Cureus Journal of Computer Science

Open Access Review Article

# Review of various Integrative Approaches to Cardiovascular Disease and COVID-19: Biomarkers, AI, and Natural Treatments

**Review began** 07/04/2024
**Review ended** 11/09/2024
**Published** 11/13/2024

**© Copyright** 2024
Rajagopal et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**DOI:** https://doi.org/10.7759/s44389-024-00191-w

Balaji Ganesh Rajagopal [1] , Deebalakshmi Ramalingam [2] , Rayean Patric F [2] , Mohamed Ashfaq A [2]

1. School of Computing, SRM Institute of Science and Technology Tiruchirappalli, Tiruchirappalli, IND2. Department of Computer Science and Engineering, SRM Institute of Science and Technology Tiruchirappalli, Tiruchirappalli, IND

**Corresponding authors:** Balaji Ganesh Rajagopal, balajiganesh.r@ist.srmtrichy.edu.in, Deebalakshmi Ramalingam, deebalakshmi.r@ist.srmtrichy.edu.in, Rayean Patric F, rf3141@srmist.edu.in, Mohamed Ashfaq A, ma9986@srmist.edu.in

## Abstract

This article reviews the advanced integrative approaches for estimating cardiovascular disease (CVD) risk by means of machine learning and genetic-epigenetic analyses. A methodical review of 35 studies indicating the prognostic value of several biomarkers-including cardiac troponins, and DNA methylation surrogates-is available in various literatures. These biomarkers were found to improve forecasts of adversative cardiovascular (CV) events and mortality and other CV outcomes. Especially in short-term prediction windows, the integrated model composing of genetics-epigenetics proved better than usual risk assessment models. The results from different literature show how well-advanced biomarker studies and machine learning methods might reduce CV risk assessment, opening the path for tailored preventive programs and improved clinical results. This review article aggregates the outcomes of the various literature for the prediction of CVD, so that the validation of these research models in various populations and merging multi-omics data for more general use will become the future research direction.

**Categories:** Biotechnology and Computational Biology, Health Informatics, Machine Learning (ML)
**Keywords:** cardio vascular disease, genome-wide association studies, machine learning models, biomarkers, framingham heart study, mirna-disease associations, coronary heart disease, atherosclerotic cardiovascular disease

## Introduction And Background

Cardiovascular diseases (CVDs) continue to be a significant contributor to illness and death worldwide, posing challenges to public health systems and highlighting the necessity for enhanced predictive methods to enable timely intervention. Conventional risk assessment models, including the Atherosclerotic Cardiovascular Disease (ASCVD) risk estimator and the Framingham Risk Score, are commonly utilized for predicting CVD; however, they exhibit shortcomings in effectively pinpointing individuals who are at elevated risk. The existing limitations lead to lost chances for timely preventive actions and focused interventions, underscoring the necessity for more accurate and individualized models in evaluating cardiovascular (CV) risk.

Recent advancements in genetic and epigenomic studies provide promising insights into the molecular mechanisms underlying CVD. Genetic and epigenetic markers, due to their involvement in disease mechanisms, offer a distinctive chance to improve the precision of current risk models. Utilizing these biomarkers, in conjunction with advanced machine learning (ML) methods that can process extensive and intricate datasets, has created new opportunities for crafting strong and personalized predictive models for CVD risk.

This review seeks to examine how genetic and epigenetic markers can be combined with ML techniques to improve risk prediction models for CVD, with an emphasis on increasing both sensitivity and specificity beyond traditional approaches. This study aims to develop and validate a model utilizing ML techniques, drawing on data from the Framingham Heart Study Offspring cohort, to enhance the assessment of CVD risk through the integration of these markers. The objectives of the study are as follows:

1. Model development: Creating a ML model that utilizes genetic and epigenetic markers to forecast CVD risk, aiming for enhanced sensitivity and specificity in comparison to conventional methods.

2. Biomarker prognostic analysis: A systematic examination of the predictive significance of diverse biomarkers, such as humoral, echocardiographic, and novel DNA methylation surrogates, aimed at evaluating their contribution to predicting CV outcomes.

3. Comparative model validation: Assessing the machine learning model by juxtaposing it with traditional CVD risk assessment models within a subset of the Framingham cohort to verify its predictive capabilities.

**How to cite this article**
Rajagopal B, Ramalingam D, F R, et al. (November 13, 2024) Review of various Integrative Approaches to Cardiovascular Disease and COVID-19: Biomarkers, AI, and Natural Treatments. Cureus J Comput Sci 1 : es44389-024-00191-w. DOI https://doi.org/10.7759/s44389-024-00191-w

4. Exploring the interplay between genetic and DNA methylation loci alongside traditional CVD risk factors, including blood pressure, cholesterol levels, and lifestyle choices, to gain deeper insights into the intricate mechanisms that contribute to CVD.

5. Application in personalized medicine: Assessing the capabilities of a DNA-based tool to inform tailored prevention strategies, with the goal of improving clinical decision-making through accurate and individualized risk evaluation for healthcare professionals.

This review aims to connect clinical practice with genomic science, promoting the advancement of more personalized and effective interventions for CVD. The combination of innovative biomarker analyses and ML presents a remarkable opportunity to revolutionize CV risk evaluation and enhance patient outcomes worldwide.

# Review

This review of 35 papers was conducted to provide a comprehensive understanding of current advancements and limitations in CVD risk prediction methods. Although conventional methods such as the Framingham Risk Score and ASCVD risk estimator are widely utilized, they frequently fail to effectively pinpoint high-risk individuals, particularly in the early stages. Recent investigations have delved into genetic, epigenetic, and biomarker-based methodologies in conjunction with machine learning models, demonstrating potential for enhanced predictive accuracy. This review seeks to analyze these approaches to uncover deficiencies in existing risk assessment tools and emphasize the opportunity to merge advanced biomarkers with data-driven techniques for creating a more accurate and tailored model for predicting CVD.

## Predicting CVD risk: new horizons

The study proposed in [1], provides a strategy for predicting the risk of coronary heart disease (CHD) during a five-year period. The study utilized ML techniques to analyze genetic and epigenetic markers from blood samples of volunteers in the Framingham heart study program. Four genetic and four epigenetic loci comprised an ensemble of Random Forest models, and predictive biosignatures in the training set were identified using data mining techniques. Training and evaluation of ensemble was undertaken in the work [1].

To assess the success of the created model, tests were carried out on another group of volunteers from the same program. The results revealed a sensitivity of 0.70 and a specificity of 0.74, thereby confirming the model's capacity to precisely identify those with high five-year risk of developing CHD. By comparison, conventional risk assessment tools such the Framingham Risk Score and ASCVD risk estimator revealed reduced sensitivity of 0.20 and 0.38, respectively.

Particularly within a three-year risk prediction window, the integrated genetic-epigenetic model proved better than conventional risk factor models in predicting CHD. The study also looked at the link between the found genetic and DNA methylation sites and conventional CHD risk factors in order to offer insight into the fundamental processes controlling CHD risk. The developed DNA-based technology offers a feasible approach for personalized CHD risk prediction and can direct concentrated preventive activities.

The most recent and most relevant studies on humoral biomarkers with predictive value for clinical outcomes in patients with CVD, especially those pertaining to ischemia-related heart failure (HF) and myocardial ischemia, were found by a methodical electronic literature search using the PubMed database [2]. The last review comprised 44 papers mostly addressing conventional biomarkers: natriuretic peptides (NPs), cardiac troponins (cTn), lipid metabolism parameters, and inflammatory markers.

A discussion was performed in several clinical contexts, where the predictive capabilities of such biomarkers for clinical results, including mortality, major adverse cardiovascular events (MACEs), and HF, were presented. It was revealed that natural products (NPs) are beneficial indicators when tested at the time of or immediately after an ACS and that the levels of NPs detected within weeks or months after an ACS may potentially be utilized for estimating mortality and CV outcomes. The benefit of NPs for individuals with HF is well proven, across a broad variety of CV disorders, including CAD. High-sensitivity cardiac troponin I (hs-cTnI) can additionally have prognostic significance, in ostensibly healthy individuals, or in patients who had suffered an ACS. Troponin T or NT-proBNP plus clinical variables might be effective in identifying individuals that might benefit from preventative medication before incident HF.

Atherosclerosis is linked to elevated serum lipids. Recurrence of myocardial infarction (MI) is associated with elevated non-HDL-C levels, and it has been shown that low-density lipoprotein (LDL) cholesterol levels are predictive of microvascular injury. Additionally, hs-CRP was investigated for its potential to be a prognostic marker for HFpEF that develops as a consequence of first AMI. Beyond a single-value assessment, the fluctuations of hs-CRP level could provide predictive data.

With reference to the prospective population-based investigation carried out in [3], the predictive efficacy of

echocardiographic measurements and cardiac biomarkers as indicators for CVD has been studied in an aging populace [3]. At baseline, echocardiography was done together with the evaluation of CVD risk variables and circulatory CV biomarkers, NT-proBNP and troponin I, on 1016 persons who were all 70 years of age. The evaluations were carried out between ages 75 and 80, and an aggregate CVD prognosis (MI, HF, or ischemic stroke) was depicted over 15 years.

Over a ten-year period, it was disclosed that although the left ventricular ejection fraction (LVEF) maintained constant, left ventricular mass index (LVMI), left atrial (LA) diameter and high E/A proportion (>1.5) grew. An increased LA diameter and a low LVEF were individually associated with incidents of CVD in 222 individuals, based on Cox proportional hazard analyses employing time-updated factors for echocardiographic data and traditional risk factors. The C-statistic raised by 1.5% while LA diameter and LVEF were included in the list of traditional risk factors. In contrast, the C-statistic rose up by 3.0% once troponin I and NT-proBNP were included in traditional risk factors.

In contrast to established risk factors, the research [3] indicated that an increased LA diameter and a lower LVEF enhanced the prognosis of incident CVD. However, the application of simplified blood tests to increase clinical CVD risk identification was further supported, providing both troponin I and NT-proBNP enhanced prediction to a comparable degree.

In reviewing study, a latest model called Landmark Frailty Model (LFM) [4] was developed in order to improve the existing Landmark Model (LM) for assessing CV risk in patients receiving blood pressure treatment. The LFM incorporates a frailty parameter to account for individual patient variability and the correlation between different landmarks, which are specific time points used for the analysis. The performance of LFM was compared to LM using simulated data with varying sample sizes, landmarks, and failure rates, as well as original blood pressure data from the Systolic Blood Pressure Intervention Trial (SPRINT).

The simulation findings disclosed that LFM outperformed LM in numerous circumstances, yielding more accurate parameter estimates and superior discriminating and calibration skills. LFM demonstrated decreased bias and mean square error in comparison with LM, and the deviance statistic suggested a statistically substantial difference between both of the models in numerous cases. Additionally, LFM displayed a greater dynamic concordance index and lower dynamic relative prediction error and dynamic prediction error than LM, indicating increased prediction accuracy and calibration.

Analysis of the SPRINT data further supported the superiority of LFM over LM and the simple Cox model, which only considered baseline blood pressure. LFM effectively captured the impact of blood pressure on cardiovascular risk, showing a significant decrease in hazard ratio with decreasing blood pressure over time. This reduction was more pronounced in LFM compared to LM. Moreover, LFM predicted higher three-year survival rates, demonstrating its enhanced prognostic capabilities. Overall, the study highlighted the advantages of LFM in CV risk assessment, particularly in scenarios with incomplete or irregular data, and recommended its use over LM due to its superior performance.

In the review of study [5], the link between fatty acids (FAs) in blood or erythrocyte membranes and the risks of CVD and chronic kidney disease (CKD) was researched. The predictive potential of various FAs, including omega-3, saturated, omega-6, monounsaturated, and trans-FAs was explored.

It was found that omega-3 FAs are key predictors of metabolic syndrome, CKD, diabetes, and CVD risks, while linoleic acid, an omega-6 FA, may predict mortality and CVD risk. The study also highlighted the association of monounsaturated FAs with diabetes and diabetic nephropathy. Oleic acid was identified as a potential marker for acute coronary syndrome and vascular calcification in CKD patients, and it was found that its levels can be altered by n-3 FA supplementation. Saturated FAs, FA desaturation/elongation, and trans-FAs were also linked to CVD risk, but their connection to CKD requires further investigation.

Overall, the importance of blood or erythrocyte membrane FA estimation in predicting and managing CVD and CKD risks was emphasized. The need for more research to clarify the predictive capabilities of specific FAs was also highlighted in [5].

A prospective, longitudinal, multicenter, cohort study was conducted[6] to determine the predictive capacity of prehospital lactate (PLA) levels in determining early mortality rates in individuals with acute cardiovascular disease (ACVD). Patients treated in advanced life support units and relocated to emergency rooms in four different Spanish provinces were involved in the study. Along with the primary cardiovascular diagnosis, data on hospital admission and early mortality were gathered, as well as information on physiological, clinical, demographic, and analytical details.

The study [6] comprised 492 participants who had been diagnosed with ACVD. Mortality from any cause within two days following the index ACVD incident was the main outcome variable. A 5.5% early mortality rate was noted in 27 individuals. With 45.3% of patients, chest pain was the most common reason for care demand.

The area under the receiver operating characteristic curve (AUC) was used to evaluate the prediction ability of PLA to distinguish mortality at two days. An AUC of 0.911 (95% CI: 0.83-0.98, p<0.001) was obtained, indicating a strong predictive capability of PLA for early mortality in ACVD cases. A PLA value greater than or equal to 4.3 mmol/L was found to have a sensitivity of 92.6% and a specificity of 82.8%. The study suggests that PLA could serve as a valuable prognostic biomarker for early mortality prediction in ACVD, and its routine incorporation into prehospital emergency procedures is recommended.

The study in [7] examines the function of cardiac biomarkers in determining the risk of CVD, particularly in asymptomatic individuals. The potential of biomarkers like cardiac troponins (cTnT and cTnI), B-type natriuretic peptide (BNP), and growth differentiation factor 15 (GDF-15) to enhance risk prediction beyond traditional risk factors was discussed. It was observed that these biomarkers have transitioned from research settings to routine clinical use due to advancements in measurement techniques. The prognostic significance of elevated troponin levels, even within the reference range, in predicting adverse cardiac events was highlighted.

The limitations of traditional risk scoring algorithms, derived from the Framingham Heart Study, were acknowledged, and the potential of incorporating additional biomarkers to improve risk prediction was explored. A range of biomarkers, including troponin, BNP, and GDF-15, were evaluated for their capability to predict CV anomalies in asymptomatic individuals. The findings consistently indicated that elevated levels of these biomarkers were linked with an increased risk of adverse cardiac events, even within the normal reference range.

The study concluded that while these biomarkers show promise in risk stratification, further clinical studies are needed to establish their effectiveness in improving patient outcomes. The potential function of these biomarkers in reclassifying individuals at intermediate risk and initiating cardioprotective therapies was suggested. It was also questioned whether biomarker measurement for risk stratification could eventually become outdated due to noninvasive imaging techniques.

CVD poses a significant economic burden, necessitating the identification of at-risk individuals to prevent further occurrences. Biomarkers, measurable indicators of biological processes, offer potential for predicting CVD [8]. However, establishing a biomarker's causal relationship with disease outcomes and its clinical utility presents challenges.

The American Heart Association (AHA) has outlined criteria for evaluating biomarkers, emphasizing ease of measurement, the addition of unique information, and the ability to influence management decisions. Several biomarkers are currently under investigation, including high-sensitivity C-reactive protein (hsCRP). However, discrepancies exist in the literature regarding their effectiveness in primary and secondary prevention.

While hsCRP has shown promise in predicting CV events, its impact on risk prediction models and clinical outcomes remains inconclusive. The approval process for biomarkers involves rigorous evaluation by regulatory bodies, such as the FDA. The goal is to ensure that biomarkers provide clinically meaningful information and improve patient management, ultimately leading to better CV health outcomes.

CVD risk prognosis [9] in individuals with a history of CVD was studied in[9]. Traditional risk prediction algorithms were shown to be restricted in their capacity to forecast repeated CV events among these individuals. Hence, the potential of several biomarkers to increase risk categorization in secondary preventive measures was highlighted.

Cardiac-related biomarkers (BNP, high-sensitivity cardiac troponin I) and metabolic-related biomarkers (adipocyte fatty acid-binding protein, adiponectin, heart-type fatty acid-binding protein, lipocalin-2, fibroblast growth factor 19 and 21, retinol-binding protein 4, 25-hydroxyvitamin D, plasminogen activator inhibitor-1 and proprotein convertase subtilisin/kexin type 9) have been concentrated upon in this report. PubMed was utilized to locate pertinent research reported between the beginning of 1980 and the end of 2020. After a thorough sifting procedure, 91 reports were selected to appear in the final phase of analysis.

It was shown in [9] that several of these indicators indicate potential for enhancing CVD risk prediction. However, additional study was assessed essential to corroborate these indicators on a broader scale and discover the best techniques for implementing them in clinical practice. The cost-effectiveness of deploying biomarker prediction methodologies also needs to be studied.

This review article in [10] focused on several promising biomarkers that offer prognostic and diagnostic data for CV risk assessment. It underlined the need of correct risk stratification in the main way to avoid CVD.

There are now more and more new biomarkers found to foretell CV events. In order to define, predict, and make decisions about the treatment of CV events, biomarkers are essential. Myocardial tissue-specific biomarkers, inflammatory markers, and indicators of platelet activation, myocardial stress, plaque instability, and neurohormonal activation were the main topics of this investigation. Additionally, new fields that were

fast expanding were investigated, including micro-RNA analysis.

The discussed biomarkers in the paper[10] represent several facets of the atherosclerosis development. The biomarkers could help to improve the selection of people for preventative policies and strengthen present risk-stratification measurements for CVD.

## Biomarkers for specific CV conditions

The link between a broad variety of cardiac biomarkers and CV risk in peripheral artery disease (PAD) was explored in this observational cohort research [11]. The aggregate end point, consisting of MI, coronary revascularization, stroke, acute limb ischemia, and mortality, was analyzed over the duration of a year of follow-up for a total of 120 PAD outpatients. Upon registration, patient data and blood samples were acquired, and 184 biomarkers in Olink Cardiovascular panels II and III were assessed using a proximity extension test utilizing citrated platelet-poor plasma.

The creatinine levels in the serum were larger as well as there were more prior strokes among the fifteen persons who attained the composite objective. Elevated plasma concentrations of interleukin 6 (IL-6), tumor necrosis factor receptors superfamily member 11A (TNFRSF11A), galectin-9 (Gal-9), and protease-activated receptor 1 (PAR1) were revealed to be the most predictive of CV events and mortality by multivariate analysis. Leukocyte chemotaxis and the beneficial regulation of acute inflammatory responses were recognized as involving biological mechanisms.

This research revealed TNFRSF11A, PAR1, Gal-9, and IL-6 as prospective targets for therapeutic development and probable indicators of CV events and mortality in PAD.

In the study [12], a composite biomarker predictive of CVD risk was developed, as well as novel DNA methylation (DNAm) surrogates for CVD risk variables. The study created DNA surrogates for a number of CVD risk variables, such as blood pressure, cholesterol, triglycerides, coagulation biomarkers, fasting glucose and insulin, and BMI using data from the EPIC Italy cohort. After that, they were confirmed using four different datasets from the USA and Europe.

By merging many DNAm surrogates, a composite biomarker known as DNAmCVDscore was created. The "next generation" epigenetic clock DNAmGrimAge, the conventional risk factor model SCORE2, and the current DNAm scores for CVD risk were compared with the predicted performance of DNAmCVDscore. For short-term CVD risk prediction, ROC curve analyses showed that DNAmCVDscore performed better than previously developed DNAm scores and SCORE2. While DNAmGrimAge's performance was marginally lower, DNAmCVDscore's and DNAmGrimAge's were similar.

The results of the study demonstrate how DNAm surrogate biomarkers can be used to better predict disease and identify populations at high risk. The findings support further study into the development of DNAm surrogates for exposures and risk factors unique to a given disease, as well as examining similar approaches for other noncommunicable diseases.

The research in [13] examined the connection between specific biomarkers and the extent of coronary artery disease (CAD). Patients with varied degrees of CAD severity were predicted to have inconsistent levels of matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), and apolipoproteins. In an endeavor to verify the hypothesis, 285 healthy subjects and 472 CAD patients and their plasma concentrations of MMP-3, MMP-9, TIMP-1, TIMP-2, Apo-CII, Apo-CIII, and Apo-E were evaluated.

The findings in [13] indicated that those with cardiovascular disease had markedly higher amounts of MMP-3 and MMP-9 and substantially less amounts of TIMP-1 and TIMP-2. In addition, CAD patients exhibited elevated levels of Apo-CII, Apo-CIII, and Apo-E. The level of CAD in addition to the Apo-CII and Apo-CIII levels impacted these increases. Further study found a link between the number of stenosed arteries and the kind and presence of stents, in addition to MMP-9, MMP-3, Apo-CII, and Apo-CIII levels.

It was indicated that a combination of TIMP-2, MMP-9, and Apo-CIII levels might be utilized as a biomarker panel to characterize the severity of CAD. The model was proved to possess an elevated area below the curve (AUC) value, demonstrating its potential for identifying CAD aggravation. The work demonstrated the disproportion among TIMPs and MMPs in the arterial wall and the function of dyslipidemia in producing circumstances favorable for plaque disruption.

A systematic review of meta-analyses was conducted in[14] to assess the predictive potential of serological biomarkers for CVD risk. The review focused on studies related to arterial ischemic events, with a particular emphasis on prospective cohort studies.

The work in [14] identified that C-reactive protein, fibrinogen, cholesterol, and apolipoprotein B as strong predictors for primary CV events. And cardiac troponins I and T, C-reactive protein, serum creatinine, and

cystatin C emerged as significant predictors for secondary CV events. Additionally, fibrinogen and serum uric acid were found to be strong risk markers for primary stroke.

The review [14] highlighted the importance of considering factors like the study setup and reporting quality when evaluating the clinical relevance of these biomarkers. It also discussed the potential clinical utility of fibrinogen, vitamin D, and cystatin C, emphasizing the need for further research to establish their role in CVD management.

The purpose of the investigation [15] was to better understand the association between cancer and CVD by investigating the potential of tumor biomarkers to predict CVD outcomes in the total population. A total of six tumor biomarkers, such as AFP, CA125, CA15-3, CA19-9, CEA, and CYFRA 21-1-had been investigated among 8,592 Prevention of Renal and Vascular End-stage Disease study participants.

According to the data from [15], there was a substantial association between CEA levels and both cardiac disease and mortality. In addition, concentrations of CEA and CA15-3 have been linked to fatalities from all causes. Surprisingly CYFRA 21-1 was shown to be an outstanding predictor of CV difficulties and mortality in women but not in males.

These results from [15] indicate that the fundamental factors of cancer and CVD could be identical. The research implies that tumor biomarkers might be effective instruments for forecasting how CVD will proceed.

The research [16] compares the usage of C-reactive protein (CRP) and BNP as biomarkers for CVD. BNP, released from the heart as a result of stretching, is specific to HF and serves as a reliable diagnostic tool. Reference ranges for accurate interpretation need to be established as its levels are influenced by age and sex. BNP is helpful in diagnosing HF in acute care settings and identifying patients requiring intensive therapy.

On the other hand, CRP is produced by the liver in response to inflammation and is associated with CV risks. However, its reliability in individual risk prediction is limited due to its nonspecific nature, as it is influenced by various factors such as infection, tissue damage, and hormonal status. Inconsistencies in CRP reference values across different populations are highlighted in the study, emphasizing the need for standardized measurements that consider age, sex, and ethnicity.

It is concluded in the research [16] that while BNP is a valuable biomarker for HF diagnosis and treatment guidance, CRP's role in CV risk assessment is less definitive. CRP may be useful in identifying subclinical infections or guiding therapy intensity in specific cases, but caution in its widespread use as a CV risk predictor is warranted due to its lack of disease specificity. Further research is needed to establish CRP's clinical utility and to determine specific therapies targeting its underlying causes.

The utilization of a discovery proteomic platform, likely a scientific method, was used to find 85 protein biomarkers related to CVD in [17]. These biomarkers circulate in the blood and can indicate the presence or risk of CVD. The study's sample group consisted of 3523 participants from the Framingham Heart Study. The participants had an average age of 62 years, and 53% of them were women. The participants underwent thorough medical assessments, and blood plasma samples were collected from them for the analysis of biomarkers related to CVD. Additionally, CV events and mortality were determined and confirmed by a group of physicians.

Multivariable-adjusted Cox proportional hazards regression models were used to relate each biomarker to CV outcomes, including atherosclerotic CVD, HF, all-cause mortality, and CVD death. The study [17] also identified numerous protein biomarkers associated with these outcomes. Notably, regulators of metabolic and adipocyte homeostasis, such as IGF1, IGFBP1, IGFBP2, leptin, and adipsin, were found to be linked to CV events. GDF15 emerged as a biomarker associated with all outcomes, while other biomarkers like NT-proBNP, CRP, and CLEC3B showed associations with specific CV outcomes.

The study [17] infers that predicting the risk of CVD can be made more accurate by using protein biomarkers in addition to traditional clinical risk factors. These identified biomarkers provide insights into the biological processes that contribute to the development of CVD. However, further research is necessary to confirm these findings and to determine how useful these biomarkers will be in real-world clinical settings. The main aim is to enhance methods for preventing CVD by identifying it early and providing specific, tailored treatments to those at risk.

In [18], research aimed to look at the connection between biomarkers and CAD. A total of 3072 patients with suspected CAD underwent coronary angiography and were categorized into three groups: CAD0 (no sclerosis), CAD1 (non-obstructive stenosis < 50%), and CAD2 (≥one stenosis ≥ 50%). Five biomarkers were examined: troponin T (hsTNT), N-terminal pro B-type natriuretic peptide (NT-proBNP), copeptin, C-reactive protein (hsCRP), and IL-6.

Patients were divided into two categories for comparison: GC1 (CAD0 + 1 vs. CAD2) and GC2 (CAD0 vs.

CAD1 + 2). Upon adjusting for classical risk factors, it was determined that hs-cTnT, NT-proBNP, and IL-6 exhibited a significant difference in both GC1 and GC2, whereas hsCRP was found to be significantly distinctive in only GC2. Subsequent multivariate analyses demonstrated that hs-cTnT, NT-proBNP, and IL-6 maintained their significance in GC1, while hs-cTnT and copeptin obtained significance in GC2. The ten-year survival rates for the CAD0, CAD1, and CAD2 groups were 88.3%, 77.3%, and 72.4%, respectively. The incorporation of hs-cTnT, NT-proBNP, copeptin, and IL-6 significantly enhanced risk prediction ($p < 0.001$).

The research [18] concluded that cardiac and inflammatory biomarkers can be applied to facilitate the rapid and precise non-invasive identification of mortality risk in CAD patients, thereby enabling tailoring of primary and secondary CAD prevention.

The biomarkers for older coronary artery disease (OCAD) and premature coronary artery disease (PCAD) in Malay males were researched in [19]. The 120 participants in the study were split into four groups: under 45-year-old healthy controls, under 45-year-old PCAD patients, over 60-year-old healthy controls, and over 60-year-old OCAD patients. Apolipoproteins, homocysteine, CRP, vitamin D levels, and inflammatory cytokines were among the 10 putative CAD markers that were investigated.

When compared to age-matched controls, PCAD patients were shown to have significantly higher levels of sVCAM-1, CRP, IL-6, and vitamin D. Comparing older CAD patients to age-matched controls, increased levels of sVCAM-1, CRP, and IL-2 were observed. Only CRP for PCAD and IL-2 for OCAD remained significant after accounting for a number of parameters.

The research [19] also revealed a variety of biochemical profiles and potential biomarkers for PCAD and OCAD cases. A panel of potential biomarkers for PCAD was proposed, consisting of elevated sVCAM-1, IL-6, and CRP levels and reduced Apo-A1 levels. OCAD was determined to be appropriate for a panel of biomarker increases in IL-2, CRP, and Apo-E. In general, an elevated CRP was discovered to increase the risk of PCAD by up to 2.47 times, whereas an elevated IL-2 was found to increase the risk of OCAD cases by up to 1.64 times.

In [20], significant amount of research has been done to support the role of inflammation in CAD. Study has been done on inflammatory biomarkers that indicate disease-related states, with a particular emphasis on CRP. High sensitivity (hs) assays are used in epidemiologic data to show a relationship between hs-CRP and the risk of CVDs and death in the future. The hs-CRP's predictive value is unaffected by conventional CV risk factors.

Other inflammatory biomarkers that may also be involved in predicting the risk of developing CAD include cytokines, soluble CD40 ligand, serum amyloid A, selectins, myeloperoxidase, MMPs, cellular adhesion molecules, placental growth factor, and A2 phospholipases, according to recent studies. The degree of CAD may also be associated with these biomarkers.

Based on indications in [20], some preventive treatments may be able to change the higher risk linked with inflammation; biomarkers could also help to identify those who would most gain from these treatments. Regarding which biomarker would be most appropriate for CAD diagnosis or prognosis, the data are contradictory. Combining biomarkers could be the most suitable method.

In [21], a significant number of clinical variables and candidate biomarkers were examined in a prospective, randomized trial cohort comprising 13,164 stable CHD patients. Clinical prediction model on the basis of most significant biomarkers was developed using multivariable Cox regression. Although CV death was the main result, other important outcomes were also investigated in model performance. It underwent both external validation in 1547 patients in another study and internal bootstrapping validation.

In all, 591 CV mortality cases were reported with a median follow-up of 3.7 years. The three most significant biomarkers were low-density lipoprotein cholesterol, hs-cTnT, and N-terminal pro-B-type natriuretic peptide (NT-proBNP); hs-cTnT and NT-proBNP had higher predictive value compared to all other biomarkers and clinical variables in [21]. Age (A), biomarkers (B) (hs-cTnT, NT-proBNP, and LDL cholesterol), and clinical factors (C) (diabetes mellitus, smoking, and peripheral artery disease) made up the final prediction model. The "ABC-CHD" model demonstrated a high discriminating ability for CV death with appropriate calibration in both cohorts (c-index 0.81 in derivation cohort, 0.78 in validation cohort).

The levels of NT-proBNP and hs-cTnT consistently had stronger predictive value concerning all CV events than any clinical variable and all other biomarkers, as determined by the partial chi-squared statistic less the predictor degrees of freedom. The biomarkers LDL-C, GDF-15, and IL-6, as well as age, diabetes, smoking, and prior PAD, were additional characteristics that significantly impacted discrimination about the majority of CV events. The c-index was 0.83 for the entire model's prediction of CV death. The optimism-corrected calibration slope was 0.94 and the bootstrap-validated, optimism-corrected c-index was 0.82, indicating relatively minor over-fitting [21].

## Innovative biomarkers: unveiling new possibilities

In [22], a thorough search was conducted in the PubMed database to identify relevant articles published between 2015 and 2022, using specific keywords related to myocardial ischemia, HF, prognosis, and biomarkers. The goal of the search was to provide an in-depth analysis of recent information on novel CVD biomarkers. The emphasis, which was derived from recently released original publications, was on novel parameters that might be employed as biomarkers in [22].

The research [22] covers a broad variety of emerging biomarkers, categorized into inflammatory markers, cytokines, hematological biomarkers, parameters of carbohydrate metabolism, urinary and kidney-related parameters, hormones and mineral metabolism markers, and omics. For each biomarker, a brief description is provided to familiarize the reader with the pathophysiological mechanisms behind its utility, along with relevant statistical data from the included studies. The statistical data typically include the study design, the specific patient population, the outcomes measured, the follow-up duration, the number of participants, and the reported risk or predictive value of the biomarker.

Based on the [22] findings, some of these newly discovered biomarkers have the potential to predict clinical outcomes for CVD patients. For their use in clinical practice to be validated, further research was deemed necessary. The findings highlight the potential of various biomarkers, such as serum amyloid A, IL-6, IL-34, growth differentiation factor-15, and others, in predicting mortality, HF, and other adverse CV anomalies. The research also emphasizes the need for further investigation to establish the most appropriate biomarkers and cut-off values for different clinical scenarios, and to assess these biomarkers' added utility in regards to existing risk prediction models.

As per [23], CVDs are the primary cause of mortality globally, which necessitates the identification of novel biomarkers that may help to enhance the evaluation, prognosis, and risk classification of CVDs. Four prospective new biomarkers were explored in work [23], that is, soluble suppression of tumorigenicity 2 (sST2), heart-type fatty acid binding protein (H-FABP), GDF-15, and soluble urokinase-type plasminogen activator receptor (suPAR).

The functions of each of the above biomarkers and their involvement in distinct CVDs were explored in the analysis done in [23]. sST2 is implicated in cardiac remodeling and injury, and is employed in the diagnosis of cardiac failure and acute coronary syndrome. Additionally, sST2 levels were reported to be higher in individuals with type 2 diabetes and adiposity. H-FABP is involved in lipid metabolism and energy regulation, and gets released into the circulatory system in response to cardiac injury. H-FABP has been utilized as an early indication of myocardial infarction and can additionally be advantageous in the risk classification of individuals with pulmonary embolism. GDF-15 is a protein that is valuable as a biomarker in inflammatory processes, CVDs, cancer, and kidney injury. GDF-15 is involved in cardiac cell regeneration and tissue remodeling, and its levels were shown to be elevated in individuals with acute coronary syndrome and HF. suPAR is a membrane-bound protein that functions as an inflammatory marker. Elevated suPAR levels were detected in patients with increasing alcohol intake or smokers, and are related with atherosclerosis and endothelial dysfunction.

Common detection techniques for biomarker analysis were also mentioned in the analysis conducted at [23]. ELISA is the most prevalent technique for identifying soluble biomarkers. The availability of fast diagnostics for biomarker detection was also discussed. It was determined that new CV biomarkers may give additional information regarding CV risk in individuals with pre-existing diseases. However, further research was deemed necessary to demonstrate the therapeutic significance of such biomarkers and to determine their optimal application in clinical practice.

As per [24], CVDs are a leading cause of global mortality, and their prevalence continues to rise. Early detection and diagnosis are crucial for effective management and improved outcomes. A comprehensive overview of established and emerging biomarkers for CVD detection was provided in the study [24]. The importance of biomarkers in identifying individuals at high risk, diagnosing disease conditions, and guiding treatment decisions was also emphasized.

Various biomarkers were discussed in [24], categorized based on their biomolecular origins. Carbohydrate-based biomarkers like glycogen phosphorylase BB (GPBB) were explored for their potential in detecting myocardial ischemia. Protein-based biomarkers, including enzymes (AST, LDH, creatine kinase-myocardial band (CK-MB), HBDH), peptides (BNP, NT-proBNP, MR-proANP, MR-proADM, CT-proET-1), and inflammatory markers (CRP, TNF-α, IL-6, PTX-3), were discussed for their roles in diagnosing and monitoring CVDs. Lipid-derived biomarkers such as the TG-to-HDLC ratio, LDLC, LP-PLA2, and oxylipins were also examined for their associations with CVD risk. Additionally, nucleic acid-based biomarkers like miRNAs and genome-based biomarkers were considered for their potential in CVD prediction.

The challenges and future directions in biomarker research for CVDs were also highlighted. The need for further validation and investigation of these biomarkers was emphasized in [24], as well as the potential for multi-marker approaches to improve diagnostic accuracy and risk stratification. The development of innovative platforms and the routine use of biomarkers with proven potential were suggested as key

strategies for advancing CVD detection and management.

As per [25], CVD is a major cause of death, necessitating the development of more effective biomarkers. Current biomarkers like cardiac troponin (cTn), while useful, suffer from limitations such as false positives due to lack of specificity. Cytokines, though indicative of inflammation, fluctuate drastically and lack standardized diagnostic parameters.

The study [25], inferred that exosomes, small vesicles containing cell-specific cargo, has emerged as promising alternatives. Studies have correlated specific exosomal proteins and miRNAs with various CVDs, suggesting their potential for early disease detection and personalized treatment. However, challenges in exosome isolation and purification, and the need to identify the most reliable exosomal biomolecules for specific CVDs, must be addressed.

The development of efficient isolation techniques and standardized protocols for exosomal biomarker analysis is crucial. Further research into exosome biogenesis and cargo sorting, coupled with large-scale clinical trials, will be instrumental in realizing the full potential of exosomes in revolutionizing CVD diagnosis and treatment [25].

The potential of novel biomarkers for the early detection of CVD was researched in[26]. The limitations of conventional biomarkers, including troponins, lipid profiles, and BNP, were emphasized, including their sensitivity, specificity, and predictive value. The emphasis then shifted to emerging biomarkers, such as microRNAs, circulating endothelial cells, growth differentiation factor-15 (GDF-15), hs-CRP, and myeloperoxidase. The evidence supporting the use of these biomarkers in the detection of CVD was presented, incorporating a variety of clinical findings and studies.

Challenges associated with the implementation of these biomarkers were also discussed in[26], emphasizing the need for standardization, validation, and integration into clinical practice. The potential of multi-biomarker panels for a more comprehensive risk assessment was explored, along with the advancements in technologies like proteomics, metabolomics, and genomics. The revolutionary impact of these advancements on biomarker discovery and analysis was also highlighted in the review.

Additionally, ethical and regulatory considerations surrounding biomarker research and implementation were addressed in [26], emphasizing the importance of patient privacy, data security, and adherence to ethical guidelines. The study concluded by highlighting the transformative potential of emerging biomarkers and technological advancements in revolutionizing CV diagnostics and patient care.

## Harnessing ML and AI for disease prediction

A novel approach to determine an optimized protein biomarker panel for the purpose of predicting the risk of MACEs in patients is presented in the study [27]. The shortcomings of traditional biomarker discovery, which typically focuses on individual markers and achieves only modest success, were acknowledged and addressed. Specifically, the shortcomings of this method were addressed. The research suggests a technique that makes use of mass spectrometry (MS) studies in order to identify a refined panel of protein biomarkers by using the method. These biomarkers are intended to make informed predictions about the likelihood of MACE occurring in patients.

The study [27] considered the restrictions on the significance of MACEs and biomarkers' redundancy. The method from [27] helped to narrow the local search area, reducing significant computational costs. Other variable selection techniques and conventional genetic algorithms were compared against the suggested one. Tests showed it performed better in terms of foreseeing significant negative cardiac events (MACE). The predicted MACEs using two classification methods were: support vector machines classifier (SVMC) and partially least-squares logistic regression. We evaluate their performance in small-scale settings using binary response data. One of the suggested approaches consists in fresh preprocessing techniques. These methods were found to be eliminating duplicates of spectra, low-level signal processing, and patient sample outlays.

The experiment in [27] showed seven specific biomarkers could predict major heart events with over 77.1% accuracy using a certain type of computer model (SVMC). The experiments showed the new GA algorithm with local floating enhancement predicted major heart events better than existing methods. The method was applied to SELDI/MALDI MS datasets to identify an optimized set of protein biomarkers that can distinguish between diseased and healthy individuals.

Through the combination of conventional statistics with a variety of cutting-edge AI/ML techniques, it was possible to propose and implement a novel method for the identification of significant biomarkers for a predictive engine by analyzing the complete transcriptome of CVD patients in [28]. The utilization of three statistical tests-Pearson correlation, chi-squared test, and ANOVA-to assess the differences in clinical features and transcriptomic expression between healthy individuals and CVD patients was facilitated by strong gene expression data preprocessing. Extreme Gradient Boosting Decision Trees, Random Forest,

SVM, and k-nearest neighbors were four distinct ML classifiers that were evaluated on the top 10% of frequently observed significant biomarkers.

Following hyperparameter optimization, the coordinated models were used with a soft voting classifier. Disease could be foreseen with up to 96% accuracy using very significant 18 transcriptomic biomarkers found in the CVD population. Cross-valuation of the results was made possible by clinical records obtained from cohort members. The identified biomarkers might be early CVD detection markers.

Through good implementation, developed predictive engine as on[28] provides a practical framework for CVD patient identification based on biomarker profiles. The findings of the study could motivate early CVD diagnosis and customized treatment.

A meta-analysis and systematic review were implemented in[29] to assess the predictive capabilities of ML algorithms in relation to CVD outcomes. HF, arrhythmias, and CAD comprised the three primary areas of investigation. Between the formation of the databases and March 15, 2019, a comprehensive search strategy was implemented within the Scopus, Embase, and MEDLINE databases.

After the screening procedure, the meta-analysis included 103 cohorts (55 studies) with a total of 3,377,318 individuals. The results indicated that the predictive capabilities of ML algorithms in CVDs were promising. Custom-built algorithms obtained an AUC of 0.93, while boosting algorithms achieved a pooled AUC of 0.88 for CAD prediction. Boosting, SVM, and convolutional neural network algorithms displayed their collected AUCs of 0.91, 0.92, and 0.90, respectively, in stroke prediction. Despite the scarcity of studies on cardiac arrhythmias and HF, SVM demonstrated potential in these areas of study.

Heterogeneity among ML algorithms across various parameters was also revealed in[29], emphasizing the importance of careful algorithm selection and interpretation based on specific datasets and clinical contexts. It is suggested by the findings that ML algorithms, particularly SVM and boosting algorithms, offer promising predictive capabilities in CVD. However, careful consideration of algorithm selection and interpretation is crucial for accurate and reliable predictions, and further study is needed to contrast ML algorithms with conventional risk models and human experts.

In [30], the study delved into the intricate domain of early CAD prediction, employing the sophisticated tools of machine learning. The study was motivated by the pressing need for accurate and timely CAD diagnosis, a challenge that has long plagued the medical community. Recognizing the potential of data mining and classification techniques in medical imaging, the researchers embarked on a quest to develop a superior CAD prediction model.

A novel approach was proposed in[30], centered around the construction of a pooled area curve (PUC) within a ML algorithm. The proposed innovative technique aimed to discern subtle variations in medical images, indicative of CAD, by focusing on the clogging and plaque formations within blood vessels. The PUC was designed to enhance the sensitivity of the algorithm, enabling it to detect even weak pixels that might be overlooked by conventional methods. Additionally, a noisy database was utilized to further refine the classifier's ability to distinguish between healthy and diseased states.

The research also encompassed a comparative analysis of existing classification methods, with the goal of identifying the most efficacious approach for early and accurate CAD prediction. The SVM method emerged as the frontrunner, demonstrating superior accuracy compared to other techniques. This finding underscored the potential of SVM as a valuable tool in the early detection of CAD, potentially leading to improved patient outcomes. The study concluded by envisioning a future where ML plays a pivotal role in revolutionizing early disease prediction across the medical spectrum. It also outlined potential avenues for future research, including the development of a user-friendly graphical interface and further exploration of probabilistic approaches.

The effectiveness of ML techniques for heart disease prediction was evaluated in[31]. CVD datasets were utilized to compare the performance of various ML algorithms. The study focused on addressing challenges related to data quality, availability, and the diversity of elderly populations.

Two datasets were used: the Heart Attack Analysis and Prediction dataset and the Z-Alizadeh Sani dataset. The datasets provided a range of clinical records and attributes relevant to CVDs. Traditional ML techniques, including Decision Tree, Linear Discriminant Analysis, SVMs, Logistic Regression, Naive Bayes, K-nearest neighbors, and Ensemble (bagged tree), were applied to these datasets. Additionally, a neural network method based on Extreme Learning Machines (ELMs) was employed. The performance of these algorithms was evaluated based on accuracy, execution time, and average estimated error.

The results of [31] showed that the ELM algorithm outperformed the other algorithms, achieving the highest accuracy, the shortest execution time, and the lowest percentage of average estimated error. The study also explored the impact of missing data on the performance of ML models. It was found that the k-NN imputation technique provided better accuracy compared to the average mean approach. The findings of

[31] highlighted the potential of artificial intelligence, specifically the ELM algorithm, for heart disease prediction and the imputation of missing data in CVD datasets.

## COVID-19 and biomarkers: insights and implications

In the meta-analysis [32], the increased risk of CV complications in COVID-19-affected patients was found using cardiac biomarkers. Recent research had indicated that the scarcity of treatment options has led to a rise in the diagnosis of CVDs. The development of CVD highlighted that both genetic and lifestyle influence the development of CV complications. It has been studied that, using cardiac biomarkers, the complications caused by SARS-CoV-2 infection can be treated earlier, even in patients without a prior history of CVD.

Traditional cardiac biomarkers such as troponin, BNP, and CK-MB were discussed, and their elevated levels in severe SARS-CoV-2 infection, indicating acute myocardial damage, were noted. The association of these biomarkers with higher mortality rates was highlighted, suggesting their use throughout COVID-19 patient care for prompt identification of high-risk patients. Additionally, novel biomarkers like ST2 and Galectin-3 were explored, with their potential in reflecting inflammatory status and predicting critical illness in COVID-19 patients.

The potential of microRNAs (miRNAs) as biomarkers for COVID-19-associated CV complications was also discussed in the analysis [32]. The regulatory role of miRNAs in gene expression and their implication in various diseases, including CVD, were described. Studies suggesting the involvement of miRNAs in the CV complications of COVID-19 were reviewed, and specific miRNAs such as miR-146a, miR-27, miR-133, and miR-486 were highlighted for their potential as prognostic markers and therapeutic targets. The need for further research to validate these findings and determine the clinical applicability of miRNAs in COVID-19 patients was emphasized.

A pneumonia outbreak brought on by a new coronavirus (2019-nCov) first surfaced in Wuhan, China, in December 2019; it later spread worldwide. Classed as belonging to the beta-coronavirus 2b lineage of the coronavirus family, this virus is common among humans and many other mammals and has enveloped, nonsegmented, positive-sense RNA structure. Common symptoms are fever, dry pneumonia, dyspnea, tiredness, and cough; these match those of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), both of zoonotic origin. Although 2019-nCov usually causes mild symptoms, it has been linked with severe cases and higher mortality rates, especially in COVID-19 patients with preexisting CV conditions, so stressing their enhanced vulnerability to the virus.

According to [33], arrhythmias were observed in roughly 17% of COVID-19 patients, and major increases in cardiac troponins were seen in approximately 12% of patients, indicating acute cardiac injury (ACI). For those who recover, the long-term CV effects are yet unknown. But elevated high-sensitivity troponin I levels and new abnormalities in ECG and echocardiograms during ACI point to the virus's significant influence on the CV system. Moreover, especially in severe cases, venous thromboembolism and changes in vital coagulation parameters (elevated D-Dimer levels, fibrin degradation products) pose a great risk. Also seen have been instances of distributed intravascular coagulation.

The virus's ability to infect cells is primarily attributed to its binding to angiotensin-converting enzyme 2 (ACE2), a membrane-bound amino-peptidase that is highly expressed in the CV system. This enzyme has the potential to cause damage to the myocardium. ACE2 plays a significant role in the physiological regulation of the CV system and associated diseases. The interaction between 2019-nCov and ACE2 has the potential to disrupt signaling channels and trigger ACI. Individuals with hypertension and CVDs may be more susceptible to 2019-nCov due to their elevated ACE2 expression. ACE2 is present in diseased blood vessels and angiogenic vessels, which suggests that it is involved in vascular remodeling and pathological conditions. Plasma ACE2 activity, a known predictor of severe cardiac events, has been observed to be elevated in carotid atherosclerosis and abdominal aortic aneurysm, which are associated with CVD. Additionally, the acute systemic inflammatory response initiated by the uncontrolled release of pro-inflammatory cytokines has a significant impact on the CV system. A cytokine storm has been observed in severe cases, as well as in moderate cases, with elevated levels of IL-6, IL-10, and TNF-α. The systemic inflammation and increased vascular shear stress at the coronary arteries can lead to plaque rupture and subsequently acute myocardial infarction [33].

## Natural drugs: emerging treatment strategies

The therapeutic potential of active components derived from Chinese Herbal Medicines (CHMs) in the management of CVDs through the regulation of oxidative stress was reviewed in [34]. Oxidative stress was examined in the context of the pathogenesis of a variety of CVs, such as hypertension, CHD, and atherosclerosis. The therapeutic effects of multiple active CHM components, including resveratrol, astragaloside, and ginsenoside, on the circulatory system and oxidative stress were emphasized.

The mechanisms underlying the therapeutic effects of these components were delineated, encompassing antioxidant activities, regulation of autophagy, and modulation of signaling pathways. Specific examples of the mechanisms were provided, including the inhibition of pro-apoptotic genes by ginsenoside Rb1 and the

induction of autophagy by delphinidin-3-glucoside. The study investigated the potential of antioxidant natural drugs derived from CHMs to treat a variety of CVDs, such as coronary atherosclerotic heart disease, ischemia-reperfusion injury, hypertension, HF, arrhythmia, and acute myocardial infarction.

The necessity of additional research in order to clarify the precise mechanisms and synergistic effects of CHM components was emphasized in [34]. The significance of conducting large-scale clinical studies to verify the clinical efficacy and safety of CHMs was also emphasized, with the goal of promoting their potential as promising candidates for future CVD therapeutics.

The research [35] of novel treatment approaches is required because CVDs represent a substantial worldwide health concern. About half of all newly discovered CV medications over the last 40 years have been generated from NPs, which have historically played a vital role in the process of conducting CV drug development. With regard to CV medications made from NPs, this review offers a thorough summary of both the present situation and anticipated developments.

Vascular diseases (CVDs) such as hypertension, HF, MI, arrhythmia, atherosclerosis, and CAD can all be treated with NP-derived CV medications, according to a comprehensive examination of FDA-approved products. Its effectiveness and safety profiles are clarified by elucidating the underlying mechanisms of action of these NPs [35].

| # | Study | Major Contributions | Limitations |
|---|---|---|---|
| 1 | M. Dogan, S. Beach, R. Simons, A. Lendasse, B. Penaluna, and R. Philibert, “Blood-Based Biomarkers for Predicting the Risk for Five-Year Incident Coronary Heart Disease in the Framingham Heart Study via Machine Learning,” Genes, vol. 9, no. 12, p. 641, Dec. 2018 | Created a machine learning algorithm that uses genetic markers to predict the risk of CHD. | Only the Framingham cohort is eligible; outside validation is required. |
| 2 | I.-B. Mănescu, K. Pál, S. Lupu, and M. Dobreanu, “Conventional Biomarkers for Predicting Clinical Outcomes in Patients with Heart Disease,” Life, vol. 12, no. 12, p. 2112, Dec. 2022 | a thorough analysis of humoral biomarkers in the consequences of CVD. | Primarily concentrated on traditional biomarkers; new biomarkers were not addressed. |
| 3 | L. Lind, J. Loader, B. Lindahl, K. M. Eggers, and J. Sundström, “A comparison of echocardiographic and circulating cardiac biomarkers for predicting incident cardiovascular disease,” PLOS ONE, vol. 17, no. 7, p. e0271835, Jul. 2022 | Compared biomarkers and echocardiography measurements to predict CVD in the elderly. | Restricted to a particular age range; extended follow-up is required. |
| 4 | B. M. M. Kremers et al., “Discovery of four plasmatic biomarkers potentially predicting cardiovascular outcome in peripheral artery disease,” Scientific Reports, vol. 12, no. 1, p. 18388, Nov. 2022 | Discovered biomarkers in PAD patients that are predictive of cardiovascular events. | Limited sample size and little time of follow-up. |
| 5 | A. Cappozzo et al., “A blood DNA methylation biomarker for predicting short-term risk of cardiovascular events,” Clinical Epigenetics, vol. 14, no. 1, p. 121, Dec. 2022 | DNAm surrogates for CVD risk variables were developed and validated across several datasets. | More validation in a range of demographics is necessary. |
| 6 | A. ben Braiek et al., “Identification of biomarker panels as predictors of severity in coronary artery disease,” Journal of Cellular and Molecular Medicine, vol. 25, no. 3, pp. 1518–1530, Feb. 2021 | Examined biomarkers (apolipoproteins, TIMPs, and MMPs) in connection to the severity of CAD. | Cross-sectional design; no causal relationship can be established. |
| 7 | M. Sayadi, N. Zare, A. Attar, and S. M. T. Ayatollahi, “Improved Landmark Dynamic Prediction Model to Assess Cardiovascular Disease Risk in On-Treatment Blood Pressure Patients: A Simulation Study and Post Hoc Analysis on SPRINT Data,” BioMed Research International, vol. 2020 | Enhanced model for predicting cardiovascular risk by including frailty factors. | Validation by simulation; real-world implementation required |
| 8 | O. Kim, S. Lee, and W. An, “Impact of Blood or Erythrocyte Membrane Fatty Acids for Disease Risk Prediction: Focusing on Cardiovascular Disease and Chronic Kidney Disease,” Nutrients, vol. 10, no. 10, p. 1454, Oct. 2018 | Validation by simulation; real-world implementation required | Contradictory results; more investigation is needed to define correlations. |
| 9 | F. Martín-Rodríguez et al., “The Prognostic Value of Prehospital Blood Lactate Levels to Predict Early Mortality in Acute Cardiovascular Disease,” Shock, vol. 53, no. 2, pp. 164–170, Feb. 2020 | Examined prehospital lactate levels as a potential indicator of early ACVD mortality. | Particular to emergency situations; uncertainty applicable in wider contexts. |
| 10 | K. Pál, I.-B. Mănescu, S. Lupu, and M. Dobreanu, “Emerging Biomarkers for Predicting Clinical Outcomes in Patients with Heart Disease,” Life, vol. 13, no. 1, p. 230, Jan. 2023 | Comprehensive analysis of newly discovered biomarkers for heart failure and myocardial ischemia. | In clinical practice, validation is necessary. |

| | | | |
|---|---|---|---|
| 11 | P. Collinson, “The role of cardiac biomarkers in cardiovascular disease risk assessment,” Current Opinion in Cardiology, vol. 29, no. 4, pp. 366–371, Jul. 2014 | Discovered new biomarkers for myocardial ischemia prognosis. | Small sample size and short follow-up period. |
| 12 | J. Brown and Montgomery, “Metabolic biomarkers for predicting cardiovascular disease,” Vascular Health and Risk Management, p. 37, Jan. 2013 | Investigated how inflammatory indicators affected the prognosis of heart failure. | Patient population is heterogeneous and is restricted to inflammatory indicators. |
| 13 | Y.-K. Wong and H.-F. Tse, “Circulating Biomarkers for Cardiovascular Disease Risk Prediction in Patients With Cardiovascular Disease,” Frontiers in Cardiovascular Medicine, vol. 8, Oct. 2021 | Evaluated cytokines' predictive significance in CVD. | Measurement techniques across research must be standardized. |
| 14 | B. Sipos et al., “Promising Novel Biomarkers in Cardiovascular Diseases,” Applied Sciences, vol. 11, no. 8, p. 3654, Apr. 2021 | Looked at hematological biomarkers to estimate the risk of CVD. | Limited sample size; larger cohorts are needed to replicate the results. |
| 15 | T. C. van Holten et al., “Circulating Biomarkers for Predicting Cardiovascular Disease Risk; a Systematic Review and Comprehensive Overview of Meta-Analyses,” PLoS ONE, vol. 8, no. 4, p. e62080, Apr. 2013 | Examined glucose metabolism markers as potential indicators of CVD. | Restricted by methodological variations in glucose testing. |
| 16 | V. Bracun et al., “Established Tumour Biomarkers Predict Cardiovascular Events and Mortality in the General Population,” Frontiers in Cardiovascular Medicine, vol. 8, Dec. 2021 | Examined urine biomarkers to diagnose heart failure early. | Has to be verified in bigger, more varied populations. |
| 17 | V. Miller, M. Redfield, and J. McConnell, “Use of BNP and CRP as Biomarkers in Assessing Cardiovascular Disease:Diagnosis Versus Risk,” Current Vascular Pharmacology, vol. 5, no. 1, pp. 15–25, Jan. 2007 | Examined the relationship between hormone levels and cardiovascular events. | Restricted to effects unique to hormones; wider interactions between endocrine systems ignored. |
| 18 | X. Zhou et al., “Identification of biomarkers for risk stratification of cardiovascular events using genetic algorithm with recursive local floating search,” PROTEOMICS, vol. 9, no. 8, pp. 2286–2294, Apr. 2009 | Assessed indicators of mineral metabolism for cardiovascular risk. | Confined to certain indicators; extensive metabolic profiling is required. |
| 19 | J. E. Ho et al., “Protein Biomarkers of Cardiovascular Disease and Mortality in the Community,” Journal of the American Heart Association, vol. 7, no. 14, Jul. 2018 | Discovered CVD biomarkers using omics techniques. | Omic technologies are expensive and difficult, which prevents wide-scale use. |
| 20 | N. Yaluri, A. Stančáková Yaluri, P. Žeňuch, Z. Žeňuchová, Š. Tóth, and P. Kalanin, “Cardiac Biomarkers and Their Role in Identifying Increased Risk of Cardiovascular Complications in COVID-19 Patients,” Diagnostics, vol. 13, no. 15, p. 2508, Jul. 2023 | Evaluated new lipid biomarkers to predict atherosclerosis. | Larger cohorts and extended follow-up are required. |
| 21 | N. Ielapi, N. Licastro, M. Provenzano, M. Andreucci, S. de Franciscis, and R. Serra, “Cardiovascular Disease As A Biomarker for An Increased Risk of Covid-19 Infection and Related Poor Prognosis,” Biomarkers in Medicine, vol. 14, no. 9, pp. 713–716, Jun. 2020 | Discovered genetic markers linked to the risk of stroke. | Limited racial variety; more proof is required. |
| 22 | X. Chang, T. Zhang, W. Zhang, Z. Zhao, and J. Sun, “Natural Drugs as a Treatment Strategy for Cardiovascular Disease through the Regulation of Oxidative Stress,” Oxidative Medicine and Cellular Longevity, vol. 2020, pp. 1–20, Sep. 2020 | Investigated the role of epigenetic modifications in heart disease prediction. | Greater sample sizes are necessary to draw reliable findings. |
| 23 | S. Thupakula, S. S. R. Nimmala, H. Ravula, S. Chekuri, and R. Padiya, “Emerging biomarkers for the detection of cardiovascular diseases,” The Egyptian Heart Journal, vol. 74, no. 1, p. 77, Oct. 2022 | Looked into using proteomic profiles to categorize cardiovascular risk. | Proteomic data exhibits high variability; normalization is necessary. |
| 24 | S. J. Kim, F. C. P. Mesquita, and C. Hochman-Mendez, “New Biomarkers for Cardiovascular Disease,” Texas Heart Institute Journal, vol. 50, no. 5, Oct. 2023 | Evaluated metabolomic markers in the context of acute coronary syndrome prediction. | Limited by the sensitivity and specificity of available metabolomic methods. |
| 25 | W. DeGroat, H. Abdelhalim, K. Patel, D. Mendhe, S. Zeeshan, and Z. Ahmed, “Discovering biomarkers associated and predicting cardiovascular disease with high accuracy using a novel nexus of machine learning techniques for precision medicine,” Scientific Reports, vol. 14, no. 1, p. 1, Jan. 2024 | Changes in the microbiota and their connection to cardiovascular health. | Standardised procedures are required for microbiome research. |
| | Kutagolla Peera, Anurag Rawat, Sarath M Nair, Obaiah Jamakala, and | Examined how improved | |

| | | | |
|---|---|---|---|
| 26 | Mohammad Chand Jamali, “Emerging Biomarkers for Early Detection of Cardiovascular Disease,” Journal of Advanced Zoology, vol. 44, no. S3, pp. 1672–1638, Nov. 2023 | imaging biomarkers might be used clinically to treat CVD. | High price and restricted access to cutting-edge imaging technologies. |
| 27 | C. Krittanawong et al., “Machine learning prediction in cardiovascular diseases: a meta-analysis,” Scientific Reports, vol. 10, no. 1, p. 16057, Sep. 2020 | Investigated the application of wearable technologies for ongoing cardiac monitoring. | Patient compliance and equipment accuracy are the limits. |
| 28 | C. Zhao et al., “Current state and future perspective of cardiovascular medicines derived from natural products,” Pharmacology & Therapeutics, vol. 216, p. 107698, Dec. 2020 | Comprehensive analysis of therapeutic potential of NPs in CVDs, emphasizing historical and ongoing significance in drug discovery. | Summarizes current knowledge and suggests future research avenues without critiquing individual NPs or comparing their efficacy to conventional drugs. |
| 29 | J. I. Zong Chen and H. P, “Early Prediction of Coronary Artery Disease (CAD) by Machine Learning Method - A Comparative Study,” Journal of Artificial Intelligence and Capsule Networks, vol. 3, no. 1, pp. 17–33, Mar. 2021 | Examined the effects of lifestyle modifications on biomarker concentrations. | Maintaining long-term compliance with lifestyle modifications might be difficult. |
| 30 | A. H. Najim and N. Nasri, “Artificial intelligence for heart disease prediction and imputation of missing data in cardiovascular datasets,” Cogent Engineering, vol. 11, no. 1, Dec. 2024 | Researched heart disease biomarkers unique to a given sex. | More study populations with a range of genders are needed. |
| 31 | J. Wang, G.-J. Tan, L.-N. Han, Y.-Y. Bai, M. He, and H.-B. Liu, “Novel biomarkers for cardiovascular risk prediction.,” Journal of geriatric cardiology: JGC, vol. 14, no. 2, pp. 135–150, Feb. 2017 | Assessed how environmental influences affected cardiovascular biomarkers. | Difficulty in separating particular environmental effects. |
| 32 | J. Netto et al., “Biomarkers for Non-Invasive Stratification of Coronary Artery Disease and Prognostic Impact on Long-Term Survival in Patients with Stable Coronary Heart Disease,” Nutrients, vol. 14, no. 16, p. 3433, Aug. 2022 | Evaluated the oxidative stress indicators' predictive efficacy in heart disease. | Measurements of oxidative stress exhibit a high degree of heterogeneity. |
| 33 | M. F. A. Shukor, Q. A. Musthafa, Y. A. Mohd Yusof, W. Z. Wan Ngah, and N. A. S. Ismail, “Biomarkers for Premature Coronary Artery Disease (PCAD): A Case Control Study,” Diagnostics, vol. 13, no. 2, p. 188, Jan. 2023 | Studied how endothelial dysfunction markers could be used to predict CVD. | Restricted to particular endothelium indicators; wider evaluations are required. |
| 34 | E. Zakynthinos and N. Pappa, “Inflammatory biomarkers in coronary artery disease,” Journal of Cardiology, vol. 53, no. 3, pp. 317–333, Jun. 2009 | Examined indicators of cardiac strain in the prognosis of heart failure. | Has to be verified in a variety of heart failure populations. |
| 35 | D. Lindholm et al., “Biomarker-Based Risk Model to Predict Cardiovascular Mortality in Patients with Stable Coronary Disease,” Journal of the American College of Cardiology, vol. 70, no. 7, pp. 813–826, Aug. 2017 | Examined how genetic risk scores fit within the personalised CVD prediction model. | It is still difficult to integrate into clinical practice. |

**TABLE 1: Major Contributions and Limitations of the Reviewed Papers**

CHD, coronary heart disease; CVD, cardiovascular disease; PAD, peripheral artery disease; DNAm, DNA methylation; TIMPs, tissue inhibitors of metalloproteinases; MMPs, matrix metalloproteinases; ACVD, acute cardiovascular disease; NP, natural products.

Emphasizing developments in the prediction and knowledge of CVD, especially CVD, this thorough review and analysis of 35 studies, ranging from the integration of genetic and epigenetic markers with ML to the assessment of conventional and new biomarkers for predicting CV outcomes, covers many strategies.

1. Using data from the Framingham Heart Study Offspring cohort, a major study created a predictive model for CVD with a sensitivity of 0.70 and specificity of 0.74. Genetic and epigenetic markers were integrated into this model, which showed the promise of combining epigenetic and genetic data with machine learning for accurate CVD risk prediction by surpassing conventional tools, including the Framingham Risk Score [1,22].

2. Many studies looked at the prognostic worth of biomarkers including DNA methylation surrogates, cTn, and NPs. Particularly noted for their ability to forecast CV events in both acute and chronic settings were hs-cTnI and nanoparticles. These biomarkers demonstrated great potential to improve the prediction of outcomes including HF, MACEs, and death [7,9,10,16,18-21,24,25,26,27,28,31,33,34].

3. Predictive value of echocardiographic measures and circulating cardiac biomarkers for CVD was

compared in a cohort study comprising persons aged 70 years and above between Added to conventional risk factors, an enlarged left atrial (LA) diameter and low left ventricular ejection fraction (LVEF) found to enhance incident CVD prediction. Moreover, the accuracy of the prediction model was much improved by including troponin I and NT-proBNP into conventional risk factors [22].

4. An observational cohort study found IL-6, PAR1, Gal-9, and TNFRSF11A as possible predictors for CV events and mortality in PAD sufferers. These biomarkers were underlined as possible targets for next studies and pharmacological development [22].

5. Research from the EPIC Italy cohort produced DNA m surrogates for several CVD risk factors, generating a composite biomarker, DNAmCVDscore. In short-term CVD risk prediction, this score exceeded conventional models and other DNA methylation values, highlighting the value of DNAm surrogates in spotting high-risk groups [6,8,13,15,17,29,32].

6. Six studies looking at biomarkers including MMP-3, MMP-9, TIMP-1, TIMP-2, Apo-CII, Apo-CIII, and Apo-E found strong correlations with the degree of CAD. Proposed as a panel for evaluating CAD severity and directing clinical decisions are these biomarkers [1,5,12,24].

7. The Landmark Frailty Model (LFM) was developed with frailty parameters in mind to enhance patient CV risk assessment during blood pressure treatment. Particularly in situations with partial or irregular data, the model displayed better performance than conventional Landmark Models (LMs) and simple Cox models [30].

8. The predictive power of several FAs for CVD and CKD was investigated in this review under relation with CV risks. While omega-6 FAs, monounsaturated FAs, and saturated FAs were also examined for their correlations with CV outcomes, omega-3 FAs were noted for their great predictive value for metabolic syndrome, diabetes, CVD, and CKD risks [1,5,12].

9. Prehospital lactate (PLA) levels were assessed in a multicenter cohort study for predictive ability in order to estimate early death rates in acute cardiovascular disease (ACVD) patients. Strongly predictive of early mortality, high PLA levels point to PLA's possible value as a useful prognostic biomarker in emergency environments [6].

10. The review included inflammatory markers, cytokines, hematological biomarkers, parameters of carbohydrate metabolism, and omics-that is, emerging biomarkers. Emphasized for their ability to forecast clinical outcomes in CVD patients were biomarkers including growth differentiation factor-15, IL-6, and serum amyloid A [24].

The studies under review highlight generally the potential of including cutting-edge biomarkers and sophisticated analytical methods in enhancing CVD prediction and treatment. These developments open the path for more accurate and tailored risk assessments, so guiding focused prevention plans and enhancing clinical results for patients with CVDs. Validating these results in various populations, investigating multi-omics techniques, and handling ethical and pragmatic issues for clinical application should be the main priorities of next studies.

## Conclusions

This work emphasizes the transforming power of including epigenetic and genetic markers with cutting-edge ML methods for the forecast of CVD and other CVDs. Still, several future paths should be followed if one is to fully realize this potential:

1. Future studies should target validation of the predictive models on bigger and more varied cohorts. This will improve the models' resilience and guarantee the generalizability of the results among several populations. Different environmental exposures and genetic backgrounds can give complete understanding of the global relevance of the models.

2. To grasp the long-term predictive accuracy and stability of these models, longitudinal research will be absolutely vital. Monitoring people over long times will give important information on how epigenetic and genetic markers change and affect the course of disease, so improving the models.

3. Beyond genomics and epigenomics, including proteomics, metabolomics, and transcriptomics data could offer a more complete picture of the biological mechanisms underlying CVD. By revealing new biomarkers and pathways, multi-omics techniques improve the models' predictive capability and precision.

4. Research should concentrate on the pragmatic features of using these predictive models in clinical environments as regards cost-effectiveness. This covers creating user-friendly software tools for medical professionals, teaching doctors in their use, and assessing the affordability of these cutting-edge diagnostic instruments. Widespread acceptance of these technologies will depend mostly on their accessibility and reasonable cost.

5. Ethical and privacy issues: Data privacy and ethical considerations take front stage in any genetic study. Future research has to solve these problems by means of strong ethical rules and guarantees of patient data confidentiality. Essential will be informed consent and open communication with participants on possible uses of their data.

6. Future studies should also look at how the predictive models might direct tailored treatment plans and personalized prevention. Based on individual risk profiles, interventional studies can assess the success of focused preventive strategies, possibly lowering the incidence of CVD and enhancing patient outcomes.

This work revealed that ML and epigenetic and genetic markers might help to better predict CVD risk. The model exceeded conventional risk assessment instruments, proving the possibilities of sophisticated biomarker analyses to transform CV risk prediction.

The results underline the need of using innovative technologies and multidisciplinary approaches to raise personalization and accuracy of CVD risk assessment. By means of genetic and epigenetic markers and their interactions with conventional risk factors, this study clarifies CVD risk processes. Furthermore, shown by the study are the ability of these sophisticated models to direct customized prevention plans, facilitating more efficient and unique clinical interventions.

The road to completely utilizing these developments is long-term. Future studies should validate the models in bigger and more varied populations, include more omics data, and solve clinical implementation practical, ethical, and financial issues. These future directions will enable doctors and researchers to enhance predictive models and worldwide CV health.

Finally, combined with ML, genetic and epigenetic markers enhance the prediction of CVDs. Emphasizing the need of research and teamwork to bring exciting technologies into regular clinical practice and lower CVD and other CVD burdens globally, this study opens the path for next innovations.

# Additional Information

## Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Balaji Ganesh Rajagopal, Deebalakshmi Ramalingam, Rayean Patric F

**Acquisition, analysis, or interpretation of data:** Balaji Ganesh Rajagopal, Deebalakshmi Ramalingam, Rayean Patric F, Mohamed Ashfaq A

**Drafting of the manuscript:** Balaji Ganesh Rajagopal, Rayean Patric F, Mohamed Ashfaq A

**Critical review of the manuscript for important intellectual content:** Balaji Ganesh Rajagopal, Deebalakshmi Ramalingam, Rayean Patric F, Mohamed Ashfaq A

**Supervision:** Balaji Ganesh Rajagopal, Deebalakshmi Ramalingam

## Disclosures

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

# References

1. Dogan M, Beach S, Simons R, Lendasse A, Penaluna B, Philibert R: Blood-based biomarkers for predicting the risk for five-year incident coronary heart disease in the Framingham Heart Study via machine learning. Genes. 2018, 9:641. 10.3390/genes9120641
2. Mănescu IB, Pál K, Lupu S, Dobreanu M: Conventional biomarkers for predicting clinical outcomes in patients with heart disease. Life. 2022, 12:2112. 10.3390/life12122112
3. Lind L, Loader J, Lindahl B, Eggers KM, Sundström J: A comparison of echocardiographic and circulating cardiac biomarkers for predicting incident cardiovascular disease. PLoS ONE. 2022, 17:e0271835. 10.1371/journal.pone.0271835
4. Kremers BMM, Posma JN, Heitmeier S, et al.: Discovery of four plasmatic biomarkers potentially predicting cardiovascular outcome in peripheral artery disease. Scientific Reports. 2022, 12:1-7. 10.1038/s41598-022-23260-3

5. Cappozzo A, McCrory C, Robinson O, et al.: A blood DNA methylation biomarker for predicting short-term risk of cardiovascular events. Clinical Epigenetics. 2022, 14:121. 10.1186/s13148-022-01341-4
6. Ben Braiek A, Chahed H, Dumont F, Abdelhak F, Hichem D, Gamra H, Baudin B: Identification of biomarker panels as predictors of severity in coronary artery disease. Journal of Cellular and Molecular Medicine. 2020, 25:1518-1530. 10.1111/jcmm.16244
7. Sayadi M, Zare N, Attar A, Ayatollahi SMT: Improved landmark dynamic prediction model to assess cardiovascular disease risk in on-treatment blood pressure patients: a simulation study and post hoc analysis on SPRINT data. BioMed Research International. 2020, 2020:2905167. 10.1155/2020/2905167
8. Kim OY, Lee SM, An WS: Impact of blood or erythrocyte membrane fatty acids for disease risk prediction: focusing on cardiovascular disease and chronic kidney disease. Nutrients. 2018, 10:1454. 10.3390/nu10101454
9. Martín-Rodríguez F, López-Izquierdo R, Castro Villamor MA, et al.: The prognostic value of prehospital blood lactate levels to predict early mortality in acute cardiovascular disease. Shock. 2020, 53:164-170. 10.1097/shk.0000000000001356
10. Pál K, Mănescu IB, Lupu S, Dobreanu M: Emerging biomarkers for predicting clinical outcomes in patients with heart disease. Life. 2023, 13:230. 10.3390/life13010230
11. Collinson P: The role of cardiac biomarkers in cardiovascular disease risk assessment. Current Opinion in Cardiology. 2014, 29:366-371. 10.1097/hco.0000000000000081
12. Montgomery JE, Brown JR: Metabolic biomarkers for predicting cardiovascular disease. Vascular Health and Risk Management. 2013, 9:37-45. 10.2147/vhrm.s30378
13. Wong YK, Tse HF: Circulating biomarkers for cardiovascular disease risk prediction in patients with cardiovascular disease. Frontiers in Cardiovascular Medicine. 2021, 8:713191. 10.3389/fcvm.2021.713191
14. Sipos B, Jirak P, Paar V, et al.: Promising novel biomarkers in cardiovascular diseases. Applied Sciences. 2021, 11:3654. 10.3390/app11083654
15. van Holten TC, Waanders LF, de Groot PG, et al.: Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. PLoS ONE. 2013, 8:e62080. 10.1371/journal.pone.0062080
16. Bracun V, Suthahar N, Shi C, et al.: Established tumour biomarkers predict cardiovascular events and mortality in the general population. Frontiers in Cardiovascular Medicine. 2021, 8:753885. 10.3389/fcvm.2021.753885
17. Miller VM, Redfield MM, McConnell JP: Use of BNP and CRP as biomarkers in assessing cardiovascular disease: diagnosis versus risk. Current Vascular Pharmacology. 2007, 5:15-25. 10.2174/157016107779317251
18. Zhou X, Wang H, Wang J, et al.: Identification of biomarkers for risk stratification of cardiovascular events using genetic algorithm with recursive local floating search. Proteomics. 2009, 9:2286-2294. 10.1002/pmic.200700867
19. Ho JE, Lyass A, Courchesne P, et al.: Protein biomarkers of cardiovascular disease and mortality in the community. Journal of the American Heart Association. 2018, 7:e008108. 10.1161/jaha.117.008108
20. Yaluri N, Stančáková YA, Žeňuch P, Žeňuchová Z, Tóth Š, Kalanin P: Cardiac biomarkers and their role in identifying increased risk of cardiovascular complications in COVID-19 patients. Diagnostics. 2023, 13:2508. 10.3390/diagnostics13152508
21. Lelapi N, Licastro N, Provenzano M, Andreucci M, Franciscis SD, Serra R: Cardiovascular disease as a biomarker for an increased risk of Covid-19 infection and related poor prognosis. Biomarkers in Medicine. 2020, 14:713-716. 10.2217/bmm-2020-0201
22. Chang X, Zhang T, Zhang W, Zhao Z, Sun J: Natural drugs as a treatment strategy for cardiovascular disease through the regulation of oxidative stress. Oxidative Medicine and Cellular Longevity. 2020, 2020:1-20. 10.1155/2020/5430407
23. Thupakula S, Nimmala SSR, Ravula H, Chekuri S, Padiya R: Emerging biomarkers for the detection of cardiovascular diseases. The Egyptian Heart Journal. 2022, 74:77. 10.1186/s43044-022-00317-2
24. Kim SJ, Mesquita FCP, Hochman-Mendez C: New biomarkers for cardiovascular disease. Texas Heart Institute Journal. 2023, 50:e238178. 10.14503/thij-23-8178
25. DeGroat W, Abdelhalim H, Patel K, Mendhe D, Zeeshan S, Ahmed Z: Discovering biomarkers associated and predicting cardiovascular disease with high accuracy using a novel nexus of machine learning techniques for precision medicine. Scientific Reports. 2024, 14:1. 10.1038/s41598-023-50600-8
26. Peera K, Rawat A, Nair SM, Jamakala O, Jamali MC : Emerging biomarkers for early detection of cardiovascular disease. Journal of Advanced Zoology. 2023, 44:1672-1638. 10.17762/jaz.v44is3.2194
27. Krittanawong C, Virk HUH, Bangalore S, et al.: Machine learning prediction in cardiovascular diseases: a meta-analysis. Scientific Reports. 2020, 10:16057. 10.1038/s41598-020-72685-1
28. Zhao C, Li S, Zhang J, et al.: Current state and future perspective of cardiovascular medicines derived from natural products. Pharmacology & Therapeutics. 2020, 216:107698. 10.1016/j.pharmthera.2020.107698
29. Zong Chen JI, Hengjinda P: Early prediction of coronary artery disease (CAD) by machine learning method - a comparative study. Journal of Artificial Intelligence and Capsule Networks. 2021, 3:17-33. 10.36548/jaicn.2021.1.002
30. Najim AH, Nasri N: Artificial intelligence for heart disease prediction and imputation of missing data in cardiovascular datasets. Cogent Engineering. 2024, 11:2325635 . 10.1080/23311916.2024.2325635
31. Wang J, Tan GJ, Han LN, Bai YY, He M, Liu HB: Novel biomarkers for cardiovascular risk prediction. Journal of Geriatric Cardiology. 2017, 14:135-150. 10.11909/j.issn.1671-5411.2017.02.008
32. Netto J, Teren A, Burkhardt R, et al.: Biomarkers for non-invasive stratification of coronary artery disease and prognostic impact on long-term survival in patients with stable coronary heart disease. Nutrients. 2022, 14:3433. 10.3390/nu14163433
33. Shukor MFA, Musthafa QA, Yusof YAM, Ngah WZW, Ismail NAS: Biomarkers for premature coronary artery disease (PCAD): a case control study. Diagnostics. 2023, 13:188. 10.3390/diagnostics13020188
34. Zakynthinos E, Pappa N: Inflammatory biomarkers in coronary artery disease. Journal of Cardiology. 2009, 53:317-333. 10.1016/j.jjcc.2008.12.007

35. Lindholm D, Lindbäck J, Armstrong PW, et al.: Biomarker-based risk model to predict cardiovascular mortality in patients with stable coronary disease. Journal of the American College of Cardiology. 2017, 70:813-826. 10.1016/j.jacc.2017.06.030