulin resistance, the inflammatory state, and reduced nitric oxide production.	Relevant metabolic biomarkers and pathways that may provide chances for early detection or metabolic processes of EH are enumerated.
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	A considerable rise in the average values and a favorable relationship between serum urate levels and the severity of hypertension, as well as between serum urate levels and CRP and IR-1	The severity of pregnancy-induced hypertension is correlated with hyperuricemia, elevated CRP and IL-1 blood levels, and these factors are significant. In pregnant women with pre-eclampsia, serum urate measurement is a sensitive, trustworthy diagnostic that correlates well with the severity of hypertension.
Chien*et.al*,[35]	2019	Original article	78	Gut microbial composition and SCFAs	Children with CAKUT had lower plasma levels of propionate, which was associated with higher concentrations of the phylum *Verrucomicrobia*, genus *Akkermansia*, and species *Bifidobacterium bifidum*.	Findings show that SCFAs produced from the gut microbiota, such as propionate and butyrate, are associated with BP abnormalities in kids with early CKD.
Ahmad *et.al*,[24]	2019	Meta-analysis of cohort studies	21 studies	CRP, hs-CRP, IL-6 and IL-1β	shown that even in the low-risk and intermediate-risk categories, the risk of hypertension rose linearly with rising circulating inflammatory markers.	Higher circulating levels of CRP, hs-CRP, and IL-6, but not IL-1, were linked to an increased risk of hypertension.
O Sun*et.al*,[33]	2018	Original article	52	Urinary PTC-EMPs	While systemic PTC-EMPs levels are unchanged in hypertensive individuals, urinary PTC-EMPs levels are elevated and may indicate renal microcirculation damage.	Urinary PTC-EMPs was useful as novel biomarkers of intrarenal capillary loss.
Sepideh*et.al*,[58]	2018	A systematic review and meta-analysis	451	hs-CRP	Compared to conventional diets, there was a larger decrease in blood hs-CRP levels.	Compared to the standard diet, following the DASH diet helps individuals' circulating serum inflammatory indicators.
Chong *et.al*,[59]	2018	Systematic Review and Meta-Analysis	746	Shear Wave Elastography (SWE)	With a summary sensitivity and specificity of 85% for the diagnosis of CSPH, SWE's diagnostic performance was not too bad.	SWE considered as a biomarker for qualification process and management of patients with Clinically Significant PH.
Dimitrios*et.al*,[23]	2014	Literature review	-	CRP, cytokines, and adhesion	Found elevated in hypertensive patients supporting the role of inflammation in the pathogenesis of hypertension	Understanding the role of inflammation in hypertension provides new insights for novel therapeutic approaches, targeting inflammation for the treatment of hypertension and its complications
Chen-Shu *et.al*,[25]	2013	Original Research	40	Vascular cytokines, total nitrite, and CyP-A	Plasma and BMI CyP-A was discovered to be one of the main causes of hypertension.	shown that plasma CyP-A plays a key role as a molecular biomarker in the early pathogenesis of EH.
Megan*et.al*,][60]	2013	Literature review	-	Serum uric acid	A strong correlation between uric acid level and essential hypertension, supporting its use in diagnosis	Use of serum uric acid level as a biomarker for diagnosis of essential hypertension in children.

A similar retrospective study performed by Pei-Shan *et.al* explained how greater serum M2BPGi levels may play a potential role in predicting the development of bacterial infection for cirrhotic individuals with PH and plasma M2BPGi levels that are positively connected with HVPG [52]. Also, in another study, Lukas *et.al,* concluded that plasma cGMP is a promising biomarker of clinically significant PH in patients with cirrhosis, especially concerning screening for esophageal varices [53].

Another similar study by Christian *et.al,* in 2014 demonstrates for the first time that miRNA-34a can mostly originate from the liver. Although higher levels of miRNA-34a may be linked to better survival at long-term follow-up in cirrhotic patients with severe PH, conventional prognostic markers are more effective at predicting survival[54]. According to Christine *et.al,* in 2017 found that liver/SSMs and biomarkers are promising tools to assess for PH in adults and children [55].

Coronavirus Disease (COVID-19)

Given that COVID-19 usually coexists with cardiovascular problems and that the virus targets the angiotensin-converting enzyme (ACE)-2 cell entering receptor, there has been much debate about how to treat patients with hypertension [61]. Angiotensin-converting enzyme 2 (ACE2) is a cell surface receptor that the SARS-CoV-2 virus binds to in order to enter human cells, causing the COVID-19 pandemic to spread over the world. As ACE2 is released into the circulation, a higher plasma level of soluble ACE2 (sACE2) may signify a higher level of cellular expression of ACE2. Male sex as well as clinical or biomarker indicators of biological ageing, cardiovascular disease, and diabetes are associated with higher sACE2 levels. It may be possible to more accurately identify persons at risk of having severe COVID-19 infection by examining the levels of GDF-15 and NT-proBNP, which are connected to a higher risk for mortality and cardiovascular disease as well as a level of sACE2[62]. Patients who had elevated cardiac damage indicators over the 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* 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

The carotid intima-media thickness, pulse wave velocity, augmentation index, and arterial wall tension of preeclamptic pregnant women were shown to be significantly higher than those of normotensive pregnant women. lateral artery Doppler and serum biomarkers can be used to assess the likelihood of hypertension and pregnancy problems, while more study is required in this field of research.Recently, research has been focused on microribonucleic acids as possible biomarkers [64]. In a study by Sakr *et.al,* in 2020 over the population of gestational hypertensives, a significant rise in the mean values of serum urate, CRP, and interleukin-1 levels was found. Serum urate levels also showed a significant link with CRP and interleukin-1, as well as a positive correlation with the degree of hypertension. The severity of pregnancy-induced hypertension correlates with hyperuricemia, elevated CRP, and interleukin-1 serum levels; these indicators may contribute to the pathophysiology of pre-eclampsia. In pregnant women with pre-eclampsia, serum urate measurement is a sensitive, trustworthy diagnostic that correlates well with the severity of hypertension [57].

Pediatric Hypertension

Gor *et.al,* in 2022 found a favorable connection between copeptin levels and blood salt levels showing serum levels of copeptin and uric acid were greater while blood potassium levels were lower in obese hypertensive kids. This means that in addition to copeptin, measuring serum levels of uric acid, potassium, and sodium may be crucial for the identification and monitoring of children with hypertension [56]. Similarly, another study conducted on pediatrics by Yanik *et.al,* and Wei *et.al,* also found a similar finding focusing on the electrolyte measurement.

Table 3: Study characteristics based on types of hypertensions

Types of hypertensions	Minor Biomarker	Types of hypertensions
Pulmonary arterial hypertension (PAH)	Plasma levels of PlGF, sVEGFR-1, TNF-α, and VEGF-D,	Pulmonary arterial hypertension (PAH)
Essential Hypertension (EH)	serum uric acid level, copeptin, serum uric acid, potassium, and sodium levels, CRP, hs-CRP and IL-6, cytokines, MCP-1, AA and IL-18,	Essential Hypertension (EH)
Portal Hypertension (PH)		Portal Hypertension (PH)

Some of the crucial preventive measures are as following

The Dietary methods to control hypertension (DASH) diet is linked to lower blood pressure and a lower risk of cardiovascular illnesses. Although interventional studies have produced mixed outcomes, it is hypothesized that DASH may also reduce systemic inflammatory indicators such as highly sensitive hs-CRP. Adherence to the DASH diet is superior to the conventional diet in improving circulating serum inflammatory indicators in adults; as a result, it may be a useful tactic to reduce inflammation. In trials lasting eight weeks or longer, there was a larger decrease in serum hs-CRP levels [58].A 4-month trial by Blumenthal et al. showed that planned diet and exercise programs given as adjuvant therapy in a cardiac rehabilitation environment result in significant drops in clinic and

ambulatory blood pressure as well as improvements in several CVD biomarkers [39].

A significant risk factor for hypertension and CVD is tobacco use. It causes metabolic reprogramming and OS in addition to changing mitochondrial function. Targeting mitochondrial OS, according to a study by Dikalov *et.al*, states that it may help treat pathological illnesses linked to tobacco use, such as endothelial dysfunction, hypertension, and cardiovascular diseases [65].

Studies evaluating Ramadan, intermittent fasting, and water-only fasting were included by Hammoud *et.al*, in 2021explain that fasting hypertension individuals, water-only fasting lowers body weight, blood pressure, and lipolytic activity without changing the average heart rate. Although there are inconsistent outcomes for body weight, blood pressure, and heart rate variability, Ramadan fasting improves lipid profiles. Given the paucity of studies in this area, additional study is needed to demonstrate the beneficial effects of fasting on people with hypertension's cardiovascular health [66].

In roughly 10% of pregnancies, hypertensive disorders of pregnancy occur. Comparing these women to parous controls who had normotensive pregnancies, it is known that these women have increased cardiovascular morbidity and mortality later in life. According to Melchiorre *et.al*, observations, prevention should begin as soon as possible after delivery by educating the women about their increased cardiovascular risk and encouraging them to control their weight, give up smoking, eat a healthy diet, and exercise every day, which are proven and affordable prevention methods [67].

RESULTS AND DISCUSSION

While discussing the various significant biomarkers which need to be taken into consideration during the diagnosis and management of various types of hypertensions are as follows

Increased endothelial dysfunction biochemical markers and decreased nitric oxide production, anomalies in glucose metabolism, and blood lipids, notably LDL-derived and VLDL-derived cholesterol measurements, are linked to the development of hypertension. Inflammation markers in hypertensive patients, including CRP, cytokines, and adhesion molecules confirm that inflammation plays an important role in the etiology of hypertension. Plasma CyP-A and numerous often reported biomarkers with recurrent patterns, such as pyruvate, lactic acid, valine, and tryptophan have the potential to serve as biomarkers of EH. In acute cardiovascular conditions, salivary biomarkers such as salivary creatinine kinase myocardial band, CRP, troponin-1, and myoglobin exhibit promising diagnostic values while myocardial injury biomarkers may be cardiac troponins, heart-type fatty acid-binding protein, and cardiac myosin binding protein-C. When evaluating hypertension and hypertension with T2DM as a complication, 8-iso-PGF2 and erythrocyte GSH could be clinically relevant.

Growth and differentiation factor-15, red cell distribution width, uric acid, creatinine, and inflammatory markers such interleukin-6, angiopoietins, and microRNAs are all prognostic indicators in PAH patients. The most used blood markers are the fibrosis-4 index and the improved liver fibrosis test, whereas the most popular elastography method for portal hypertension is vibration-controlled transient elastography. HVPG, the gold standard for determining portal pressure and plasma cGMP is a promising biomarker of clinically significant PH in patients with cirrhosis. Liver/SSMs are promising tools to assess for PH in adults and children. The severity of pregnancy-induced hypertension correlates with hyperuricemia, elevated CRP, and interleukin-1 serum levels. In pregnant women with pre-eclampsia, serum urate measurement is a sensitive, trustworthy diagnostic that correlates well with the severity of hypertension. Along with Copeptin, serum levels of uric acid, potassium, and sodium may be crucial for the identification and monitoring of children with hypertension.

CONCLUSION

For diagnostic as well as management purposes biomarkers play an important role owing to the potentiality for the minimization of the morbidity and mortality rate related to various types of hypertensions and could be the future of primordial prevention, needs further studies and technologies for the upliftment of medical information and reduction in the treatment cost as well as the better therapeutic outcome to improve in the quality of life of patients and their sufferings. Additionally, a DASH diet, improvement in the sedentary lifestyle, and fasting properly would be beneficial for the management of hypertension..

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Conflict of interest

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