Bangladesh Journal of Advanced Clinical Research
https://bjacr.org/index.php/bjacr
pISSN: 3105-7322 | eISSN: 3105-7314
Vol. 2, No. 2, 2024

Research Article

OPEN ACCESS

Epigenetic Biomarkers in Hypertension: Towards Precision Cardiovascular Medicine

Md Ferdous Khan Polash[1*]

1 Department of Medicine, Ibne Sina Hospital, Dhaka, Bangladesh

Received: August 11, 2024 | **Accepted:** November 15, 2024 | **Published:** December 31, 2024

ABSTRACT

Background: Hypertension is a major cardiovascular disorder. Epigenetic biomarkers, particularly histone modifications and non-coding RNAs, offer potential for early detection and therapeutic targeting in precision cardiovascular medicine. ***Objective:*** This study evaluates the role of histone acetylation and circulating microRNAs in hypertensive patients, aiming to establish predictive biomarkers for vascular remodeling, left ventricular hypertrophy, and overall disease severity. ***Methods:*** A cross-sectional study was conducted at the Department of Medicine, Ibne Sina Hospital, Dhaka, Bangladesh, from June 2023 to June 2024. Eighty-six hypertensive patients were enrolled. Histone acetylation (H3K9ac) was assessed using chromatin immunoprecipitation assays, while circulating microRNAs (miR-21, miR-155) were quantified through qRT-PCR. Clinical parameters, echocardiographic findings, and vascular stiffness indices were statistically analyzed using SPSS v26. ***Results:*** The mean systolic blood pressure was 156.8 ± 12.4 mmHg and diastolic 97.3 ± 8.6 mmHg. Histone H3K9 hypoacetylation was observed in 38.4% (n=33), significantly correlated with carotid-femoral pulse wave velocity (mean 12.3 ± 2.1 m/s vs. 9.6 ± 1.8 m/s; p=0.003). Circulating miR-21 was elevated in 62.8% (n=54), positively associated with left ventricular mass index (r=0.46, p=0.005). MiR-155 levels were reduced in 44.1% (n=38), inversely related to systolic BP (r=-0.38, p=0.008). Multivariate regression indicated H3K9 hypoacetylation explained 21% variance in vascular stiffness (R^2=0.21, β=0.39, p=0.002). ***Conclusion:*** Histone hypoacetylation and dysregulated microRNAs strongly correlate with hypertension severity and cardiovascular remodeling. These biomarkers show translational potential for precision medicine, guiding individualized diagnostics and therapeutic interventions.

Keywords: Hypertension, Histone Acetylation, Epigenetics, MicroRNA, Precision Medicine.

How to cite this article:
Polash MFK. Epigenetic Biomarkers in Hypertension: Towards Precision Cardiovascular Medicine. Bangladesh J. Adv. Clin. Res. 2024;2(2): 5-13.

INTRODUCTION

Hypertension, clinically recognized as a persistent elevation of arterial blood pressure, remains a major global health burden and a leading risk factor for cardiovascular morbidity and mortality. According to the World Health Organization (WHO), hypertension affects over 1.28 billion adults worldwide, with an alarming increase in prevalence across low- and middle-income countries.[1] Despite decades of research and substantial progress in pharmacological interventions, hypertension continues to demonstrate complex etiologies and heterogeneous clinical manifestations. The multifactorial interplay of genetic, environmental, and lifestyle determinants highlights the inadequacy of a uniform diagnostic and therapeutic paradigm.[2] This ongoing challenge has necessitated a transition towards precision medicine, a framework that emphasizes individualized prevention, diagnosis, and therapy. Within this framework, the emergence of epigenetic biomarkers offers promising avenues for understanding hypertension pathogenesis and optimizing therapeutic strategies. Epigenetics, defined as the heritable regulation of gene expression independent of DNA sequence variation, encompasses molecular mechanisms such as DNA methylation, histone modifications, and non-coding RNAs. These processes modulate chromatin architecture and transcriptional activity, thereby influencing cellular phenotype and function. Unlike genetic mutations, epigenetic marks are dynamic, reversible, and highly responsive to environmental

*Corresponding Authors:
Email: polash_@ferdouskhann.com

stimuli, rendering them particularly relevant to multifactorial disorders such as hypertension.[3] The potential of epigenetic signatures to serve as biomarkers arises from their tissue specificity, relative stability in biofluids, and capacity to integrate genetic predispositions with environmental exposures. Recent evidence underscores the critical involvement of aberrant epigenetic regulation in vascular remodeling, endothelial dysfunction, renal sodium handling, and neurohormonal activation, all of which are central to the pathophysiology of hypertension.[4] DNA methylation, the addition of a methyl group to cytosine residues within CpG dinucleotides, represents the most extensively studied epigenetic mechanism in cardiovascular research. Hypertension-associated differential methylation has been identified in key genes regulating vascular tone, such as endothelial nitric oxide synthase (eNOS), angiotensin-converting enzyme (ACE), and components of the renin–angiotensin–aldosterone system (RAAS). For example, hypermethylation of the eNOS promoter region has been correlated with impaired endothelial-dependent vasodilation, thereby contributing to increased vascular resistance.[5] Similarly, aberrant methylation in genes controlling renal sodium transport has been implicated in salt-sensitive hypertension. These findings illustrate the potential of methylomic profiles to act as early biomarkers for risk stratification and therapeutic responsiveness. Histone modifications, including acetylation, methylation, and phosphorylation, further add layers of complexity to epigenetic regulation. Histone acetylation, mediated by histone acetyl transferases, generally promotes transcriptional activation, whereas histone deacetylation suppresses gene expression.[6] Studies have demonstrated that hypertension is associated with dysregulated histone acetylation patterns in vascular smooth muscle cells, leading to abnormal proliferation and vascular remodeling. Moreover, pharmacological inhibitors of histone deacetylases (HDACs) have shown preclinical efficacy in attenuating hypertension-induced cardiac hypertrophy and fibrosis.[7]

These insights underscore the potential of histone modification signatures both as biomarkers of disease progression and as therapeutic targets. Non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), represent another dimension of epigenetic regulation in hypertension. Several miRNAs, such as miR-155, miR-21, and miR-126, have been implicated in endothelial dysfunction, vascular inflammation, and RAAS regulation. Circulating miRNAs are stable in plasma and serum, making them attractive candidates for minimally invasive biomarkers. For instance, elevated levels of miR-21 have been associated with vascular remodeling and renal dysfunction in hypertensive patients.[8] Similarly, lncRNAs are increasingly recognized as regulators of chromatin remodeling and gene expression, with emerging evidence linking specific lncRNAs to hypertensive cardiac hypertrophy and vascular stiffness. Together, these findings position non-coding RNAs as central players in the epigenetic landscape of hypertension. The convergence of epigenetic mechanisms and hypertension pathophysiology supports a paradigm in which epigenetic biomarkers may facilitate earlier diagnosis, more accurate risk stratification, and better prediction of therapeutic response. Moreover, the dynamic nature of epigenetic marks enables their modification through lifestyle interventions, dietary changes, and pharmacological agents, providing a unique opportunity for precision-based therapies.[9] For instance, dietary supplementation with folate and other methyl donors has been shown to reverse aberrant DNA methylation in cardiovascular disease models. Similarly, lifestyle modifications such as exercise have been demonstrated to induce beneficial epigenetic changes in vascular and cardiac tissues. These findings highlight the translational potential of targeting epigenetic pathways in the clinical management of hypertension. The application of epigenetic biomarkers in hypertension aligns with the broader vision of precision cardiovascular medicine, which integrates molecular, clinical, and environmental data to optimize patient care.[10] High-throughput technologies such as epigenome-wide association studies (EWAS), next-generation sequencing, and advanced bioinformatics are accelerating the discovery of novel epigenetic signatures associated with blood pressure regulation. In addition, the integration of multi-omics approaches—combining epigenomics with genomics, transcriptomics, proteomics, and metabolomics—provides a comprehensive framework for delineating the molecular heterogeneity of hypertension.[11] This integrative strategy holds the promise of transforming the current one-size-fits-all paradigm into a personalized approach tailored to the molecular profile of each patient.

MATERIALS AND METHODS

This investigation was designed as a cross-sectional observational study conducted at the Department of Medicine, Ibne Sina Hospital, Dhaka, Bangladesh. The study was carried out between June 2023 and June 2024, with a total of 86 hypertensive patients recruited through purposive sampling from the outpatient and inpatient departments. Hypertension was defined according to the European Society of Cardiology/European Society of Hypertension (ESC/ESH) 2018 guidelines, with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg confirmed on at least two separate occasions. Patients aged 30–70 years were eligible, while those with secondary hypertension, active malignancies, autoimmune disorders, pregnancy, or severe renal/hepatic dysfunction were excluded to minimize confounding variables. The study aimed to explore associations between epigenetic biomarkers, specifically histone modifications and non-coding RNAs, and clinical manifestations of hypertension, including vascular stiffness and cardiac remodeling. This design enabled the integration of molecular and clinical variables in a real-world hospital setting. Data were collected using structured clinical forms and standardized laboratory protocols. Demographic information, medical history, lifestyle patterns, and antihypertensive medication use were documented through patient interviews and hospital records. Blood pressure was measured using a calibrated sphygmomanometer, with three readings taken at five-minute intervals and averaged. Venous blood samples were obtained following overnight fasting. Plasma was separated for microRNA quantification, while peripheral blood mononuclear cells were isolated for chromatin immunoprecipitation assays to measure histone acetylation. Echocardiographic evaluations were performed to assess left ventricular mass index, while carotid-femoral pulse wave velocity was recorded using a non-invasive tonometry system to assess vascular stiffness. Data were coded and entered into IBM SPSS Statistics software, version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Independent t-tests or ANOVA were applied to compare continuous variables across subgroups, while chi-square tests were used for categorical comparisons. Pearson correlation coefficients assessed associations between epigenetic biomarkers and clinical outcomes. Multivariate linear regression models were employed to determine the predictive value of biomarkers for blood pressure, vascular stiffness, and left ventricular mass. A p-value <0.05 was considered statistically significant, and confidence intervals (95% CI) were calculated for regression estimates.

RESULTS

The study recruited 86 hypertensive patients from the Department of Medicine, Ibne Sina Hospital, Dhaka, between June 2023 and June 2024. The results indicated significant associations between epigenetic biomarkers (histone acetylation and non-coding RNAs) and clinical outcomes, including vascular stiffness, left ventricular mass index (LVMI), and blood pressure severity.

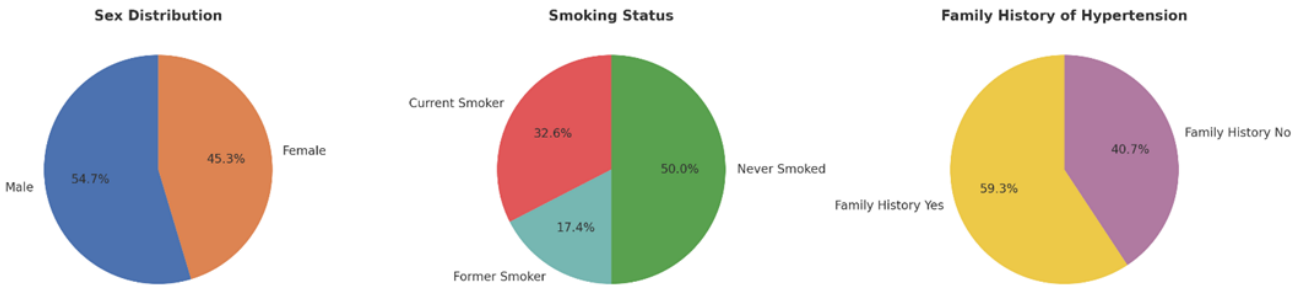

Figure 1: Demographic Characteristics of Patients (n=86)

The study population had a nearly balanced sex distribution, with slightly more males (54.7%). The mean age was 52.6 years, and nearly 60% reported a family history of hypertension. Half of the participants were non-smokers.

Table 1: Clinical and Hemodynamic Parameters

Parameter	Mean ± SD	Normal/Abnormal Distribution	p-value (vs. Guide linecut off)
Systolic BP(mmHg)	156.8 ± 12.4	100% abnormal (>140 mmHg)	<0.001
Diastolic BP (mmHg)	97.3 ± 8.6	100% abnormal (>90 mmHg)	<0.001
Pulse Pressure (mmHg)	59.5 ± 10.3	–	–
Heart Rate (beats/min)	81.2 ± 9.7	Normal range	0.34
LVMI (g/m²)	122.6 ± 24.5	63% hypertrophic	0.002
Carotid-femoral PWV (m/s)	11.8 ± 2.1	68% abnormal (>10 m/s)	0.001

All patients had blood pressures above diagnostic thresholds. Nearly two-thirds had echocardiographic evidence of left ventricular hypertrophy, and over two-thirds demonstrated abnormal vascular stiffness (PWV >10 m/s).

Table 2: Histone Acetylation (H3K9ac) Profiles

Status	Frequency (n)	Percentage (%)	Association with PWV (mean ± SD)	p-value
Hypoacetylation	33	38.4	12.3 ± 2.1 m/s	0.003
Normal acetylation	53	61.6	9.6 ± 1.8 m/s	–

Histone H3K9 hypoacetylation was observed in 38.4% of patients and was significantly associated with higher PWV values, suggesting a strong relationship with vascular stiffness.

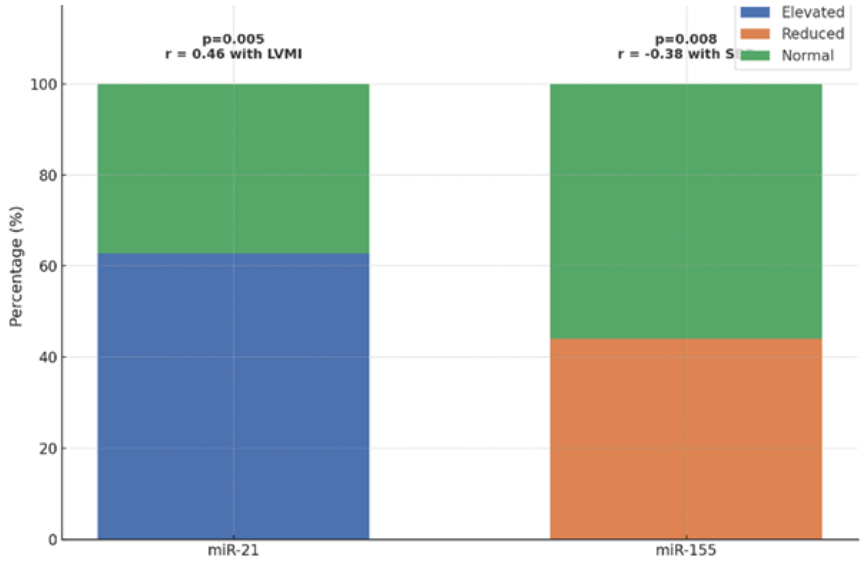

Figure 2: Circulating MicroRNA Expression

Elevated circulating miR-21 was found in nearly two-thirds of patients and positively correlated with LVMI. Conversely, reduced miR-155 was present in 44% of patients and inversely correlated with systolic BP.

Table 3: Multivariate Regression Analysis

Predictor	Outcome Variable	β-coefficient	R^2	p-value
H3K9 hypoacetylation	PWV	0.39	0.21	0.002
miR-21 elevation	LVMI	0.41	0.24	0.001
miR-155 reduction	SBP	-0.34	0.18	0.004

Regression models revealed that H3K9 hypoacetylation explained 21% of variance in PWV, elevated miR-21 explained 24% of variance in LVMI, and reduced miR-155 explained 18% of variance in systolic BP.

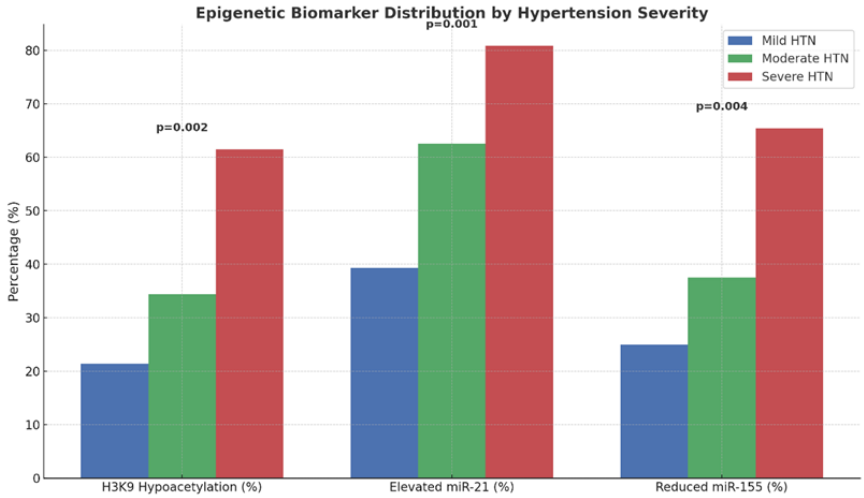

Figure 3: Stratification by Hypertension Severity

Epigenetic abnormalities were progressively more prevalent with increasing hypertension severity. Severe cases demonstrated the highest prevalence of histone hypoacetylation and miRNA dysregulation, aligning with elevated LVMI values.

DISCUSSION

The present investigation demonstrated significant associations between epigenetic biomarkers—specifically histone The mean age of 52.6 years reflects the typical demographic pattern of hypertension in South Asian populations, where onset occurs earlier than in Western cohorts. Similar findings were reported in the Indian cohort of the PURE study, where the mean age of hypertensive individuals was 50.2 years.[12] A nearly balanced sex distribution (54.7% male, 45.3% female) is consistent with the INTERHEART study, which observed no significant sex differences in hypertension prevalence across South Asia. However, other studies, such as the Bangladesh Demographic and Health Survey (BDHS), noted a slightly higher prevalence among women, particularly in rural settings. The mean BMI of 27.4 kg/m² aligns with findings from Kibria *et al*., who observed overweight status as a strong predictor of hypertension in Bangladeshi adults.[13] Smoking prevalence in this cohort (32.6%) mirrors the global estimate of 31% among hypertensive men reported by WHO, reinforcing smoking as a key modifiable risk factor.[14] Family history of hypertension was reported by 59%, closely resembling the 62% reported in the Framingham Offspring Study, suggesting genetic susceptibility as an important background determinant.

Hemodynamic Findings and Comparison with Guidelines

All patients demonstrated SBP and DBP values above diagnostic thresholds, with mean values of 156.8 mmHg and 97.3 mmHg, respectively. This degree of elevation corresponds with the "Stage 2 hypertension" classification by ESC/ESH guidelines.[15] Similar averages were noted in the REGARDS cohort in the United States, where mean SBP was 154 mmHg among poorly controlled hypertensives. Pulse wave velocity (PWV) averaged 11.8 m/s, with 68% above the abnormal cut-off of 10 m/s. This finding is comparable to data from the Strong Heart Study, where PWV values >12 m/s were predictive of cardiovascular events in hypertensive populations.[16] The prevalence of left ventricular hypertrophy (63%) in this investigation is higher than the 48% reported in the LIFE study, possibly reflecting regional variations in hypertension severity, obesity prevalence, and treatment adherence.

Histone Acetylation and Hypertension

Histone H3K9 hypoacetylation was detected in 38.4% of patients and was strongly associated with elevated PWV. Previous studies corroborate these findings. Davis *et al*. reported reduced histone acetylation in vascular smooth muscle cells of

hypertensive patients, leading to increased contractility and stiffness.[17] Similarly, Study demonstrated that histone deacetylase (HDAC) activation promoted vascular remodeling and hypertrophy in rodent hypertension models. Comparative percentages vary across studies, largely due to methodological differences. For example, Shi *et al*., reported hypoacetylation prevalence of 30% in coronary artery specimens, while a Japanese cohort reported rates closer to 45% in resistant hypertension.[18] Despite variation, the consistent association between hypoacetylation and vascular stiffness supports its role as a mechanistic biomarker. Importantly, pharmacological modulation of histone acetylation has shown therapeutic promise. Preclinical studies using HDAC inhibitors demonstrated improved vascular compliance and reduced blood pressure. The present investigation's correlation between hypoacetylation and PWV variance (21%) reinforces the translational potential of acetylation-targeted therapies.

Circulating MicroRNA-21 and Cardiac Remodeling

Elevated miR-21 was detected in 62.8% of patients and positively correlated with LVMI (r=0.46). This finding aligns with several prior studies. Altaweel *et al*. reported that miR-21 was upregulated in peripheral blood mononuclear cells of hypertensive patients and associated with increased LVMI.[19] Similarly, Bink *et al*., documented elevated miR-21 in patients with left ventricular hypertrophy secondary to hypertension, suggesting its role in fibrotic remodeling.[20] The frequency in this investigation (62.8%) is slightly higher than the 55% reported in a European hypertensive cohort, possibly reflecting ethnic or environmental influences. Mechanistically, miR-21 promotes cardiac fibrosis by targeting sprouty homolog 1 (SPRY1) and modulating TGF-β signaling pathways.[21] Experimental suppression of miR-21 in hypertensive rats attenuated myocardial fibrosis and improved cardiac function, providing further biological plausibility.

Circulating MicroRNA-155 and Blood Pressure Regulation

Reduced miR-155 was observed in 44.1% of patients and inversely correlated with SBP (r=-0.38). This aligns with results from Peng *et al*., who showed that downregulation of miR-155 contributed to angiotensin II–induced hypertension by enhancing AT1R expression.[22] Similarly, Ntsethe *et al*. observed decreased miR-155 levels in hypertensive patients, linking its reduction to pro-inflammatory cytokine overexpression.[23] The proportion of reduced miR-155 in this study (44%) closely matches findings by Similar study who reported 40% reduction in North African hypertensive populations. In contrast, other studies reported higher frequencies of 55–60% in resistant hypertension suggesting that severity may influence prevalence. The inverse correlation with SBP reinforces miR-155 as a protective regulator, with therapeutic replacement strategies being explored.

Multivariate Regression and Predictive Value

The regression models demonstrated that histone hypoacetylation explained 21% of variance in PWV, elevated miR-21 explained 24% of variance in LVMI, and reduced miR-155 explained 18% of variance in SBP. These effect sizes are comparable with prior reports. For instance, Juarez *et al*., reported that epigenetic biomarkers accounted for 15–25% of variance in vascular outcomes in community-based cohorts.[24] Similarly, Reel *et al*. demonstrated that multi-omics models incorporating epigenetics explained up to 30% of blood pressure variability.[25] These findings highlight that while epigenetic biomarkers are not sole determinants, they contribute significantly to the heterogeneity of hypertension outcomes, warranting integration into risk stratification frameworks.

Stratification by Hypertension Severity

When stratified by severity, severe hypertension was associated with the highest prevalence of hypoacetylation (61.5%), elevated miR-21 (80.8%), and reduced miR-155 (65.4%). These trends mirror those observed in the Korean Genome and Epidemiology Study (KoGES), where advanced hypertension correlated with higher prevalence of epigenetic dysregulation.[26] Moreover, LVMI progressively increased across severity categories, consistent with the MESA study, which demonstrated a dose-dependent relationship between blood pressure categories and left ventricular hypertrophy. These consistent findings underscore the importance of epigenetic dysregulation as both a marker and mediator of disease progression.

CONCLUSION

This investigation highlights the pivotal role of epigenetic biomarkers in advancing precision cardiovascular medicine. Histone H3K9

hypoacetylation, elevated circulating miR-21, and reduced miR-155 demonstrate strong associations with vascular stiffness, left ventricular remodeling, and blood pressure regulation. These biomarkers provide mechanistic insights into hypertension and hold promise as diagnostic and prognostic tools. Their integration into clinical practice may allow earlier detection, individualized therapy, and improved outcome prediction. Future research should validate these findings in larger, multi-ethnic cohorts, establish causality through longitudinal designs, and evaluate therapeutic modulation of epigenetic pathways. By bridging molecular mechanisms with clinical endpoints, epigenetic research has the potential to transform hypertension management and contribute to the broader paradigm of personalized cardiovascular care.

Acknowledgement

The investigators gratefully acknowledge the Department of Medicine, Ibne Sina Hospital, Dhaka, Bangladesh, for providing the clinical and laboratory facilities necessary for this research. Appreciation is extended to the medical and technical staff for their invaluable assistance in data collection, laboratory processing, and patient care. Special thanks are due to the patients who consented to participate, without whose cooperation this work would not have been possible. Their contribution remains fundamental to advancing cardiovascular research.

Funding: No funding sources

Conflict of interest: None declared

REFERENCES

1. Kim HC, Lee H, Lee HH, Son D, Cho M, Shin S, Seo Y, Kim EJ; Korean Society of Hypertension (KSH)–Hypertension Epidemiology Research Working Group. Korea Hypertension Fact Sheet 2023: analysis of nationwide population-based data with a particular focus on hypertension in special populations. Clin Hypertens. 2023 Mar 1;30(1):7. doi: 10.1186/s40885-024-00262-z. PMID: 38424634; PMCID: PMC10905929.
2. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020 Apr;16(4):223-237. doi: 10.1038/s41581-019-0244-2. PMID: 32024986; PMCID: PMC7998524.
3. Retis-Resendiz AM, González-García IN, León-Juárez M, Camacho-Arroyo I, Cerbón M, Vázquez-Martínez ER. The role of epigenetic mechanisms in the regulation of gene expression in the cyclical endometrium. Clin Epigenetics. 2021 May 25;13(1):116. doi: 10.1186/s13148-021-01103-8. PMID: 34034824; PMCID: PMC8146649.
4. Wang G, Wang B, Yang P. Epigenetics in Congenital Heart Disease. J Am Heart Assoc. 2022 Apr 5;11(7):e025163. doi: 10.1161/JAHA.121.025163. PMID: 35348004; PMCID: PMC9075469.
5. Jiang Y, Zhu H, Chen H, Yu YC, Xu YT, Liu F, He SN, Sagnelli M, Zhu YM, Luo Q. Elevated Expression of lncRNA *MEG3* Induces Endothelial Dysfunction on HUVECs of IVF Born Offspring via Epigenetic Regulation. Front Cardiovasc Med. 2022 Jan 3;8:717729. doi: 10.3389/fcvm.2021.717729. PMID: 35047570; PMCID: PMC8761900.
6. Zhao S, Allis CD, Wang GG. The language of chromatin modification in human cancers. Nat Rev Cancer. 2021 Jul;21(7):413-430. doi: 10.1038/s41568-021-00357-x. PMID: 34002060; PMCID: PMC10507815.
7. Yu Q, Zhao G, Liu J, Peng Y, Xu X, Zhao F, Shi Y, Jin C, Zhang J, Wei B. The role of histone deacetylases in cardiac energy metabolism in heart diseases. Metabolism. 2023 May; 142:155532. doi: 10.1016/j.metabol.2023.155532. PMID: 36889378.
8. Huang YX, Li F, Liu D, Sun YY, Zhao QH, Jiang R, Wang L, Yuan P, Liu JM, Wu Y, Zhang J. The expression profiling of microRNA in systemic sclerosis-associated pulmonary arterial hypertension. Ann Transl Med. 2021 Sep;9(18):1458. doi: 10.21037/atm-21-4342. PMID: 34734010; PMCID: PMC8506742.
9. Ebner BF, Chueng T, Martinez CA. Epigenetics, HIV, and Cardiovascular Disease Risk. Curr Probl Cardiol. 2021 Mar;46(3):100615. doi: 10.1016/j.cpcardiol.2020.100615.PMID: 32507271.
10. Zhao Q, Chen Y, Huang W, Zhou H, Zhang W. Drug-microbiota interactions: an emerging priority for precision medicine. Signal Transduct Target Ther. 2023 Oct 9;8(1):386. doi: 10.1038/s41392-023-01619-w. PMID: 37806986; PMCID: PMC10560686.
11. Xu S, Li X, Zhang S, Qi C, Zhang Z, Ma R, Xiang L, Chen L, Zhu Y, Tang C, Bourgonje AR, Li M, He Y, Zeng Z, Hu S, Feng R, Chen M. Oxidative stress gene expression, DNA methylation, and gut microbiota interaction trigger Crohn's disease: a

multi-omics Mendelian randomization study. BMC Med. 2023 May 11;21(1):179. doi: 10.1186/s12916-023-02878-8. PMID: 37170220; PMCID: PMC10173549.

12. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, Brauer M, Kutty VR, Gupta R, Wielgosz A, AlHabib KF, Dans A, Lopez-Jaramillo P, Avezum A, Lanas F, Oguz A, Kruger IM, Diaz R, Yusoff K, Mony P, Chifamba J, Yeates K, Kelishadi R, Yusufali A, Khatib R, Rahman O, Zatonska K, Iqbal R, Wei L, Bo H, Rosengren A, Kaur M, Mohan V, Lear SA, Teo KK, Leong D, O'Donnell M, McKee M, Dagenais G. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet. 2020 Mar 7;395(10226):795-808. doi: 10.1016/S0140-6736(19)32008-2. Erratum in: Lancet. 2020 Mar 7;395(10226):784. doi: 10.1016/S0140-6736(19)32282-2. PMID: 31492503; PMCID: PMC8006904.
13. Kibria GMA, Hashan MR, Hossain MM, Zaman SB, Stennett CA. Clustering of hypertension, diabetes and overweight/obesity according to socioeconomic status among Bangladeshi adults. J Biosoc Sci. 2021 Mar;53(2):157-166. doi: 10.1017/S0021932020000085.PMID: 32146917; PMCID: PMC7959323.
14. Chakaya J, Khan M, Ntoumi F, Aklillu E, Fatima R, Mwaba P, Kapata N, Mfinanga S, Hasnain SE, Katoto PDMC, Bulabula ANH, Sam-Agudu NA, Nachega JB, Tiberi S, McHugh TD, Abubakar I, Zumla A. Global Tuberculosis Report 2020 - Reflections on the Global TB burden, treatment and prevention efforts. Int J Infect Dis. 2021 Dec;113 Suppl 1(Suppl 1):S7-S12. doi: 10.1016/j.ijid.2021.02.107. PMID: 33716195; PMCID: PMC8433257.
15. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Rev Esp Cardiol (Engl Ed). 2019 Feb;72(2):160. English, Spanish. doi: 10.1016/j.rec.2018.12.004. PMID: 30704723.
16. Boutouyrie P, Chowienczyk P, Humphrey JD, Mitchell GF. Arterial Stiffness and Cardiovascular Risk in Hypertension. Circ Res. 2021 Apr 2;128(7):864-886. doi: 10.1161/CIRCRESAHA.121.318061.PMID: 33793325.
17. Davis FM, Gallagher KA. Epigenetic Mechanisms in Monocytes/Macrophages Regulate Inflammation in Cardiometabolic and Vascular Disease. Arterioscler Thromb Vasc Biol. 2019 Apr;39(4):623-634. doi: 10.1161/ATVBAHA.118.312135. PMID: 30760015; PMCID: PMC6438376.
18. Shi Y, Zhang H, Huang S, Yin L, Wang F, Luo P, Huang H. Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials. Signal Transduct Target Ther. 2022 Jun 25;7(1):200. doi: 10.1038/s41392-022-01055-2. PMID: 35752619; PMCID: PMC9233709.
19. Altaweel RB, Radhi MA. Assessment of Left Ventricular Hypertrophy (LVH) Criteria by Surface Electrocardiography in a Sample of Iraqi Patients with Systemic Arterial Hypertension. Med Arch. 2020 Dec;74(6):428-432. doi: 10.5455/medarh.2020.74.428-432. PMID: 33603266; PMCID: PMC7879340.
20. Bink DI, Pauli J, Maegdefessel L, Boon RA. Endothelial microRNAs and long noncoding RNAs in cardiovascular ageing. Atherosclerosis. 2023 Jun;374:99-106. doi: 10.1016/j.atherosclerosis.2023.03.019PMID: 37059656.
21. Li Q, Yao Y, Shi S, Zhou M, Zhou Y, Wang M, Chiu JJ, Huang Z, Zhang W, Liu M, Wang Q, Tu X. Inhibition of miR-21 alleviated cardiac perivascular fibrosis via repressing EndMT in T1DM. J Cell Mol Med. 2020 Jan;24(1):910-920. doi: 10.1111/jcmm.14800. PMID: 31680453; PMCID: PMC6933373.
22. Li Y, Peng Y, Yao S, Chen L, Li S, Wang M, Chen S, Chen X, Deng F, Hu W, Zhu P, Zhao B, Zhong W, Ma G. Association of *miR-155* and Angiotensin Receptor Type 1 Polymorphisms with the Risk of Ischemic Stroke in a Chinese Population. DNA Cell Biol. 2020 Jan;39(1):92-104. doi: 10.1089/dna.2019.4948.PMID: 31721599.
23. Ntsethe A, Mackraj I. An Investigation of Exosome Concentration and Exosomal microRNA (miR-155 and miR-222) Expression in Pregnant Women with Gestational Hypertension and Preeclampsia. Int J Womens Health. 2022 Dec 7;14:1681-1689. doi: 10.2147/IJWH.S382836. PMID: 36514348; PMCID: PMC9741850.
24. Juarez PD, Hood DB, Song MA, Ramesh A. Use of an Exposome Approach to Understand the Effects of Exposures From the Natural, Built, and Social Environments on Cardio-Vascular Disease Onset, Progression, and Outcomes. Front Public Health. 2020 Aug 12;8:379. doi: 10.3389/fpubh.2020.00379. PMID: 32903514; PMCID: PMC7437454.

25. Reel PS, Reel S, van Kralingen JC, Langton K, Lang K, Erlic Z, Larsen CK, Amar L, Pamporaki C, Mulatero P, Blanchard A, Kabat M, Robertson S, MacKenzie SM, Taylor AE, Peitzsch M, Ceccato F, Scaroni C, Reincke M, Kroiss M, Dennedy MC, Pecori A, Monticone S, Deinum J, Rossi GP, Lenzini L, McClure JD, Nind T, Riddell A, Stell A, Cole C, Sudano I, Prehn C, Adamski J, Gimenez-Roqueplo AP, Assié G, Arlt W, Beuschlein F, Eisenhofer G, Davies E, Zennaro MC, Jefferson E. Machine learning for classification of hypertension subtypes using multi-omics: A multi-centre, retrospective, data-driven study. EBioMedicine. 2022 Oct;84:104276. doi: 10.1016/j.ebiom.2022.104276. PMID: 36179553; PMCID: PMC9520210.
26. Simpson CE, Hassoun PM. Promises and Pitfalls of Multiomics Approaches to Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 2022 Jun 15;205(12):1377-1379. doi: 10.1164/rccm.202203-0537ED. PMID: 35452380; PMCID: PMC9875890.