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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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The target readership includes academic members, specialists, residents, and general practitioners working in the fields of adult cardiology, pediatric cardiology, cardiovascular surgery and internal medicine.

The editorial and publication processes of the journal are conducted in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the European Association of Science Editors (EASE), the Committee on Publication Ethics (COPE) and the HEART Group.

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2. Main Text
3. Tables, Graphs and Figures
4. Copyright Transfer Form
5. Author Contribution Form
6. ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

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Information about the authors and their institutions should not be included in the main text, tables, figures and video documents. Since submitted manuscripts are evaluated by the reviewers through the online system, personal identification is excluded in the interests of unbiased interpretation. Thus, only information about the manuscript as specified below should be included on the title page. For each type of manuscript, it is mandatory to upload a title page as a separate Microsoft Word document through the online submission system. The title page should include the names of the authors with their latest academic degrees, and the name of the department and institution, city and country where the study was conducted. If the study was conducted in several institutions, the affiliation of each author must be specified with symbols. The correspondence address should contain the full name of the corresponding author, postal and e-mail addresses, phone and fax numbers. If the content of the manuscript has been presented before, the name, date and place of the meeting must be noted. Disclosure of conflict of interest, institutional and financial support, author contributions, acknowledgments, and ORCID iDs of the authors should be included on the title page.

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The manuscripts submitted to our journal are classified and evaluated according to the manuscript types stated below. During preliminary evaluation, the editors assess whether a manuscript's format and sub-headings are prepared in accordance with the journal's guidelines. Therefore, it is important that authors check the accuracy of the main text in terms of the following.

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- **Original investigation**
- **Editorial comment**
- **Review**
- **Education**
- **Scientific letter**
- **Case report**
- **Original image**
- **Letter to the editor**
- **Publication ethics**
- **Scientific puzzle**
- **Miscellaneous articles**

B. References

C. Special Terms and Conditions

A. Manuscript types

- **Original Research**
- Title
- Highlights: Each submission should be accompanied by 3 to 5 "highlight points" which should emphasize the most striking results of the study and highlight the message that is intended to be conveyed to the readers. It should be limited to 70 words.
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Statistical Analysis: Statistical analysis should be conducted in accordance with the guidelines on reporting statistical data in medical journals [Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93 and Lang T, Altman D. Basic statistical reporting for articles published in clinical medical journals: the SAMPL Guidelines. In: Smart P, Maisonneuve H, Polderman A (editors). Science Editors' Handbook, European Association of Science Editors, 2013.]. The software used for statistical analysis must be described. Data must be expressed as mean ± standard deviation when parametric tests are used to compare continuous variables. For nonparametric tests, data must be expressed as median (minimum-maximum) or percentiles (25th and 75th percentiles). In advanced and complex statistical analyses, relative risk (RR), odds ratio (OR) and hazard ratio (HR) must be supported by confidence intervals and p values. The outcomes of statistical analyses and interpretation of the results must be in evidence-based scientific language (Editors of Heart Group journals. Statement on matching language to the type of evidence used in describing outcomes data. Anatolian Journal of Cardiology 2012;12:709).

- **Editorial Comment**

Authors are selected and invited by the Editor-in-Chief. This type of manuscript aims at providing a brief commentary on an article published in the journal by a researcher who is an authority in the relevant field or by the reviewer of the article.

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NOTE 1: Case reports that include video images have a better chance of publication.

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Book with Single Author: Cohn PF. *Silent Myocardial Ischemia and Infarction*. 3rd ed. New York: Marcel Dekker; 1993.

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Scientific or Technical Report: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: October 1994. Report No: HHSIGOE 169200860.

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Epub ahead of print articles: Aksu HU, Ertürk M, Gül M, Uslu N. Successful treatment of a patient with pulmonary embolism and biatrial thrombus. *Anatolian J Cardiol*. December 26, 2012. doi: 10.5152/akd.2013.062. [Epub ahead of print].

Manuscript published in electronic format: Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis (serial online)*. l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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Drawings should be performed by professionals. No grey colours should be used.
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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Dirty Earth-Diseased Hearts

In this issue we publish a very important review by Münzel et al from Germany titled 'Dirty Earth, Diseased Hearts: Soil, Water, and Plastic Pollution in the Cardiovascular Exposome'. They conclude that reducing soil, water, and plastic pollution must become a central pillar of cardiovascular prevention through enforceable, lifecycle-based policies that protect human health. Thanks to Prof. Münzel et al.

The hemoglobin–albumin–lymphocyte–platelet (HALP) score is an emerging nutritional–inflammatory biomarker. Although minimally invasive valve surgery (MIVS) offers advantages over sternotomy, current prediction models such as EuroSCORE II and STS-PROM may not fully capture perioperative vulnerability. Evidence evaluating whether HALP predicts early postoperative recovery in MIVS remains limited. This is the issue that Zengin et al from Türkiye tried to solve.

Transcatheter aortic valve implantation is an established alternative for patients with severe aortic stenosis who are unsuitable for surgical valve replacement. Conscious sedation is preferred to preserve spontaneous respiration and patient cooperation. So Gürsoy Çirkinoğlu and Şahinkaya from Türkiye invetigated the best sedation type during this operation.

Cardiac troponin T (cTnT) and NT-proBNP are key biomarkers reflecting myocardial injury and hemodynamic load in heart failure or after cardiac surgery. However, data on their postoperative course in pediatric HeartMate 3 recipients are limited. Ön et al from Türkiye aimed to evaluate the clinical significance of postoperative changes in these biomarkers in these pediatric patients.

As age increases, the body's immune system gradually exhibits a chronic, low-grade activation state, known as inflammatory aging, characterized by a sustained increase in levels of inflammatory cells and mediators in peripheral blood. This state can damage the vascular endothelial function, accelerate the process of atherosclerosis, and significantly increase the risk of CVD death. Therefore, finding biomarkers that can reflect chronic low-grade inflammation is of great significance for CVD risk management in the elderly. Sun et al from China used the aggregate index of systemic inflammation fort his purpose.

The optimal treatment strategy for isolated side branch lesions remains uncertain. In their study, Akın et al from Türkiye aimed to evaluate the safety and efficacy of drug-coated balloon angioplasty for the treatment of de novo isolated side branch stenosis.

And a case report, letters, e-page original...

I hope this new issue of our journal will be interest of our readers.

EDITORIAL

Çetin Erol

Editor-in-Chief, Ankara, Türkiye

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Dirty Earth, Diseased Hearts: Soil, Water, and Plastic Pollution in the Cardiovascular Exposome

ABSTRACT

Healthy soils and clean water are essential for human survival, yet, both are increasingly compromised by chemical and plastic pollution. This preventable crisis causes an estimated 9 million premature deaths each year, including about 0.9 million linked to soil pollution and 1.3 million to water pollution. In 2019 alone, pollution contributed to 5.5 million cardiovascular deaths, underscoring its role in the global burden of non-communicable disease. A key under-recognized driver is the rapid rise in plastic production and plastic-associated chemicals. Global plastic output has increased more than 250-fold since 1950 and is projected to nearly triple by 2060, while less than 10% is effectively recycled. As highlighted by the Lancet Countdown on health and plastics, plastics threaten human health across their lifecycle, from fossil fuel extraction to waste, fragmentation, and environmental persistence. Soils and water systems are increasingly contaminated by heavy metals, pesticides, persistent synthetic chemicals, and micro- and nanoplastics. These pollutants degrade soil, reduce agricultural productivity, contaminate food chains, and spread through aquatic ecosystems, thereby amplifying disease risk. Micro- and nanoplastics have been detected in human blood, placenta, brain, and cardiovascular tissues, raising concern about biological effects. These exposures are drivers of cardiovascular disease. Despite their chemical diversity, they converge on shared mechanisms, including oxidative stress, inflammation, endocrine disruption, and circadian dysregulation. Their persistence reflects policy failure. Reducing soil, water, and plastic pollution must become a central pillar of cardiovascular prevention through enforceable, lifecycle-based policies that protect human health.

Keywords: Cardiovascular disease, endothelium, environment, oxidative stress, plastic pollution, soil pollution, water pollution

INTRODUCTION

Healthy soils and clean water are fundamental to human health and planetary stability. Soil, often overlooked in medicine, underpins food production, ecosystem integrity, water regulation, and carbon storage, thereby mitigating climate change. Yet, soil degradation already threatens the health and livelihoods of 3.2 billion people worldwide;[1] while more than 2 billion people live under conditions of water stress, a number projected to rise with climate change and population growth.[2]

Pollution of soil, water, and air is a major and escalating global health threat.[3] The Lancet Commission on Pollution and Health identified pollution as responsible for approximately 9 million premature deaths in 2019, 16% of all global deaths, and 268 million disability-adjusted life-years (DALYs).[4,5] Air pollution remains the leading contributor, causing up to 8.3 million deaths annually,[6,7] whereas water pollution disproportionately affects infant mortality.[4] Soil pollution contributes substantially to disease burden across the life course. [4,8]

An emerging and insufficiently addressed dimension is plastic pollution. As highlighted by the Lancet Countdown on health and plastics, plastic production has increased more than 250-fold since 1950, with profound health risks across its lifecycle, from fossil fuel extraction to waste accumulation. Micro- and nanoplastics, now detected in human tissues,[9] represent a new class of pervasive environmental contaminants.

INVITED REVIEW

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Notably, ~70% of pollution-related diseases are non-communicable, with cardiovascular diseases accounting for more than 60% of this burden.[10] Despite this, environmental drivers are largely neglected in global non-communicable disease (NCD) strategies. Across diverse exposures, shared mechanisms, including oxidative stress, inflammation, neuroendocrine activation, and circadian disruption—link pollution to cardiometabolic and neuropsychiatric disease.[5,11-15]

Soil and water pollution, though less visible than air pollution, involves complex mixtures of heavy metals, pesticides, synthetic chemicals, pathogens, and plastic waste originating from industry, agriculture, fossil fuels, and urbanization. More than 90% of pollution-related disease and deaths occur in low- and middle-income countries [16] (Figure 1).

This review examines the links between soil and water pollution and human health, with a focus on cardiovascular disease.

Soil and Water: The Living Foundations of Health and Survival

Healthy soil and water are foundational to human health, food security, and ecosystem stability. Soil underpins nearly 95% of global food production and provides about 78% of per capita caloric intake directly from crops, with an additional 20% derived from land-based systems dependent on soil. Beyond food, soil supplies essential nutrients, filters water, and supports biodiversity critical for nutrient cycling, carbon storage, and disease regulation. It is also the second-largest active carbon sink after the oceans and provides materials for infrastructure, fuel, and fiber. However, soil health is increasingly threatened by pollution, including heavy metals, pesticides, and macro- and microplastics, as well as by deforestation and overfertilization.

Oceans, covering more than 70% of Earth's surface and containing 97% of its water, are equally vital. They regulate climate by absorbing 90% of excess heat and about one-third of carbon dioxide emissions,[17] produce atmospheric oxygen through marine microorganisms,[18,19] and sustain global economies and food systems.[20] They are essential for human well-being, particularly in coastal and low-income regions.[21-23]

Despite their importance, oceans are increasingly threatened by climate change, acidification, biodiversity loss, and pollution.[20,24-27] Rising water demand, urbanization, and industrialization further degrade freshwater systems, with an estimated 80% of wastewater globally released untreated, disproportionately affecting low-income countries and posing major risks to human health and ecosystems.

HIGHLIGHTS

- Chemical and plastic pollution causes an estimated 9 million deaths per year,
- Global plastic output is projected to tiple by 2060 based on the actual levels.

CHEMICAL CONTAMINATION OF SOIL AND WATER: SHARED MOLECULAR PATHWAYS DRIVING CARDIOVASCULAR DISEASE

Chemical Contamination as a Systemic Health Hazard

Contamination of soil and water is a major but often underestimated determinant of human health. According to a WHO assessment, exposure to selected chemicals caused an estimated 2 million deaths and 53 million DALYs in 2019, exceeding the previous estimate of 1.6 million deaths and 45 million DALYs in 2016.[28] The substances involved include heavy metals, organic solvents, polycyclic aromatic hydrocarbons (PAHs), benzene, pesticides, and highly persistent "forever chemicals" such as perfluorinated and polyfluorinated alkyl substances (PFAS).[28] Although these chemicals are classically linked to cancer and respiratory disease, they also contribute importantly to cardiovascular morbidity and mortality.[28] This threat is not theoretical: biomonitoring studies have detected hundreds of such compounds, sometimes at concerning concentrations, in the general European population [29]and in the United States.[30]

Shared Molecular Pathways of Toxicity

Despite their diverse chemical structures, many pollutants act through a limited number of shared pathophysiological pathways, most prominently oxidative stress, inflammation, metabolic dysregulation, endothelial dysfunction, and circadian disruption (Figure 2).

Pesticides and Endocrine-Disrupting Chemicals

Pesticides activate the aryl hydrocarbon receptor, leading to the release of thromboinflammatory mediators such as interleukin-1β, plasminogen activator inhibitor-2, and transforming growth factor-α (Figure 2). More broadly, pesticides and other endocrine-disrupting chemicals promote chronic low-grade inflammation.[31] hydrocarbon receptor activation also induces xenobiotic-metabolizing enzymes, including cytochrome P450 1A1 and 1B1 and glutathione S-transferase A1. In parallel, altered glucose metabolism activates muscarinic receptor signaling and the citric acid cycle, increasing diacylglycerol generation and thereby activating protein kinase C and the phagocytic NADPH oxidase NOX2, with subsequent reactive oxygen species (ROS) formation.[32]

Pesticides additionally impair potassium homeostasis and ATP-sensitive potassium channel activity, leading to mitochondrial dysfunction, mitochondrial ROS formation, and altered calcium signaling. They may react with protein thiol groups, causing electrophile adduct formation and sulfoxidation that disrupt multiple enzymatic pathways. Disturbed insulin signaling, including altered expression of insulin receptor substrate 2, glucose transporter 2, and glucokinase, links pesticide exposure to metabolic disease. Some pesticides also form DNA adducts, cause strand breaks, induce mutagenic base modifications, and promote adverse epigenetic changes. Halogenated solvents may exert toxicity partly through disruption of cardiac ion channels.[33]

Metals and Metalloids

Cadmium, lead, and mercury alter antioxidant gene expression, including superoxide dismutase and catalase, and

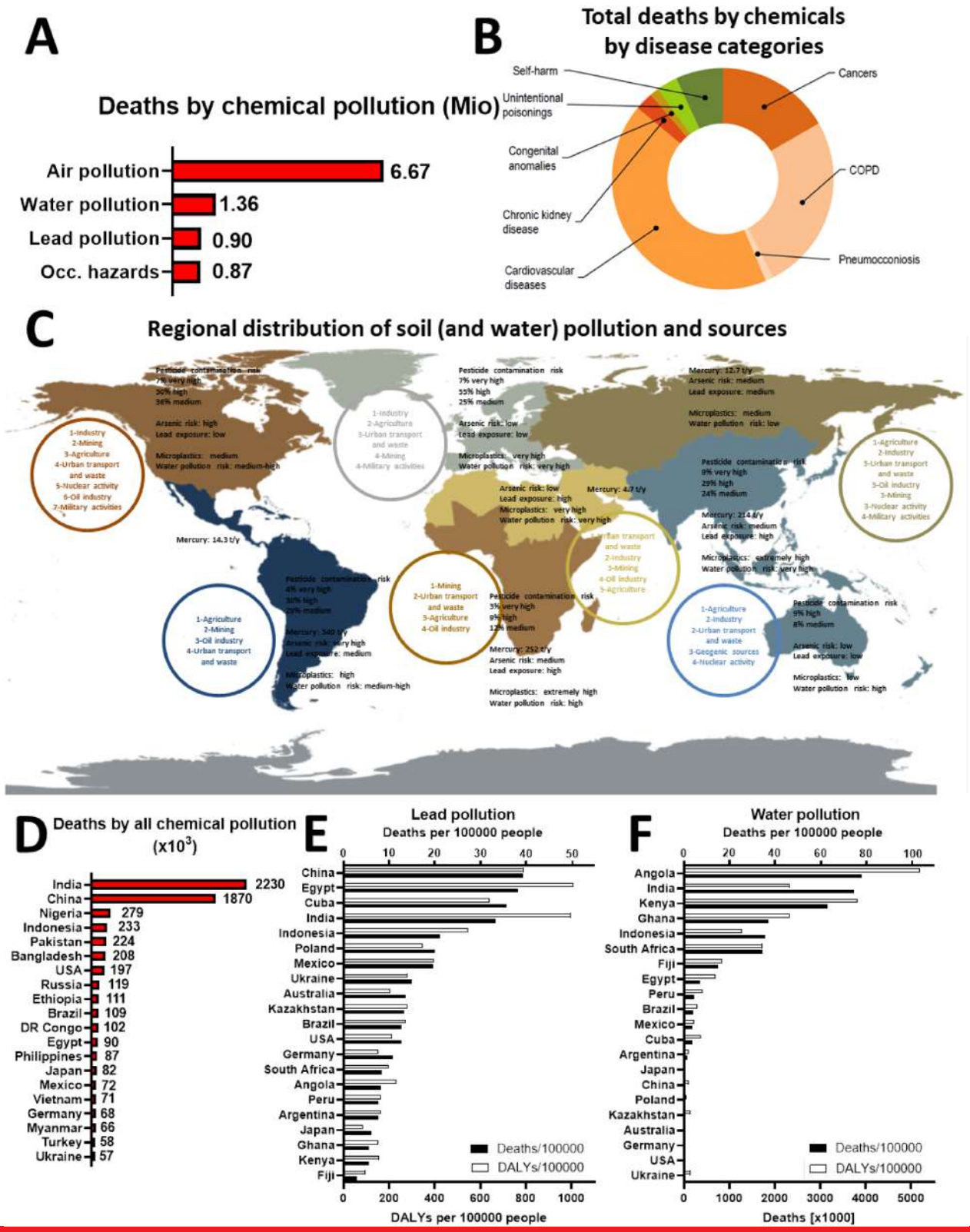

Figure 1. Estimated global annual deaths by all sources of chemical pollution (A)[3,4] and the disease entities being associated with these deaths (B).[28] (C) Regional distribution of chemical soil (and water pollution) with the major sources like industry, mining, and agriculture.[16] The chemical pollution levels and risk scores were summarized from different chemical pollution exposure maps (the sources can be provided by the authors at request). (D) Deaths by all chemical pollution—ranking by top 20 countries.[16] Population-related rates of death and disability-adjusted life-years for lead pollution as a typical soil pollutant (E) and for water pollution (unsafe water source including chemical hazards) (F), listed for 20 representative countries of different WHO regions.[198] With permission from[3,28] (CC BY-NC-ND, CC BY-NC-SA). Graph[8] modified with permission.

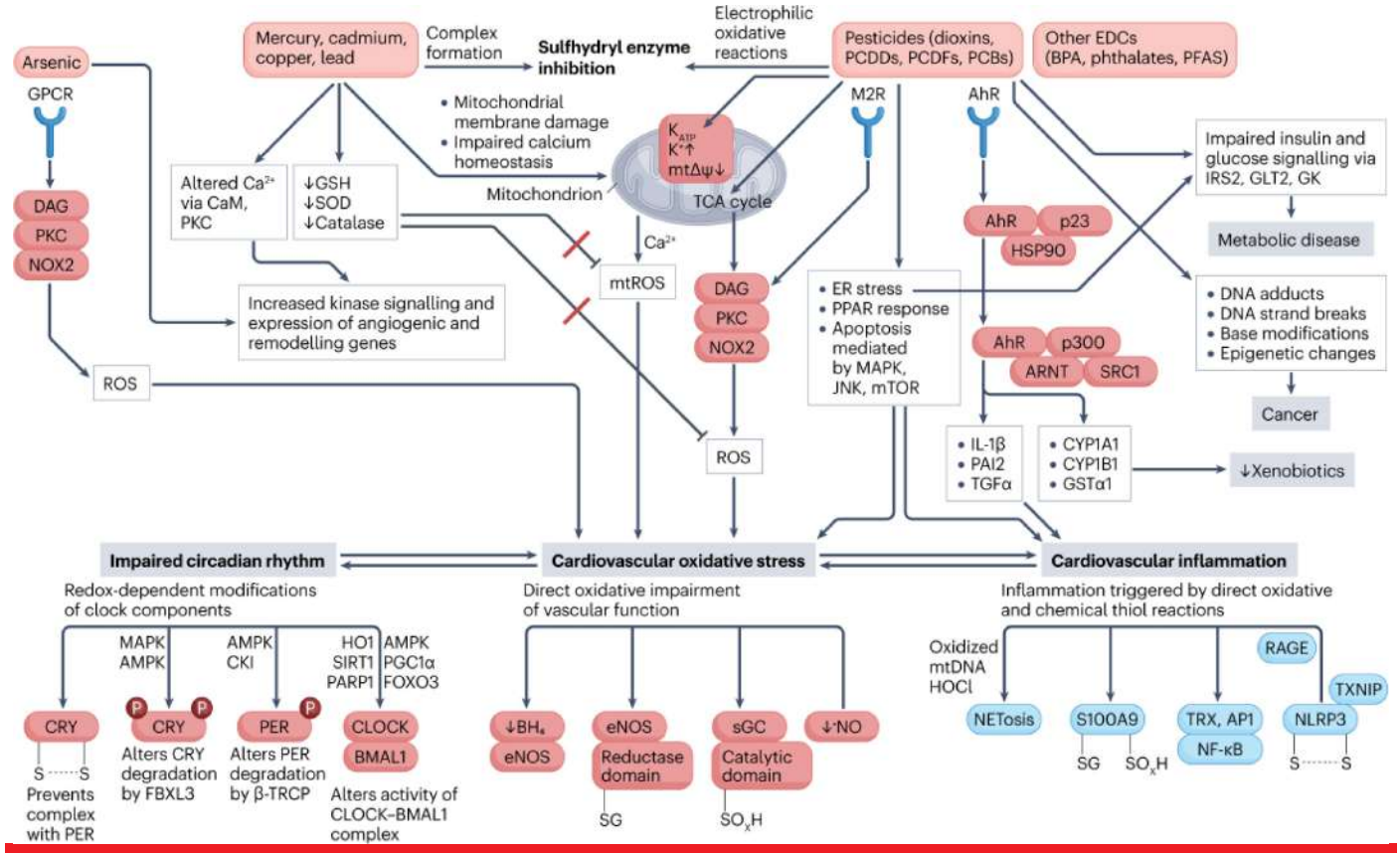

Figure 2. Cellular pathophysiology of metals/metalloids and pesticides. Details and explanation of abbreviations in the text. Pathomechanisms summarized[38] for arsenic, for lead,[35] for cadmium,[34] and[32] for pesticides. Oxidative mechanisms of endothelial/vascular dysfunction summarized.[40] Activating redox mechanisms for inflammation summarized.[41] Other pathomechanisms summarized[13] for heavy metals and[31] for pesticides or other endocrine-disrupting chemicals. PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PCBs, polychlorinated biphenyls; -SG, S-glutathionylation; -SO_xH, sulfoxidation; -S-S-, disulfide bridge. Graph[8] modified with permission.

reduce intracellular glutathione levels, thereby weakening cellular antioxidant defenses and promoting oxidative stress through redox cycling, Fenton-like chemistry, and lipid peroxidation.[34,35] These mechanisms provide a plausible link to ferroptosis-associated cardiovascular injury.[36] Heavy metals also bind thiol groups in proteins and enzymes, thereby impairing enzymatic function.

For methylmercury, one of the earliest toxic processes is the reaction with endogenous thiol and selenol groups, producing stable complexes that impair protein function.[37] Lead also damages membranes, including mitochondrial membranes, and perturbs calcium homeostasis, thereby further increasing mitochondrial ROS formation. Arsenic, although technically a metalloid, behaves similarly to heavy metals and can activate G-protein-coupled receptors, leading to NOX2 activation and downstream oxidative injury.[38] Cadmium has also been shown to activate phosphoinositide 3-kinases/protein kinase B (PI3K/Akt) signaling, a pathway implicated in cardiotoxicity and remodeling.[39]

From Oxidative Stress to Vascular Injury

A central consequence of pollutant-induced ROS generation is vascular dysfunction. Oxidative depletion of tetrahydrobiopterin and S-glutathionylation of endothelial nitric oxide synthase (eNOS) can render the enzyme inactive or uncoupled, thereby reducing nitric oxide bioavailability and worsening endothelial dysfunction.[40] Protein kinase C (PKC)-dependent inhibition of eNOS phosphorylation may further contribute to its inactivity. In parallel, sulfoxidation of soluble guanylyl cyclase impairs vasodilatory signaling, while direct reaction of nitric oxide with superoxide forms peroxynitrite, a strong oxidant that amplifies oxidative damage in addition to depleting nitric oxide.

ROS also activate inflammatory signaling cascades.[41] Examples include neutrophil extracellular trap formation through hypochlorous acid generation and oxidation of mitochondrial DNA, a potent damage-associated molecular pattern. Thiol oxidation can activate nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) via thioredoxin oxidation or activator protein 1 (AP-1) activation. The NLR family pyrin domain containing 3 (NLRP3) inflammasome may be triggered by thiol oxidation, disulfide bridge formation, or activation of thioredoxin-interacting protein. Signaling through receptor for advanced glycation end products is likewise redox-sensitive. Toxic metals, metalloids, and

pesticides can therefore directly engage redox-sensitive inflammatory machinery.

Taken together, oxidative stress and inflammation represent the major mechanistic bridge between pollutant exposure and cardiovascular injury, as emphasized by previous reviews [5,13,31] and by meta-analytic evidence linking pesticide exposure to oxidative stress biomarkers.[42] Additional pathways include metallothionein-1 induction,[43] interleukin 6 (IL-6) release through mitogen-activated protein kinase 3/1 (ERK1/2) activation,[44] suppression of antioxidant enzymes, and uncoupling of mitochondrial respiration.[5] Methylmercury further promotes thrombosis and inflammatory activation.[45] Importantly, heavy metals and organic pollutants also disrupt circadian regulation; cadmium chronotoxicity is a notable example.[46,47] Antioxidant cotreatment can partly attenuate these effects, again underscoring the role of oxidative stress.[48] Copper, even at low concentrations, can also induce ROS generation and lipid peroxidation and may promote endothelial dysfunction through interaction with homocysteine.[49-51]

CHEMICAL POLLUTANTS AND THEIR DISEASE BURDEN

Broad Health Effects Beyond the Cardiovascular System

Chemical contaminants in soil and water can be broadly divided into inorganic pollutants, such as metals and metalloids, and organic pollutants, such as persistent industrial chemicals and pesticides. Both groups have major implications for human health.

Arsenic, cadmium, lead, and mercury are associated with cardiovascular disease, neurodevelopmental injury, and cancer.[4,52-54] Organic contaminants such as polychlorinated biphenyls (PCBs), PAHs, and volatile organic compounds are linked to cancer, reproductive toxicity, and neurological disease.[55-58] Dioxins remain a concern because of their persistence and toxicity.[59,60] PCBs, although banned in many settings, continue to persist in the environment and are linked to endocrine disruption and cancer.[61,62] PFAS are highly persistent and contribute to endocrine and neurodevelopmental effects.[63] Pesticides bioaccumulate and are increasingly associated with chronic diseases, including cancer and asthma.[64]

Metals as Cardiovascular Toxicants

Exposure to toxic metals such as arsenic, lead, cadmium, mercury, and copper has become a major public-health issue.[65-67] Arsenic and cadmium are classified as group I human carcinogens. Chronic exposure to these substances is linked not only to cancers of the bladder, kidney, liver, lung, and skin, but increasingly also to cardiovascular disease. Methylmercury is a potent neurotoxicant,[68] yet it also appears relevant to vascular disease. Arsenic and coexisting metals can independently increase cardiovascular risk.[49] The key point is that even low to moderate exposure levels, common in many populations, are increasingly associated with adverse cardiovascular outcomes.

Pesticides and Endocrine-Disrupting Chemicals

Organophosphate insecticides such as malathion, chlorpyrifos, diazinon, and parathion are designed to inhibit acetylcholinesterase and primarily target the nervous system. Yet, their adverse effects extend beyond neurotoxicity. Persistent organochlorines such as dichlorodiphenyltrichloroethane (DDT), chlorinated industrial chemicals such as PCBs, dioxins, PFAS, and related compounds remain important due to persistence, bioaccumulation, and endocrine disruption. The Stockholm Convention banned many persistent organic pollutants,[69] but legacy contamination remains widespread.

Dioxins are particularly toxic and have been associated with insulin resistance and type 2 diabetes.[70-72] Dioxin-like PCBs are linked to hypertension, hypertriglyceridemia, glucose intolerance, obesity, and diabetes.[5] Polybrominated diphenyl ethers can alter thyroid function and are associated with metabolic syndrome and diabetes.[73] PFAS act as endocrine disruptors and are increasingly implicated in obesity, dyslipidemia, and diabetes,[74-76] with occupational studies also suggesting increased mortality from diabetes and cerebrovascular disease.[77] Bisphenol A (BPA) and phthalates also disrupt endocrine function and may promote cardiovascular disease through adverse effects on lipids, obesity, and diabetes.[74,75]

CARDIOVASCULAR DISEASE AS A SENTINAL OUTCOME OF CHEMICAL EXPOSURE HIDDEN CARDIOTOXINS IN THE MODERN CHEMICAL ERA

A major concern is that known hazards likely represent only the tip of the iceberg. More than 300,000 synthetic chemicals have been introduced over the past decades, and many remain inadequately tested for cardiovascular toxicity.[78,79] These substances are present in consumer products, food chains, indoor environments, and ecosystems, resulting in widespread exposure.[80,81] Weak regulation and incomplete toxicity testing mean that many cardiotoxic effects may only become apparent through epidemiological observation. Figure 3 summarizes major cardiovascular complications linked to chemical exposure.

Epidemiological Evidence: Metals

Evidence linking metals to cardiovascular disease is extensive (Table 1). Historical observations described excess hypertension and stroke among lead-exposed workers.[67,82] Later studies confirmed that even low blood lead concentrations are associated with hypertension.[83,84] Cohort studies subsequently showed higher all-cause and cardiovascular mortality with elevated blood lead levels [85,86](Figure 4). In patients with type 2 diabetes, both blood lead and cadmium were associated with increased all-cause and cardiovascular mortality.[87] Blood selenium and cadmium were also associated with heart failure and mortality, indicating that mixtures of metals may modify risk.[88]

Cadmium exposure has been associated with coronary artery disease, peripheral arterial disease, atherosclerosis, stroke, and cardiovascular mortality.[67,89] Even low urinary cadmium concentrations have been linked to increased cardiovascular risk. Studies examining multiple metals together found associations with both all-cause and cardiovascular mortality.[90] Particularly striking is the estimate that lead exposure may

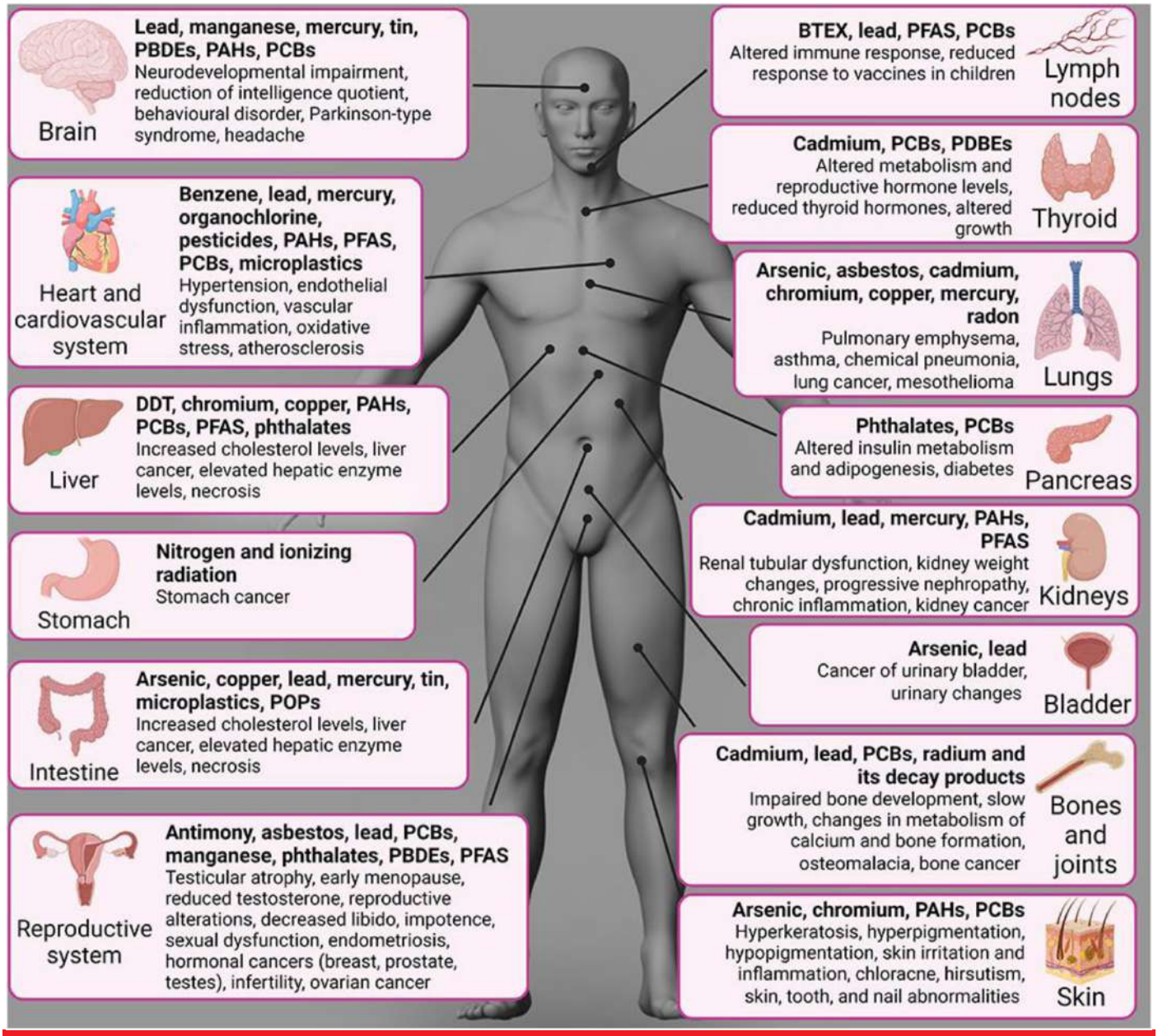

Figure 3. Main effects of soil contaminants on human health, indicating the organs or systems affected and the contaminants causing them. BTEX, refers to the chemicals benzene, toluene, ethylbenzene, and xylene; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PFAS, per- and polyfluoroalkyl substances; POPs, persistent organic pollutants. Adapted from the report of the Food and Agriculture Organization of the United Nations (created from data in the Agency for Toxic Substances and Disease Registry[199] and Campanale et al[200]), https://www.fao.org/3/cb4894en/online/src/html/chapter-04-3.html. Graph[8] modified with permission.

have been responsible for 5.5 million cardiovascular deaths worldwide in 2019.[91]

Mercury exposure has been linked to reduced heart rate variability, hypertension, carotid thickening, accelerated atherosclerosis, myocardial infarction, and cardiovascular mortality.[92] Cobalt toxicity has long been known from "beer drinkers cardiomyopathy" [93] and from occupational exposure in hard-metal industries.[94] Arsenic shows strong dose–response relationships with carotid atherosclerosis, hypertension, ischemic heart disease, diabetes, and peripheral vascular disease.[67,95-97] Copper has also been linked to cardiovascular disease.[98]

Epidemiological Evidence: Pesticides, Plastics, and Endocrine Disruptors

A growing number of epidemiological studies implicate BPA and related plastic chemicals in cardiovascular disease (Table 2). Higher urinary BPA has been associated with prevalent cardiovascular diagnoses,[99] and subsequent studies linked BPA, bisphenol F (BPF), and bisphenol S (BPS) with prevalent cardiovascular disease, hypertension, or

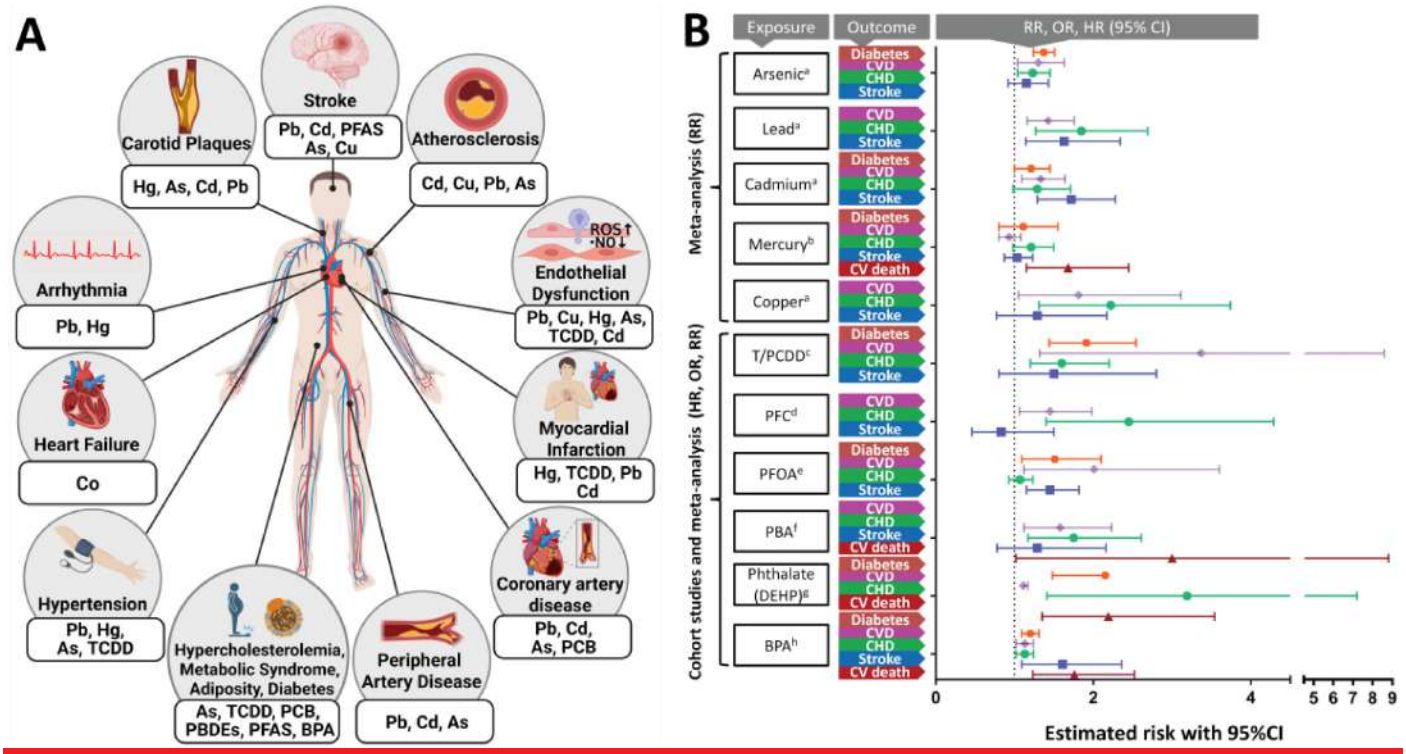

Figure 4. (A) Cardiovascular side effects of toxic chemicals. Graph[8] modified with permission using biorender.com. (B) Association of metals and pesticides with cardiovascular risk. Data taken from a meta-analysis for all metals[a] except mercury[b] (highest versus lowest tertile or highest versus lowest)[36,67] and from cohort studies for pesticides [c] (2nd highest versus lowest quartile, exposed versus unexposed),[201,202] [d] (highest versus lowest quartile),[203-205] [e] (highest versus lowest quartile or quintile),[193,206,207] [f] (highest versus lowest tertile).[208,209] T/PCDD, dioxins; PFC, per- and polyfluorinated chemicals; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PBA, phenoxybenzoic acid; PCB, polychlorinated biphenyls; PBDE, polybrominated diphenyl ethers; BPA, bisphenol-A. Graph[210] modified with permission.

heart failure.[100-104] These findings suggest that replacement bisphenols may not be safer than BPA.

Additionally, PCBs, dioxins, and organophosphates were also associated with cardiac toxicity in epidemiological studies. Acute poisoning by organophosphates can cause profound cardiac toxicity, including bradycardia, ST-segment elevation, conduction abnormalities, QT prolongation, torsade de pointes, and ventricular arrhythmias.[105] High-level exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has been associated with increased mortality from ischemic heart disease and other cardiovascular conditions.[106] Among PCBs, the most cardiotoxic appear to be dioxin-like congeners such as PCB-126.[72,106,107]

Summary Perspective

Chemical contamination of soil and water is not only an environmental problem but a major cardiovascular threat. Heavy metals, pesticides, persistent organic pollutants, and endocrine-disrupting chemicals act through shared mechanisms, especially oxidative stress, inflammation, endothelial dysfunction, and circadian disruption, to drive vascular injury and chronic disease. Although the evidence base is strongest for lead, cadmium, arsenic, mercury, BPA, PFAS, dioxins, and related compounds, many additional cardiotoxic chemicals likely remain unidentified. The burden is therefore likely underestimated, particularly in regions with weak regulation and high cumulative exposure.

MICRO- AND NANOPLASTICS AS EMERGING SOIL AND WATER CONTAMINANTS

A Rapidly Expanding Pollution Problem

Plastic production has increased dramatically over the past decades, from less than 2 million tons in 1950 to about 460 million tons today, with roughly half of all plastic ever produced manufactured since 2002. Without major policy change, production is projected to double by 2040 and triple by 2060, with especially steep growth expected in low- and middle-income countries.[108] At the same time, plastic leakage into the environment has risen sharply. Global plastic waste entering ecosystems is estimated at 44 million tons per year, while the accumulation of plastics in rivers, lakes, and oceans is expected to more than triple by 2060.[108] Most visible plastic waste initially appears as macroplastic debris, but this is only part of the problem. Environmental weathering, abrasion, oxidation, hydrolysis, and photodegradation progressively fragment larger plastic items into smaller particles that disperse widely through soil and water systems.

These particles are now classified according to size as plastic nanoparticles (≤100 nm), nanoplastics (100-1000 nm),

microplastics (1 μm to <1000 μm), mesoplastics, macroplastics, and megaplastics.[109] Of these, micro- and nanoplastics are of greatest toxicological concern because of their biological mobility, persistence, and capacity to interact with cells and tissues[110] (Figure 5). Their widespread presence in soils, inshore waters, rivers, and oceans has raised growing concern not only because of ecological damage but also because of their possible implications for human cardiovascular health. Plastic contamination of seafood and drinking water represents an important route of human exposure, especially for populations that depend heavily on marine food sources.[111] Recent work from the *Lancet Countdown on health and plastics* reinforces this concern by framing plastics as a life-cycle threat to human health, spanning fossil fuel extraction, polymer production, product use, waste generation, and environmental breakdown into micro- and nanoplastics. It also highlights that less than 10% of plastics are recycled and that plastic-related health losses now exceed US$1.5 trillion annually, underscoring the scale of the problem beyond purely environmental metrics.

Mechanisms of Micro- and Nanoplastic Toxicity

Micro- and nanoplastics are not inert particles. At high concentrations, they are directly cytotoxic and can induce cell death through necrosis or regulated pathways.[112] Surface-active agents and additives associated with these particles can disrupt plasma membranes and alter cell signaling. Small nanoparticles, in particular, are readily taken up by cells through endocytosis.[113,114] Once internalized, they may destabilize endosomal membranes, interfere with intracellular trafficking, and damage subcellular organelles such as mitochondria.[115,116] Their accumulation within endosomes and lysosomes can also impair macroautophagy, thereby disturbing cellular quality control mechanisms.[117] In some circumstances, micro- and nanoplastics may stimulate autophagic responses; in others, they may trigger autophagy-associated cell death.[118]

A recurring feature of particle toxicity is the induction of cellular stress. Experimental studies have shown activation of stress pathways such as adenosine monophosphate (AMP)-activated protein kinase in exposed organisms.[119,120] This response is closely linked to excess generation of reactive oxygen species,[121] derived either from damaged mitochondria or from activation of NADPH oxidases.[122] As with classical air pollutants and chemical toxicants, oxidative stress appears to be a central pathway by which micro- and nanoplastics impair vascular and metabolic homeostasis.

These particles also activate innate immune pathways. Damage-associated molecular patterns generated by cellular injury can stimulate Toll-like receptor signaling, resulting in sterile inflammation even in the absence of infection.[123,124] Local inflammatory responses can recruit immune cells, amplify cytokine release, and promote tissue damage. Evidence from aquatic species indicates that nanoparticles can activate innate immune defense systems,[125] and analogous processes are likely to occur in mammalian and human cells.

Plastic Particles as Carriers of Chemical Toxicity

An additional concern is that plastic particles are not only toxic in themselves but also function as carriers for a wide variety of hazardous chemicals. Approximately half of the weight of many manufactured plastics consists of additives, including phthalates, bisphenols, flame retardants, PFAS, PCBs, and heavy metals. These compounds are added to impart flexibility, durability, color, fire resistance, or water repellence, but many are carcinogenic, endocrine-disrupting, neurotoxic, or metabolically harmful. Because many additives are not covalently bound to the polymer matrix, they can leach from plastic particles into the surrounding environment or directly into biological tissues. Thus, micro- and nanoplastics act as mobile vectors for chemical exposure, potentially amplifying toxicity through combined particle and chemical effects.[126,127] This concern is emphasized in the *Lancet Countdown on health and plastics*, which describes plastics as complex chemical materials whose health effects extend far beyond visible debris and include systemic exposure to plastic-associated chemicals throughout the lifecycle.

Cardiovascular Effects of Micro- and Nanoplastics

Although human data remain limited, experimental evidence suggests that micro- and nanoplastics can adversely affect the cardiovascular system through several mechanisms. In vitro studies show that nanoplastics can induce premature endothelial senescence through upregulation of p53, p21, and p16, all key mediators of cell-cycle arrest and vascular aging.[128] Exposure of isolated pig coronary arteries to polystyrene nanoplastics caused endothelial dysfunction, downregulation of endothelial nitric oxide synthase, and increased oxidative stress, mediated in part through the NADPH oxidase/sirtuin (SIRT) pathway.[128] These findings strongly parallel the redox-dependent vascular injury observed with more established pollutants.

Animal studies support these observations. In mice, ingestion of polystyrene beads increased adiposity and promoted cardiometabolic disease.[129] In Wistar rats, microplastics triggered cardiomyocyte pyroptosis via oxidative stress and NLRP3/caspase-1 signaling and promoted cardiac fibrosis through activation of Wnt/β-catenin signaling and apoptosis.[130,131] Other studies have shown that polystyrene nanoplastics can cause vascular injury, structural endothelial damage, coagulation abnormalities, and prothrombotic changes mediated through Janus kinase 1/signal transducer and activator of transcription 3 (JAK1/STAT3)/tissue factor signaling.[132] Additional reported effects include altered heart rate, impaired cardiac function, hemolysis, pericardial effusion, myocardial fibrosis, and a prothrombotic phenotype.[109,133]

Taken together, these data suggest that micro- and nanoplastics can damage the cardiovascular system at multiple levels: by impairing endothelial function, promoting oxidative stress and inflammation, activating inflammasome signaling, accelerating vascular aging, and enhancing thrombosis. In mechanistic terms, they resemble a hybrid toxic exposure, part particle, part chemical mixture, part inflammatory trigger.

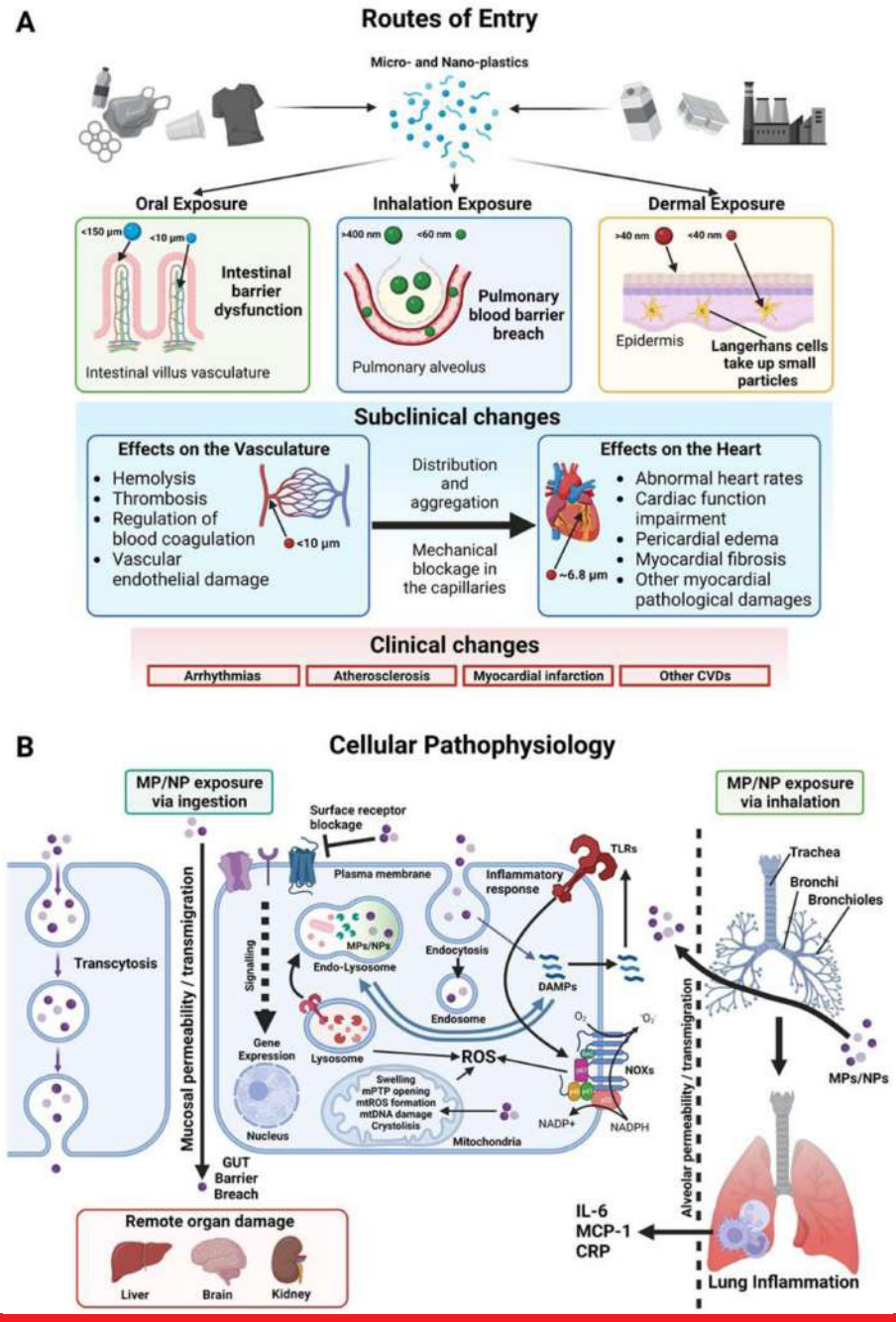

Figure 5. (A) The exposure routes, toxicological, subclinical, and clinical effects of MNPs on the cardiovascular system. Graph[8] modified with permission using biorender.com. (B) Scheme of pathomechanisms of micro- and nanoplastics (MP/NP) toxicity (combination of experimentally confirmed pathomechanisms of MP/NP as well as anticipated processes established for airborne ultrafine and fine particulate matter particles). MPs/NPs uptake is mainly based on ingestion and inhalation. MPs/NPs can, on one hand, increase mucosal and alveolar permeability, allowing transmigration of the particles (e.g. via gut barrier breach or transcytosis). On the other hand, severe lung inflammation caused by MP/NP interaction with phagocytic cells will cause the release of inflammatory cytokines such as IL-6, MCP-1, and CRP to the circulation. Once reaching the circulation and end organs, MPs/NPs can impair signaling via cell surface receptors and thereby cause changes in nuclear gene expression. Endocytosis of MPs/NPs will lead to the formation of endolysosomes, release of damage-associated molecular patterns (DAMPs), and thereby activation of Toll-like receptor (TLR)-mediated inflammatory signaling and oxidative stress. NPs can also directly penetrate into mitochondria and cause multiple functional damages via swelling, cristolysis, opening of the mitochondrial permeability transition pore (mPTP), mitochondrial DNA (mtDNA) damage, and mitochondrial reactive oxygen species formation. Oxidative stress may arise from the NADPH oxidases (NOXs) and damaged mitochondria. Redrawn and modified from Yong et al[112] with permission. © 2020 by the authors (Licensee MDPI, Basel, Switzerland). This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license. Graph[8] modified with permission using biorender.com.

Human Exposure and Translational Relevance

Direct evidence in humans is still emerging, but recent findings are troubling. Micro- and nanoplastics have now been detected in human blood,[134] supporting the view that these particles can cross biological barriers and enter the circulation. Human evidence has also advanced beyond exposure detection alone. A recent systematic review of in vivo human studies concluded that micro- and nanoplastics are detectable across multiple human organs and are already linked, albeit not yet definitively, to inflammation and functional impairment, while underscoring major methodological heterogeneity and the urgent need for standardized exposure assessment and prospective cohort studies.[135] Particularly relevant for cardiovascular medicine, Marfella and colleagues showed that the presence of micro- and nanoplastics in carotid atheromas was associated with a significantly increased risk of the composite endpoint of myocardial infarction, stroke, or death during follow-up, providing the first prospective human evidence linking plaque-associated plastic particles with adverse cardiovascular outcomes.[136] This clinical signal is reinforced by a paired-sample analysis showing that microplastics were detected in all blood and carotid plaque samples, with higher concentrations in plaques than in blood, and that several polymer types were associated with adverse lipid markers, providing further support for systemic exposure and vascular tissue accumulation.[137] The Lancet Countdown on health and plastics further documents that micro- and nanoplastics have been found in human breastmilk, liver, kidney, colon, placenta, lung, spleen, brain, heart, and great vessels, reinforcing the plausibility of direct cardiovascular effects and the need for a precautionary approach.[138] Broader recent reviews have also reinforced the view that exposure through ingestion and inhalation is widespread and that micro- and nanoplastics should increasingly be regarded as credible contributors to chronic disease risk, even though causal inference remains constrained by small study sizes, variable analytical methods, and the lack of large-scale longitudinal studies.[139,140]

ENVIRONMENTAL DRIVERS OF SOIL AND WATER DEGRADATION

Deforestation and Ecosystem Disruption

Deforestation, the large-scale removal of forests, is a major driver of environmental degradation with far-reaching implications for climate, biodiversity, and human health. It is primarily driven by agricultural expansion, logging, mining, and urbanization. Forests play a critical role in carbon sequestration, and their removal releases large amounts of stored carbon dioxide, thereby accelerating climate change. In addition, deforestation disrupts hydrological cycles, altering rainfall patterns and increasing the risk of both droughts and floods.

The ecological consequences are profound. Forest loss leads to biodiversity decline, threatening ecosystem services such as pollination, pest regulation, and soil fertility. These disruptions have direct implications for food security and agricultural productivity. Indigenous and local communities, particularly in regions such as the Amazon and Central Africa, are disproportionately affected, often facing displacement, loss of livelihoods, and erosion of cultural identity.

Although deforestation may yield short-term economic benefits through timber extraction and agricultural expansion, it undermines long-term ecosystem services, including water purification, soil stability, and climate regulation.[141] Increasingly, policy approaches emphasize sustainable forestry, land-use regulation, reforestation, and recognition of ecosystem services in economic decision-making.

Wildfires, particularly in South America, further amplify these effects. The Amazon region, which contains approximately 21% of the world's remaining forests, is increasingly affected by fires linked to deforestation and land degradation.[142] These fires not only release greenhouse gases but also reduce the capacity of forests to absorb them, creating a feedback loop that accelerates climate change.[143] Alarmingly, deforestation levels of 20%-25% may push the Amazon toward an irreversible tipping point, transforming it into a non-forest ecosystem and disrupting regional and global hydrological cycles.[143]

Deforestation also has direct health consequences. Biomass burning releases particulate matter and toxic gases, contributing to cardiovascular and respiratory disease. Moreover, increased human–wildlife contact raises the risk of zoonotic disease transmission, including Ebola and vector-borne diseases such as malaria and dengue.[144] Loss of forest resources further undermines nutrition, water access, and traditional medicine systems.

Airborne Dust and Soil-Derived Particles

Airborne soil particles represent an underappreciated pathway linking soil degradation to human health. Agricultural activities, construction, and unpaved surfaces release dust into the atmosphere, while natural sources, particularly desert regions, generate large quantities of wind-blown (aeolian) dust. The "dust belt" extending from North Africa through the Middle East to Central Asia is the largest global source,[145] contributing 30%-50% of atmospheric aerosol loading.[146]

Although often considered "natural," a substantial proportion of dust emissions is influenced by human activity, including land degradation and desertification. The relative contribution of anthropogenic sources varies geographically, ranging from ~8% in North Africa to ~75% in Australia.[147] Dust particles can be transported over long distances, affecting populations far from their origin (Figure 6).

Health impacts are significant. Assuming similar toxicity to urban particulate matter, desert dust contributes to approximately 1.8% of global cardiopulmonary mortality, rising to 15%-50% in regions close to major dust sources.[148] Climate change is expected to increase dust emissions, making it an increasingly important component of air pollution.[149]

Mechanistically, inhaled dust particles induce oxidative stress and inflammation in the respiratory system, damaging the air–blood barrier.[150] Smaller particles can enter the circulation, triggering systemic inflammatory responses

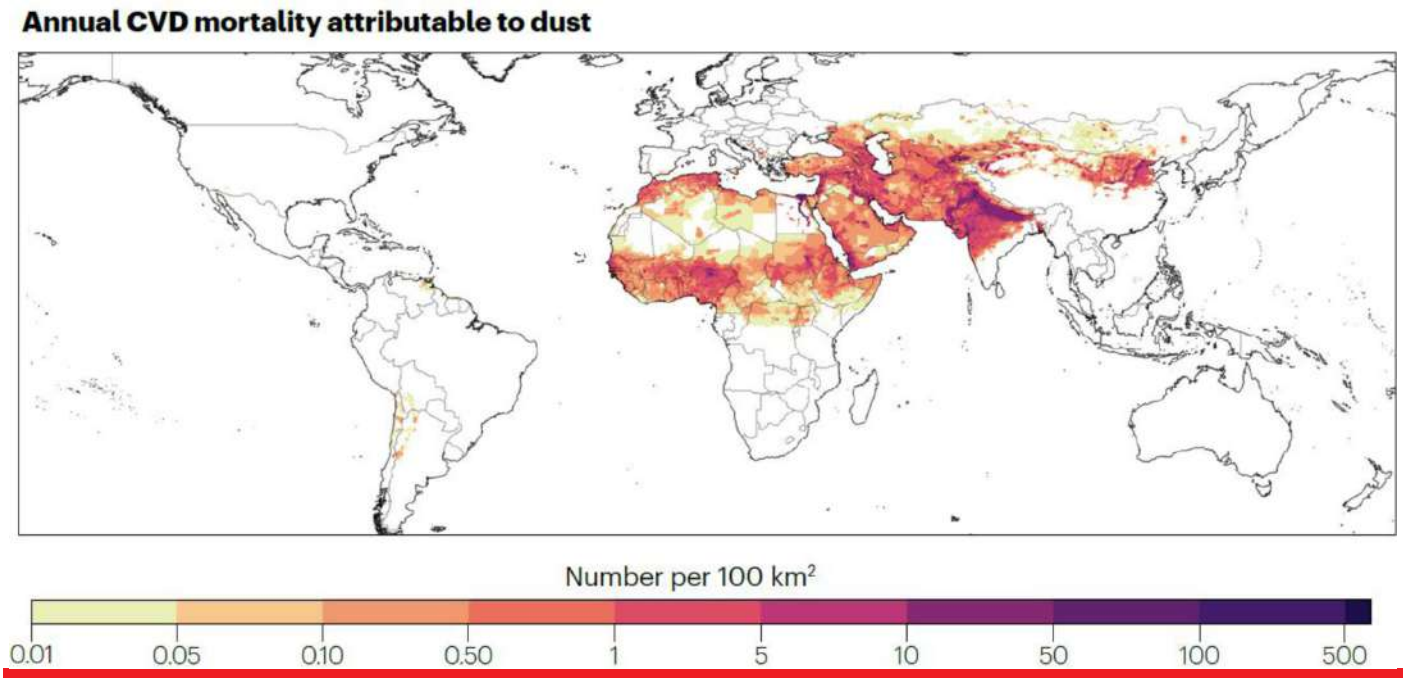

Figure 6. Annual cerebrovascular (stroke) plus ischemic heart disease mortality per area of 10 × 10 km² from exposure to aeolian dust (total CVD mortality). CVD, cardiovascular diseases. Graph[8] modified with permission.

and affecting cardiovascular and cerebrovascular systems.[151,152] Importantly, the toxicity of dust is enhanced by interaction with anthropogenic pollutants. During atmospheric transport, dust particles accumulate acids, metals, and secondary pollutants, increasing their oxidative potential.[153,154]

Epidemiological evidence supports these findings. Dust exposure has been associated with acute myocardial infarction,[155] and meta-analyses show increased cardiovascular mortality with rising dust concentrations.[152] A 10 μg/m³ increase in PM10 from desert dust is associated with a ~2% increase in cardiovascular mortality risk. However, most studies focus on short-term exposure, and long-term effects remain insufficiently understood.

Overfertilization and Nitrogen Cycle Disruption

Human activities have profoundly altered the global nitrogen cycle, primarily through synthetic fertilizer production (Haber–Bosch process), livestock farming, and fossil fuel combustion.[156,157] While reactive nitrogen is essential for plant growth, excessive inputs lead to widespread environmental and health impacts.

Overfertilization results in eutrophication of soils and water bodies, groundwater contamination with nitrates, and atmospheric release of ammonia (NH_3). Ammonia contributes to the formation of fine particulate matter (PM2.5) by reacting with sulfur and nitrogen oxides, particularly in regions with intensive agriculture. In Europe, East Asia, and parts of North America, agricultural ammonia emissions contribute substantially to PM2.5-related mortality, estimated at 20%-40%.[158,159] Given that nearly half of air pollution-related deaths are due to cardiovascular disease,[7] overfertilization indirectly contributes to CVD burden.

Excess nitrogen also leads to acidification, biodiversity loss, and emission of nitrous oxide (N_2O), a potent greenhouse gas that contributes to climate change and stratospheric ozone depletion.[160]

At the individual level, elevated nitrate and nitrite levels have been linked to cardiovascular mortality. Studies show that increased serum nitric oxides (NOx) concentrations are associated with a higher risk of cardiovascular death.[161,162] In a cohort study, elevated NOx levels were associated with nearly doubled cardiovascular mortality risk (HR 1.98, 95% CI=1.10-3.58).[163] These findings highlight the importance of nitrogen pollution as both an environmental and clinical concern.

Urban Design and Environmental Exposure

Urbanization is a defining feature of the modern exposome. Currently, 55% of the global population lives in cities, a proportion projected to reach 68% by 2050, with the majority residing in low- and middle-income countries.[164] While urban environments provide access to healthcare and infrastructure,[165] they also concentrate environmental exposures.

Unhealthy city design contributes to pollution through traffic emissions, industrial activity, and inadequate waste management.[13,166] High levels of nitrogen dioxide, sulfur dioxide, and particulate matter increase the risk of cardiovascular disease, cancer, and neurodegenerative conditions.[3,4]

The lack of green spaces exacerbates these risks. Vegetation improves air quality, reduces heat, and supports mental health, yet many urban areas remain heavily built-up with limited greenery.[167,168] Soil contamination from industrial activities introduces heavy metals and chemicals into urban environments, which can enter the food chain or groundwater.[169]

Urban heat islands, caused by heat absorption from buildings and asphalt—further increase cardiovascular risk, particularly during heatwaves.[168] Car-centric infrastructure reduces physical activity, contributing to obesity, diabetes, and CVD.[170]

Urban runoff carries pollutants, including microplastics and PFAS, into water systems.[5] In addition, noise, overcrowding, and lack of access to natural environments negatively affect mental health.[15]

Sustainable urban planning, emphasizing green spaces, active transport, public transit, and pollution control, is therefore a critical strategy for reducing environmental health risks.[171]

Climate Change as a Cross-Cutting Driver

Climate change acts as a multiplier of environmental risks, affecting soil, water, and air quality simultaneously. Soils are a major carbon reservoir, storing more carbon than the atmosphere,[172] but climate change is altering soil moisture, increasing erosion, and accelerating desertification.[173]

Rising temperatures and extreme weather events mobilize pollutants, increase water contamination, and promote the spread of pathogens. Floods can redistribute contaminants, while droughts concentrate pollutants in water sources.

Climate change also affects air quality. Higher temperatures promote the formation of ozone and secondary particulate matter, while drought conditions increase dust emissions and wildfire frequency.[174,175] Wildfires release large amounts of particulate matter and toxic metals, with significant cardiovascular impacts.

Heat itself is a major cardiovascular stressor. Non-optimal temperatures contribute to more than 7.6% of cardiovascular deaths in Europe.[176] Heat exposure increases heart rate, blood viscosity, and inflammatory responses, exacerbating existing cardiovascular and respiratory diseases.[177] Combined exposure to heat and air pollution further amplifies health risks.[178]

Urban populations are particularly vulnerable due to heat island effects, high pollution levels, and limited adaptive capacity.

Key Concept

Deforestation, airborne dust, overfertilization, urbanization, and climate change are interconnected drivers of soil and water degradation. Through shared pathways—including oxidative stress, inflammation, and ecosystem disruption—these environmental changes contribute substantially to cardiovascular disease and global health risk.

CURRENT GAPS AND FUTURE PRIORITIES

Despite growing recognition of environmental pollution as a major driver of cardiovascular disease, substantial knowledge gaps remain. Human exposure levels across different environmental compartments, soil and water, are still incompletely characterized, particularly for complex mixtures of pollutants. Dose–response relationships are often poorly defined, especially at low, chronic exposure levels that are most relevant for the general population. Moreover, while epidemiological evidence is robust for some exposures such as air pollution and toxic metals, it remains limited or heterogeneous for many other environmental contaminants and combined exposures.

A major limitation is that much of the current evidence base derives from experimental models, including cellular systems and animal studies, rather than large-scale human investigations. However, these studies consistently point toward a convergence of biological effects across diverse pollutants. Key mechanisms include oxidative stress, endothelial dysfunction, inflammation, metabolic dysregulation, pyroptosis, fibrosis, and prothrombotic signaling. The remarkable consistency of these pathways across different environmental stressors strongly supports their biological relevance and argues against considering any single pollutant in isolation.

Future research must move beyond single-exposure paradigms and address the complexity of real-world conditions. Priorities include:

- Quantification of environmentally realistic exposure levels across populations;
- Investigation of chronic low-dose and cumulative effects over the life course;
- Improved understanding of tissue distribution and bioaccumulation;
- Assessment of mixture effects and interactions between chemical and non-chemical stressors;
- Generation of long-term epidemiological data linking environmental exposures to cardiovascular outcomes;
- Development of advanced analytical tools for biomonitoring and exposome research.

Importantly, the absence of complete scientific certainty should not delay action. The history of environmental health repeatedly demonstrates that waiting for definitive causal proof at the population level can result in substantial and preventable disease burden. A precautionary approach is therefore warranted.

Key Concept

Environmental pollutants in soil and water, ranging from metals and pesticides to persistent synthetic chemicals and complex mixtures, act through shared biological pathways, including oxidative stress, inflammation, endothelial dysfunction, vascular aging, fibrosis, and thrombosis. These mechanisms provide a unifying framework linking environmental exposure to cardiovascular disease. Given their global prevalence, persistence, and capacity to interact within the human exposome, these pollutants represent a major, yet still under-recognized, modifiable cardiovascular risk factor.

INTERCONNECTED PATHWAYS: SOIL-WATER-AIR TRANASFER AND THE EXPOSOME

Environmental Compartments are Not Isolated

Soil, water, and air are tightly interconnected environmental compartments that continuously exchange pollutants. Contaminants released into soil rarely remain confined;

instead, they are mobilized through leaching, runoff, volatilization, and resuspension, thereby entering aquatic systems and the atmosphere. This dynamic exchange creates a complex and evolving mixture of exposures that shape the human exposome across the life course.

Agricultural practices represent a major pathway for such transfer. Pesticides, fertilizers, and industrial contaminants accumulate in soil and are transported into rivers, lakes, and groundwater through rainfall and irrigation. Similarly, contaminated sediments can release pollutants back into water systems under changing environmental conditions, prolonging exposure. Industrial emissions deposited onto soil surfaces can later be resuspended into the air as particulate matter, contributing to inhalational exposure.[3]

This continuous cycling of pollutants implies that exposure assessment based on a single environmental medium is inherently incomplete. Instead, individuals are exposed to mixtures of pollutants across multiple pathways: ingestion (food and water), inhalation (airborne particles), and dermal contact, often simultaneously and chronically.

The Exposome Framework: from Single Pollutants to Mixtures

The concept of the exposome provides a useful framework to understand these complex interactions. It captures the totality of environmental exposures across the lifespan, integrating chemical, physical, and biological stressors with social and behavioral determinants. Soil and water pollution are therefore not isolated phenomena but integral components of a broader environmental risk architecture that includes air pollution, noise, heat, and light exposure.

Importantly, co-exposure is the rule rather than the exception. Individuals living in urban or industrialized environments are often exposed simultaneously to heavy metals, endocrine-disrupting chemicals, microplastics, air pollutants, and non-chemical stressors. These combined exposures may interact in additive, synergistic, or even antagonistic ways, complicating risk assessment and potentially amplifying health effects.[5]

Recent epidemiological and experimental studies increasingly support the concept that mixtures of pollutants exert stronger biological effects than individual exposures. For example, combined exposure to metals and air pollution has been associated with enhanced oxidative stress and vascular dysfunction, suggesting convergence on shared mechanistic pathways.[179]

Shared Biological Pathways Across Environmental Stressors

A striking feature of environmental risk factors is the convergence of biological mechanisms across seemingly unrelated exposures. Whether triggered by chemical pollutants, particulate matter, noise, or psychosocial stress, a limited set of core pathways appears to mediate disease development.

Central among these are oxidative stress, inflammation, endothelial dysfunction, autonomic imbalance, and activation of the hypothalamic–pituitary–adrenal axis. Increased sympathetic activity and stress hormone release can further amplify vascular injury and metabolic dysregulation. These processes lead to impaired nitric oxide signaling, increased vascular tone, prothrombotic states, and structural vascular changes.

Circadian disruption represents another unifying mechanism. Environmental exposures, including heavy metals, endocrine disruptors, and artificial light, can interfere with circadian gene expression and biological rhythms, thereby affecting metabolism, blood pressure regulation, and inflammatory responses.[46,131] This may provide an additional link between environmental stressors and cardiometabolic disease.

The convergence of these pathways supports the concept of a "final common pathway" of environmental cardiotoxicity, in which diverse exposures ultimately lead to similar vascular and systemic outcomes.

Vulnerable Populations and Environmental Injustice

The burden of environmental exposure is not equally distributed. More than 90% of pollution-related disease and death occurs in low- and middle-income countries.[16] Rapid urbanization, weak regulatory frameworks, and limited infrastructure for waste management and pollution control contribute to disproportionately high exposure levels in these regions.

Within countries, vulnerable populations, including children, the elderly, and socioeconomically disadvantaged groups, are often more heavily exposed and more susceptible to adverse health effects. Occupational exposures further increase risk in specific groups, such as agricultural workers, miners, and industrial laborers.

Early-life exposure is of particular concern. Developmental windows represent periods of heightened vulnerability during which environmental insults can have long-lasting effects on organ systems, including the cardiovascular and nervous systems. Evidence suggests that prenatal and early childhood exposure to pollutants may predispose individuals to cardiovascular disease later in life.

Climate Change as an Amplifier of Pollution Exposure

Climate change interacts with soil and water pollution in multiple ways, often exacerbating exposure and health risks. Rising temperatures can increase the volatilization of chemicals and accelerate the degradation of plastics into micro- and nanoplastics. Extreme weather events, such as floods and droughts, can mobilize pollutants from contaminated soils into water systems or concentrate them in shrinking water supplies.

Drought conditions may increase reliance on contaminated groundwater, while flooding can disperse industrial and agricultural contaminants over wide areas. In addition, climate-driven changes in ecosystems can alter the distribution and bioaccumulation of pollutants in food chains.

Heat stress itself is a cardiovascular risk factor and may act synergistically with chemical exposures to increase disease risk. Thus, climate change does not represent a separate challenge but rather an amplifier of existing environmental health threats.

Implications for Risk Assessment and Prevention

The interconnected nature of environmental exposures has important implications for both research and policy. Traditional risk assessment approaches, which focus on single pollutants in isolation, are insufficient to capture the complexity of real-world exposures. There is a need for integrated approaches that consider mixtures, multiple exposure pathways, and cumulative risk over time.

From a prevention perspective, this implies that effective strategies must address the broader environmental system rather than individual pollutants alone. Reducing emissions, improving waste management, regulating chemical production, and redesigning urban environments are all necessary components of a comprehensive approach.

Importantly, environmental interventions often yield co-benefits. Measures that reduce pollution, such as transitioning to clean energy, promoting sustainable agriculture, and improving urban design, can simultaneously mitigate climate change, enhance biodiversity, and reduce cardiovascular risk.

Key Concept

Soil, water, and air pollution are interconnected components of a unified environmental exposome. Their combined effects, mediated through shared biological pathways such as oxidative stress and inflammation, drive cardiovascular and systemic disease. Addressing these risks requires integrated, multisectoral strategies that move beyond single-exposure paradigms.

POLICY PREVENTION, AND CLINICAL IMPLICATIONS

Environmental Pollution as a Preventable Cardiovascular Risk Factor

The evidence presented in this Review makes clear that soil, water, and plastic pollution are not only environmental concerns but major, modifiable drivers of cardiovascular disease. Despite this, environmental exposures remain largely absent from clinical guidelines and global prevention strategies for NCDs. Current frameworks continue to prioritize individual lifestyle factors while underestimating structural and environmental determinants of health.[10]

This imbalance represents a critical gap. Unlike many traditional risk factors, environmental exposures are largely involuntary and unequally distributed. As such, they require population-level interventions rather than individual behavioral change. Addressing pollution is therefore not only a matter of environmental protection but a central pillar of cardiovascular prevention.

Policy Failure and the Need for Systemic Change

The persistence of widespread chemical and plastic pollution reflects systemic policy failures. More than 300,000 synthetic chemicals are in global use, yet only a small fraction have been adequately tested for long-term toxicity, including cardiovascular effects.[78,126] Regulatory frameworks are often fragmented, slow to respond, and insufficiently precautionary.

In addition, the true health costs of pollution are largely externalized. Industrial production, fossil fuel use, and plastic manufacturing generate substantial economic benefits for producers while shifting health and environmental costs onto societies, particularly vulnerable populations. The *Lancet Countdown on health and plastics* highlights that plastics alone are associated with health-related economic losses exceeding US$1.5 trillion annually, underscoring the magnitude of these hidden costs. (Figure 7)

A paradigm shift is urgently needed, from reactive regulation to proactive, precautionary governance. This includes stricter chemical safety testing, transparency regarding chemical composition, and lifecycle-based regulation of pollutants from production to disposal.

Priority Actions for Policy and Public Health

Effective prevention of pollution-related cardiovascular disease requires coordinated, multisectoral action. Key priorities include:

- **Reducing emissions at the source** through stricter regulation of industrial chemicals, pesticides, and plastic production.
- **Transitioning to clean energy systems**, thereby simultaneously reducing air, soil, and water contamination.
- **Improving waste management and circular economy strategies**, particularly for plastics.
- **Protecting water resources** through improved monitoring, filtration, and infrastructure.
- **Strengthening international agreements**, including implementation of the European Union Zero Pollution Action Plan and the development of a legally binding Global Plastics Treaty (see the following).

These measures are not only technically feasible but also highly cost-effective when considering the substantial healthcare costs associated with pollution-related disease.

The Role of Clinicians and the Healthcare System

Healthcare professionals have a critical role in addressing environmental determinants of cardiovascular disease. Clinicians should recognize pollution as a major cardiovascular risk factor, comparable in importance to smoking, hypertension, and diabetes, and incorporate environmental exposure into risk assessment and patient counseling.

At the individual level, clinicians can:

- Educate patients about environmental risks and mitigation strategies
- Identify vulnerable populations, including those with high occupational or residential exposure.
- Advocate for preventive measures, such as improved indoor air quality and reduced exposure to contaminated food and water.

At the collective level, healthcare professionals and scientific societies should:

- Advocate for stronger environmental policies
- Integrate environmental risk factors into clinical guidelines
- Support research on environmental determinants of disease

Figure 7. Quantifiable economic losses due to soil pollution. Adapted.[172]

- Engage with policymakers to promote evidence-based regulation

Healthcare systems themselves must also reduce their environmental footprint, as they contribute significantly to greenhouse gas emissions and waste generation.

RESEARCH PRIORITIES AND RESEARCH GAPS

Despite growing evidence, important gaps remain. These include limited data on long-term, low-dose exposure, insufficient understanding of mixture effects, and a lack of large-scale epidemiological studies linking soil and water pollutants to cardiovascular outcomes.

Future Research Should Prioritize

- Improved exposure assessment using biomonitoring and exposome approaches
- Mechanistic studies linking environmental exposures to cardiovascular endpoints
- Longitudinal cohort studies assessing cumulative exposure and disease risk
- Interventional studies evaluating the impact of pollution reduction on cardiovascular outcomes

Bridging these gaps will be essential to strengthen causal inference and inform policy.

A Call to Action: From Evidence to Implementation

The science is now sufficiently robust to justify immediate action. Waiting for absolute certainty risks perpetuating preventable disease and death. The history of public health, from tobacco control to air pollution regulation, demonstrates that early intervention saves lives.

Environmental pollution represents a global cardiovascular risk factor of unprecedented scale. Addressing it requires coordinated action across sectors, disciplines, and political boundaries. Policies that reduce pollution will yield substantial co-benefits, including improved cardiovascular health, reduced healthcare costs, climate mitigation, and enhanced ecosystem resilience.

Policy Frameworks and Economic Burden of Pollution Control

The scale of soil and water pollution poses not only a major health threat but also a profound economic challenge. In the European Union alone, soil degradation is estimated to cost more than €50 billion annually.[180] Approximately 2.8 million potentially contaminated sites have been identified, many of them legacy "brownfield" areas with unclear ownership, suggesting that the true burden is likely underestimated.[181]

Table 1. Cardiovascular Diseases and Outcomes Associated with Metal Exposure in Epidemiological Studies

First Author, Year	Total Sample Size	Exposure	Outcome	Risk Estimate
Schober, 2006 [85]	n = 9,757	Blood lead	All-cause and CVD mortality	Using blood lead levels < 5 microg/dL as the referent, RR of mortality from all causes was 1.24 (95% CI 1.05-1.48) for those with blood levels of 5-9 microg/dL and 1.59 (95% CI, 1.28-1.98) for those with blood levels > or = 10 microg/dL. The magnitude of risk was similar for deaths due to cardiovascular disease.
Lanphear, 2018 [86]	n = 14,289	Blood lead	All-cause, CVD, ischemic heart disease mortality	An increase in the concentration of lead in blood from 1.0 μg/dL to 6.7 μg/dL was associated with all-cause mortality (HR 1.37, 95% CI 1.17-1.60), CVD mortality (1.70, 1.30-2.22), and ischemic heart disease mortality (2-08, 1.52-2.85).
Tsoi, 2021[185]	n = 39,477	Blood lead	Prevalent hypertension	Using quartile 1 as reference, higher blood lead levels were associated with increased odds of hypertension (Quartile 4 OR 1.22, 95% CI 1.09-1.36).
Cook, 2022[186]	n = 15,036	Blood lead	CVD and heart disease mortality	Participants with high lead level (vs. low level) had an increased risk of death from all CVD (HR 1.35, 95% CI 1.03-1.77). Moderate and high lead levels showed an increased risk of death from heart disease (1.37, 1.04-1.81 and 1.60, 1.21- 2.13, respectively). A linear association with all CVD and heart disease deaths was observed (1.08, 1.00- 1.16 and 1.09, 1.02-1.16, respectively, per 1-unit increase in lead levels).
Zhu, 2022 [87]	n = 7,420 for blood lead and n = 5,113 for blood cadmium	Blood lead and cadmium	All-cause and CVD mortality	The geometric mean (interquartile range) concentrations of blood lead and cadmium were 19.6 (11.8, 35.0) μg/L and 0.39 (0.21, 0.60) μg/L, respectively, among patients with type 2 diabetes. Comparing extreme quartiles, the HR of all-cause mortality were 1.51 (1.25-1.82) for blood lead and 1.58 (1.22-2.03) for blood cadmium. The HRs of CVD mortality were 2.27 (1.54-3.34) for blood lead and 1.78 (1.04-3.03) for blood cadmium.
Lee, 2011[187]	n = 1,908	Blood cadmium	Prevalent ischemic heart disease, stroke, and hypertension	An interquartile range (IQR) increase in blood cadmium was found to be associated with an increased risk for ischemic heart disease (OR 2.1, 95% CI 1.3-3.4), and hypertension only among men (OR 1.4, 95% CI 1.1-1.8). No association was observed with stroke.
Tellez-Plaza, 2013 [89]	n = 3,348	Urine cadmium	Incident CVD	HRs comparing the 80th to the 20th percentile of urine cadmium concentrations were 1.43 for cardiovascular mortality (95% CI 1.21-1.70) and 1.34 for CHD mortality (1.10-1.63). HRs for incident cardiovascular disease, coronary heart disease, stroke, and heart failure were 1.24 (1.11-1.38), 1.22 (1.08-1.38), 1.75 (1.17-2.59), and 1.39 (1.01-1.94), respectively.
Li, 2022 [188]	n = 39,865	Blood cadmium	All-cause and CVD mortality	Compared with the lowest quantile of cadmium exposure level group, the HRs in the highest quantile cadmium exposure level group were 1.73 (95% CI 1.52-1.97) for all-cause mortality and 1.72 (95% CI 1.28-2.30) for CVD mortality.
Tellez-Plaza, 2012 [189]	n = 8,989	Blood and urine cadmium	All-cause and CVD mortality	HRs for blood and urine cadmium were 1.50 (95% CI 1.07-2.10) and 1.52 (95% CI 1.00-2.29), respectively, for all-cause mortality, 1.69 (95% CI 1.03- 2.77) and 1.74 (95% CI 1.07- 2.83) for CVD mortality, 1.98 (95% CI 1.11- 3.54) and 2.53 (95% CI 1.54-4.16) for heart disease mortality, and 1.73 (95 CI 0.88-3.40) and 2.09 (95% CI 1.06-4.13) for CHD mortality.
Xing, 2023 [88]	n = 15,689	Blood selenium and cadmium	Prevalent heart failure and CVD and all-cause mortality	Low blood selenium (OR 0.952) and high blood cadmium (OR 1.345) were associated with heart failure. HRs for all-cause mortality was 0.76 (95% CI 0.65-0.88)for high selenium levels compared to low selenium levels. Taking the low cadmium levels as reference, HR for all-cause mortality among high cadmium levels was 1.68 (95% CI 1.44-1.96). Association between selenium, cadmium, and cardiovascular mortality was similar to that of all-cause mortality.

(*Continued*)

Table 1. Cardiovascular Diseases and Outcomes Associated with Metal Exposure in Epidemiological Studies (Continued)

First Author, Year	Total Sample Size	Exposure	Outcome	Risk Estimate
Nigra, 2021[190]	n = 4,990	Urinary total arsenic	Heart disease mortality	HR of heart disease mortality for an increase in urinary total arsenic was 1.20 (0.83-1.74).
Sun, 2021[191]	n = 17,294	Blood mercury	All-cause and CVD mortality	Mean (SD) blood mercury concentration was 1.62 (2.46) μg/L. Comparing the highest with the lowest quartile of blood mercury concentration, the HRs were 0.82 (0.66-1.05) for all-cause mortality and 0.90 (0.53-1.52) for CVD related mortality.
Isiozor, 2023[192]	n = 1,911	Serum copper	CVD mortality	Copper concentrations (mg/l) were categorized into quartiles (<1.0; 1 to <1.1; 1.1 to <1.21; ≥1.21). Using the first quartile as reference, the HR for CVD death in second, third and fourth quartiles were 1.45 (1.05-2.01), 1.69 (1.25-2.27), and 1.68(1.23-2.29), respectively.
Duan, 2020[90]	n = 26,056	Blood lead, cadmium, and mercury and urine barium, cadmium, cobalt, cesium, molybdenum, lead, antimony, titanium, tungsten, and uranium	All-cause and CVD mortality	The blood metal mixture was associated with all-cause mortality (RR 1.38, 95% CI 1.25-1.51) and CVD mortality (RR 1.43, 95% CI 1.06-1.94). The urinary metal mixture was associated with an increased risk of all-cause mortality (RR 1.48, 95% CI 1.30-1.68).

Globally, the financial gap for restoring and protecting ecosystems remains substantial. Achieving Sustainable Development Goal 14—focused on conserving oceans and marine resources—will require approximately US$174.5 billion annually, compared with current investments of only US$25.5 billion, leaving a funding gap of nearly US$149 billion per year.[182] This underscores the urgent need for increased investment in pollution prevention, particularly targeting plastic contamination at its source.

In response, the European Commission has introduced the Zero Pollution Action Plan as a core element of the European Green Deal.[183] Its 2050 vision aims to reduce pollution to levels no longer harmful to human health or ecosystems. Interim 2030 targets include reducing premature deaths from air pollution by 55%, cutting plastic waste at sea by 50% and environmental microplastics by 30%, halving pesticide use and nutrient losses, improving biodiversity by 25%, reducing noise exposure by 30%, and significantly lowering waste generation.[183]

A comparable regulatory framework exists in the United States through the Environmental Protection Agency (EPA), which implements major legislative instruments such as the Clean Air Act, Clean Water Act, Toxic Substances Control Act, Resource Conservation and Recovery Act, and Superfund program to regulate pollutants, manage hazardous waste, and remediate contaminated sites.[184]

Together, these frameworks highlight both progress and persistent gaps. Closing the implementation and funding deficits will be essential to reduce pollution exposure and achieve meaningful health gains.

CONCLUSIONS

Soil, water, and plastic pollution represent a largely invisible but profoundly important driver of global cardiovascular disease. This Review highlights that these environmental exposures are not isolated ecological concerns but central determinants of human health, contributing substantially to the global burden of NCD. The evidence is now compelling: pollutants originating from industrial, agricultural, and urban sources permeate ecosystems, enter the human body through multiple pathways, and converge on a limited set of biological mechanisms, including oxidative stress, inflammation, endothelial dysfunction, and metabolic disruption, that ultimately promote cardiovascular injury.

A key insight is the interconnected nature of environmental compartments. Soil, water, and air continuously exchange contaminants, creating complex exposure mixtures that define the human exposome. This interconnectedness challenges traditional single-exposure frameworks and underscores the need for integrated, systems-level approaches in both research and prevention. Importantly, emerging contaminants such as micro- and nanoplastics exemplify how modern environmental changes introduce new and poorly understood risks with potentially far-reaching cardiovascular implications.

Despite these advances, environmental determinants remain underrepresented in cardiovascular prevention

Table 2. Cardiovascular Diseases and Outcomes Associated with Pesticides and Other Endocrine-Disrupting Exposures in Epidemiological Studies

Lang, 2008[99]	n = 1,455	Urinary BPA	Prevalent CVD	Higher urinary BPA concentrations were associated with cardiovascular diagnoses (OR per 1-SD increase in BPA concentration, 1.39; 95% CI 1.18-1.63).
Shankar, 2012[193]	n = 745	Urinary BPA	Peripheral arterial disease	OR for peripheral arterial disease associated with the highest versus lowest tertile of urinary BPA was 2.69 (95% CI 1.02-7.09).
Sturgeon, 2016[194]	n = 5,080	Urinary phthalate metabolite	CVD mortality	No association between CVD mortality and individual urinary phthalate metabolites was observed. HRs comparing the highest to lowest quartile ranged from 0.73 (0.5-1.2) for mono-ethyl phthalate to 1.4 (0.8-2.5) for mono-(2-ethyl-5-hydroxyhexyl) phthalate.
Bao, 2020[195]	n = 3,883	Urinary BPA	All-cause and CVD mortality	HRs comparing highest vs lowest tertile of urinary BPA levels were 1.49 (95% CI 1.01-2.19) for all-cause mortality and 1.46 (95% CI 0.67-3.15) for cardiovascular disease mortality.
Cai, 2020[196]	n = 9,139	Urinary BPA	Prevalent CVD	In quartile analysis, highest level of urinary BPA was associated with increased prevalence of myocardial infarction (OR 1.73, 95% CI 1.11-2.69) and stroke (1.61, 1.09-2.36), when compared with those at the lowest quartile. Per unit (μg/g creatinine) increment in ln-transformed BPA concentration was shown to be significantly associated with 19%, 19%, 25%, 29%, 20%, and 16% increased ORs of prevalence of congestive heart failure, CHD, angina pectoris, MI, stroke and total CVD among total participants, respectively.
Moon, 2021[100]	n = 11,857	Urinary BPA	Prevalent CVD	OR between BPA and CVD was 1.13 (95% CI 1.02-1.24).
Wang, 2022[101]	n = 1,267	Urinary BPF and BPS	Prevalent CVD	The third tertile concentration of BPS increased the risk of total CVD (OR: 1.99, 1.16-3.40). BPS was positively associated with the risk of coronary heart disease, and the third tertile concentration of BPS increased the CHD risk by 2.22 times (1.04-4.74). No significant association was observed between BPF and CVD.
Chen, 2022[102]	n = 8,164	Urinary BPA, BP-3, and triclosan	Prevalent CVD	OR of CVD 1.09 (95% CI 1.01-1.18) per 1-unit increasement in log-transformed urinary BPA. Compared with the lowest quartile (< 0.9), the OR was 1.30 (1.03-1.65) in the highest quartile (> 3.8). No associations were found for BP-3 and triclosan.
Moreno-Gómez-Toledano, 2022[103]	n = 3,701	Urinary BPF and BPS	Prevalent congestive heart failure and hypertension	BPF showed a statistically significant relationship with congestive heart failure (OR 1.15, 95% CI 1.01-1.30). BPS was positively correlated with hypertension (OR 1.09, 95% CI 1.02-1.17).
Lu, 2023[104]	n = 3,502	Urinary BPA, BPF, and BPS	Prevalent CVD	The highest level of urinary BPA (≥2.5 ng/ml) was significantly associated with a higher CVD prevalence (OR 1.58; 95% CI 1.08-2.3) among all participants in the quartile analysis. Higher levels of urinary BPF were positively associated with CVD prevalence in females (Q2: 1.81, 1.03-3.18; Q4: 1.73, 1.07-2.79) and in the elderly population (Q3: 1.7, 1.16-2.48). No associations were found between urinary BPS levels and CVD.
Chen, 2023[42]	n = 1,467	Urinary BPA	Prevalent blood pressure and hypertension	When the concentration of BPA was in Q4, diastolic blood pressure was increased by 2.08 mm Hg. At the same time, compared to participants in the first quartile (Q1), those from the fourth quartile (Q4) of BPA concentrations had 21% higher odds of hypertension (compared to the lowest quartile, Q1).
Chen, 2023[197]	n = 9,243	Urinary BPA	Cardiovascular and all-cause mortality	Compared to the lowest BPA quartile group, HRs of the highest BPA quartile group were 1.76 (95% CI, 1.23-2.52) for cardiovascular mortality and 1.21 (95% CI, 0.98-1.49) for all-cause mortality.

BP-3, benzophenone-3; BPA, bisphenol A; BPF, bisphenol F; bisphenol S; CHD, coronary heart disease.

strategies and clinical guidelines. This gap reflects not a lack of evidence, but a lag in translation from science to policy and practice. Unlike traditional risk factors, environmental exposures are largely involuntary, unequally distributed, and driven by structural forces, necessitating population-level interventions and strong regulatory action.

The implications are clear. Reducing pollution is one of the most powerful and cost-effective strategies to prevent cardiovascular disease on a global scale. Measures targeting emissions, chemical safety, waste management, and sustainable urban and agricultural practices offer substantial co-benefits for climate, ecosystems, and human health.

At the same time, clinicians and scientific societies must play a more active role in recognizing, communicating, and addressing environmental risks.

Ultimately, protecting soil and water quality is not only an environmental imperative but a medical one. Cardiovascular health cannot be achieved without a healthy environment. Integrating environmental protection into the core of cardiovascular prevention represents a critical step toward a more comprehensive, equitable, and future-oriented approach to global health.

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The HALP Score and Its Association with Respiratory and Intensive Care Outcomes After Minimally Invasive Valve Surgery: The MINI-HALP Study

ABSTRACT

Background: The hemoglobin–albumin–lymphocyte–platelet (HALP) score is an emerging nutritional inflammatory biomarker. Although minimally invasive valve surgery (MIVS) offers advantages over sternotomy, current prediction models such as EuroSCORE II and STS-PROM may not fully capture perioperative vulnerability. Evidence evaluating whether HALP predicts early postoperative recovery in MIVS remains limited.

Methods: This single-center retrospective study included 139 adults undergoing MIVS between January 2020 and June 2025. Patients were stratified based on the median HALP value (≤42.2 vs. >42.2). Baseline characteristics, operative data, and postoperative outcomes were compared. Correlations between HALP and operative risk indices (STS and EuroSCORE II), ventilation duration, intensive care unit (ICU) stay, and hospitalization length were assessed using Spearman's analysis. Receiver-operating characteristic curves evaluated the ability of HALP to predict prolonged intubation and ICU stay.

Results: Higher HALP scores were associated with younger age, better functional status, and lower STS and EuroSCORE II values. Patients with HALP >42.2 had shorter intubation time (9.7 ± 13.3 vs. 16.6 ± 27.2 hours, $P = .013$) and ICU stay (2.3 ± 2.7 vs. 3.1 ± 3.0 days, $P = .021$). All in-hospital deaths occurred in the low-HALP group. The HALP score showed inverse correlations with STS ($r = -0.351$), EuroSCORE II ($r = -0.296$), intubation time ($r = -0.236$), and ICU duration ($r = -0.231$) (all $P < .01$). No significant association was observed with hospitalization time.

Conclusions: A low preoperative HALP score was associated with prolonged ventilation, extended ICU stay, and increased early mortality after MIVS. The HALP reflects biological resilience beyond conventional risk models and may serve as an accessible adjunct for risk stratification. Prospective multicenter studies are needed to confirm these findings and support its incorporation into clinical decision-making.

Keywords: HALP score, ICU stay, minimally invasive valve surgery, risk stratification

INTRODUCTION

The HALP score, first proposed by Chen et al in 2015, integrates hemoglobin, albumin, lymphocyte, and platelet counts into a single index reflecting both nutritional and immune status.[1] This score quantifies the balance between hematologic and metabolic components of systemic health, offering a simple composite indicator derived from routine laboratory parameters.[1] Since its introduction, HALP has been recognized as a composite biomarker linking systemic inflammation, nutritional reserve, and long-term outcomes across various clinical settings.[1] Although the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) and Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) models remain standard tools for surgical risk estimation, both were originally developed in large sternotomy populations and perform inconsistently in minimally invasive valve surgery (MIVS) cohorts.[2-4]

Recent validation studies have shown that, despite reasonable discrimination, these models frequently overpredict operative mortality and show poor

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calibration for the patient selection and procedural characteristics of MIVS.[2,3] Consequently, growing evidence supports the need for procedure-specific or recalibrated risk algorithms better aligned with outcomes in minimally invasive valve surgery.[3,4] In parallel, MIVS has gained widespread adoption as a less invasive alternative to conventional sternotomy; however, evidence regarding its impact on postoperative respiratory and intensive care outcomes remains heterogeneous.[5-9] Several meta-analyses and cohort studies have reported shorter mechanical ventilation times and reduced intensive care unit (ICU) length of stay after MIVS, yet these benefits are not uniformly demonstrated across all surgical subtypes or institutional protocols.[5,6,8] Recent investigations suggest that the observed improvements may be driven more by enhanced perioperative pathways and early extubation protocols than by the surgical access itself.[7,9] Collectively, these findings underscore the heterogeneity of existing evidence and highlight the need for procedure-specific evaluation of postoperative recovery metrics in the minimally invasive era.[5-9]

Despite growing interest in composite nutritional and inflammatory indices, evidence linking the HALP score to postoperative respiratory outcomes and intensive care trajectories remains extremely limited, particularly in the context of minimally invasive valve surgery. Furthermore, established risk prediction systems such as EuroSCORE II and STS-PROM, which were calibrated in full-sternotomy cohorts, often fail to accurately reflect perioperative risk in this surgical subset. Therefore, the present study aimed to evaluate the association between preoperative HALP score and prolonged mechanical ventilation and ICU stay following minimally invasive valve surgery, and to determine whether this hematologic–nutritional index could provide incremental prognostic insight beyond traditional surgical risk models.

HIGHLIGHTS

- This study is the first to evaluate the prognostic value of the hemoglobin–albumin–lymphocyte–platelet (HALP) score in minimally invasive valve surgery (MIVS).
- Patients with low preoperative HALP scores (≤42.2) experienced significantly longer intubation times, extended intensive care unit stays, and all in-hospital deaths occurred exclusively in this group.
- The HALP score showed a significant inverse correlation with established surgical risk indices, including STS and EuroSCORE II, indicating that lower HALP reflects higher predicted operative risk.
- Hemoglobin–albumin–lymphocyte–platele provides additional prognostic insight beyond conventional risk models by capturing nutritional–inflammatory status and biological resilience, which directly influence perioperative recovery.
- Given its simplicity, accessibility, and strong association with postoperative outcomes, HALP may serve as a useful adjunct for preoperative risk stratification in MIVS.

METHODS

Study Design

This single-center, observational, retrospective cohort study was conducted between June 2021 and April 2025 at a tertiary cardiovascular surgery center. A total of 139 consecutive patients who underwent minimally invasive valve surgery during the study period were included in the analysis. The hemoglobin, albumin, lymphocyte, and latelet (HALP) score, a composite nutritional and inflammatory index, was calculated using the following formula: hemoglobin (g/L) × albumin (g/L) × lymphocyte count (/L) ÷ platelet count (/L)[1]. The study population was divided into 2 groups according to the median HALP score (≤42.2 vs. >42.2) to investigate the association between preoperative nutritional-inflammatory status and perioperative outcomes.

All adult patients (≥18 years) who underwent elective minimally invasive aortic, mitral, or tricuspid valve surgery via thoracotomy or mini-sternotomy were eligible for inclusion. Demographic, clinical, laboratory, echocardiographic, and procedural variables were retrieved from institutional electronic medical records and operative reports. Patients were excluded if they had active infective endocarditis, urgent surgery, concomitant coronary artery bypass grafting (CABG) or aortic surgery, emergency procedures for acute aortic dissection or rupture, prior valve surgery within 6 months, hematologic malignancies, chronic inflammatory or autoimmune diseases, severe hepatic dysfunction, chronic renal failure requiring dialysis, or incomplete preoperative laboratory data. The study was approved by the institutional ethics committee (Ethics Committee Approval no: TABED-1/1688/2025-24/09/2025) and conducted in accordance with the Declaration of Helsinki.

Definitions and Outcomes

All perioperative and postoperative variables were defined according to established international consensus guidelines. Postoperative acute kidney injury (AKI) was defined as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or ≥1.5 times baseline within 7 days, in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[10] Postoperative stroke was defined as a new focal neurological deficit lasting more than 24 hours and confirmed by imaging and classified as disabling or non-disabling based on residual neurological impairment.[11]

Re-exploration was defined as reopening of the surgical site for causes such as bleeding, tamponade, or prosthetic valve dysfunction, whereas reoperation or reintervention denoted any subsequent valve surgery or catheter-based procedure performed after the index operation.[12] Infective endocarditis was diagnosed using the modified Duke criteria.[13]

Prolonged intubation was defined as mechanical ventilation lasting ≥24 hours, and prolonged ICU stay as ICU duration ≥2 days following surgery.[14] Prolonged hospitalization was defined as total postoperative length of stay >7 days.[15] Mortality included both cardiac and non-cardiac deaths occurring during the index hospitalization; cardiovascular mortality referred specifically to death due to myocardial

infarction, heart failure, fatal arrhythmia, or valve-related complications.[16]

All outcome data, including mortality and postoperative complications, were obtained from institutional electronic records and cross-checked against national healthcare databases.

Statistical Analysis

The normality of distribution for continuous variables was assessed using both graphical methods and the Shapiro–Wilk test. Continuous variables are expressed as mean ± standard deviation (SD) or median (minimum–maximum), as appropriate, whereas categorical variables are presented as frequencies and percentages. Comparisons between groups classified according to the HALP score (≤42.2 vs. >42.2) were performed using the independent samples *t*-test for normally distributed variables and the Mann–Whitney *U*-test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Because no universally accepted cut-off value for the HALP score exists in cardiac or minimally invasive valve surgery populations, the median HALP value of the cohort (42.2) was used to provide an unbiased, data-driven stratification. This approach ensured balanced group sizes and minimized the risk of misclassification or selection bias associated with externally derived thresholds. In addition, receiver operating characteristic (ROC) curve analyses were conducted to further evaluate the predictive ability of the HALP score for prolonged intubation time, ICU stay, and total hospitalization duration. The area under the curve (AUC) with corresponding 95% CIs was calculated, and the optimal discriminatory threshold of the HALP score was identified using Youden's index.

The relationships between the HALP score and perioperative parameters, including STS, EuroSCORE II, intubation time, ICU stay, and hospitalization duration, were assessed using Spearman's rank correlation coefficient. All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2024 software. A 2-tailed *P*-value <.05 was considered statistically significant.

RESULTS

This single-center study included 139 consecutive patients who underwent minimally invasive valve surgery and were categorized according to the median HALP score (≤42.2 vs. >42.2). Baseline demographic, clinical, and echocardiographic characteristics are summarized in Table 1. The mean age was significantly lower in the high-HALP group than in the low-HALP group (50.28 ± 14.58 vs. 56.16 ± 12.01 years, $P=.033$). Body surface area was higher among patients with HALP >42.2 (1.93 ± 0.18 vs. 1.85 ± 0.20 m^2, $P=.015$). The proportion of male patients was greater in the high-HALP group (62.3% vs. 42.9%, $P=.022$). NYHA class I-II was more frequent among those with HALP >42.2 (91.3% vs. 75.7%, $P=.013$), whereas preoperative atrial fibrillation was more common in the low-HALP group (35.7% vs. 20.3%, $P=.043$). Other baseline variables were comparable between the groups (Table 1).

Preoperative laboratory and surgical characteristics of the study cohort are presented in Table 2. Hemoglobin (14.08 ± 1.33 vs. 12.40 ± 1.59 g/dL, $P<.001$), platelet (229.65 ± 70.23 vs. 291.94 ± 66.53 $\times10^3$/μL, $P<.001$), and albumin (43.84 ± 3.41 vs. 41.80 ± 3.69 g/L, $P=.001$) values significantly differed across the groups. STS (1.24 ± 1.13 vs. 1.90 ± 1.37, $P<.001$) and EuroSCORE II (0.91 ± 0.52 vs. 1.31 ± 1.08, $P=.002$) were lower in patients with higher HALP scores. The rates of aortic valve replacement (49.3% vs. 30.0%, $P=.020$) and right anterior thoracotomy (34.8% vs. 18.6%, $P=.031$) were higher in the high-HALP group, while conventional right thoracotomy was more frequent in the low-HALP group (68.6% vs. 50.7%, $P=.032$). Other procedural parameters were similar between the 2 groups (Table 2).

Postoperative outcomes according to HALP categories are summarized in Table 3. Postoperative sinus rhythm was observed more frequently in the high-HALP group (98.6% vs. 90.0%, $P=.033$), whereas pacemaker implantation was required more often among patients with low HALP (10.0% vs. 1.4%, $P=.033$). Intubation time (9.70 ± 13.34 vs. 16.59 ± 27.16 hours, $P=.013$) and ICU stay (2.30 ± 2.69 vs. 3.06 ± 2.99 days, $P=.021$) were shorter in the high-HALP group. All-cause in-hospital mortality occurred exclusively in patients with HALP ≤42.2 (8.6% vs. 0%, $P=.015$). The remaining postoperative complications were comparable between the 2 groups (Table 3).

Correlation analyses between HALP and perioperative parameters are presented in Table 4. The HALP score showed a significant inverse correlation with both STS ($r=-0.351$, $P<.001$) and EuroSCORE II ($r=-0.296$, $P<.001$). Figure 1 illustrates these relationships between HALP score and operative risk indices. The HALP was also inversely correlated with intubation time ($r=-0.236$, $P=.005$) and ICU stay ($r=-0.231$, $P=.006$), while no significant correlation was found with total hospitalization duration ($r=-0.113$, $P=.187$) (Figure 2).

Subgroup analysis revealed that patients with prolonged intubation (≥24 hours), extended ICU stay (≥2 days), or hospitalization ≥7 days had lower HALP scores, although these differences did not reach statistical significance (Table 5).

DISCUSSION

This study is the first to investigate the prognostic significance of the HALP score in patients undergoing MIVS. The major findings of the present study are summarized as follows: (1) patients with lower preoperative HALP scores (≤42.2) exhibited significantly longer intubation time and ICU stay compared with those with higher HALP scores (>42.2); (2) all in-hospital deaths occurred exclusively in the low-HALP group, suggesting a potential link between impaired nutritional–inflammatory status and early postoperative mortality; (3) the HALP score demonstrated a significant inverse correlation with both established surgical risk indices, namely the STS and EuroSCORE II, indicating that lower HALP values parallel higher predicted surgical risk; and (4) the HALP score was inversely associated with perioperative recovery parameters, including ventilation and intensive care duration, whereas no significant relationship was

Table 1. Comparison of Demographic, Clinical, and Echocardiographic Characteristics by HALP Score Groups

Variables	HALP Score ≤42.2 (n = 70)	HALP Score >42.2 (n = 69)	*P*
Age (years)	56.16 ± 12.01	50.28 ± 14.58	**.033**
Body surface area (m^2)	1.85 ± 0.20	1.93 ± 0.18	**.015**
Sex (Male), n (%)	30 (42.9)	43 (62.3)	.022
Smoking, n (%)	20 (28.6)	24 (34.8)	.431
Hypertension, n (%)	27 (38.6)	23 (33.3)	.520
Hyperlipidemia, n (%)	11 (15.7)	14 (20.3)	.483
Diabetes mellitus, n (%)	8 (11.4)	13 (18.8)	.222
COPD, n (%)	10 (14.3)	7 (10.1)	.456
ASCV), n (%)	6 (8.6)	6 (8.7)	.979
Chronic kidney disease (CKD), n (%)	1 (1.4)	0 (0.0)	.504
Heart failure (HF), n (%)	4 (5.7)	1 (1.4)	.187
Previous cardiac surgery, n (%)	11 (15.7)	8 (11.6)	.480
Previous MVR, n (%)	4 (5.7)	4 (5.8)	.633
Previous AVR, n (%)	1 (1.4)	0 (0.0)	.504
Previous AVR + MVR, n (%)	2 (2.9)	1 (1.4)	.505
Other previous surgery, n (%)	2 (2.9)	1 (1.4)	.505
History of MI, n (%)	1 (1.4)	1 (1.4)	.748
History of PCI, n (%)	3 (4.3)	4 (5.8)	.492
History of TIA or stroke, n (%)	3 (4.3)	2 (2.9)	.507
History of IE, n (%)	1 (1.4)	1 (1.4)	.999
NYHA functional class, n (%)			
I–II	53 (75.7)	63 (91.3)	**.013**
III–IV	17 (24.3)	6 (8.7)	
Left ventricular ejection fraction (LVEF, %)	57.03 ± 7.15	58.32 ± 6.66	.235
LVEDD, mm	5.03 ± 0.73	5.19 ± 0.73	.157
LVESD, mm	3.37 ± 0.72	3.46 ± 0.69	.385
IVS, mm	1.11 ± 0.25	1.15 ± 0.25	.355
Preoperative sinus rhythm, n (%)	45 (64.3)	55 (79.7)	**.043**
Preoperative atrial fibrillation, n (%)	25 (35.7)	14 (20.3)	**.043**

Values are expressed as mean ± standard deviation (SD) or median (minimum–maximum), as appropriate. Bold values indicate statistically significant differences ($P < .05$).
ASCVD, atherosclerotic cardiovascular disease; AVR, aortic valve replacement; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; IE, infective endocarditis; IVS, interventricular septum; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MI, myocardial infarction; MVR, mitral valve replacement; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

observed with total hospitalization time. Collectively, these findings suggest that the HALP score, an easily obtainable preoperative biomarker, may provide complementary prognostic insight beyond conventional risk prediction models in patients undergoing MIVS.

The relationship between systemic inflammatory burden and postoperative recovery has been consistently demonstrated across different cardiac populations. For example, cohorts with active infective endocarditis—characterized by heightened inflammatory activity—exhibit significantly longer ICU stays and higher early mortality.[17] These observations highlight that biological vulnerability plays a key role in early postoperative trajectories, independent of procedural complexity. The HALP score integrates hematologic, nutritional, and inflammatory domains that together influence perioperative resilience and postoperative recovery. Malnutrition and hypoalbuminemia impair wound healing and reduce oncotic pressure, while anemia and lymphopenia limit oxygen delivery and immune response. These factors collectively weaken physiologic reserve, leading to delayed recovery and prolonged ventilation and ICU stay.[18,19] Thus, HALP provides a comprehensive reflection of the host's biologic fitness, independent of procedural complexity.

Mechanistically, each HALP component has a biologically plausible role in postoperative outcomes. Anemia and hypoalbuminemia reduce tissue oxygenation and protein synthesis, lymphopenia reflects immune exhaustion, and platelet activation contributes to thrombo-inflammatory injury.[20] These mechanisms explain the observed association between low HALP and prolonged mechanical ventilation or ICU stay: patients entering surgery with a diminished nutritional–inflammatory reserve exhibit impaired cardiopulmonary adaptation and slower recovery following anesthesia and cardiopulmonary bypass.

Table 2. Comparison of Preoperative Laboratory and Surgical Characteristics by HALP Score Groups

Variables	HALP Score ≤42.2 (n = 70)	HALP Score >42.2 (n = 69)	*P*
Hemoglobin (g/dL)	12.40 ± 1.59	14.08 ± 1.33	**<.001**
Neutrophil count (×10³/μL)	4.69 ± 1.62	4.48 ± 1.35	.561
Platelet count (×10³/μL)	291.94 ± 66.53	229.65 ± 70.23	**<.001**
Monocyte count (×10³/μL)	0.44 ± 0.14	0.45 ± 0.13	.515
Total cholesterol (mg/dL)	177.76 ± 35.76	174.22 ± 46.42	.317
Albumin (g/L)	41.80 ± 3.69	43.84 ± 3.41	**.001**
Creatinine (mg/dL)	0.87 ± 0.24	0.88 ± 0.17	.390
Aortic valve replacement (AVR), n (%)	21 (30.0)	34 (49.3)	**.020**
Mitral valve replacement (MVR), n (%)	33 (47.1)	29 (42.0)	.544
Tricuspid valve replacement (TVR), n (%)	10 (14.3)	4 (5.8)	.096
MVR + TVR, n (%)	2 (2.9)	0 (0.0)	.252
AVR + MVR, n (%)	2 (2.9)	1 (1.4)	.505
Right anterior thoracotomy (RAT), n (%)	13 (18.6)	24 (34.8)	.031
Infra-axillary approach, n (%)	1 (1.4)	2 (2.9)	.495
J-shaped sternotomy, n (%)	8 (11.4)	8 (11.6)	.592
Right thoracotomy, n (%)	48 (68.6)	35 (50.7)	.032
STS score	1.90 ± 1.37	1.24 ± 1.13	**<.001**
EuroSCORE II	1.31 ± 1.08	0.91 ± 0.52	**.002**
Cardiopulmonary bypass time (min)	153.97 ± 59.14	146.81 ± 44.94	.487
Aortic cross-clamp time (min)	104.16 ± 37.94	104.01 ± 30.88	.642

Values are expressed as mean ± standard deviation (SD) or median (minimum–maximum), as appropriate. Bold values indicate statistically significant differences ($P < .05$).
CPB, cardiopulmonary bypass; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HGB, hemoglobin; PLT, platelet count; RAT, right anterior thoracotomy; STS, Society of Thoracic Surgeons; TVR, tricuspid valve replacement; Xcl, aortic cross-clamp; AVR, aortic valve replacement; MVR, mitral valve replacement.

Table 3. Comparison of Postoperative Outcomes by HALP Score Groups

Variables	HALP Score ≤42.2 (n = 70)	HALP Score >42.2 (n = 69)	*P*
Postoperative sinus rhythm, n (%)	63 (90.0)	68 (98.6)	**.033**
Postoperative atrial fibrillation, n (%)	13 (18.6)	8 (11.6)	.251
Postoperative pacemaker requirement, n (%)	7 (10.0)	1 (1.4)	**.033**
Intubation time (hours)	16.59 ± 27.16	9.70 ± 13.34	**.013**
ICU stay (days)	3.06 ± 2.99	2.30 ± 2.69	**.021**
Hospital stay (days)	8.43 ± 5.46	8.06 ± 7.60	.183
Re-exploration, n (%)	8 (11.6)	4 (5.8)	.227
Postoperative bleeding, n (%)	6 (8.6)	1 (1.4)	.060
Postoperative stroke, n (%)	1 (1.4)	0 (0.0)	.504
Postoperative disabling stroke, n (%)	0 (0.0)	0 (0.0)	-
Paravalvular leak, n (%)	1 (1.4)	1 (1.4)	.748
Myocardial infarction (MI), n (%)	0 (0.0)	0 (0.0)	-
Vascular complication, n (%)	2 (2.9)	0 (0.0)	.252
Postoperative acute kidney injury (AKI), n (%)	3 (4.3)	3 (4.3)	.999
Infective endocarditis, n (%)	1 (1.4)	1 (1.4)	.999
Reintervention/Reoperation, n (%)	10 (14.3)	4 (5.8)	.096
Rehospitalization, n (%)	19 (27.9)	20 (29.4)	.850
All-cause mortality, n (%)	6 (8.6)	0 (0.0)	**.015**
Cardiovascular mortality, n (%)	3 (4.3)	0 (0.0)	.125

Values are expressed as mean ± standard deviation (SD) or median (minimum–maximum). Bold values indicate statistically significant differences ($P < .05$).
AKI, acute kidney injury; ICU, intensive care unit; MI, myocardial infarction.

Table 4. Correlation Between HALP Score and STS, ESII, Intubation Time, ICU Stay, and Hospitalization Duration

Variables	*r*	*P*
STS	−0.351	**<.001**
EuroSCORE II	−0.296	**<.001**
Intubation time (hours)	−0.236	**.005**
ICU stay (days)	−0.231	**.006**
Hospitalization duration (days)	−0.113	.187

r; Spearman's correlation coefficient. Bold values indicate statistically significant differences ($P < .05$).
HALP, hemoglobin, albumin, lymphocyte, and platelet; STS, Society of Thoracic Surgeons; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; ICU, intensive care unit.

In line with Demir et al[21] who demonstrated that lower preoperative HALP scores were strongly associated with in-hospital and long-term mortality after tricuspid valve surgery, the results extend the prognostic value of HALP to the minimally invasive valve surgery setting. Although Demir et al did not examine respiratory parameters or perioperative recovery indices such as intubation duration, ICU stay, or hospital length of stay, the study demonstrates that reduced HALP scores are closely linked to prolonged intubation and extended ICU stay in the early postoperative period. This novel observation suggests that impaired nutritional–inflammatory reserve may hinder postoperative respiratory recovery, supporting the broader concept that HALP reflects systemic vulnerability rather than operative complexity. The consistent association between lower HALP values and adverse early recovery metrics in the cohort therefore complements prior evidence linking HALP to increased postoperative risk in other cardiac surgery populations.

Similarly, Koyuncu and Koyun[22] showed that reduced HALP scores strongly predicted 30-day mortality after CABG, a setting characterized by greater ischemic and inflammatory

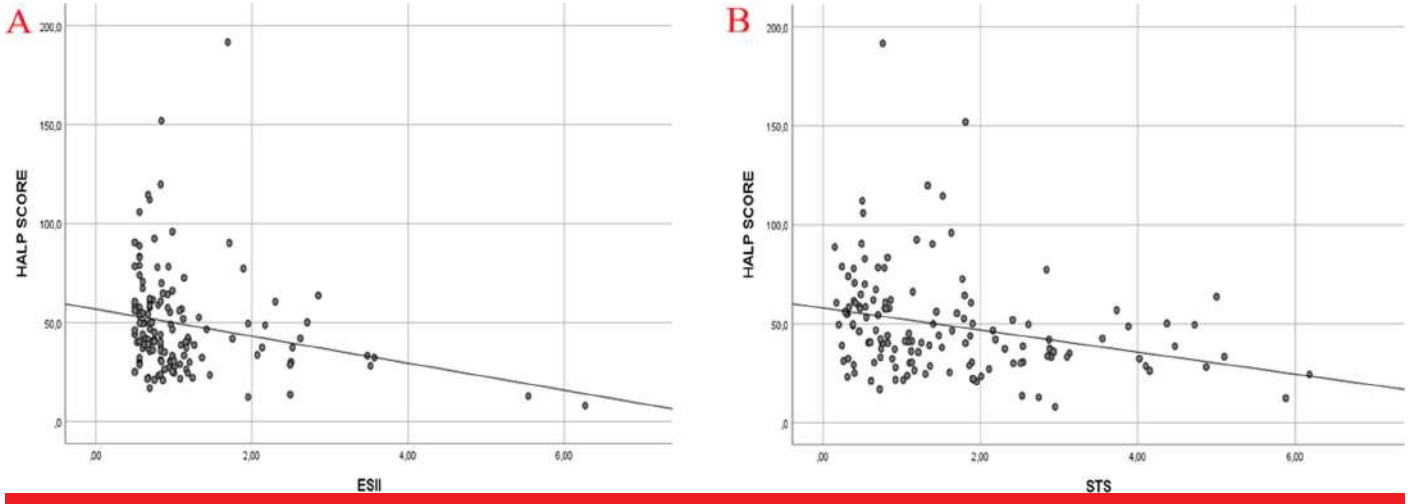

Figure 1. Preoperative HALP score distribution in the study cohort. HALP, Hemoglobin, Albumin, Lymphocyte, Platelet; ESII, EuroSCORE II; STS, Society of Thoracic Surgeons Score.

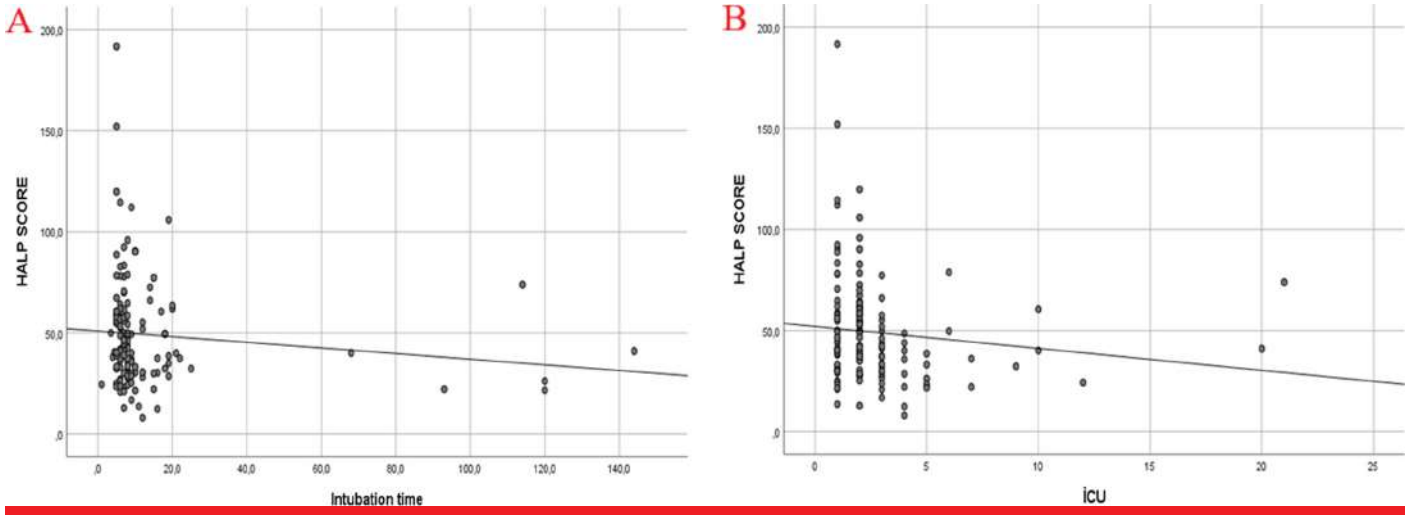

Figure 2. Association between preoperative HALP score and postoperative outcomes. HALP, Hemoglobin, Albumin, Lymphocyte, Platelet; ESII, EuroSCORE II; STS, Society of Thoracic Surgeons score.

Table 5. Comparison of HALP Scores According to Intubation Time, ICU Stay, and Hospitalization Duration Classifications

Variables	Classification	Mean ± SD	Median (Min-Max)	*P*
Intubation time	<24 hours	49.76 ± 26.60	43.8 (8.0-191.7)	.105
	≥24 hours	36.74 ± 18.19	32.3 (21.6-73.9)	
ICU stay	<2 days	54.64 ± 33.94	45.0 (13.6-191.7)	.314
	≥2 days	46.09 ± 20.72	41.9 (8.0-119.8)	
Hospitalization duration	<7 days	52.07 ± 28.25	46.6 (16.8-191.7)	.184
	≥7 days	45.41 ± 23.48	40.5 (8.0-152.0)	

HALP, hemoglobin, albumin, lymphocyte, and platelet; ICU, intensive care unit; SD, standard deviation.

burden. Their findings align with the results and are biologically supported by prior studies demonstrating that malnutrition, anemia, and inflammation impair oxygen transport and delay wound healing.[23,24]

Altunova et al[25] further expanded this relationship by reporting that low HALP values were associated with higher mortality following endovascular aortic repair (EVAR). The findings complement these observations by demonstrating that HALP deterioration manifests early as impaired respiratory recovery—prolonged intubation and extended ICU stay—potentially preceding late adverse outcomes.

Traditional surgical risk models such as EuroSCORE II and STS remain valuable tools for mortality prediction but perform inconsistently in minimally invasive cardiac surgery. In a large minimally invasive mitral valve surgery (MIMVS) cohort, Moscarelli et al[2] reported that EuroSCORE II achieved good discrimination yet consistently overpredicted mortality in low-risk patients. More recently, Berretta et al[26] showed that both STS and EuroSCORE II preserved discriminative capacity but lacked calibration in MIMVS. The findings are consistent with these observations: patients with lower HALP values had both higher predicted surgical risk and worse early recovery metrics, suggesting that HALP provides non-redundant, patient-centered information that captures biological dimensions absent from anatomy-based risk models.

Integrating HALP into preoperative evaluation may enhance risk stratification and help identify patients who could benefit from nutritional or anti-inflammatory optimization before surgery. Such tailored strategies may improve early postoperative recovery without adding procedural risk.

Study Strengths and Limitations

The main strength of the study is its first-in-field evaluation of the HALP score as a preoperative prognostic biomarker, uniquely focused on early respiratory recovery and ICU outcomes in a MIVS population. This study has several limitations that should be acknowledged. First, it was a single-center, retrospective analysis with a relatively limited sample size, which may restrict the generalizability of the findings. Second, the HALP score was calculated from baseline preoperative laboratory data; although this approach reflects real-world clinical practice, future prospective studies with serial perioperative measurements could provide deeper insight into the temporal dynamics of nutritional and inflammatory status. Third, long-term follow-up data were not available, preventing evaluation of the prognostic value of HALP for late morbidity and survival after valve surgery. Finally, the study cohort included patients undergoing different minimally invasive approaches and valve types, which may introduce heterogeneity in operative complexity and recovery time. Although all procedures were performed by the same surgical team using standardized protocols, minimizing inter-operator variability.

CONCLUSION AND RECOMMENDATIONS

In conclusion, a low preoperative HALP score—indicating impaired nutritional and inflammatory status—was independently associated with prolonged mechanical ventilation and ICU stay in patients undergoing minimally invasive valve surgery. The HALP integrates hemoglobin, albumin, lymphocyte, and platelet levels into a single, objective index that reflects biological resilience beyond anatomical or procedural risk factors. Unlike traditional models such as STS and EuroSCORE II, which emphasize surgical complexity, HALP captures host-related vulnerability that directly influences perioperative outcomes. Its simplicity and accessibility support its use as a complementary biomarker for preoperative risk stratification, warranting further validation in larger, multicenter cohorts.

Ethics Committee Approval: The study was approved by the Ankara Bilkent City Hospital Ethics Committee (Ethics Committee Approval No: TABED-1/1688/2025; Date: 24/09/2025) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Hemodynamic Safety of Dexmedetomidine-Fentanyl Sedation During TAVI

ABSTRACT

Background: Transcatheter aortic valve implantation (TAVI) is an established alternative for patients with severe aortic stenosis who are unsuitable for surgical valve replacement. Conscious sedation is preferred to preserve spontaneous respiration and patient cooperation. Dexmedetomidine, a selective α_2-adrenergic agonist, provides sedation, analgesia, and sympatholysis with minimal respiratory depression, making it suitable for high-risk TAVI patients.

Methods: We retrospectively analyzed 53 patients who underwent TAVI under dexmedetomidine-based sedation at a single center between January and July 2025. Patients received an initial loading dose of dexmedetomidine (1 µg/kg over 15 minutes) and fentanyl (1 µg/kg), followed by dexmedetomidine infusion (0.2-1.2 µg/kg/h) to achieve a Ramsay Sedation Score of 3-4 and bispectral index (BIS) 70-80. Hemodynamic parameters were recorded at baseline (T0), post-loading (T1), 10 minutes post-loading (T2), and end of procedure (T3). Hemodynamic compromise was defined as a >30% decrease in systolic or mean arterial pressure(MAP) <65 mm Hg.

Results: The mean age was 76.4 ± 7.3 years, with 58.5% female; all patients were ASA III–IV. Mean arterial pressure (MAP) remained above 65 mm Hg at all time points, with the greatest decrease at T2. Systolic and MAP reductions were consistently below the 30% threshold. Postoperative complications included pacemaker implantation in 2 patients, transient contrast-induced nephropathy in 1, and temporary inotropic support in 4. No anesthesia-related respiratory complications occurred.

Conclusions: Dexmedetomidine combined with fentanyl provides safe and effective sedation for TAVI, maintaining hemodynamic stability and spontaneous respiration. This sedation protocol minimizes perioperative risks and may improve procedural safety in high-risk patients.

Keywords: Conscious sedation, dexmedetomidine, fentanyl, hemodynamic stability, sedation, TAVI, transcatheter aortic valve

ORIGINAL INVESTIGATION

INTRODUCTION

Degenerative calcific aortic stenosis is the most frequent valvular heart disease in Western countries, with a prevalence of about 3% after the age of 75.[1] In severe cases, surgical valve replacement is the standard treatment; however, approximately 30% of these patients are not candidates for surgery due to limited life expectancy and advanced comorbidities. Up to one-third of patients who require lifesaving surgical aortic valve replacement are denied surgery due to a high operative mortality rate.[2] In this patient group, transcatheter aortic valve implantation (TAVI) is considered a life-saving alternative,[3] and this procedure can be performed under conscious sedation. Controlled hypotension is achieved during valve implantation or balloon procedures via a transvenous pacemaker. Transvenous pacing is often used during TAVI procedures to achieve controlled hypotension during valve implantation or balloon valvuloplasty.[4]

Conscious sedation during TAVI aims to prevent pain and discomfort while allowing patient communication.[5] In patients with respiratory instability, severe orthopnea, or those who cannot tolerate sedation, orotracheal intubation and general anesthesia may be necessary during TAVI procedures.

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Dexmedetomidine is a sedative agent with anxiolytic, hypnotic, analgesic, and sympatholytic properties, making it suitable for sedation during TAVI procedures.[6]

It exerts its effects through α_2-adrenergic receptors in the central, peripheral, and spinal cord, without affecting GABA receptors.[7] Dexmedetomidine's ability to maintain spontaneous respiration and patient cooperation makes it a preferred choice in sedative procedures, especially in high-risk patients. Moreover, animal studies have demonstrated that dexmedetomidine protects the heart from ischemic injury, stabilizes cardiac electrophysiology, and prevents arrhythmias.[8] However, its potential to cause bradycardia should be considered, as it may lead to hemodynamic instability in patients with severe aortic stenosis.

This retrospective study aimed to evaluate our institutional experience with dexmedetomidine-based sedation in patients undergoing TAVI.

METHODS

This single-center retrospective study was conducted after obtaining approval from the Local Ethics Committee (decision no. 2025/412, dated 27/08/2025). The need for written informed consent was waived by the ethics committee due to the retrospective nature of the study using the electronic medical records and perioperative anesthesia documents. Data were recorded from the electronic medical records and perioperative anesthesia documents. Patients with missing data, those who received general anesthesia, patients whose anesthesia method was changed for any reason, and those who received sedation techniques other than the routine institutional protocol were excluded from the study.

In our routine protocol, patients undergoing TAVI routinely receive standard ASA monitoring, including invasive arterial pressure monitoring and bispectral index (BIS) monitoring. For sedation, an initial intravenous dose of fentanyl (1 µg/kg) and dexmedetomidine (1 µg/kg over 15 minutes) is administered, followed by a dexmedetomidine infusion at 0.2-1.2 µg/kg/min for maintenance of sedation. If bradycardia occurs during the procedure, the infusion rate is reduced or an alternative anesthetic agent is administered. The maintenance dose is titrated to achieve a Ramsay Sedation Score of 3-4 and a BIS value between 70 and 80.

HIGHLIGHTS

- Dexmedetomidine-fentanyl sedation maintained stable hemodynamics during transcatheter aortic valve implantation (TAVI).
- No anesthesia-related respiratory complications were observed.
- Conversion to general anesthesia was not required in any patient.
- Postoperative complications were minimal and manageable.
- This sedation protocol may enhance safety in high-risk TAVI patients.

Data Collection and Hemodynamic Assessment

Patient demographics, including age, sex, weight, American Society of Anesthesiologists (ASA) physical status classifications, comorbidities, ejection fraction, hospital length of stay, intensive care unit stay, and 1-week and 1-month mortality were recorded. From anesthesia monitoring forms, data on the type of anesthesia administered, drugs used, pre-procedural blood pressure, heart rate, and peripheral oxygen saturation were collected, as well as intra-procedural hemodynamic parameters following drug administration, complications related to anesthesia or the procedure.

Hemodynamic effects after drug administration were assessed by changes in systolic and mean arterial pressures (MAPs). A decrease of more than 30% from baseline in systolic or MAP, or a systolic arterial pressure below 90 mmHg or MAP below 65 mm Hg, was considered a hemodynamic compromise. Baseline hemodynamic data were recorded as T0, hemodynamic parameters after dexmedetomidine administration as T1, measurements 10 minutes after completion of drug administration as T2, and hemodynamic parameters at the end of the procedure as T3.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics Standard Concurrent User V30 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation (SD).

A 1-sample *t*-test was used to compare the sample means with pre-determined reference values. A ≥30% decrease in systolic blood pressure and MAP was defined as the clinically significant threshold. Additionally, a reference value of 65 mm Hg for MAP was considered. In all analyses, a *P*-value of $< .05$ was considered statistically significant.

RESULTS

During the specified study period, data from 68 patients were collected. Of these, 4 patients received general anesthesia, 2 patients developed cardiac arrest due to mechanical complications following valve opening and were switched to general anesthesia, and 2 patients could not receive dexmedetomidine due to bradycardia. Additionally, 5 patients were excluded due to incomplete data. Consequently, data from 53 patients who received sedation and analgesia with dexmedetomidine were analyzed (Figure 1). The mean age of the patients was 76.4 ± 7.3 years, with 58.5% female and 41.5% male. All patients were classified as ASA III or ASA IV (52.8% and 47.2%, respectively). Comorbidities of the patients were diabetes mellitus (66%), coronary artery disease (39.6%), hypertension (32.1%), heart failure (32.1%), chronic obstructive pulmonary disease (11.3%), renal disease (11.3%), and obstructive sleep apnea syndrome (1.9%). Demographic data are presented in Table 1.

The mean systolic arterial pressure of the patients was highest at T0 and lowest at T2 (T0: 150 [25], T1: 110 [18], T2: 100 [15], and T3: 130 [26]). At all time points, the MAP remained above 65 mm Hg. The hemodynamic parameters and sedation scores of the patients are summarized in Table 2.

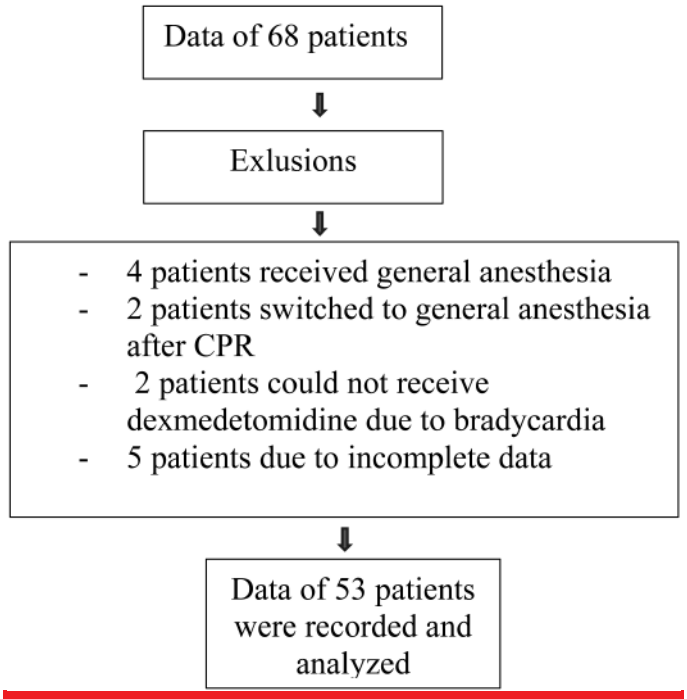

Figure 1. Flow chart.

The mean MAP after drug administration was 86.08 ± 10.6 mm Hg at T1 (difference: +21.07; 95% CI: 18.15-24.00; t(52) = 14.436; $P < .001$), 79.70 ± 12.25 mm Hg at T2 (difference: +14.69; 95% CI: 11.32-18.08; t(52) = 8.731; $P < .001$), and 92.09 ± 13.73 mm Hg at T3 (difference: +27.09; 95% CI: 23.31-30.88; t(52) = 14.358; $P < .001$) (Table 3).

The decrease in MAP after drug administration was significantly lower than the 30% reference value at all time points (Table 4). The mean decrease at T1 was 17.44% ± 15.17% ($P < .001$), at T2 it was 7.17% ± 10.29% ($P < .001$). At T3, the mean change was −7.93% ± 17.51%, indicating that MAP increased by approximately 8 mmHg instead of decreasing ($P < .001$).

Table 1. Demographic Data

Age, years	76.4 ±7.3
Weight	75 [18.5]
EF median	60 [13]
Gender (%)	
Female	31 (58.5)
Male	22 (41.5)
ASA status (%)	
ASA-III	28 (52.8)
ASA IV	25 (47.2)
Comorbidities %	
Diabetes mellitus	35 (66.0)
Coronary artery disease	21 (39.6)
Hypertension	17 (32.1)
Heart failure	17(32.1)
COPD	6 (11.3)
Renal disease	6 (11.3)
OSAS	1 (1.9)
ECG	
SR	48 (90.6)
AF	5 (9.4)
Procedure time (min)	55 [20]

Data are presented as median (IQR), mean ± SD or number (% percentage).
AF, atrial fibrillation; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; ECG, electrocardiography; OSAS, obstructive sleep apnea syndrome; SR, sinus rhythm.

The decrease in systolic arterial pressure after drug administration varied according to time points when compared with the 30% decrease reference value (Table 5). At T1, the mean decrease was 21.94 ± 9.55%, which was significantly lower than 30% ($P < .001$). At T2, the mean decrease was 28.01% ± 14.46%, showing no significant difference from 30% ($P = .161$). At T3, the mean decrease was 14.30% ± 15.32%, significantly lower than 30% ($P < .001$).

The mean intensive care unit (ICU) stay of the patients was 1.94 ± 1.72 days, and the total hospital stay was 5.3 ±

Table 2. Hemodynamic Parameters and Sedation Score at Different Time Points

Time	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (beats/min)
T0	154.02 ± 22.6	81.47 ± 10.8	105.58 ± 12.57	81.58 ± 12.5
T1	119 ± 21.3	69.6 ± 8.07	86.08 ± 10.62	67.17 ± 9.9
T2	100.9 ± 18.3	65.06 ± 11.8	79.7 ± 12.2	63.21 ± 9.3
T3	130.53 ± 22.9	73.09 ± 10.5	92.09 ± 13.7	74.75 ± 12.3

Data are presented as mean ± SD, based on distribution. Normality was assessed using the Kolmogorov–Smirnov test.
DBP, diastolic blood pressure; HR, heart rate; MAP, mean blood pressure; SBP, systolic blood pressure; T0, baseline; T1, after loading dose; T2, 10 minutes later; T3, end of the procedure.

Table 3. Comparison of MAP with Reference Value (65 mm Hg)

MAP	Mean ± SD	Mean Difference (mm Hg)	95% CI	t (df)	*P*
T1	86.08 ± 10.6	+21.07	18.15-24.00	14.436 (52)	< .001
T2	79.70 ± 12.25	+14.69	11.32-18.08	8.731 (52)	< .001
T3	92.09 ± 13.73	+27.09	23.31-30.88	14.358 (52)	< .001

$P < .05$ was considered statistically significant.
CI, confidence interval; MAP, mean arterial pressure; SD, standard deviation; t (df), *t*-test statistic and degrees of freedom.

Table 4. MAP Change Compared to 30% Reference Decrease

MAP decrease	Mean ± SD	Mean Difference (%)	95% CI	t (df)	*P*
T1	17.44 ± 15.17	−12.56	−−16.74-8.38	−6.026 (52)	< .001
T2	7.17 ± 10.29	−22.82	−25.65-−19.98	−16.132 (52)	< .001
T3	−7.93 ± 17.51	−37.93	−42.75-−33.10	−15.76 (52)	< .001

P < .05 was considered statistically significant.
CI, confidence interval; MAP, mean arterial pressure; t (df), *t*-test statistic and degrees of freedom; SD, standard deviation.

Table 5. SBP Change Compared to 30% Reference Decrease

SBP decrease	Mean ± SD	Mean Difference (%)	95% CI	t (df)	*P*
T1	21.94 ± 9.55	−8.056	−10.69-−5.42	−6.141(52)	< .001
T2	28.01 ± 14.46	−1.985	−5.97-2.001	−0.999 (52)	.161
T3	14.30 ± 15.32	−15.69	−19.92-−11.47	−7.456 (52)	< .001

P < .05 was considered statistically significant.
CI, confidence interval; t (df), *t*-test statistic and degrees of freedom; SBP, systolic blood [ressure; SD, standard deviation.

2.55 days. Postoperatively, 2 patients required pacemaker implantation due to heart block, 1 patient developed transient contrast-induced nephropathy, and 4 patients received temporary inotropic support. No patient required inotropic support prior to valve opening. No anesthesia-related complications were observed.

DISCUSSION

Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist that has gained widespread use in sedative procedures due to its unique pharmacological profile. Unlike traditional sedatives such as propofol or benzodiazepines, dexmedetomidine provides sedation while preserving respiratory drive, allowing patients to remain arousable and cooperative during procedures. Its anxiolytic, hypnotic, and sympatholytic properties make it particularly valuable in procedures where patient cooperation and spontaneous respiration are essential, including dental sedations, endoscopic interventions, fiberoptic interventions, minor surgical procedures, and cardiac catheterizations.[9-12]

In recent years, dexmedetomidine has also been increasingly investigated as a sedative agent in patients undergoing TAVI. Compared to agents such as propofol, midazolam, and remifentanil, dexmedetomidine has been associated with more stable hemodynamic parameters and lower rates of respiratory depression, which are critical considerations in this high-risk population.[6,13,14] Mayr et al[13] compared dexmedetomidine with a combination of propofol-opioid during transfemoral TAVI and found that dexmedetomidine offered better hemodynamic support, less need for conversion to general anesthesia, and more favorable gas exchange parameters.[13] Another more recent systematic review by Chowdhury et al[15] compared dexmedetomidine vs. propofol for sedation in adult patients undergoing cardiac procedures and reported that dexmedetomidine demonstrated superior respiratory safety—fewer incidents of respiratory depression—while maintaining hemodynamic stability. Moreover, its sympatholytic effects may attenuate peri-procedural stress responses, further supporting its role as a preferred agent in TAVI procedures. Song et al[16] reported that in patients undergoing TAVI, the use of dexmedetomidine was associated with significant reductions in myocardial injury markers such as troponin I and CK-MB, suggesting a potential cardioprotective role. This finding indicates that in procedures with high cardiac stress, such as TAVI, dexmedetomidine may provide not only effective sedation but also myocardial protection.

In the context of TAVI, especially in elderly patients with severe aortic stenosis and multiple comorbidities, sedation management poses significant challenges. Hemodynamic instability, respiratory depression, and procedural complications are major concerns. Our study demonstrates that a combination of dexmedetomidine and fentanyl provides effective sedation while maintaining MAP above clinically significant thresholds and avoiding significant drops in systolic blood pressure. Importantly, no anesthesia-related respiratory complications occurred, highlighting the safety of this regimen in a vulnerable patient population.

These findings align with previous reports suggesting that dexmedetomidine offers superior hemodynamic and respiratory safety compared to traditional sedatives. The absence of severe perioperative complications, along with stable hemodynamics and preserved patient cooperation, underscores the clinical relevance of this sedation strategy.

Clinically, this study provides practical evidence that dexmedetomidine-fentanyl sedation can be safely implemented in routine TAVI procedures in patients at high perioperative risk. This approach may contribute to reduced hemodynamic stress and improved overall procedural safety. Our results may guide anesthesiologists in optimizing sedation protocols for elderly, high-risk TAVI patients, reinforcing the importance of individualized, hemodynamically stable sedation strategies in structural heart interventions.

Study Limitations

This study is retrospective and single-center, with a modest sample size. Future prospective, multicenter studies are warranted to confirm these findings and to further assess the impact of dexmedetomidine-fentanyl sedation on clinical outcomes such as long-term cardiovascular events and hospital resource utilization.

CONCLUSION

In conclusion, dexmedetomidine combined with fentanyl provides safe and effective sedation for TAVI, maintaining hemodynamic stability and spontaneous respiration. This regimen minimizes perioperative risk, improves procedural safety in high-risk patients, and represents a clinically relevant alternative to general anesthesia.

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Ethics Committee Approval: This study was approved by the Ethics Committee of İzmir City Hospital (Approval No.: 225/412; Date: August 27, 2025).

Informed Consent: No informed consent was obtained from the patients due to the retrospective design of the study, and the requirement for informed consent was waived by the Local Ethics Committee.

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Author Contributions: Concept – G.G.C.; Design – G.G.C.; Supervision – H.H.S.; Resources – G.G.C.; Materials – H.H.S.; Data Collection and/or Processing – G.G.C.; Analysis and/or Interpretation – G.G.C.; Literature Search – G.G.C.; Writing – G.G.C.; Critical Review – H.H.S.

Declaration of Interests: The authors have no conflicts of interest to declare.

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The Postoperative Course of Troponin T and NT-proBNP Levels in the Pediatric Population Implanted with the HeartMate 3 Device

ABSTRACT

Background: Cardiac troponin T (cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are key biomarkers reflecting myocardial injury and hemodynamic load in heart failure or after cardiac surgery. However, data on their postoperative course in pediatric HeartMate 3 (HM3) recipients are limited. This retrospective case series of ten pediatric patients aimed to evaluate the clinical significance of postoperative changes in these biomarkers.

Methods: This retrospective case series included pediatric patients who underwent left ventricular assist device (LVAD) implantation between 2022 and 2024 at the center. Clinical and laboratory data were retrospectively obtained from medical records.

Results: Ten patients with dilated cardiomyopathy (PEDIMACS profiles 1-3) were included. The median preoperative cTnT level was 98.5 [IQR 42.5-236.5] ng/L. Median postoperative cTnT levels were 182.6 [IQR 88.3-342.9] ng/L at 1 month, 54.0 [IQR 32.0-92.0] ng/L at 6 months, and 43.2 [IQR 25.8-71.4] ng/L at 12 months. Median B-type natriuretic peptide (BNP) levels were 7510 [IQR 5350-10850] ng/L preoperatively, 4122 [IQR 2963-7288] ng/L at 1 month, 853 [IQR 520.3-1426] ng/L at 6 months, and 1041 [IQR 619.8-1524] ng/L at 12 months. The mean intensive care unit (ICU) stay was 24.1 ± 16.3 days. Troponin levels returned to normal by postoperative month 6 in all but 2 patients. Spearman analysis showed a significant positive correlation between preoperative cTnT and ICU stay ($\rho = 0.687$, $P = .028$).

Conclusion: In pediatric HM3 recipients, cTnT and NT-proBNP levels reflect postoperative myocardial recovery and may serve as clinically useful indicators associated with intensive care duration.

Keywords: Bridge to heart transplantation, dilated cardiomyopathy, HeartMate 3, left ventricular assist device, NT-proBNP, pediatric heart failure, troponin T

INTRODUCTION

Pediatric heart failure, although relatively uncommon during childhood, is a serious clinical condition associated with high morbidity and mortality. In patients who progress to end-stage heart failure, heart transplantation remains the most effective and definitive treatment option. However, the limited availability of suitable organ donors has led to the increasing use of ventricular assist devices (VADs) in the pediatric population as a bridge-to-transplantation therapy. In addition, in conditions such as myocarditis or systemic diseases, VADs can also be used to support myocardial recovery or serve as destination therapy.[1,2]

In recent years, advancements in VAD technology have transformed these devices from temporary bridge therapies into durable treatment options that prolong survival and enhance functional capacity.[3] These devices aim to maintain systemic circulation, preserve end-organ perfusion, and reduce the adverse multiorgan effects of heart failure until transplantation becomes feasible. Nevertheless, repeated hospitalizations, infection, bleeding, thrombosis, and right ventricular failure remain major complications that limit the widespread clinical use of VAD therapy.[4,5]

ORIGINAL INVESTIGATION

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The HeartMate 3 (HM3) device (Abbott Corp., USA) is a new-generation left ventricular assist device (LVAD) that provides continuous centrifugal blood flow through complete magnetic levitation technology. With these technological features, it aims to reduce the incidence of pump thrombosis, hemolysis, and embolic complications.[6,7] However, due to its size, which poses anatomical limitations in small children, the use of HM3 in the pediatric population has so far been reported only by a limited number of centers.[8]

During the postoperative recovery period following VAD implantation, cardiac biomarkers—particularly cardiac troponin T (cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) serve as important clinical indicators for monitoring myocardial stress and hemodynamic improvement. Although numerous studies have investigated these parameters in the adult population, data regarding long-term biochemical changes in pediatric patients remain limited.[9]

Myocardial injury after cardiac surgery may develop due to several factors, including prolonged cardiopulmonary bypass time, inadequate cardioprotection, systemic inflammatory response, or direct myocardial trauma. In this process, the troponin complex is considered one of the most sensitive and specific biomarkers of myocardial injury.[10-12] Troponin T levels usually begin to rise within 3-6 hours after myocardial injury, peak at 12-24 hours, and then gradually decline.[13] With these characteristics, it represents a clinically valuable parameter for assessing postoperative myocardial stress and recovery.

In adult populations, troponin levels have been reported to possess prognostic value in predicting cardiac complications, mortality, and intensive care unit stay duration.[12-14] However, in pediatric patients, the dynamics and prognostic significance of troponin T levels following LVAD implantation have not yet been well defined.

Another biomarker used in the assessment of heart failure is B-type natriuretic peptide (BNP) and its inactive fragment, NT-proBNP, which reflect ventricular wall stress and volume overload. These biomarkers are widely used in adults for the diagnosis, risk stratification, and prognostic evaluation of heart failure. However, in the pediatric population, standard reference ranges and cutoff values have not yet been clearly established due to age and body surface area–related variability. Furthermore, BNP and NT-proBNP are particularly sensitive for detecting postoperative right ventricular dysfunction, which represents one of the most important complications after left ventricular assist device implantation in children with dilated cardiomyopathy. Global cardiac hypokinesia and altered ventricular loading conditions may predispose these patients to right ventricular failure, making postoperative management challenging. Therefore, evaluation of NT-proBNP levels during the postoperative period may provide clinically relevant insight into hemodynamic changes and ventricular adaptation following mechanical circulatory support.[7,8,15-18]

In this study, the postoperative course of troponin T and NT-proBNP levels was retrospectively evaluated in pediatric patients implanted with the HM3 device. The timing of normalization of these biomarkers and their possible associations with intensive care unit stay duration were analyzed, and the findings were discussed in the context of the existing literature.

HIGHLIGHTS

- Troponin T and N-terminal pro-B-type natriuretic peptide levels reflect postoperative myocardial recovery in pediatric HeartMate 3 recipients.
- A significant correlation was found between preoperative troponin T levels and intensive care unit stay duration.
- Biomarker normalization by 6 months indicates improved ventricular unloading and recovery.
- Genetic cardiomyopathies may cause delayed biochemical recovery.
- Troponin T can serve as a potential prognostic marker in pediatric left ventricular assist device management.

METHODS

This retrospective case series included pediatric patients who were diagnosed with advanced heart failure between 2022 and 2024, listed for heart transplantation, and implanted with a LVAD as a bridge to transplantation. All patients were followed at the center. The study was approved by the Ege University Medical Research Ethics Committee (Approval No.: 25-6.1T/16; Date: 26.06.2025). Demographic data (age, sex, and body weight), primary diagnoses, PEDIMACS profiles, and pre- and post-operative clinical parameters were retrospectively reviewed from medical records. All patients were diagnosed with dilated cardiomyopathy, and the HM3 (Abbott Corp., USA) was used as the mechanical circulatory support device.

In each patient, serum high-sensitivity cardiac troponin T (hs-cTnT) and NT-proBNP levels were assessed preoperatively and during postoperative follow-up at 1 week, and at 1, 3, 6, and 12 months.

Troponin T levels were measured using an electrochemiluminescence immunoassay (ECLIA) method on Roche Diagnostics Elecsys 2010 or Cobas e601 platforms. The measurement range was 3-10000 ng/L, with an upper reference limit of 14 ng/L.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were also determined using the ECLIA principle on the Roche Cobas e601 analyzer. The measurement range was 5-35,000 ng/L, and the upper reference limit was accepted as 125 ng/L.

Venous blood samples were collected, centrifuged, and analyzed within 24 hours while stored at 2-8°C. All measurements were performed under the same laboratory conditions without changes to the device or calibration standards.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed with the Shapiro–Wilk test.

Non-normally distributed variables were summarized as median (minimum–maximum).

Correlation analysis: The relationship between serum TnT and NT-proBNP levels and the duration of intensive care unit (ICU) stay was evaluated using the Spearman correlation test.

Changes in troponin T levels measured preoperatively and at postoperative day 1, day 3, day 7, day 14, and at 1, 3, 6, and 12 months were analyzed using the Friedman non-parametric repeated-measures analysis of variance, given the small sample size and non-normal distribution of the data. When a significant overall time effect was detected, post-hoc pairwise comparisons were performed using the Wilcoxon signed-rank test with Bonferroni correction to evaluate at which postoperative time point troponin T levels converged with preoperative values. Group comparisons: Based on the mean ICU stay (24 days), patients were divided into 2 groups as "short-stay" (<24 days) and "long-stay" (≥24 days). Differences in biochemical parameters between the 2 groups were analyzed using the Mann–Whitney *U*-test. A *P*-value of $< .05$ was considered statistically significant.

RESULTS

A total of 10 patients were included in the study; 4 (40%) were male and 6 (60%) were female. The ages ranged from 8 to 17 years, with a median age of 13 years [IQR 10.5-14.75]. All patients were diagnosed with dilated cardiomyopathy, and their PEDIMACS profiles ranged from 1 to 3. Genetic testing revealed Carvajal syndrome in 1 patient and Limb-Girdle muscular dystrophy in another. All cases were supported with the HM3 device. The mean ICU stay duration was 24.1 ± 16.3 days. During follow-up, 1 patient died on postoperative day 18.

Correlation analysis demonstrated a positive but not statistically significant relationship between BNP levels and ICU stay duration ($r = 0.667$, $P = 0.071$). In contrast, a significant positive correlation was found between preoperative troponin T levels and ICU stay duration ($r = 0.687$, $P = 0.028$). Patients with ICU stay durations longer than the mean value (24 days) had significantly higher preoperative troponin T levels (Mann–Whitney *U*-test, $P = 0.016$). The demographic and clinical characteristics of the patients, as well as their ICU stay durations, are summarized in Table 1.

Table 1. Demographic Data and Pediatric ICU Stay Durations

Case	Age	Weight (kg)	Sex	ICU Stay (Days)	Diagnosis
1	15	32.0	Male	31	Limb-Girdle muscular dystrophy
2	13	28.0	Female	5	DCM
3	12	40.0	Female	11	DCM
4	10	24.0	Female	29	DCM
5	17	46.0	Male	12	DCM
6	14	42.0	Female	36	Carvajal syndrome
7	8	19.0	Male	59	DCM
8	10	26.0	Female	9	DCM
9	16	52.0	Female	23	DCM
10	13	nan	Male	20	DCM

Most patients were diagnosed with dilated cardiomyopathy (DCM). One patient had Carvajal syndrome and 1 had Limb-Girdle muscular dystrophy.
ICU, intensive care unit.

In the preoperative period, troponin T (cTnT) levels ranged from 15 to 589 ng/L, with a median of 98.5 ng/L [IQR 42.5-236.5]. The highest preoperative troponin level was observed in the patient with Limb-Girdle muscular dystrophy carrying a homozygous mutation in the SGCA gene (Case 1). On postoperative day 1, cTnT levels ranged from 554 to 23254 ng/L, with a median of 1104.5 ng/L [IQR 818.8-2663.3]; the highest level was recorded in the patient with Carvajal syndrome (Case 6). On postoperative day 7, troponin levels ranged from 320 to 1890 ng/L, with a median of 880 ng/L [IQR 620-1320].

At 1 month postoperatively, cTnT levels ranged from 18 to 1580 ng/L, with a median of 48 [IQR 32-105]; at 3 months, values ranged from 7 to 45 ng/L, with a median of 18 ng/L [IQR 10-25]. At 6 months, cTnT levels were between 5 and 38 ng/L, with a median of 12 ng/L [IQR 7-18], and at 12 months, they ranged from 4 to 33 ng/L, with a median of 10 ng/L [IQR 6-14]. The temporal changes of postoperative troponin and NT-proBNP levels by day are presented in Table 2, and their

Table 2. Postoperative Troponin T Levels by Time Point

Case	Preop TnT	Postop Day 1 TnT	Postop Day 7 TnT	Postop 1M TnT	Postop 3M TnT	Postop 6M TnT	Postop 12M TnT
1	27	554	686	63	16.0	17.0	23.0
2	21	770	547	56	31.0	29.0	20.0
3	18	773	878	54	11.0	6.0	5.0
4	20	1008	1192	71	12.0	12.0	5.0
5	15	3344	2648	120	19.0	11.0	8.0
6	589	23254	4742	207	662.0	25.0	191.0
7	44	956	467	54	16.0	14.0	21.0
8	19	1545	1058	99	9.0	8.0	11.0
9	25	1589	476	70	15.0	11.0	10.0
10	16	3036	2123	1580	nan	nan	nan

Troponin T levels peaked immediately after surgery and decreased progressively, approaching the normal range in most patients within 6-12 months.

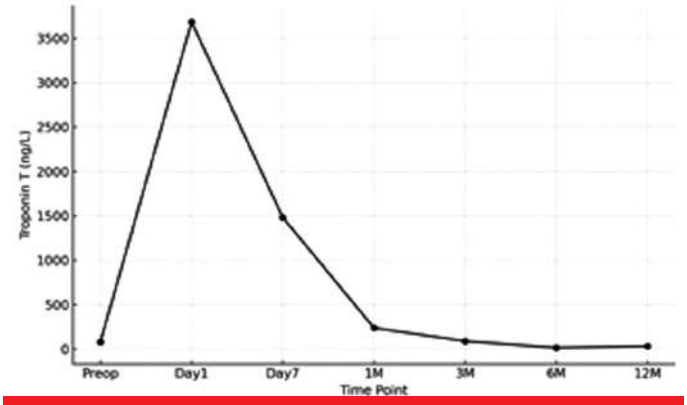

Figure 1. Postoperative 1-year trajectory of patients' cardiac troponin T (cTnT) levels. (This figure illustrates the temporal trend of serum troponin T concentrations throughout the first postoperative year.)

monthly trends are illustrated in Figure 1. Consistent with these descriptive findings, Friedman analysis demonstrated a statistically significant change in troponin T levels over time across the preoperative and postoperative measurements (overall time effect). In post hoc pairwise comparisons (Wilcoxon signed-rank tests with Bonferroni correction), troponin T showed an early postoperative increase followed by a gradual decline, approaching preoperative values during mid- to long-term follow-up.

On postoperative day 1, NT-proBNP levels ranged from 3130 to 23693 ng/L, with a median of 11138 ng/L [IQR 5889-15724]. On postoperative day 7, NT-proBNP levels ranged from 2800 to 20400 ng/L, with a median of 9020 ng/L [IQR 6400-13250]. At 1 month, levels ranged from 1650 to 8900 ng/L, with a median of 4600 ng/L [IQR 3250-5800]. At 3 months, NT-proBNP levels were between 665 and 1887 ng/L, with a median of 1071 ng/L [IQR 725-1550]. At 6 months, levels ranged from 180 to 1887 ng/L, with a median of 853 ng/L [IQR 450-1268], and at 12 months, from 222 to 2105 ng/L, with

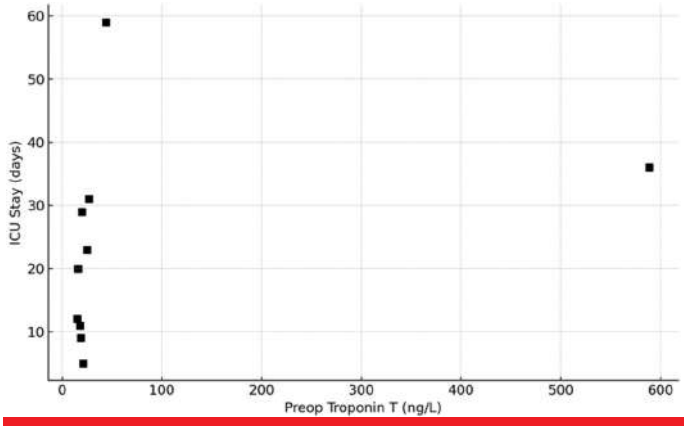

Figure 2. Correlation between preoperative troponin T levels and intensive care unit (ICU) stay duration. (The scatter plot demonstrates the relationship between preoperative cTnT values and postoperative ICU length of stay, with the regression/LOWESS line indicating the overall trend.)

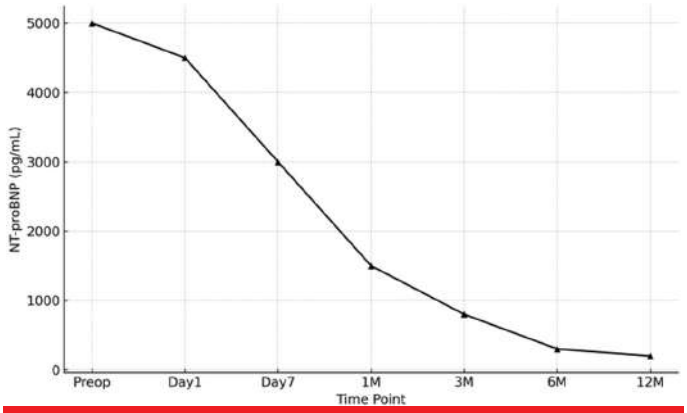

Figure 3. Postoperative 1-year trajectory of patients' N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. *(NT-proBNP declined markedly within the first 6 months and then stabilized.)*

a median of 980 ng/L [IQR 445-1480]. The temporal changes in NT-proBNP levels are shown in Figures 2 and 3.

The duration of ICU stay ranged from 5 to 59 days, with a mean of 24.1 ± 16.3 days. According to Spearman correlation analysis, postoperative day 1 NT-proBNP levels showed a positive but statistically non-significant correlation with ICU stay duration ($\rho = -0.395$, $P = .258$) (Figure 4).

When patients were grouped according to ICU stay duration, those in the long-stay group (≥24 days, n = 5) had preoperative troponin T levels ranging from 45 to 589 ng/L, with a median of 275 (IQR 125-512). In this group, a positive correlation was observed between troponin T levels and ICU stay duration (Spearman $\rho = 0.872$, $P = .054$).

In the short-stay group (<24 days, n = 5), preoperative troponin T levels ranged from 15 to 128 ng/L, with a median of 54 [IQR 32-92]. In this group, a negative correlation was found between troponin T levels and ICU stay duration (Spearman $\rho = -0.900$, $P = .037$) (Table 3).

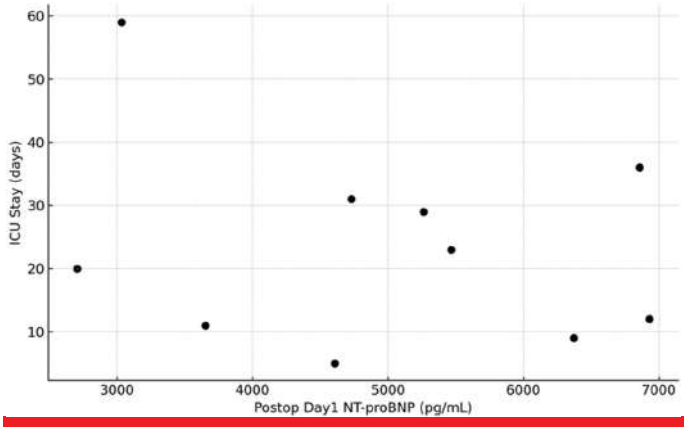

Figure 4. Correlation of postoperative day 1 N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and intensive care unit (ICU) stay duration. (A positive trend was observed, though statistical significance was not reached.)

Table 3. Spearman Correlation Analysis Between Preoperative Troponin T Levels and ICU Stay Duration in Patient Subgroups With Short and Long ICU Stay

Group	Spearman's rho (ρ)	*P*	Interpretation
All patients (n = 10)	0.687	.028	Significant positive correlation
Long ICU stay (≥ 24 days, n = 5)	0.872	.054	Strong positive correlation, borderline significance
Short ICU stay (< 24 days, n = 5)	−0.900	.037	Strong negative correlation, statistically significant

ICU, intensive care unit.

DISCUSSION

This study is one of the few to investigate the relationship between postoperative changes in troponin T (cTnT) and NT-proBNP levels and the duration of ICU stay in pediatric patients implanted with a HM3 LVAD. The findings provide a comprehensive evaluation not only of the temporal changes in these biomarkers during the postoperative period but also of their associations with demographic and clinical parameters.

The study included 10 patients aged between 10 and 16 years, with a median age of 13 years [IQR 10.5-14.75]. Body weights ranged from 23 to 52 kg, with a median of 31 kg [IQR 27-36]. Sixty percent of the patients were female and 40% were male. All patients were diagnosed with dilated cardiomyopathy, and their PEDIMACS profiles ranged between 1 and 3.

This demographic distribution is consistent with previous pediatric mechanical circulatory support series reported in the literature. Bhatia et al[1] reported a similar age range in their series of 11 patients, most of whom were diagnosed with dilated cardiomyopathy, demonstrating that both HeartMate 2 and HM3 devices could be safely used in this population. Similarly, data from the PEDIMACS registry presented by Rossano et al[19] indicated an increasing use of device support among patients aged 6-17 years, with lower mortality rates compared with younger pediatric groups.[18]

In the center, pediatric patients with advanced heart failure, particularly those who are inotropic-dependent with low PEDIMACS profiles, undergo routine daily laboratory monitoring in both the preoperative and postoperative intensive care setting. As part of this standard clinical follow-up, daily cTnT and NT-proBNP measurements are available for all patients. For the purposes of this study, we selected biomarker values obtained on postoperative days 1, 3, 7, and 14, and subsequently at 1, 3, 6, and 12 months. These specific time points correspond to the institution's structured postoperative monitoring schedule, which is designed to evaluate early myocardial injury, stabilization, and longer-term myocardial recovery after LVAD implantation. Therefore, the chosen sampling intervals reflect routine clinical practice and provide representative markers of both acute and chronic postoperative trajectories.

In the preoperative period, troponin T levels in all patients were above the upper reference limit, ranging from 15 to 589 ng/L, with a median value of 98.5 ng/L [IQR 42.5-236.5]. This finding indicates that myocardial cell injury was already present before device implantation. Lipshultz et al[12] reported that troponin T levels reflect the severity of myocardial damage in pediatric heart failure patients. Similarly, Licka et al[13] and Collinson et al[14] demonstrated a strong correlation between troponin elevation and myocyte necrosis.

On postoperative day 1, troponin T levels ranged from 554 to 23.254 ng/L, with a median of 1.104 ng/L [IQR 818.8-2.663]. A marked early postoperative rise was observed in all patients, followed by a decline at 1 month and a gradual return toward normal reference levels between 6 and 12 months. Ragusa et al[9] similarly reported that troponin T levels increase in the early period following VAD implantation and subsequently show a progressive decline. Immer et al[10] noted that postoperative troponin elevation correlates with cardiopulmonary bypass duration and surgical complexity. Lasocki et al[11] and Babuin and Jaffe[20] also emphasized that elevated troponin levels represent the biochemical manifestation of early myocardial injury. The trend observed in the series is consistent with the literature and suggests that myocardial stress gradually decreases following device implantation, likely due to the reduction in ventricular wall tension provided by mechanical unloading. These findings should be interpreted as reflecting general temporal trends rather than definitive time-specific conclusions, particularly in light of the limited sample size. Nevertheless, the observed postoperative decline in troponin T levels is consistent with the expected pattern of myocardial recovery following mechanical ventricular unloading. Preoperative BNP levels ranged from 3201 to 16322 ng/L, with a median of 7510 ng/L [IQR 5350-10850] ng/L. Elevated BNP levels are associated with left ventricular volume overload and increased intracardiac pressures. Braunwald[21] and Sarhene et al[15] reported that BNP possesses both diagnostic and prognostic value in heart failure, while York et al[16] emphasized its significant association with mortality. In this context, the high BNP values observed in this study can be interpreted as a biochemical indicator of ventricular dysfunction in the pre-implantation period.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels on postoperative day 1 ranged from 3130 to 23693 ng/L, with a median of 11138 ng/L [IQR 5889-15724] ng/L, demonstrating a marked decline by the first postoperative month. The median NT-proBNP level was 853 ng/L [IQR 450-1268] ng/L at 6 months and 980 ng/L [IQR 445-1480] ng/L at 12 months. The early postoperative elevation in BNP is primarily attributed to surgical stress and hemodynamic loading.[15,20,21] In adult LVAD series, BNP levels have been reported to reflect improvements in ventricular function following device implantation.[15,16] The 2022 AHA/ACC/HFSA heart failure guideline published by Heidenreich et al[18] recommends the use of BNP for risk stratification and monitoring in heart failure management. However, in pediatric populations,

standardization remains challenging due to age and body surface area–related variability in reference values.

The duration of ICU stay ranged from 5 to 59 days, with a mean of 24.1 ± 16.3 days. Correlation analysis revealed a statistically significant positive relationship between preoperative troponin T levels and ICU stay duration ($\rho = 0.687$, $P = .028$). In contrast, postoperative day 1 NT-proBNP levels showed a positive but statistically non-significant correlation with ICU stay duration ($\rho = -0.395$, $P = 0.258$). These findings suggest that patients with a greater degree of preoperative myocardial injury experience a longer postoperative recovery period. Similarly, Immer et al,[10] Boroński et al,[22] and Mildh et al[23] reported correlations between troponin levels, postoperative morbidity, and ICU length of stay. The Mann–Whitney U-test also demonstrated significantly higher preoperative troponin T levels in the long-stay group ($P = .016$), supporting this association.

Delayed normalization of troponin T levels was observed in patients with genetic cardiomyopathies. In two cases diagnosed with Carvajal syndrome and Limb-Girdle muscular dystrophy, troponin T levels remained above the reference range even at the sixth postoperative month. This finding suggests that genetic etiology may contribute to delayed myocardial recovery. Boroński et al[22] also reported that postoperative troponin elevation may be associated with the inflammatory response. Therefore, the interpretation of troponin levels should consider not only myocardial necrosis but also potential contributions from inflammatory processes and genetic background.

Despite these valuable observations, certain limitations should be acknowledged. First, the small sample size inherently restricts the statistical power of the analyses and limits the generalizability of the findings. In addition, although the use of the mean ICU stay of 24 days as a cutoff was clinically reasonable, the small number of patients may have influenced the robustness of this stratification. Therefore, interpretations regarding ICU stay–biomarker associations should be approached with caution.

Beyond ICU stay, additional patient outcomes were also evaluated. One patient died due to progressive multiple organ dysfunction that had already developed by the time of presentation. This patient presented to the emergency department at an end-stage, with markedly elevated renal and hepatic function tests secondary to severe heart failure, and was already progressing toward multiple organ dysfunction; under these circumstances, despite LVAD implantation, the patient could not be stabilized and died on postoperative day 18. Another patient, who was later found to have Carvajal syndrome based on a genetic result consistent with arrhythmogenic right ventricular dysplasia, experienced gradually worsening right ventricular failure despite LVAD support and died from severe right ventricular dysfunction in the twentieth postoperative month while awaiting heart transplantation. No significant postoperative complications were observed in the remaining patients during their intensive care or early postoperative course.

This study represents one of the few datasets demonstrating the temporal changes of troponin T and NT-proBNP levels and their clinical correlations in the pediatric HM3 population. The findings indicate that troponin T may serve as a biochemical marker of postoperative recovery, whereas NT-proBNP primarily reflects early hemodynamic loading. Larger, multicenter, and prospective studies are warranted to better define the prognostic value and clinical utility of these biomarkers in pediatric LVAD patients.

CONCLUSION

In pediatric patients implanted with the HM3 left ventricular assist device, troponin T (TnT) and NT-proBNP levels reflect postoperative myocardial recovery and may serve as clinically useful indicators associated with intensive care unit stay duration. The early postoperative rise in TnT levels, followed by gradual normalization within 6-12 months, can be interpreted as evidence of ventricular decompression and hemodynamic improvement achieved through mechanical support.

However, in cases where TnT levels normalize more slowly, underlying genetic cardiomyopathies and persistent inflammatory processes should be carefully investigated.

This study is original in demonstrating a significant correlation between preoperative TnT levels and postoperative intensive care unit stay duration, suggesting that this biomarker may serve as a potential prognostic indicator in pediatric LVAD patients.

Future studies with larger sample sizes, prospective designs, and multicenter participation are warranted to more clearly define the clinical utility and prognostic value of TnT and NT-proBNP levels in the management of this patient population.

Study Limitations

Despite these valuable observations, certain limitations should be acknowledged. First, the small sample size (n = 10) inherently limits the statistical power of the analyses and restricts the generalizability of the findings. Therefore, the results should be interpreted as exploratory observations rather than definitive conclusions. In addition, although serial troponin T and NT-proBNP measurements were available up to 12 months postoperatively, the limited number of patients may have reduced the ability to detect subtle differences between individual postoperative time points.

Artificial Intelligence (AI) Statement: Artificial Intelligence–assisted technologies (such as ChatGPT, OpenAI) were used solely for language editing and formatting assistance. The authors are fully responsible for the scientific content of the manuscript.

Ethics Committee Approval: This study was approved by the Ege University Medical Research Ethics Committee (Approval No.: 25-6.1T/16; Date: 26.06.2025).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept & Design – Ş.Ş.Ö., Z.Ü.T., E.D., M.Ö.; Supervision – M.Ö., T.Y., Ç.E., O.N.T.; Resources & Materials – M.Y., B.B.A., H.K., B.K.B., A.T., P.Y., K.C.; Data Collection/Processing – Ş.Ş.Ö., Z.Ü.T., E.D., M.Y., B.B.A., H.K.; Analysis/Interpretation – Ş.Ş.Ö., E.D., Z.Ü.T., H.H., E.L.; Literature Search & Writing – Ş.Ş.Ö., E.D., Z.Ü.T.; Critical Review – M.Ö., T.Y., Ç.E., O.N.T., H.H., E.L., B.K.B.

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The Relation Between the Aggregate Index of Systemic Inflammation and the Mortality Rate of Cardiovascular Disease in the Elderly Population

ABSTRACT

Background: Cardiovascular disease (CVD) is a leading cause of death in older adults and is closely associated with inflammation. The aggregate index of systemic inflammation (AISI), a novel biomarker, may predict CVD mortality in this population. To analyze the association between AISI levels and CVD mortality in the older population.

Methods: This study was based on the National Health and Nutrition Examination Survey (NHANES) database. By constructing weighted Kaplan–Meier (K-M) survival curves and Cox proportional hazards models, the link between AISI levels and CVD mortality rate were analyzed in the elderly. The restricted cubic spline (RCS) was applied to elucidate the non-linear link. A random survival forest model was constructed to assess the predictive value of multiple variables.

Results: One thousand three hundred nineteen CVD death events were recorded. The weighted K-M survival curve manifested that the CVD mortality risk was considerably higher in the highest tertile group than in the lowest tertile. In the model with full adjustments, each one-unit increase in AISI was associated with a 1.52-fold higher risk of death (HR = 1.52, 95% CI: 1.30-1.76, $P < .001$), and a non-linear relationship was detected (P-nonlinear = .0001). When AISI was above the threshold of 263.43, the CVD mortality risk was significantly elevated (HR = 1.99, 95% CI: 1.59-2.49, $P < .001$). No significance was observed below this threshold. AISI had the highest predictive value for CVD mortality in the elderly.

Conclusion: The AISI is an effective indicator for predicting the CVD mortality risk in the elderly, especially when AISI reaches high levels.

Keywords: Aggregate index of systemic inflammation, cardiovascular disease mortality, elderly, National Health and Nutrition Examination Survey

ORIGINAL INVESTIGATION

INTRODUCTION

The health status and disease management of the elderly have become a focus of public health due to the growing worldwide aging population. Cardiovascular disease (CVD) contributes to the largest global death toll among the elderly,[1] causing widespread concern. As of 2019, the number of CVD patients in 204 countries and regions has climbed from 271 million in 1990 to 523 million, with an additional 6.5 million CVD deaths, making it a leading global cause of death.[2] Inflammation plays a central driving role in the occurrence and development of CVD, not only as a common pathological basis for various CVD,[3,4] but also as a key bridge connecting aging and CVD mortality risk. As age increases, the body's immune system gradually exhibits a chronic, low-grade activation state, known as inflammatory aging, characterized by a sustained increase in levels of inflammatory cells and mediators in peripheral blood.[5] This state can damage the vascular endothelial function, accelerate the process of atherosclerosis, and significantly increase the risk of CVD death.[6] Therefore, finding biomarkers that can reflect chronic low-grade inflammation is of great significance for CVD risk management in the elderly.

In recent years, the aggregate index of systemic inflammation (AISI) has received widespread attention as an emerging comprehensive inflammatory indicator, consisting of neutrophil count, platelet count, monocyte count, and lymphocyte

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count.[7] Compared to traditional inflammatory markers such as C-reactive protein (CRP) and white blood cell count, AISI may be able to more comprehensively evaluate the inflammatory status of the body. C-reactive protein can effectively reflect acute inflammatory response, but it is susceptible to interference from short-term infections and other factors.[8] White blood cell count is too general to distinguish specific components of the inflammatory response.[9] In contrast, AISI synchronously captures 3 interrelated pathophysiological networks: innate immunity (neutrophils, monocytes), adaptive immunity (lymphocytes), and thrombus inflammation interaction (platelets).

Therefore, the mechanism by which AISI affects CVD mortality may work synergistically through 3 core pathological pathways. Congenital immune overactivation (neutrophils and monocytes) directly leads to endothelial damage and progression of atherosclerosis.[10,11] Platelet-mediated thrombotic inflammatory cycle significantly increases the risk of acute occlusive events.[12] Lymphocytes can accelerate the formation of atherosclerotic lesions by affecting immune regulation.[13] The increase of AISI may reflect the triple hazards of pro-inflammatory, thrombotic, and immune imbalance, which together promote the occurrence of fatal CVD events. Moreover, a great positive linkage between AISI and the prevalence of hypertension has been discovered,[14] making AISI a new predictor of hypertension.[15] In addition, AISI can predict the mortality rate of stroke patients[16] and the mortality rate of patients with chronic obstructive pulmonary disease combined with COVID-19 infection.[17] However, AISI's role in predicting elderly people's CVD mortality has not been fully elucidated.

The objective of this study was to explore the link between AISI and CVD mortality in the elderly by analyzing a large sample size of data from the National Health and Nutrition Examination Survey (NHANES). Based on existing research progress, the hypothesis was proposed that there is an independent positive correlation between AISI and CVD mortality rate in the elderly population, and this correlation exhibits a non-linear threshold effect. It was intended to reveal the potential value of AISI in predicting CVD mortality in the elderly and provide a theoretical basis for future clinical applications.

HIGHLIGHTS

- This article reveals for the first time that there is a significant non-linear positive correlation between aggregate index of systemic inflammation (AISI) and the risk of cardiovascular disease (CVD) death in the elderly population, and the threshold point is determined to be 263.43.
- This article innovatively uses Cox regression and random survival forest models to mutually verify the reliability of AISI as an independent predictor of CVD mortality risk in the elderly population.
- The AISI has the potential to serve as a simple and easily accessible auxiliary tool for timely identification of high-risk CVD populations in the elderly population in clinical practice.

METHODS

Study Population from National Health and Nutrition Examination Survey

The population data used in this study were available through the NHANES database,[18] which is a publicly available, de-identified dataset. The NHANES is a comprehensive study conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) to examine the nutrition and health of the noninstitutionalized U.S. population through a multistage and stratified sampling method. All data were approved by the NCHS Ethics Review Committee; therefore, no additional ethical approval was required.

The link between AISI and CVD mortality in the elderly was probed using survey data from 10 cycles from 1999 to 2018 (n = 101 316). The exclusion criteria are as follows: (1) excluding participants younger than 60 (n = 82 229); (2) excluding participants with lacking or invalid AISI data (n = 2164); and (3) excluding participants with missing data on other covariate variables (n = 3401). A total of 13 522 elderly subjects were studied. The specific process of subject screening is displayed in Figure 1.

Independent Variable

The calculation of AISI was based on indicators in the whole blood cell count. The blood sampling followed the NHANES standardized protocol: venous blood samples were taken on an empty stomach for more than 8 hours and were collected at a mobile examination center. The complete blood cell count was measured using a Beckman Coulter automatic blood analyzer to ensure data reliability.[19]

AISI = neutrophil count × platelet count × monocyte count/lymphocyte count.[7]

Dependent Variable

The National Death Index records as of December 31, 2019 were the reference for us to determine the mortality outcomes. The underlying causes of mortality were assessed by the International Statistical Classification of Diseases, 10th Revision (ICD-10).

Variables

Covariates in this investigation included gender, body mass index (BMI), ethnicity, education level, poverty income ratio (PIR), red blood cell (RBC) count, diabetes, smoking, white blood cell (WBC) count, alcohol consumption, hypertension, hemoglobin, and mean RBC volume. Subjects fell into 3 distinct PIR categories: low income (PIR $\leq$ 1.3), moderate income (1.3 < PIR $\leq$ 3.5), and high income (PIR > 3.5).[20] Body mass index was calculated as weight (kg) divided by the square of height (m), and classified as obese (>30 kg/m^2), overweight (25-30 kg/m^2), and underweight/healthy weight (< 25 kg/m^2).[21] Smoking status was grouped into 3 groups based on the smoking history and current smoking behavior of the subjects: never smokers (reporting a total of less than 100 cigarettes smoked), former smokers (reporting a total of 100

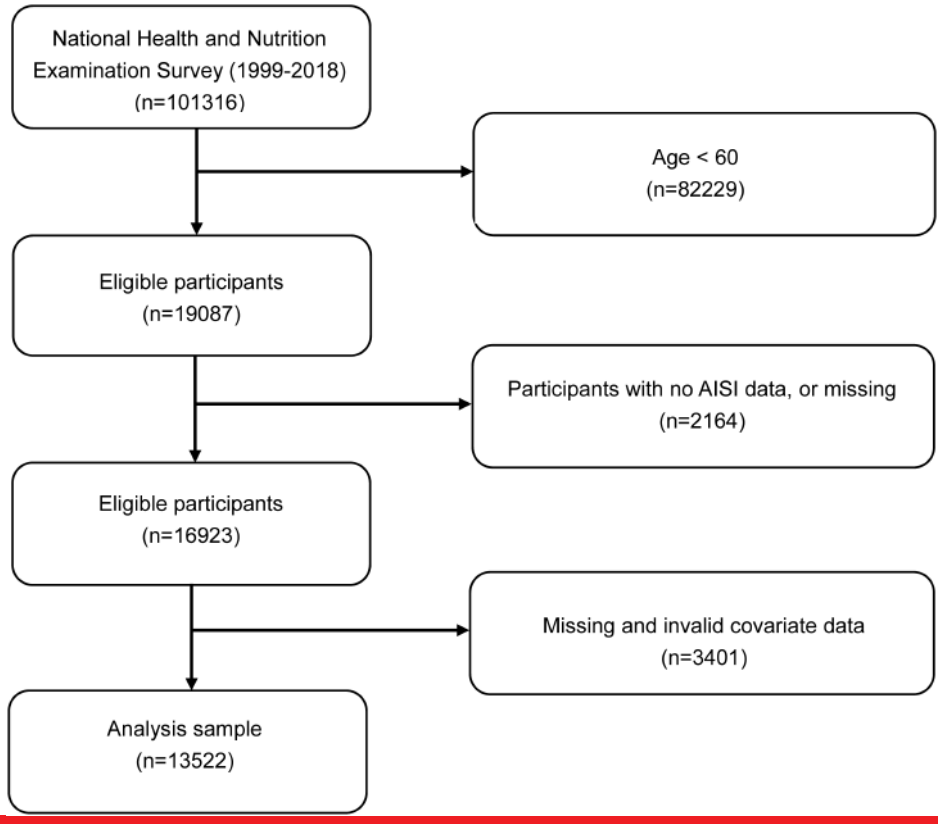

Figure 1. Flowchart of NHANES participant screening.

or more cigarettes smoked but currently not smoking), and current smokers (reporting a total of 100 or more cigarettes smoked and still smoking).[22] Drinking at least 12 drinks per year was defined as alcohol consumption.[23] Participants with diabetes were defined as having any of the following conditions: (1) glycated hemoglobin (HbA1C) concentration >6.5%; (2) fasting blood glucose level ≥126 mg/dL; (3) self-reported diabetes; and (4) currently taking antidiabetic medication to lower blood sugar.[24,25] High blood pressure was determined to be any of the following: (1) systolic blood pressure ≥ 140 mm Hg; (2) diastolic blood pressure ≥ 90 mm Hg; (3) self-reported hypertension; and (4) taking antihypertensive medication.[26]

Statistical Analysis

We completed all statistical analyses in this work by using R software (V4.4.1). The *tableone* package was employed to create the baseline table, which was based on the AISI-weighted tertile grouping and the characteristics of the total population. The sample size and its proportion [n (%)] were utilized to express the categorical variables in the statistical analysis, while the mean and standard deviation [mean (SD)] were utilized to express the continuous variables. Then, the continuous variable AISI with a non-normal distribution was logarithmically transformed for easy analysis.

The *jskm* package was utilized to plot the weighted Kaplan–Meier (K-M) survival curve based on the AISI weighted tertile grouping of subjects, describe the survival status of subjects, and evaluate the distinction between groups through the log-rank test. A Cox proportional hazard model was set up considering complex sampling by utilizing the *survey* package and the *survival* package, and the model was gradually adjusted to dig out the link between AISI and CVD mortality in the elderly. Based on biological relevance, variables were included and the variance inflation factor was calculated using the *car* package. The results were all <5, indicating no significant over-adjustment (Supplementary Table 1). Subgroup analysis was conducted based on stratification of gender, BMI, smoking, alcohol, diabetes, and hypertension to examine the independent effects of AISI. The crude model did not adjust for confounding factors. In Model 1, adjustments were added to gender, BMI, smoking, education level, PIR, race, and alcohol consumption. Model 2 had adjustments for all covariates (BMI, race, smoking, gender, education level, alcohol consumption, PIR, hypertension, WBC count, diabetes, hemoglobin, mean RBC volume, and RBC count). Furthermore, a trend test was launched to examine the linkage between the AISI-weighted tertiles and CVD mortality rates. If $P < .05$, statistical significance was indicated.

In the model with adjustment for all covariates, a restricted cubic spline (RCS) analysis was conducted by utilizing the *rms* package to illuminate the nonlinear relationship between AISI and CVD mortality in the elderly population. A 2-part linear regression model was set up to display threshold effects.

The *randomForestSRC* package was used to construct a random survival forest (RSF) model and evaluate the predictive value of multiple variables on CVD mortality in elderly individuals. The parameters were set to ntree = 1000 (number of trees), nodesize = 25 (minimum size of terminal nodes), splitrule = logrank (rule for survival splitting),

importance = TRUE (calculate variable importance), proximity = TRUE (calculate neighbor matrix), and cv = TRUE (cross-validation). The NHANES survey weights were normalized (weights = WEIGHT/mean (weight)) and incorporated into the model to consider complex sampling designs. The dataset was divided into a training set (70%) and a testing set (30%). The contribution of each variable was presented by utilizing the *ggRandomForests* package.

Time-dependent ROC curves were calculated using the *timeROC* package and the model's predictive accuracy was evaluated at different time points (3, 5, and 10 years). To quantify the incremental predictive value brought by incorporating AISI into the baseline model, prediction models were constructed with and without AISI. Further, the predictive performance of the 2 models were evaluated using the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) continuous models.[27]

Sensitivity analysis was conducted to ensure the robustness of the results: (1) As NHANES aims to represent the health status of the non-institutionalized American population, participants with acute or chronic inflammatory conditions were not excluded from this study. However, in order to assess the impact of related confounding factors, participants with hepatitis B virus infection, self-reported cancer, or rheumatoid arthritis were excluded, and 8632 participants were included for weighted Cox regression analysis. (2) After removing blood parameters, Model 3 was constructed for weighted Cox regression analysis. Model 3 adjusted for gender, race, BMI, educational level, PIR, smoking, drinking, diabetes, and hypertension.

RESULTS

Baseline Characteristics

To probe into the relationship between AISI and CVD mortality in the elderly, 13 522 samples from NHANES 1999-2018 were included. Of these, 1319 (8.5%) died from CVD. According to the AISI-weighted tertiles of the subjects, there were 364 deaths (6.5%) in Group T1, 413 deaths (7.9%) in Group T2, and 542 deaths (11.1%) in Group T3. Compared to participants in the lowest tertile of AISI, those with higher AISI were always male, former and current smokers, obese (BMI $\geq$ 30), and individuals with comorbidities such as diabetes and hypertension. Additionally, the levels of WBC count, RBC count, and hemoglobin in subjects with higher AISI were considerably higher than those in subjects with the lowest tertile (Table 1).

Relation Between Aggregate Index of Systemic Inflammation and Cardiovascular Disease Mortality in the Elderly

The weighted K-M survival curve manifested the survival probability trend in AISI-weighted tertile groups. The mortality risk was highest in the T3 group over time ($P < .001$), but no significant difference in the risk of CVD death between T1 and T2 was detected ($P = .180$) (Figure 2A). Next, the Cox proportional hazard model was utilized to further dissect the link between AISI and CVD mortality in the elderly. In the unadjusted model (Crude model), when the AISI variable increased by 1 unit, the risk of death increased by 1.60 times (HR = 1.60, 95% CI: 1.41-1.81, $P < .001$). In Model 1, adjustments were added to confounding factors, finding the significant trend (HR = 1.49, 95% CI: 1.31-1.69, $P < .001$). In Model 2 (all covariates adjusted), when the AISI variable increased by 1 unit, the risk of death increased by 1.52 times (HR = 1.52, 95% CI: 1.30-1.76, $P < .001$). The trend test demonstrated that among the 3 models, as the interquartile range of AISI increased, the CVD mortality risk in the elderly significantly elevated (Table 2). The results of subgroup analysis showed that after adjusting for all confounding variables, AISI was positively correlated with CVD mortality risk in the elderly population in all subgroups ($P < .005$), indicating that the independent effect of AISI was consistent and robust across different subgroups (Supplementary Table 2). The results of both sensitivity analyses showed that after adjusting for all confounding variables, AISI was still positively correlated with the risk of CVD mortality in the elderly population ($P < .05$) (Supplementary Tables 3 and 4).

Nonlinear Relationship Between Aggregate Index of Systemic Inflammation and Cardiovascular Disease Mortality Rate in the Elderly Population

Further, the threshold effect model was applied and RCS to probe into the nonlinear link between AISI and CVD mortality rate in the elderly, revealing a significant overall trend between AISI and the CVD mortality risk (P-overall <.0001). With increasing AISI, the CVD mortality risk in the elderly was greatly elevated. A non-linear link between AISI and CVD mortality in the elderly was detected (P-non-linear = .0001) (Figure 2B).

The threshold effect results implied no statistically significant link with the risk of CVD mortality in the elderly when AISI < 263.43 ($P = .6$). When AISI $\geq$ 263.43, a significant positive correlation with the risk of CVD mortality in elderly individuals was discovered (HR = 1.99, 95% CI: 1.59-2.49, $P < .001$). Furthermore, the Wald test revealed statistically significant differences between the 2 groups ($P < .001$) (Table 3).

Prognostic Value of Aggregate Index of Systemic Inflammation

We developed an RSF model to examine the value of AISI in predicting CVD mortality in the elderly. The results demonstrated that AISI was the most effective predictor of CVD mortality in the elderly compared to other variables (Figure 3A). Furthermore, the performance of RSF and Cox models was compared and evaluated using C-index: the C-index of RSF was 0.691, while that of the Cox model was 0.725. This indicates that the Cox model has slightly better overall discriminative ability than RSF, but RSF has more advantages in capturing nonlinear relationships and variable interactions.[28]

Subsequently, the predictive performance of the model was tested using the ROC curves. The model had AUC values of 0.729, 0.711, and 0.749 for predicting CVD mortality in elderly individuals at 3, 5, and 10 years, respectively, suggesting that the RSF model possessed good predictive ability (Figure 3B).

Table 1. Baseline Characteristics of Included Subjects

Characters	Total	T1 (<211.25)	T2 (211.25-365.14)	T3 (≥365.14)	*P*
Overall	13 522	4998 (33.3)	4314 (33.3)	4210 (33.3)	
Gender					<.001
Male	6809 (45.4)	2310 (40.0)	2149 (45.1)	2350 (51.0)	
Female	6713 (54.6)	2688 (60.0)	2165 (54.9)	1860 (49.0)	
Race					<.001
Mexican American	1967 (3.7)	766 (4.4)	680 (3.8)	521 (2.9)	
Other Hispanic	1003 (3.3)	434 (4.1)	309 (3.1)	260 (2.7)	
Non-Hispanic White	7239 (80.7)	1990 (72.6)	2450 (82.5)	2799 (87.0)	
Non-Hispanic Black	2518 (7.7)	1418 (12.9)	647 (6.2)	453 (4.1)	
Other race	795 (4.6)	390 (6.0)	228 (4.4)	177 (3.3)	
BMI (kg/m^2)					<.001
<25	3510 (26.0)	1309 (27.3)	1070 (24.3)	1131 (26.2)	
25-30	5115 (37.3)	1946 (39.3)	1640 (38.1)	1529 (34.5)	
>30	4897 (36.8)	1743 (33.4)	1604 (37.6)	1550 (39.3)	
Alcohol					.119
No	4454 (29.8)	1716 (30.8)	1428 (30.2)	1310 (28.4)	
Yes	9068 (70.2)	3282 (69.2)	2886 (69.8)	2900 (71.6)	
Smoke					<.001
Never	6448 (48.0)	2630 (53.9)	2049 (47.2)	1769 (43.0)	
Past	5357 (40.4)	1824 (37.5)	1740 (41.7)	1793 (42.1)	
Now	1717 (11.5)	544 (8.6)	525 (11.1)	648 (14.9)	
Education					.014
Less than high school	2424 (9.1)	935 (9.4)	813 (9.1)	676 (8.7)	
High school or equivalent	5221 (37.9)	1860 (35.2)	1640 (38.7)	1721 (39.9)	
College or above	5877 (53.0)	2203 (55.4)	1861 (52.2)	1813 (51.4)	
PIR					.001
Low	3848 (18.1)	1497 (18.5)	1186 (17.3)	1165 (18.3)	
Medium	5775 (41.8)	2029 (39.4)	1860 (40.8)	1886 (45.1)	
High	3899 (40.2)	1472 (42.0)	1268 (41.9)	1159 (36.6)	
Diabetes					<.001
No	9743 (76.5)	3635 (78.8)	3150 (77.8)	2958 (72.9)	
Yes	3779 (23.5)	1363 (21.2)	1164 (22.2)	1252 (27.1)	
Hypertension					<.001
No	2634 (22.1)	1070 (26.3)	833 (21.2)	731 (18.9)	
Yes	10 888 (77.9)	3928 (73.7)	3481 (78.8)	3479 (81.1)	
WBC (1000 cells/μL)	7.11 ± 3.42	6.09 ± 5.05	6.94 ± 1.53	8.31 ± 2.17	<.001
RBC (1000 cells/μL)	4.57 ± 0.48	4.53 ± 0.47	4.59 ± 0.46	4.60 ± 0.50	<.001
Hemoglobin (g/dL)	14.09 ± 1.40	13.97 ± 1.32	14.17 ± 1.36	14.14 ± 1.51	<.001
Mean cell volume (fL)	91.22 ± 5.11	91.33 ± 5.24	91.24 ± 4.88	91.08 ± 5.20	.136
CVD mortality					<.001
Alive	12 203 (91.5)	4634 (93.5)	3901 (92.1)	3668 (88.9)	
Deceased	1319 (8.5)	364 (6.5)	413 (7.9)	542 (11.1)	

n (%) represented the categorical variable and mean (sd) represented the continuous variable. n was unweighted. n (%), mean, and SD were weighted.
BMI, body mass index; CVD, cardiovascular disease; PIR, poverty-income ratio; RBC, red blood cell; WBC, white blood cell.

The Incremental Value of Aggregate Index of Systemic Inflammation Prediction Model

We used a weighted Cox model (Model 3) to construct models with and without AISI and evaluated predictive performance using Harrell's C-index and time-dependent AUC (3, 5, and 10 years). The results showed that the C-index of the model containing AISI was 0.741, which was higher than that of 0.733 in the model without AISI. The time-dependent AUC showed that the model containing AISI had better predictive performance at 3 years (0.765

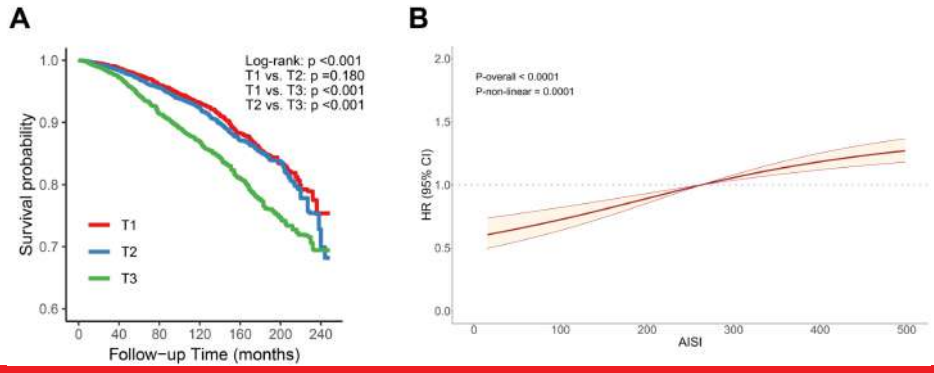

Figure 2. Weighted K-M survival curves (A) and RCS model (B) of AISI and CVD mortality in elderly individuals. The RCS model was adjusted for gender, race, BMI, education level, PIR, smoking, alcohol consumption, diabetes, hypertension, WBC count, RBC count, hemoglobin, and mean RBC volume. Take-home messages: (A) The highest CVD mortality risk in the T3 group; (B) A nonlinear increase in CVD mortality risk with rising AISI. AISI, aggregate index of systemic inflammation; CVD, cardiovascular disease; BMI, body mass index; PIR, poverty-income ratio; WBC, white blood cell; RBC, red blood cell.

Table 2. The Associations Between AISI and Cardiovascular Mortality in Elderly Individuals

	HR (95% CI), *P*		
Characteristic	**Crude Model**	**Model 1**	**Model 2**
CVD mortality			
AISI (continuous)	1.60 (1.41-1.81), <.001	1.49 (1.31-1.69), <.001	1.52 (1.30-1.76), <.001
AISI (categorical)			
T1	Ref.	Ref.	Ref.
T2	1.13 (0.95-1.35), .162	1.09 (0.92-1.29), .314	1.10 (0.93-1.31), .266
T3	1.81 (1.53-2.14), <.001	1.62 (1.36-1.93), <.001	1.58 (1.30-1.93), <.001
P for trend	<.001	<.001	<.001

The Crude model did not adjust for confounding factors. In Model 1, adjustments were made for gender, race, BMI, education level, PIR, smoking, and alcohol consumption. Model 2 had adjustments for all covariates, including gender, race, BMI, education level, PIR, smoking, alcohol consumption, diabetes, hypertension, WBC count, RBC count, hemoglobin, and mean RBC volume.
AISI, aggregate index of systemic inflammation; BMI, body mass index; CVD, cardiovascular disease; PIR, poverty-income ratio.

vs. 0.751), 5 years (0.757 vs. 0.745), and 10 years (0.753 vs. 0.747) (Figure 4).

In addition, the AISI model showed a statistically significant improvement in predictive ability compared to the baseline model (without AISI). The estimated value of IDI was greater than 0, and at 10 years, the model's integrated discriminative ability was improved by a net 1.5% (IDI = 0.015, $P < .001$). The estimated values of continuous NRI were between 0.160 and 0.178, and the *P*-values were significant (Supplementary Table 5). In summary, the IDI and NRI results clearly quantified and confirmed that AISI provides significant incremental predictive value independent of traditional risk factors, particularly in improving the accuracy of risk stratification.

DISCUSSION

In this nationally representative large-scale study, a significant positive relation between AISI and CVD mortality in the elderly population was revealed for the first time. The threshold effect analysis further demonstrated that when AISI reached or exceeded 263.43, the elderly had a considerably elevated risk of CVD mortality. In addition, the RSF model also verified AISI as a strong indicator for predicting CVD mortality in the elderly.

Mounting studies have revealed that chronic inflammation is essential for the pathogenesis of atherosclerosis and other CVDs.[3,4] Atherosclerosis is the leading cause of CVD worldwide.[29] In the initial stage of atherosclerosis, low-density lipoprotein cholesterol enters the subendothelial space, undergoes oxidation and aggregation, and the oxidative modification induces endothelial cells to express cell adhesion molecules, recruiting T lymphocytes and monocytes into the inflamed arterial wall.[30] Monocytes subsequently differentiate into macrophages and secrete pro-inflammatory

Table 3. Threshold Effect Analysis of AISI on CVD Mortality in Elderly Individuals

Outcomes	**HR (95% CI), *P***
AISI	
Cutoff	
<263.43	1.08 (0.80-1.46), .6
≥263.43	1.99 (1.59-2.49), <.001
P for Wald test	<.001

Adjustments were made for gender, race, BMI, education level, PIR, smoking, alcohol consumption, diabetes, hypertension, WBC count, RBC count, hemoglobin, and mean RBC volume.
AISI, aggregate index of systemic inflammation; BMI, body mass index; CVD, cardiovascular disease; PIR, poverty-income ratio.

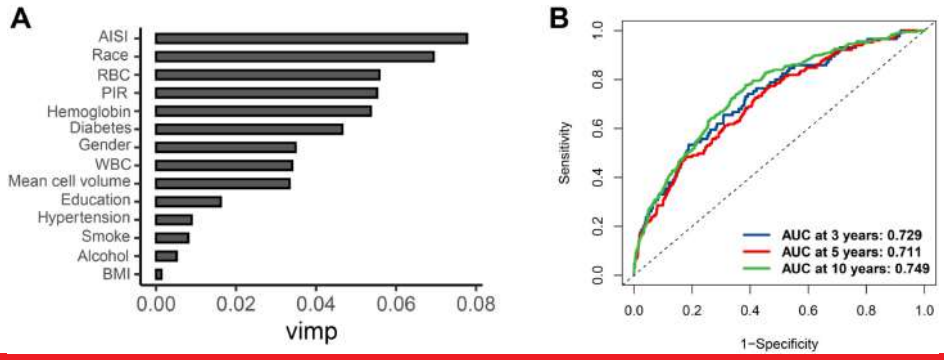

Figure 3. Prognostic value of AISI for CVD mortality in elderly individuals. (A) Prognostic value of AISI for CVD mortality in elderly individuals using the random survival forest model. (B) ROC curves of the random survival forest model. Take-home messages: (A) AISI is the best indicator for predicting CVD mortality risk; (B) The predictive model incorporating AISI exhibits strong predictive capability. AISI, aggregate index of systemic inflammation; CVD, cardiovascular disease; BMI, body mass index; PIR, poverty-income ratio; WBC, white blood cell; RBC, red blood cell.

cytokines (IL-12, IL-1α, IL-6, IL-1β, etc.), resulting in local inflammation, further boosting plaque formation and atherosclerosis.[31]

Inflammatory biomarkers are positively linked with the risk and mortality rate of CVD. A prospective study demonstrated that higher levels of CRP are associated with an elevated risk of heart failure in CVD patients.[32] Another Mendelian randomization study revealed that genetically determined elevated levels of CRP increase the risk of hypertension-related heart disease by 21%.[33] As an indicator of systemic inflammation, the neutrophil-to-lymphocyte ratio is remarkably positively associated with CVD mortality in patients with diabetes, rheumatoid arthritis, and hypertension.[25,34,35] Another marker of inflammation is the platelet-to-lymphocyte ratio (PLR), with high levels of PLR elevating the risks of all-cause mortality and CVD mortality in maintenance hemodialysis patients.[36] The AISI integrates multiple blood cell parameters related to inflammation, including neutrophils, platelets, monocytes, and lymphocytes, comprehensively reflecting the body's systemic inflammatory status, rather than relying solely on a single indicator. The AISI has been confirmed as an effective indicator for assessing cardiovascular risk in patients with acute coronary syndrome receiving percutaneous coronary intervention, with higher AISI levels closely linked with elevated cardiovascular event risk.[37] An elevated mortality rate in stroke patients has been revealed to be connected with high AISI.[16] Additionally, AISI is an essential predictor of restenosis and mortality following carotid endarterectomy.[38] The results coincided with the former findings that higher AISI levels significantly correlate with CVD mortality in the elderly.

It was considered that individuals with higher AISI levels often have more complications (such as diabetes and obesity), so the association between AISI and CVD mortality may be disturbed by such factors. To verify whether AISI has an independent predictive effect on comorbidities, a multicollinearity diagnosis was performed using the variance inflation factor, and the results confirmed that there was no serious collinearity issue between AISI and other comorbidities. Further subgroup analysis revealed that AISI maintained stable predictive ability in different clinical feature populations, supporting its robustness as an independent predictor.

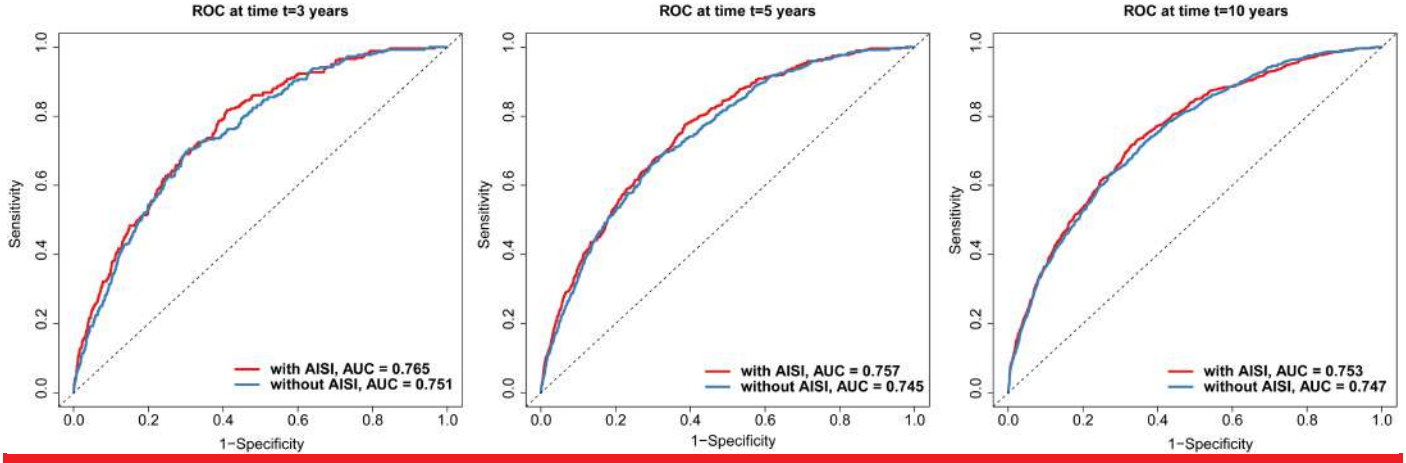

Figure 4. Prognostic value of AISI for CVD mortality in elderly individuals (Comparison between the model with AISI and the model without AISI). Take-home messages: The prediction model containing AISI has better predictive value. AISI, aggregate index of systemic inflammation; CVD, cardiovascular disease.

Based on the above analysis, AISI is not just a substitute indicator for known risk factors, but more likely an independent risk marker that can reflect the potential immune-inflammatory status of the body.

The threshold effect analysis uncovered that the CVD mortality in the elderly population significantly rose when AISI reached or exceeded 263.43 (HR = 1.99), indicating that for every unit increase in AISI, the relative risk of CVD occurrence increased by 99%. No significant statistical significance was detected below this threshold. This suggested that the CVD mortality rate in the elderly population significantly rose only when the inflammatory state reached a certain level. The weighted K-M survival curves also confirmed this finding, demonstrating a significantly elevated risk of CVD death only in the highest tertile (T3) group, with no obvious difference in CVD mortality risk observed between the T1 and T2 groups. These findings echo a former study revealing that as AISI exceeds 507.45, the mortality rate of stroke patients significantly rises with the increase of AISI values.[16] Therefore, the work further supported the potential value of AISI as an indicator for CVD mortality prediction in the elderly, especially in the presence of high inflammation. This suggests that AISI may serve as a practical risk assessment tool in clinical practice. Clinical doctors can use this threshold to quickly identify high-risk elderly patients with elevated inflammation levels and significantly increased CVD risk. However, it should be noted that the AISI cutoff value (263.43) can only be used for risk stratification and is not an accurate value for clinical decision-making. In addition, AISI also has the potential to optimize existing risk prediction models. Based on the results of the RSF model, AISI has been identified as an important variable for predicting CVD mortality in the elderly population. ROC curve and incremental predictive value analysis further indicated that incorporating AISI into the model significantly improves its predictive performance, which may lead to better management of CVD risk in the elderly. Most importantly, AISI can be calculated from routine blood tests. It can assist clinical doctors in assessing cardiovascular risk without the need for additional testing. It is low-cost and easy to operate, exhibiting outstanding advantages.

A hallmark of aging is systemic chronic inflammation, a phenomenon known as inflammation.[39] The factors secreted by senescent cells are collectively referred to as senescence-related secretory phenotypes, which not only accelerate the progression of chronic inflammation but also trigger senescence in normal cells.[40] Long-term inflammation can trigger fibrosis in the heart and blood vessels,[41,42] thereby elevating the risk of CVD. The growth in AISI may reflect this inflammatory aging state in the elderly, making AISI a strong predictor of CVD mortality risk. However, the predictive value of AISI in CVD mortality risk in other age groups has not been fully dissected, awaiting further studies in the future.

Although this study offered evidence supporting AISI as an indicator for predicting CVD mortality risk in the elderly, certain shortcomings persist. First, though this prospective cohort study had a large sample size and lasted for a long follow-up period, a causal relationship cannot be established due to the nature of observational studies. Individuals with preclinical or undiagnosed subclinical CVD may already have more severe systemic inflammatory states in their bodies, leading to elevated levels of AISI. In this case, the increase in AISI may be a result of potential CVD rather than the cause, which could affect the interpretability of the research results. Secondly, the research focuses on the elderly population in the United States, and caution should be exercised when generalizing the research results to other healthcare environments, younger populations, or populations in other countries, as there may be differences in lifestyle, access to medical resources, and disease prevalence among different regions or age groups. Thirdly, NHANES only provides a single record of laboratory blood cell count and cannot evaluate changes in AISI over time, which may not reflect the average level of long-term follow-up. In future research, measurements of AISI can be repeated at multiple time points to explore the relationship between the dynamic changes of AISI and the risk of CVD in elderly people. Lastly, although the independent predictive value of AISI has been validated through various statistical methods, there may still be other confounding factors that have not been considered, such as dietary details, genetic factors, etc., that may affect the results. Therefore, future large-scale clinical trials are recommended to validate the findings of this study.

CONCLUSION AND RECOMMENDATIONS

This study found that AISI is an independent predictor of CVD mortality risk in the elderly population, especially for those at high AISI levels (AISI $\geq$ 263.43). Therefore, AISI has the potential to serve as an objective and easily accessible auxiliary tool for the timely identification of high-risk populations in clinical practice, and can also be integrated into other CVD risk assessment models, which may optimize the predictive value of prediction models.

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Supplementary Table 1. VIF of variables for multivariate cox regression

Characters	VIF
AISI	1.074
Gender	1.162
Race	1.070
BMI	1.036
Education	1.101
PIR	1.066
Smoke	1.060
Alcohol	1.099
Diabetes	1.056
Hypertension	1.022
WBC	1.026
RBC	3.950
Hemoglobin	3.744
Mean cell volume	2.629

AISI, Aggregate index of systemic inflammation; BMI, Body Mass Index; PIR, Poverty-Income Ratio; WBC, White Blood Cell; RBC, Red Blood Cell; VIF, variance inflation factor.

Supplementary Table 2. Subgroup analysis based on stratifications of gender, BMI, smoking, alcohol, diabetes, and hypertension

	HR (95% CI), *P*
Participants	**Model 2**
Gender	
Male	1.51 (1.23-1.85), <0.001
Female	1.49 (1.23-1.80), <0.001
BMI	
<25	1.42 (1.15-1.75), <0.001
25-30	1.45 (1.17-1.79), <0.001
>30	1.74 (1.32-2.28), <0.001
Smoke	
No	1.49 (1.20-1.86), <0.001
Yes	1.49 (1.19-11.86), <0.001
Alcohol	
No	1.49 (1.18-1.89), <0.001
Yes	1.49 (1.22-1.83), <0.001
Diabetes	
No	1.42 (1.21-1.67), <0.001
Yes	1.73 (1.32-2.25), <0.001
Hypertension	
No	1.46 (1.04-2.04), 0.027
Yes	1.51 (1.29-1.77), <0.001

The model adjusted for gender, race BMI, educational level, PIR, smoking, drinking, diabetes, hypertension, white blood cell count, red blood cell count, hemoglobin and mean red blood cell volume. BMI, Body Mass Index; PIR, Poverty-Income Ratio.

Supplementary Table 3. The associations between AISI and cardiovascular mortality in elderly individuals (after excluding participants with hepatitis B virus infection, self-reported cancer, or rheumatoid arthritis)

	HR (95% CI), *P*		
Characteristic	**Crude model**	**Model 1**	**Model 2**
CVD mortality			
AISI (continuous)	1.45 (1.24-1.70), <0.001	1.35 (1.13-1.60), <0.001	1.37 (1.13-1.67), 0.002

The Crude model did not adjust for confounding factors; Model 1 adjusted for gender, race BMI, educational level, PIR, smoking and drinking; Model 2 adjusted for gender, race BMI, educational level, PIR, smoking, drinking, diabetes, hypertension, white blood cell count, red blood cell count, hemoglobin and mean red blood cell volume. Abbreviation: AISI, Aggregate index of systemic inflammation; BMI, Body Mass Index; PIR, Poverty-Income Ratio; CVD, Cardiovascular Disease.

Supplementary Table 4. The associations between AISI and cardiovascular mortality in elderly individuals (after removing blood parameters)

	HR (95% CI), *P*
Characteristic	**Model 3**
CVD mortality	
AISI (continuous)	1.47 (1.29-1.67), <0.001

Model 3 adjusted for gender, race BMI, educational level, PIR, smoking, drinking, diabetes, and hypertension. Abbreviation: AISI, Aggregate index of systemic inflammation; BMI, Body Mass Index; PIR, Poverty-Income Ratio; CVD, Cardiovascular Disease.

Supplementary Table 5. The incremental value of the AISI prediction model

Time Point	Metric	Point estimation	95% (CI)	*P*
3 years	IDI	0.007	[0.001, 0.011]	<0.001
	Continuous NRI	0.178	[0.033, 0.218]	<0.001
5 years	IDI	0.011	[0.001, 0.014]	<0.001
	Continuous NRI	0.172	[0.037, 0.214]	<0.001
10 years	IDI	0.015	[0.003, 0.020]	<0.001
	Continuous NRI	0.160	[0.031, 0.183]	<0.001

The Model adjusted for gender, race BMI, educational level, PIR, smoking, drinking, diabetes, and hypertension. Abbreviation: AISI, Aggregate index of systemic inflammation; IDI, Integrated Discrimination Improvement; NRI, Net Reclassification Improvement.

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Safety Profile of Drug-Coated Balloon Angioplasty for Isolated Side Branch Lesions: A Single-Center Experience

ABSTRACT

Background: The optimal treatment strategy for isolated side branch (SB) lesions remains uncertain. In this study, the aim was to evaluate the safety and efficacy of drug-coated balloon (DCB) angioplasty for the treatment of de novo isolated SB stenosis.

Methods: This single-center, retrospective study included patients with symptomatic isolated SB occlusion who underwent percutaneous coronary intervention using DCB. The primary endpoint was procedural success, and the secondary endpoint was the occurrence of major adverse cardiac events, defined as death from all causes, myocardial infarction, target vessel revascularization, or revascularization of target lesions.

Results: Forty-eight patients were included between April 2022 and June 2025. The mean age was 62.8 ± 13.9 years, and the majority were male (n = 35, 72.9%). The cohort exhibited a high cardiovascular risk profile. Procedural success was achieved in 97.9% (n = 47). Thrombolysis in myocardial infarction grade 3 flow was obtained in all patients, with a mean residual stenosis of 26% ± 14.9. One patient (2.1%) required bailout stenting, and no cases of acute thrombosis were observed. During a mean follow-up of 423 days, 8 patients (16.7%) underwent repeat coronary angiography for angina, 6 patients (12.5%) required additional medical therapy, and 1 patient (2.1%) experienced myocardial infarction.

Conclusion: These findings suggest that, with appropriate lesion preparation and patient selection, DCB angioplasty represents a safe and feasible revascularization strategy for isolated SB occlusions. However, larger, controlled, and long-term studies are needed to confirm these results.

Keywords: Coronary bifurcation, drug-coated balloon, isolated side branch stenosis, percutaneous coronary intervention

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INTRODUCTION

Isolated side branch (SB) stenosis in coronary artery disease represents one of the most challenging lesion subsets in interventional cardiology. Compared with non-bifurcation lesions, these lesions are associated with a higher risk of ischemic events. The small vessel diameter, close anatomical relation with the main vessel, and difficulty in maintaining main vessel flow during the procedure make treatment decisions complex. As these lesions constitute less than 5% of all bifurcation lesions, the rarity and unique characteristics of Medina 0.0.1 bifurcation lesions result in limited evidence regarding optimal treatment strategies and necessitate an individualized approach.[1,2]

In recent years, drug-coated balloon (DCB) technology has emerged as an innovative stentless option that provides homogeneous local drug delivery, accelerates vessel healing, reduces neointimal proliferation, and preserves physiological vasomotion.[3,4] The use of DCBs in coronary bifurcation lesions offers several advantages. First, compared with plain old balloon angioplasty, DCBs can potentially enhance the procedural success of a provisional strategy.[5,6] Second, DCBs maintain the original carina anatomy and reduce both procedural complexity and the complications related to permanent metallic implants. Third, DCBs allow for late lumen enlargement.[7] Lastly, despite their relatively small diameter (usually ≤2.75 mm), SBs supply a significant myocardial area; thus, several studies

have shown that DCBs are at least as effective as drug-eluting stents in the treatment of small vessels.[8–11]

METHODS

Study Design and Participants

Between April 2022 and June 2025, all patients who underwent coronary angiography for stable angina, unstable angina, or acute coronary syndrome were screened. Patients with isolated SB *de novo* occlusion (Medina, 0.0.1) identified as the culprit lesion and treated with DCB were included (n = 48). The follow-up period ranged from 155 to 858 days (mean, 423 days). Follow-up of 32 patients was conducted face-to-face through outpatient clinic visits. Clinical information of 16 patients—who were not followed up at the center—was obtained through the national database and telephone contact. These patients were asked whether they experienced chest pain after the procedure and whether they were using any new medication or had undergone coronary angiography. This study is designed as a hypothesis-generating retrospective observational cohort evaluating procedural safety and feasibility rather than a comparative efficacy trial. Ethical approval was obtained from the Ethics Committee of Lokman Hekim University (University of Health Sciences) (Approval No.: 2025/148, dated May 30, 2025). All procedures were performed in accordance with the Declaration of Helsinki.

Definitions

Vessel Stenosis Parameters

Minimal lumen diameter (MLD): Diameter at the narrowest point of the stenosis (mm).

Reference vessel diameter (RVD): Calculated as the diameter of the normal vessel segment immediately distal to the stenosis.

Percent diameter stenosis (DS%): $DS\% = (1 - MLD/RVD) \times 100$.

Major Adverse Cardiac Events (MACE): According to the Academic Research Consortium definitions, MACE is defined as: 1) Death from all causes (including isolated cardiac death), 2) myocardial infarction (MI), and 3) target vessel revascularization or revascularization of target lesions (TLR).

HIGHLIGHTS

- The success of drug-coated balloon (DCB) treatment of isolated side branch (SB) occlusions depends on appropriate lesion preparation.
- Drug-coated balloon treatment of isolated SB occlusions offers the advantages of shorter procedure times, less radiation exposure, and less contrast material use.
- No risk of acute thrombosis has been identified with DCB application in isolated SB occlusions.
- Drug-coated balloon treatment is a promising treatment strategy for patients with Medina 0.0.1 lesions who experience chest pain despite medical treatment.

Myocardial infarction: Defined as cardiac enzymes ≥ 3× upper normal limit.

Definition of successful procedure: Following DCB application; residual stenosis <30% (<20% in some studies), thrombolysis in myocardial infarction (TIMI) grade 3 flow, absence of acute vessel closure, no severe dissection (≥ type C), and no elastic recoil or flow-limiting dissection in the branch ostium.

Procedure

For isolated SB lesions identified as the culprit, predilation was performed with semi-compliant or non-compliant balloons. After adequate lesion preparation, DCB angioplasty was performed if the following angiographic criteria were met: TIMI flow grade 3, residual stenosis ≤30%, and absence of dissection ≥type C. A DCB matched 1 : 1 to the vessel diameter was inflated at nominal pressure for at least 60 seconds. In patients who experienced chest discomfort during DCB inflation, the balloon was deflated for 15 seconds and then reinflated twice for 30 seconds each. All DCB procedures were performed using SeQuent Please NEO (B. Braun Medical, Melsungen, Germany).

Statistical Analysis

Descriptive statistics for continuous variables are expressed as mean ± SD or median (interquartile range). Categorical variables are presented as counts (n) and percentages (%), and 95% CIs were calculated using the Wilson method. The primary safety endpoints were periprocedural complications which consisted of dissection, bailout stenting, acute thrombosis, and periprocedural myocardial infarction. Owing to the small sample size and multiple comparisons, the analysis was considered hypothesis generating. All analyses were performed using Python 3.11 (pandas, statsmodels).

RESULTS

A total of 48 patients with isolated SB occlusion (Medina 0.0.1) treated only with DCB were included in this study. The baseline demographic and clinical characteristics are detailed in Tables 1 and 2. The mean age of the patients was 62.8 ± 13.9 years, and the population was predominantly male (n = 35, 72.9%). The cohort exhibited a high-risk profile, with a significant prevalence of cardiovascular risk factors. Hypertension was present in 75% (n = 36) of patients, hyperlipidemia in 87.5% (n = 42), and current smoking in 75% (n = 36). Diabetes mellitus was diagnosed in half of the patients (n = 24, 50%), with 20.8% (n = 10) of the total cohort requiring insulin therapy. The clinical history revealed a substantial burden of coronary artery disease. A majority of patients had a history of prior percutaneous coronary intervention (PCI) (n = 30, 62.5%) and myocardial infarction (n = 27, 56.2%). A smaller proportion had undergone prior coronary artery bypass grafting (n = 4, 8.3%) or had a history of stroke (n = 4, 8.3%). The mean left ventricular ejection fraction was 50.3% ± 10.4, indicating predominantly preserved to mildly reduced systolic function (Table 2).

The primary clinical presentation for the index procedure was unstable or stable angina pectoris in 87.5% (n = 42) of cases, while the remaining 12.5% (n = 6) presented with an acute

Table 1. Demographic Characteristics, Clinical, and Laboratory Findings

Variables	Mean ± SD (n = 48)
Age (years)	62.8 ± 13.9
Height (cm)	169.2 ± 8.7
Weight (kg)	82.1 ± 12.9
Ejection fraction (%)	50.2 ± 10.4
Hemoglobin (g/dL)	13.3 ± 2.3
Hematocrit, %	39.7 ± 4.5
Platelets (10^5/μL)	244.4 ± 74.1
White blood cells	8.9 ± 3.2
Creatinine (mg/dL)	1.4 ± 0.2
Urea (mg/dL)	41.4 ± 25.4
Glucose (mg/dL)	152.7 ± 55.5
LDL cholesterol (mg/dL)	94.5 ± 53.9
HDL cholesterol (mg/dL)	41.2 ± 12.8
Triglycerides (mg/dL)	166.1 ± 83.9
Total cholesterol	170.0 ± 59.2
Number of antianginal drugs	1.5 ± 0.6

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

coronary syndrome. The most frequently treated vessel was the left anterior descending artery/diagonal branches (n = 23, 47.9%), followed by the left circumflex artery (LCx) (n = 13, 27.1%) and obtuse marginal branches (n = 10, 20.8%). Angiographic analysis demonstrated a high degree of lesion severity. The mean baseline stenosis of the treated vessel was greater than 90%, with 47.9% exhibiting stenosis of 95% or greater. All patients underwent lesion preparation with predilation prior to DCB application. Non-compliant balloons were used for predilation in 60.4% (n = 29) of cases, while semi-compliant balloons were used in 39.6% (n = 19). The mean diameter of the primary predilation balloon was 2.28 ± 0.51 mm. The average number of DCBs used per patient was 1.1 ± 0.4. The mean diameter and length of the primary DCB were 2.54 ± 0.47 mm and 23.9 ± 7.5 mm, respectively. The DCB was inflated to a mean pressure of 8 atm for an average duration of 63.5 ± 11.9 seconds. The procedural and angiographic outcomes were highly successful. As documented in the provided literature, achieving optimal lesion preparation is paramount for DCB success. In this cohort, post-procedural TIMI flow was grade 3 in all 48 patients. The mean residual stenosis after the DCB procedure was 26% ± 14.9, meeting the generally accepted criterion of <30% for a successful angiographic result (Tables 3 and 4).

Table 2. Demographic Characteristics

Variables	n (%)
Sex (male)	35 (72.9)
Angina	45 (93.8)
PCI history	30 (62.5)
CABG history	4 (8.3)
MI history	27 (56.2)
HT	36 (75)
Stroke history	4 (8.3)
DM	24 (50)
Insulin	10 (20.8)
HLP	42 (87.5)
Smoking	36 (75)

CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; DM, Diabetes Mellitus; HLP, hyperlipidemia; HT, hypertension.

Table 3. Pre-Procedure Angiographic Findings

Variables	Mean ± SD (n = 48)
Predilation balloon diameter 1 (mm)	2.28 ± 0.51
Predilation balloon diameter 2 (mm)	2.3 ± 0.7
Predilation balloon diameter 3 (mm)	2.5
Number of DCB balloons used	1.1 ± 0.4
DCB 1 diameter (mm)	2.54 ± 0.47
DCB 1 length (mm)	23.8 ± 7.5
DCB 2 diameter (mm)	2.5 ± 0.3
DCB 2 length (mm)	28 ± 9
DCB 3 diameter (mm)	2.7
DCB 3 length (mm)	15
Predilation inflation count	1.6 ± 0.6
Inflation pressure (atm)	8
DCB inflation time (s)	63.5 ± 11.9
TIMI flow after balloon	3
Residual stenosis after DCB (%)	26 ± 14.9

DCB, drug-coated balloon; TIMI, thrombolysis in myocardial infarction.

Procedural Complications and Clinical Outcomes

The overall procedural success rate was 97.9% (n = 47) (Figure 1). Although type A/B coronary dissections were observed in 35.4% (n = 17) of procedures, the incidence of flow-limiting dissections requiring intervention was minimal. This finding is further supported by the fact that bailout stenting, which is the primary remedy for a failed DCB-only strategy, was required in only 1 patient (2.1%) (Table 4). No instances of post-DCB acute thrombosis were recorded. In-hospital and short-term clinical outcomes were also favorable. There was 1 reported case of post-procedural death (2.1%) and 1 case of post-procedural MI (2.1%). No strokes were observed. At follow-up, 16.7% (n = 8) of patients underwent a subsequent coronary angiography, and 12.5% (n = 6) reported post-procedural angina (Table 5).

DISCUSSION

In this study, DCB angioplasty was found to be a safe and feasible therapeutic option for one of the most technically demanding lesion types in interventional cardiology, specifically isolated SB occlusion (Medina 0.0.1), treated without stent implantation.

As Medina 0.0.1 lesions account for only 3%-5% of all bifurcations, clinical evidence remains scarce, and an individualized approach is needed. Compared with other bifurcation patterns, isolated SB lesions present several technical difficulties: the risk of main vessel injury during SB intervention,

Table 4. Angiographic Findings

Variables		n (%)
Presentation	ACS	6 (12.5)
	USAP/SAP	42 (87.5)
Treated vessel	LAD/Diagonal	23 (47.9)
	LCX	13 (27.1)
	OM	10 (20.8)
	RCA PI	2 (4.2)
Stenosis degree	100	6 (12.5)
	99	10 (20.8)
	98	3 (6.2)
	95	4 (8.3)
	90	13 (27.1)
	85	2 (4.2)
	80	8 (16.7)
	70	2 (4.2)
Stenosis 2 vessel	LAD/Diagonal	3 (75)
	LCX	1 (25)
Stenosis 2 degree	90	1 (25)
	95	2 (50)
	99	1 (25)
Stenosis 3 vessel	LCX	1 (100)
Stenosis 3 degree	98	1 (100)
Predilation balloon type	NC	29 (60.4)
	SC	19 (39.6)
Bailout stent	No	47 (97.9)
	Yes	1 (2.1)
Dissection	Type A-B	17 (35.4)
Post-DCB acute thrombosis		0
Outcome, successful		47 (97.9)

ACS, acute coronary syndrome; DCB, drug-coated balloon; NC, non-compliant; SAP, stable angina pectoris; SC, semi-compliant; USAP, unstable angina pectoris; LAD, left anterior descending; LCX, left circumflex artery; OM, obtuse margin; RCA, right coronary artery; PL, posterolateral.

a fibrocalcific plaque structure with high recoil potential and limited acute gain,[12] and a small vessel diameter that increases the risk of restenosis and stent thrombosis.[13] Recent

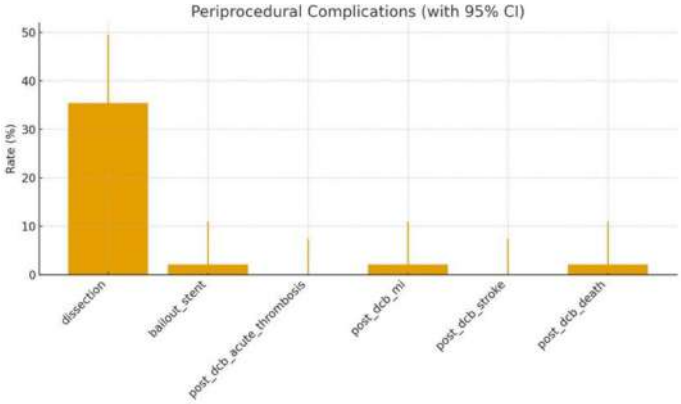

Figure 1. Overall procedural success rate of drug-coated balloon (DCB) angioplasty in isolated side branch lesions.

Table 5. Post–Drug-Coated Balloon Follow-Up

Variables	n (%)
Post-DCB CAG	8 (16.7)
Post-DCB angina	6 (12.5)
Post-DCB death	1 (2.1)
Post-DCB stroke	0
Post-DCB MI	1 (2.1)

CAG, coronary angiography; DCB, drug-coated balloon; MI, myocardial infarction.

registry-based studies have shown that lesions involving only the SB ostium (Medina 0.0.1) were associated with the worst 1-year outcomes compared with other subtypes.[14] This finding highlights the ongoing challenge of determining the optimal PCI strategy for isolated SB lesions.

In previous studies evaluating Medina 0.0.1 lesions treated with either stent implantation or medical therapy, MACE rates were found to be high. A recent meta-analysis comparing 1-stent and 2-stent strategies in Medina 0.0.1 lesions found similar rates of MACE between the 2 techniques.[15] Nonetheless, the overall risk of adverse events remains relatively high. Brueck et al[16] reported that interventional treatment of isolated diagonal branch lesions resulted in higher rates of rehospitalization and reintervention for angina

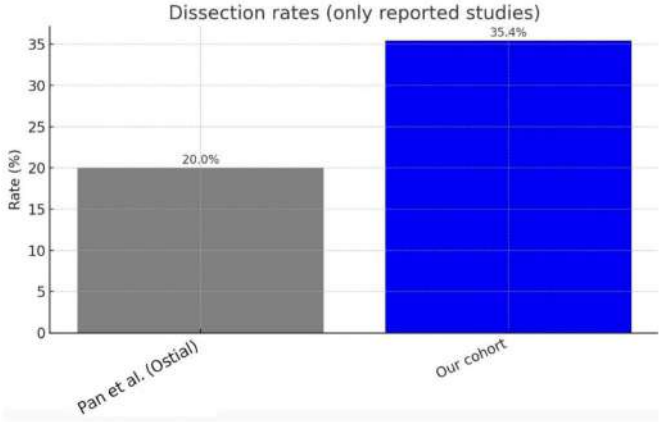

Figure 2. Distribution of dissection rates reported in different studies.

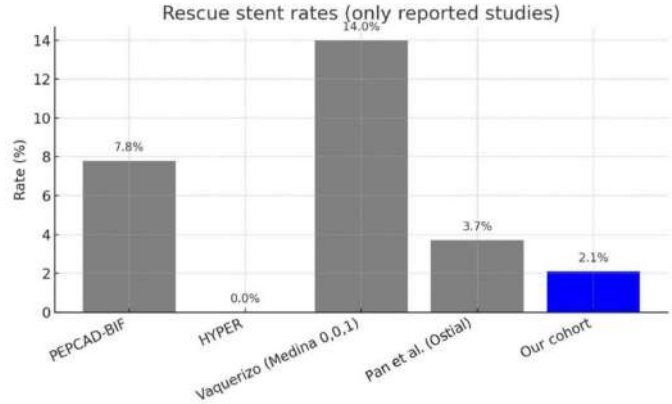

Figure 3. Comparison of bailout stent rates across published trials.

compared with conservative therapy.These findings suggest that patient selection may be more crucial than the specific PCI technique used.

Certain complications may occur in patients undergoing DCB treatment. Regarding type A-B coronary dissections, the incidence in this study (35.4%) was comparable to that reported by Gitto et al[17] (39.1%).In ostial-focused studies by Pan et al,[18] only flow-limiting dissections (type C or higher) were reported, with an incidence of approximately 20%. Most dissections are clinically insignificant and heal spontaneously. The inherent fragility of ostial and bifurcation regions predisposes them to dissection. Two-stent strategies may further increase the risk of SB injury, reinforcing the importance of meticulous lesion preparation and DCB sizing (Figure 2). When non-flow-limiting dissections remain after DCB treatment, the majority of dissections heal biologically over time without any significant adverse impact on late lumen loss or target vessel failure/MACE. Advanced optical coherence tomography (OCT) studies support the notion that DCB promotes healing at the dissection site and reduces neointimal hyperplasia. In this study, 35.4% of dissections that occurred were not flow-limiting, therefore not treated with a stent.[17,19]

In cases of flow-limiting dissection, treatment with bailout stenting may be necessary. In this cohort, the bailout stent rate was 2%, which is lower than that reported in the DCB-BIF (~4%) and PEPCAD-BIF (7.8%) trials.[20,21] No bailout stenting was reported in the HYPER study, whereas the Vaquerizo series reported a rate of 14%.[22,23] Thus, the current findings fall within the lower-to-mid range of reported rates in the literature (Figure 3). Another potential complication, periprocedural myocardial infarction, occurred at a lower rate in this study (2%) than in DCB-BIF (4.6%) and DEBUT (6.8%), and it was similar to that observed in HYPER (2%).[21,23] Evidence suggests that optimal lesion preparation before DCB angioplasty reduces MACE and spontaneous MI compared with uncoated balloon angioplasty.[20]

When these results—in the absence of acute thrombosis, 97.9% procedural success, and low adverse event rates—are considered alongside these data, DCB angioplasty appears to be a safe and feasible approach for Medina 0.0.1 lesions. The present findings align with those of Erdoğan et al[24], who treated major branches of the left main trunk with ostial DCB. Furthermore, this study obtained similar results to the PICCOLETO II – Side Branch Sub-Study, BASKET-SMALL 2 Sub-Analysis, DEBSIDE Study, and PEPCAD-BIF Trial, all of which evaluated DCB treatment outcomes in isolated SB occlusions.[9,21,25,26]

Study Limitations

This study has several limitations. This study is designed as a hypothesis-generating retrospective observational cohort evaluating procedural safety and feasibility rather than a comparative efficacy trial. It is a retrospective, single-center study with a limited number of patients and no control group. The absence of intravascular imaging (Intravascular Ultrasound-OCT) and pre/post-procedure physiological evaluation (fractional flow reserve) is another limitation. Furthermore, direct comparison of angiographic outcomes was not possible because routine follow-up angiography was not performed. Despite these constraints, the available follow-up data provide meaningful insight into the safety and feasibility of DCB angioplasty in this specific lesion subset.

CONCLUSION

This single-center, retrospective study with a small sample size demonstrates that DCB angioplasty can be performed safely and feasibly in isolated SB lesions, with low complication rates. Bailout stenting and periprocedural MI were uncommon, and most dissections were minor. Proper lesion preparation and patient selection are key to procedural success. Larger, prospective studies with longer follow-up are needed to validate these results.

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Lokman Hekim University (University of Health Sciences) (Approval No.: 2025/148; Date: May 30, 2025).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Artificial Intelligence: The authors declare that they did not use artificial intelligence (AI)-supported technologies (such as Large Language Models [LLM], chatbots, or visual generators) in the production of the work.

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Primary Cardiac Chondroma Presenting as a Left Atrial Mass: An Exceptionally Rare Case Report

CASE REPORT

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INTRODUCTION

Primary cardiac tumors are rare clinical entities with a prevalence of approximately 0.02% in autopsy studies. Of these, about 75% are benign and 25% are malignant. Benign tumors include myxoma, papillary fibroelastoma, fibroma, lipoma, and hemangioma, whereas angiosarcoma is the most common malignant type. These tumors may remain asymptomatic and be incidentally detected or they may present with systemic, embolic, or cardiac symptoms such as dyspnea and palpitations.[1-3]

Chondromas are benign, slow-growing tumors composed of mature hyaline cartilage, most frequently found in the small bones of the hands and feet.[4] Visceral chondromas are extremely rare and are most often associated with Carney's triad, involving pulmonary chondromas as one of its components.[5]

The origin of chondroid differentiation in primary cardiac tumors remains unclear, as cartilage is not a normal constituent of human cardiac tissue. Previous studies have suggested that chondrocyte-like cells may emerge in the context of valvular myxomatous degeneration through aberrant osteogenic differentiation and endochondral ossification processes, particularly involving the mitral valve.[6] In the present case, however, the lesion did not originate from the mitral valve, making this mechanism unlikely.

The differential diagnosis of cardiac masses containing cartilaginous elements includes primary or metastatic chondrosarcoma, teratoma, and myxoma with focal chondroid differentiation.

Recent advances in cardiac imaging modalities—including echocardiography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)—have substantially improved the detection and characterization of cardiac masses, facilitating more accurate differentiation between benign and malignant lesions and enabling better surgical planning.[7,8] Although data on cardiac chondroid tumors are limited, for extracardiac cartilaginous lesions, MRI criteria were shown to be useful in differentiating benign or atypical cartilaginous lesions from high-grade chondrosarcomas, with benign lesions typically demonstrating well-defined margins, homogeneous internal architecture, and high signal intensity on T2-weighted images, whereas malignant tumors more often exhibit infiltrative growth patterns, heterogeneous signal characteristics, and aggressive imaging features.[9] Despite these advancements, primary cardiac chondroma remains extraordinarily rare, with only 4 cases reported in the literature to date. Herein, an additional case of primary cardiac chondroma presenting as a left atrial mass, highlighting the diagnostic challenges, imaging features, and surgical considerations associated with this exceptional entity.

CASE REPORT

A 79-year-old male presented with progressive shortness of breath and palpitations over the preceding month. Transthoracic echocardiography (TTE) revealed a 3.5 × 4.5 cm mass occupying the left atrium. The patient had an unintentional weight loss of approximately 6-7 kg in 1 month. His past medical history

included benign prostatic hyperplasia (BPH) but no other chronic illnesses. Transesophageal echocardiography (TEE) and thoracic CT demonstrated a homogeneous mass with irregular margins attached to the atrial roof, extending into the pulmonary veins, but not the left ventricle (Figure 1). Echocardiography reveals the morphology and mobility of the mass, as shown in Videos 1 and 2. Despite the large size of the mass, no significant hemodynamic compromise was detected. Doppler echocardiographic assessment revealed no evidence of transmitral inflow obstruction, and estimated pulmonary artery pressures were within normal limits. The pulmonary veins were closely abutted by the mass; however, no radiological or functional evidence of pulmonary venous stenosis or obstruction was observed. Electrocardiography revealed T-wave inversions in the precordial leads. Laboratory evaluation showed borderline elevations of Cancer Antigen 19-9 (CA 19-9) and prostate-specific antigen, as well as subclinical hypothyroidism. Thyroid ultrasound revealed no nodules. Abdominopelvic CT identified bilateral renal cortical cysts and simple hepatic cysts. Prostate MRI was consistent with BPH. The PET CT was performed to further characterize the lesion and to exclude malignancy, given the patient's unintentional weight loss and the irregular morphology of the mass on cross-sectional imaging. The absence of fluorodeoxyglucose uptake supported a benign etiology and helped differentiate the lesion from metabolically active malignant cardiac tumors.

No specific radiological feature unique to cardiac chondroma was identified; however, the lesion appeared as a relatively homogeneous mass without invasive characteristics, favoring a benign process. Although the margins appeared irregular on CT, this finding was interpreted as tumor contours rather than true infiltrative growth, as there was no evidence of myocardial invasion or destruction of adjacent structures. Coronary angiography showed normal coronary anatomy.

A multidisciplinary team decided to proceed with surgical intervention. During surgery, a firm, fixed mass was visualized, attached to the left atrial roof and extending toward the pulmonary veins and left ventricle. Complete resection was not feasible due to dense adhesion to surrounding cardiac tissues (Figure 2A). Three biopsy samples were taken.

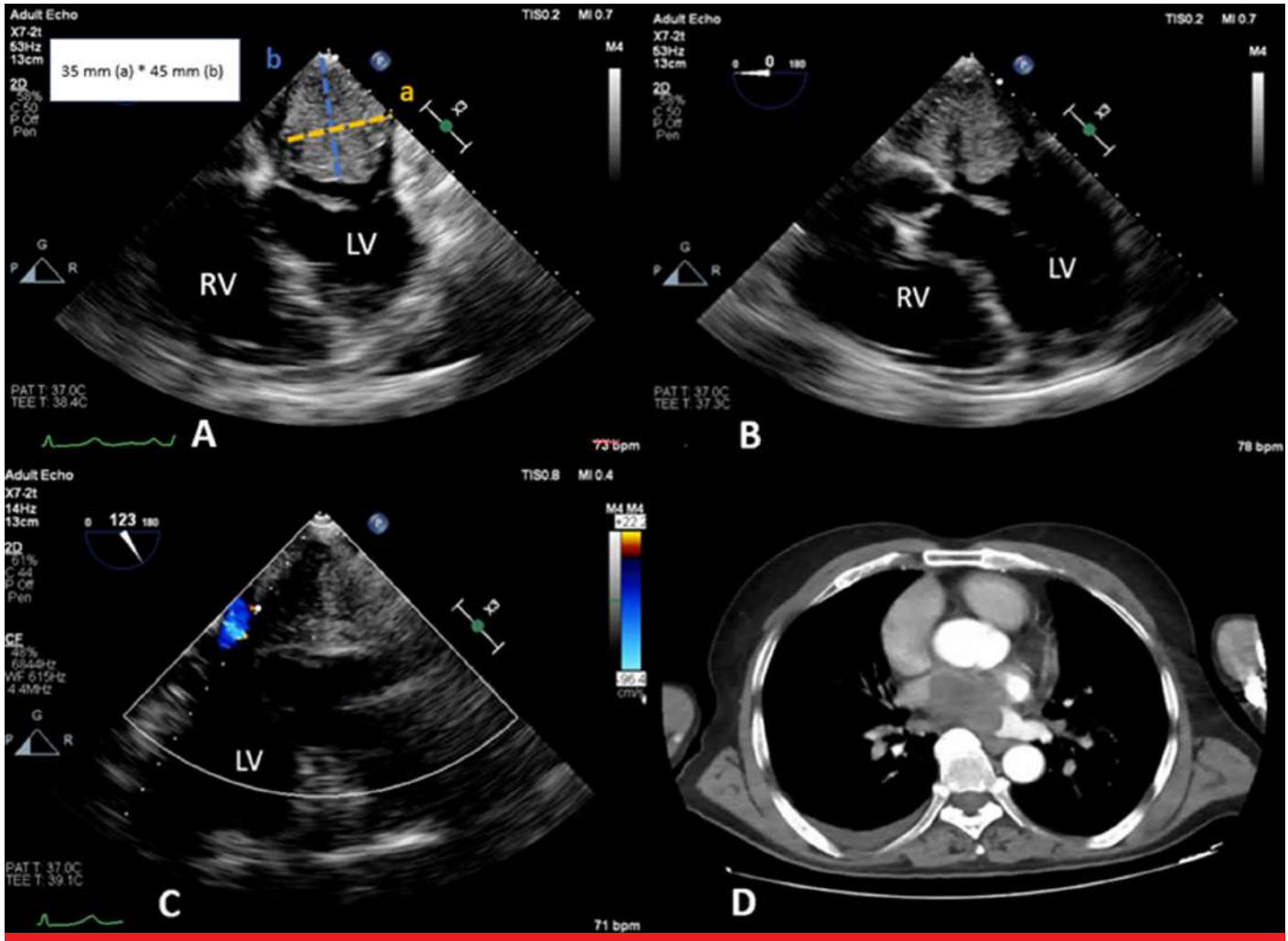

Figure 1. (A, B, C) Preoperative transesophageal echocardiography image demonstrating a cardiac mass. (D) Preoperative thoracic computed tomography image demonstrating a cardiac mass.

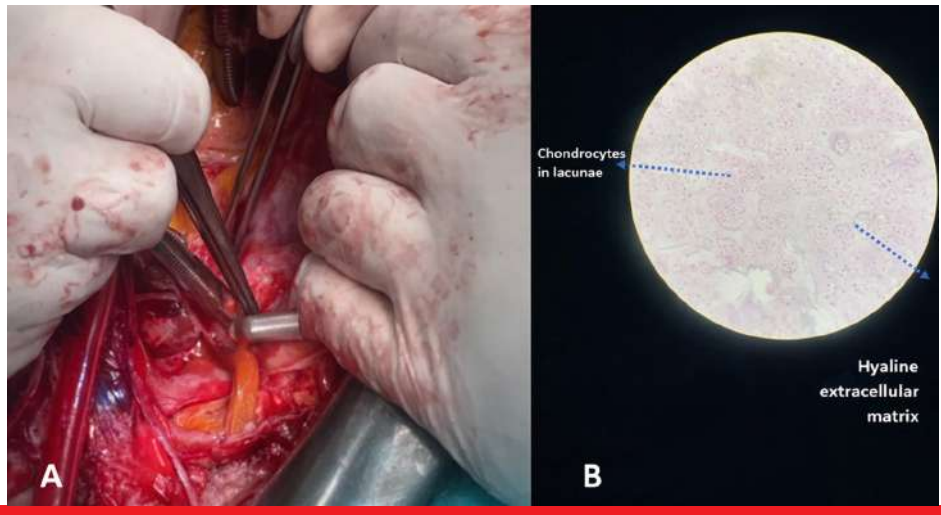

Figure 2. (A) Intraoperative image shows the occupation of the left atrium by the tumor. (B) Histopathological view showing mature cartilaginous tissue consistent with primary cardiac chondroma (hematoxylin–eosin staining, magnification × 10).

Histopathological analysis revealed mature hyaline cartilage consistent with primary cardiac chondroma (Figure 2B).

DISCUSSION

Primary cardiac tumors are rare clinical entities, and primary cardiac chondroma is one of the rarest forms. Most benign cardiac tumors are asymptomatic until they cause obstruction, embolization, or arrhythmia. Clinical presentation depends on tumor size, growth rate, and location within the heart.[1,2]

Only 4 previous cases of primary cardiac chondroma have been documented. The first case described by Vigraizer et al in 1973, involving a 55-year-old man with heart failure and myocardial infarction; autopsy revealed a 4 × 5 cm benign chondroma in the left atrium.[10] Dralle et al in 1994 reported a 36-year-old man presented with dyspnea and palpitations; a 2.5 × 1.6 cm tricuspid valve mass was surgically excised and diagnosed as chondroma. The patient had an uneventful postoperative course.[11] Sebire et al in 2004 reported a 16-year-old boy presented with superior vena cava obstruction and heart failure; the patient died postoperatively due to hemodynamic instability.[12] The most recent case published by Koskinas et al in 2011, a 62-year-old male with acute pulmonary edema was incidentally found to have a cardiac mass, later confirmed as chondroma after excision.[13]

On imaging, chondromas generally present as well-circumscribed, homogeneous masses that may contain calcifications but lack aggressive features, whereas chondrosarcomas tend to demonstrate infiltrative growth, heterogeneous internal architecture, destruction of adjacent structures, and increased metabolic activity on PET. Histopathologically, chondromas are characterized by mature hyaline cartilage with low cellularity, uniform chondrocytes, absence of nuclear atypia, and lack of mitotic activity, in contrast to chondrosarcomas, which exhibit increased cellularity, pleomorphism, hyperchromatic nuclei, and mitotic figures.[9] In the present case, the absence of fluorodeoxyglucose uptake on PET CT and the presence of mature hyaline cartilage without atypia supported a benign diagnosis.

Surgical management was particularly challenging due to the firm adherence of the mass to the left atrial roof and its extension toward the pulmonary veins and adjacent myocardial structures. Complete resection was deemed unsafe because attempted radical excision carried a substantial risk of atrial wall disruption, pulmonary venous injury, and postoperative atrial arrhythmias resulting from involvement of critical atrial conduction pathways. Therefore, a conservative surgical strategy with partial excision and biopsy was preferred to minimize the risk of structural compromise and life-threatening complications.

Given the incomplete resection, long-term clinical and imaging follow-up is of paramount importance. Although cardiac chondromas are benign and slow-growing tumors, residual tumor tissue may pose a risk of progressive obstruction, arrhythmia, or local recurrence over time, necessitating close surveillance.

Although not performed in this case, cardiac MRI may provide valuable additional information in the evaluation of chondroid cardiac tumors.

This case emphasizes the importance of thorough preoperative imaging and a multidisciplinary approach for management of rare cardiac tumors.

CONCLUSION

Primary cardiac chondroma is an exceptionally rare benign tumor that may mimic other intracardiac masses. Despite its benign histological features, its location within vital cardiac structures can make surgical excision challenging and may result in life-threatening complications.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Declaration of Interests: The authors have no conflict of interest to declare.

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Videos 1, 2: Preoperative transesophageal echocardiography demonstrating a cardiac mass within the left atrium.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Concerns Regarding the Interpretation of Triglyceride-Glucose Index as a Protective Factor in Hypertrophic Cardiomyopathy

LETTER TO THE EDITOR

To the Editor,

We read with interest the article by Liu et al[1] investigating the association between the triglyceride-glucose (TyG) index and outcomes in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF). While the study is notable for its large sample size, we have significant reservations regarding the interpretation of the TyG index as a protective factor.

The central claim that a higher TyG index reflects beneficial metabolic remodeling is not supported by recent mechanistic evidence. On the contrary, studies indicate that increased myocardial glucose utilization in HCM is a marker of underlying mitochondrial dysfunction and an inadequate energy state, not an adaptive protection.[2,3] For example, research by Vaniya et al[2] demonstrates that this metabolic shift co-occurs with significant lipid peroxidation and cardiolipin damage, hallmarks of metabolic distress. Another study describes a self-perpetuating cycle of decline in HCM where such metabolic changes ultimately worsen diastolic function.[3] This directly contradicts the proposed framework of protective adaptation.

A critical flaw is the lack of genetic data, which severely limits the interpretability of the findings. Metabolic disturbances in HCM are highly genotype specific.[2] The observed protective association could be entirely confounded by the uneven distribution of genetic subtypes within the cohort, rather than representing a true biological effect.

Furthermore, the results starkly contradict the established literature in general HFpEF populations, where a high TyG index is a consistent marker of insulin resistance, inflammation, and worse prognosis.[4,5] The authors' explanation for this reversal in HCM patients is not substantiated by a plausible biological mechanism.

Methodologically, the study is underpowered to assess the relationship with sudden cardiac death, a paramount endpoint in HCM, due to the low event count. The diagnostic criteria for HFpEF, reliant on an N-terminal pro-B-type natriuretic peptide (NT-proBNP) cut-off not validated in HCM, also introduces potential bias.

In summary, the assertion of a protective TyG index is premature. The observed association must be interpreted with extreme caution, considering the conflicting mechanistic data, unaddressed genetic heterogeneity, and inconsistency with broader HFpEF research. Future studies integrating genetic data, myocardial metabolic phenotyping, and TyG trajectories are needed to clarify whether TyG reflects true protective metabolic flexibility or serves as a surrogate marker of unmeasured disease characteristics.

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Reply to the Letter to the Editor: "Concerns Regarding the Interpretation of Triglyceride-Glucose Index as a Protective Factor in Hypertrophic Cardiomyopathy"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the authors of the letter for their thoughtful commentary[1] on our recent article[2] about the association between triglyceride-glucose (TyG) index and prognosis of patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF). We appreciate the opportunity to address the points raised.

We acknowledge that the association we observed between the TyG index and the prognosis of patients with HCM and HFpEF appears counterintuitive when viewed through the lens of general cardiometabolic pathophysiology. The readers note that in broader HFpEF populations, an elevated TyG index typically signifies insulin resistance and is associated with worse outcomes. However, we believe the unique metabolic milieu of HCM warrants a distinct interpretation.

Firstly, we agree that increased glucose utilization in HCM has been linked to mitochondrial stress. However, the biological response to metabolic stress is not monolithic. In the context of HCM with increased left ventricular pressure load, a substrate switch toward glucose oxidation may represent a compensatory adaptation to maintain myocardial energy production when fatty acid oxidation becomes inefficient. This concept of metabolic remodeling as a transient compensatory mechanism, rather than solely a marker of dysfunction, is supported by prior work in cardiac energetics.[3,4] While the studies by Vaniya et al[5] and Wijnker et al[6] highlight associated pathology, they do not preclude the possibility that this metabolic shift could be linked to a phenotype with slower progression or different mortality drivers in a specific clinical context. Our mediation analysis, showing N-terminal pro B-type natriuretic peptide as a significant mediator, suggests that the TyG index may indirectly reflect a hemodynamic or neurohormonal profile with a more favorable prognosis in this particular cohort.

Secondly, we fully concur that the lack of genetic data is a significant limitation. Genetic heterogeneity undoubtedly influences metabolic phenotype in HCM. However, the observed association remained significant after adjusting for numerous clinical covariates, including family history. While genetic confounding cannot be ruled out, our findings generate a hypothesis that merits testing in genetically characterized cohorts. We did not claim definitive causality but reported a novel association that could guide future, more detailed investigation.

Thirdly, the apparent contradiction with the general HFpEF literature underscores the specificity of the HCM-HFpEF population. HCM is a primary myocardial disease with distinct pathophysiology, whereas most HFpEF studies enroll patients with secondary hypertrophy due to hypertension or metabolic syndrome. Applying findings from 1 population directly to the other may be inappropriate. Our study precisely aimed to explore whether established biomarkers behave differently in this distinct entity.

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Finally, concerning methodological points, we acknowledged the limited power for the sudden cardiac death analysis due to the low event rate and called for further studies. Regarding the N-terminal pro B-type natriuretic peptide cutoff, we used a widely accepted guideline-recommended threshold for HFpEF diagnosis, while also transparently noting its potential limitation in HCM as a study limitation. The consistency of our results across multiple adjusted models and the competing risk analysis adds robustness to the primary findings for all-cause and cardiovascular mortality.

In conclusion, we agree that labeling the TyG index as universally "protective" is premature. We welcome the reader's call for integrated studies incorporating genetics, longitudinal TyG trajectories, and advanced metabolic phenotyping. It is through such rigorous, multifaceted research that we can determine whether this association reflects adaptive metabolic flexibility, uncovers a novel HCM subtype, or is confounded by unmeasured factors.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Remarkable Indices in Predicting Atherosclerotic Cardiovascular Disease

LETTER TO THE EDITOR

To the Editor,

We read with great interest the article by Song et al titled "Triglyceride-Glucose Index and the Risk of Calcific Aortic Valve Stenosis" and would like to congratulate the authors for highlighting the role of metabolic risk markers in valvular heart diseases.[1] Calcific aortic valve disease and atherosclerotic cardiovascular disease (ASCVD) share similar risk factors and pathogenic mechanisms, leading to comparable clinical outcomes. Therefore, the use of novel approaches and newly developed indices may enable more effective diagnosis, treatment, and follow-up strategies for both clinical conditions. The triglyceride–glucose (TyG) index is a well-known parameter frequently used to assess ASCVDs. We aim to contribute an alternative perspective by integrating this widely used index with several novel indices documented in the literature. In the pathophysiology of ASCVDs, metabolic problems such as insulin resistance, dyslipidemia, and visceral obesity, along with endocrine dysfunction, play a major role.[2,3] New indices have been developed to quantitatively evaluate these risk factors. We know that these indices work through different metabolic pathways. Although ASCVD risk factors are already described in detail in clinical guidelines, combining markers like low-density lipoprotein, triglycerides, and body mass index (BMI) or integrating them with new parameters may improve risk prediction. In the literature, particularly in premature atherosclerosis, various disease groups have been clearly defined, and efforts have been made to develop predictive models before clinical disease onset. Therefore, we aimed to contribute to this topic by integrating our recent publications with updated evidence from the literature. Several studies have evaluated metabolic processes across different diseases using indices such as the TyG index and the C-reactive protein (CRP)-TyG index.[4,5] The TyG index serves as a simple surrogate marker of insulin resistance, while CRP reflects systemic inflammation. The Body Roundness Index (BRI) is an indicator of central obesity, and thyroid-stimulating hormone (TSH) represents thyroid function. Accordingly, the combined assessment of metabolic (TyG), anthropometric (BRI), and endocrine (TSH) markers may offer a valuable approach for improving the prediction of ASCVD risk. In our research, we aimed to examine the combined use of these markers and share our results. In our pilot study on patients with subclinical hypothyroidism, BRI values were significantly higher in those who developed coronary artery disease (CAD), while a new index we developed, BRITSH, was significantly lower in the same group.[6] In hypothyroid patients, BRI showed high performance in predicting CAD (area under the curve (AUC) 86%), and BRITSH showed moderate predictive value (AUC 67%). In multivariate logistic regression analysis, the BRITSH ratio, along with age, diabetes, high-sensitivity CRP, and non-high-density lipoprotein cholesterol, was found to be an independent predictor of CAD. These findings suggest that the BRITSH index, which combines body composition and thyroid function, may be more helpful than traditional measures in predicting CAD risk in hypothyroid patients. In another study, we investigated the TyG-BRI index and its ability to predict in-hospital mortality in elderly patients with ST-elevation myocardial infarction (STEMI). Among octogenarians (≥80 years), those who died during hospitalization had significantly higher TyG-BRI values than survivors.[7] Each unit increase in

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TyG-BRI was associated with a 32% higher risk of in-hospital mortality. A TyG-BRI cutoff value of >30.7 had 83% sensitivity and 67% specificity in predicting mortality. Our results showed that the TyG-BRI index, which can be calculated from routine laboratory and body measurements, may provide independent, low-cost risk prediction beyond traditional risk factors in elderly STEMI patients. This suggests that combining metabolic and body composition indicators may improve risk stratification in older adults. The prognostic value of TyG and combined indices has been studied in various clinical settings. For example, in a recent study of 1095 patients with hypertrophic cardiomyopathy and preserved ejection fraction heart failure, surprisingly, those in the highest TyG quartile had lower long-term all-cause and cardiovascular mortality compared to those with lower TyG values.[8] Furthermore, combining multicomponent parameters may improve the prediction of cardiovascular disease risk (Figure 1). In fact, combining clinical, biochemical, and vascular imaging markers has been shown to significantly improve the detection of asymptomatic atherosclerosis.[9] In conclusion, BRI may help to fill the gap left by BMI in capturing body composition in ASCVD risk prediction. The combined use of metabolic-endocrine indices like TyG-BRI and BRITSH can improve risk classification and provide meaningful contributions to clinical practice. These integrated approaches better reflect the risk caused by metabolic disorders and visceral adiposity and may guide more personalized preventive strategies.

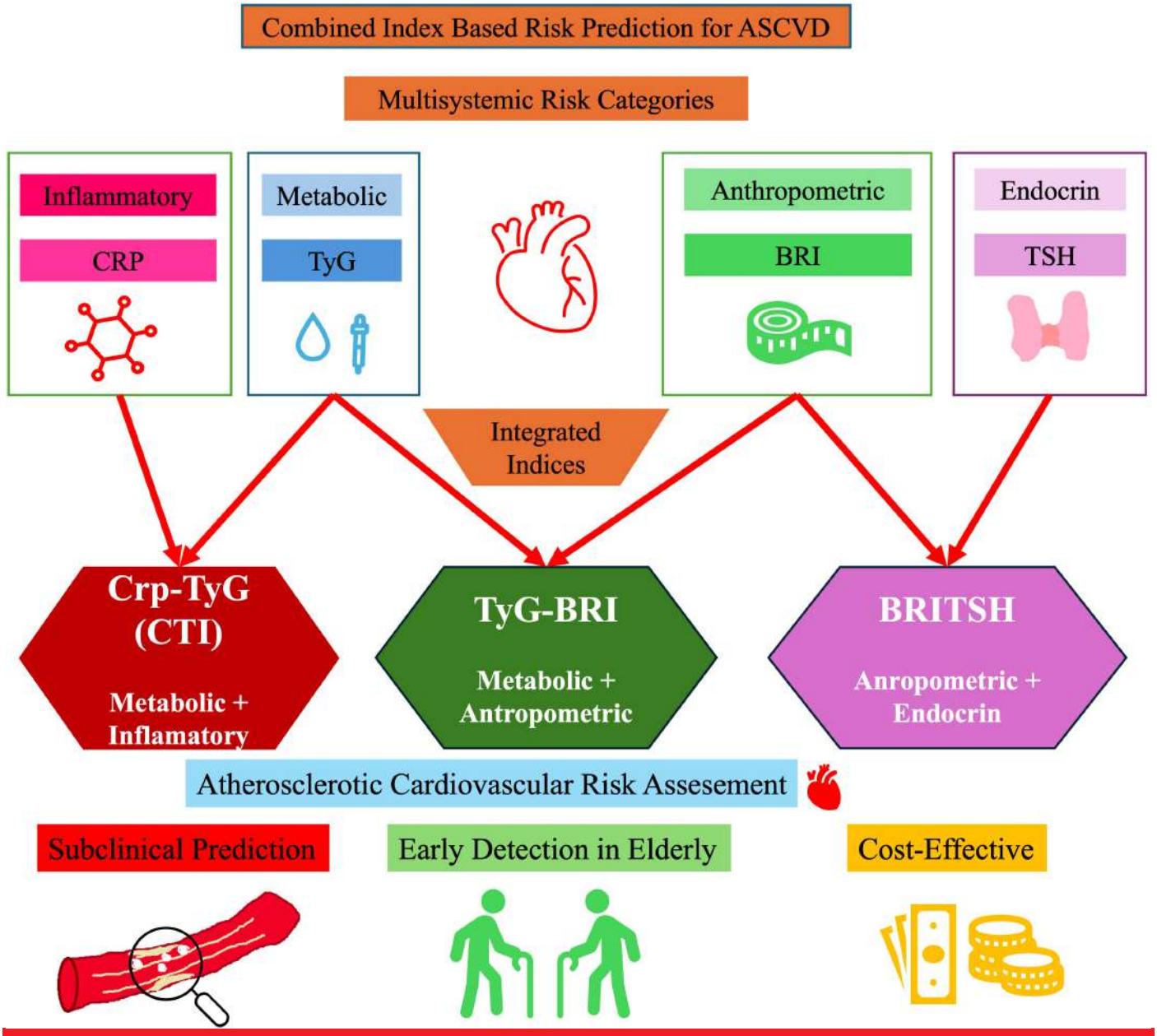

Figure 1. Integrated indices for ASCVD prediction. ASCVD, atherosclerotic cardiovascular diseases; BRI, Body Roundness Index; CRP, C-reactive protein; TSH, thyroid-stimulating hormone; TyG, triglyceride–glucose.

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Reply to the Letter to the Editor: "Remarkable Indices in Predicting Atherosclerotic Cardiovascular Disease"

LETTER TO THE EDITOR
REPLY

To the Editors,

We thank the readers[1] of the letter for their interest in our study (Triglyceride-Glucose Index and the Risk of Calcific Aortic Valve Stenosis: A Bidirectional Mendelian Randomization Study) and their constructive comments on the role of metabolic indices in cardiovascular risk stratification.[1,2] We appreciate the opportunity to respond and further discuss the integration of novel biomarkers in atherosclerotic cardiovascular disease (ASCVD) prediction.

We agree that traditional risk factors, while foundational, may not fully capture the complex metabolic and anthropometric contributors to ASCVD. The readers rightly highlight the potential of combined indices such as TyG-BRI and BRITSH in refining risk assessment, particularly in specific patient subgroups like those with subclinical hypothyroidism or elderly STEMI patients. Their pilot data suggesting the utility of BRITSH in hypothyroid patients and TyG-BRI in octogenarian STEMI are noteworthy and align with the growing interest in multimodal risk evaluation.[3,4]

In our own work, we have observed that the triglyceride-glucose (TyG) index—while commonly linked to insulin resistance and adverse outcomes—may exhibit context-dependent associations, as seen in certain heart failure phenotypes.[1] This reinforces the readers' point that biomarkers should be interpreted within specific pathophysiological and clinical contexts. The integration of metabolic (TyG), anthropometric (BRI), and endocrine (TSH) markers represents a logical step toward more personalized risk prediction.[5]

We also support the notion that composite indices could help overcome limitations of traditional measures such as body mass index, especially in capturing visceral adiposity and its metabolic consequences. The referenced studies, including those on CRP-TyG and TyG-BRI, underscore the additive prognostic value of combining routinely available parameters.[4,6]

However, we wish to emphasize the importance of external validation and prospective confirmation before these indices are widely adopted in clinical practice. Variability in population characteristics, comorbidities, and treatments may influence their generalizability. Furthermore, as the authors note, future studies should explore whether such indices improve hard clinical endpoints beyond existing risk scores.

In conclusion, we commend the authors for their contribution to the evolving discourse on ASCVD risk prediction. Their proposed integrated approach—bridging metabolism, body composition, and endocrine function—holds promise for enhancing risk stratification and guiding tailored prevention strategies.

We look forward to further research in this area and thank the editors for facilitating this scholarly exchange.

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Methodological Concerns Regarding Cardioprotective Effects of PCSK9 Inhibition in Diabetic Rats

LETTER TO THE EDITOR

To the Editor,

We read with interest the recent article by Zhang et al[1] investigating the cardioprotective effects of alirocumab and atorvastatin in a rat model of type 2 diabetes mellitus (T2DM) with myocardial ischemia-reperfusion (I/R) injury. While the findings are potentially valuable, we wish to raise several methodological concerns that fundamentally affect the interpretation and validity of the conclusions.

First, the induction of T2DM using 150 mg/kg streptozotocin is unusually high. As detailed in a comprehensive practical guide, the standard dose range for establishing a T2DM model in rats is 25 to 35 mg/kg, administered after a high-fat diet to induce partial beta-cell dysfunction.[2] Doses of 50 to 65 mg/kg are reserved for inducing type 1 diabetes, while doses exceeding 65 mg/kg cause near-complete and irreversible beta-cell ablation.[2] The 150 mg/kg dose is therefore overwhelmingly toxic and would produce a phenotype consistent with severe type 1 diabetes, not T2DM.[1] This is corroborated by the authors' own data showing significantly reduced insulin and C-peptide levels in diabetic rats. The mechanistic claims regarding metabolic modulation must be reconsidered given that the observed beta-cell destruction is likely irreversible.

Second, the absence of a sham-operated control group represents a critical oversight. The non-diabetic I/R and T2DM+I/R groups underwent thoracotomy with coronary ligation, while the "Control" group consisted of naive animals. Without a sham group undergoing thoracotomy without ligation, it is impossible to distinguish inflammatory and metabolic changes attributable to true I/R injury from those resulting from surgical trauma alone.

Third, the 2-hour reperfusion duration is relatively shorter to show apoptotic and inflammatory changes to peak following I/R injury. The authors' TUNEL and caspase-3 data at 2 hours may not capture the full extent of injury or the true therapeutic efficacy of the interventions. Evidence for longer reperfusion indicates that many key apoptotic and inflammatory pathways continue to evolve beyond 2 hours.[3]

Fourth, the finding that atorvastatin downregulates PCSK9 expression is biologically paradoxical. Careskey et al demonstrated conclusively that atorvastatin (40 mg/day) significantly increases circulating PCSK9 levels in humans by 34% compared with baseline and placebo.[4] This occurs because statins upregulate SREBP-2, a transcription factor that activates both the LDL receptor and PCSK9 genes.[4] The authors present their contradictory finding as "novel evidence" without mechanistic explanation, implying potential errors in assay design or data interpretation.[1]

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Finally, no pharmacokinetic bridging data are provided to justify whether the 10 mg/kg/week alirocumab dose in rats achieves plasma concentrations comparable to therapeutic human doses.[1] Without measured drug levels, extrapolation to clinical efficacy remains speculative.

While the study addresses an important clinical question, these methodological limitations collectively compromise the translational reliability of the findings.

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Tetralogy of Fallot with Left Common Carotid Artery Arising from the Main Pulmonary Artery: A Rare Combination

E-PAGE ORIGINAL IMAGE

A 13-year-old female patient presented with a 2 month history of precordial bulge, without cyanosis, syncope, developmental delay, or family history of genetic disorders. Echocardiography showed right ventricular outflow tract obstruction, severe pulmonary stenosis (Figure 1A), a ventricular septal defect, and overriding of the aorta (Figure 1B), confirming the diagnosis of tetralogy of Fallot (TOF). In addition, echocardiography revealed a right-sided aortic arch (RAA) and an anomalous vascular structure connecting to the main pulmonary artery (MPA). Color Doppler imaging demonstrated continuous blood flow within this vessel (Figure 1C). Further computed tomography angiography with 3D reconstruction revealed the RAA and anomalous origin of the left common carotid artery (LCCA) from the MPA, with proximal segment tortuosity (Figure 1D and E). Consequently, a comprehensive cerebral evaluation was conducted for the patient, and time-of-flight magnetic resonance angiography of the brain showed well-developed intracranial segments of the

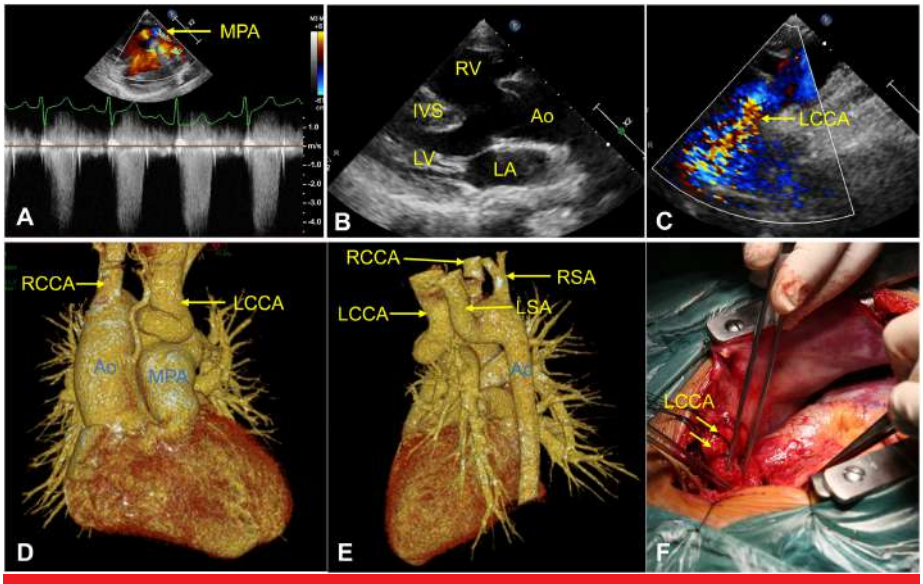

Figure 1. (A) Echocardiography showing severe pulmonary stenosis. (B) Echocardiography revealing ventricular septal defect and overriding of the aorta. (C) Color Doppler imaging demonstrating continuous blood flow within this vessel connecting to the main pulmonary artery. (D, E) Computed tomography angiography with 3D reconstruction reveals the anomalous origin of the left common carotid artery (LCCA) from the main pulmonary artery (MPA) and the right-sided aortic arch gives rise sequentially to the RCCA, RSA, LSA. (F) Intraoperative photograph showing the anomalous origin of the LCCA from the MPA. MPA, main pulmonary artery; LV, left ventricle; LA, left atrium; RV, right ventricle; IVS, Interventricular Septum; AO, aorta; LCCA, left common carotid artery; RCCA, right common carotid artery; RSA, right subclavian arteries; LSA, left subclavian arteries.

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bilateral vertebral arteries, basilar artery, and right posterior communicating artery. Subsequently, the patient underwent TOF corrective surgery with concomitant ligation of the aberrant LCCA (Figure 1F). The patient's oxygen saturation increased from 92% preoperatively to 100% postoperatively, and the patient was discharged 20 days after surgery and showed good recovery at the 6-month follow-up.

Anomalous origin of the LCCA from the MPA associated with TOF is an exceptionally rare combination of congenital abnormalities. Although this anomaly has been reported in association with 22q11.2 deletion syndrome or charge association,[1] genetic testing was not pursued in this patient owing to poor economic condition in her family. Imaging to confirm adequate brain blood supply is essential when determining the suitability of carotid ligation. Therefore, multimodality imaging plays an essential role in both definitive diagnosis and surgical planning for such anomalies.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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