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Together, these studies highlight the critical role of integrating diverse data types and utilizing advanced machine learning and deep learning techniques to enhance the predictive modelling of CVDs, ultimately aiding in early intervention, personalized treatment strategies, and improved patient outcomes.

Specific Biomarkers and their Roles

Biomarkers are measurable indicators of some biological state or condition and can provide valuable insights into the underlying pathophysiology of cardiovascular diseases. In the context of cardiovascular diseases, biomarkers can be used to assess the risk of developing the disease, detect the presence of the disease, monitor the progression of the disease, and guide treatment decisions. Table 1 is compiled from many published reports and provides a list of the biomarkers based on different pathophysiological processes of heart diseases.

Table 1: Biomarkers based on different Pathophysiological processes. This table is compiled from several published reports.

Pathophysiological Process	Biomarkers
Inflammation	CRP, ST2, TNF-a, GDF-15, FAS, LP-A2, YKL-40, IL-1, Osteoprotegerin, Cytokines, Adiponectin, TREM-1, TLR-4, HMGB-1, RAGE, Danger associated molecular patterns (DAMPs), Oncostatin M, Serpins
Oxidative stress	Oxidized-LDL, Myeloperoxidase, Urinary biopyrrins, Urinary and plasma isoprostanes, urinary 8-hydroxyl-2-deoxyguanosine, Plasma malondialdehyde
Neurohormonal therapy	Norepinephrine, Renin, Angiotensin-II, Aldosterone, Arginine vasopressin, Copeptin, Endothelin -1, Urocortin, MR-proADM.
Extracellular matrix remodeling	MMP-2,3,9. TIMP1, IL-6, Collagen propeptides, N-terminal collagen type III peptide, Myostatin, Syndecan-4, Galectin-3, Oncostatin M, Serpins,
Myocyte injury	BNP, NT-proBNP, MR- proANP, sST2, GDF-15
Myocardial stretch	Troponin-T, Troponin-I, Myosin light chain kinase I, Heart-type FA binding protein, CKMB, HSP60

Cardiac Troponins and Natriuretic Peptides

Cardiac troponins (cTnI and cTnT) and natriuretic peptides (NPs) are widely recognized biomarkers of myocardial injury and dilation, respectively, because of their specific functions and diagnostic capabilities in cardiovascular diseases (CVD). When myocardial cells are damaged, cardiac troponins are released into the bloodstream, making them highly specific indicators of myocardial injury, such as acute myocardial infarction [57]. High-sensitivity tests for troponins can even identify minor myocardial injuries, which are essential for early detection and risk assessment in various clinical scenarios, including COVID-19, where elevated troponin levels have been associated with higher mortality rates and the need for mechanical ventilation [58-60]. Troponins also play a significant role in evaluating myocardial injury in hospitalized COVID-19 patients, with their increase indicating underlying pathological processes that can be further explored through cardiovascular magnetic resonance imaging [61]. In hypertrophic cardiomyopathy, increased levels of cTnI and creatine kinase-MB (CK-MB) are associated with poorer prognoses, emphasizing their importance in predicting adverse outcomes and guiding preventive actions, such as implantable cardioverter defibrillator implantation [62]. Conversely, natriuretic peptides, including B-type natriuretic peptide (BNP) and its precursor NT-proBNP, are discharged in response to myocardial stretch and volume overload, reflecting myocardial dilation and severity of heart failure [63]. These peptides are particularly valuable in the diagnosis and treatment of heart failure as they offer additional prognostic insights beyond traditional clinical features. For example, NT-proBNP levels significantly enhance the prognostic precision of troponin models in forecasting mortality and severe complications in COVID-19 patients [58-60].

The physiological distinctions in the production, release, and breakdown of these biomarkers between males and females further complicate their clinical interpretation, highlighting the necessity for sex-specific considerations in their application [64]. Moreover, integrating these biomarkers into risk prediction models enables more accurate identification of individuals at risk of future cardiovascular events, potentially leading to earlier initiation of preventive therapies [63]. Despite their well-established roles, the specificity of troponins for MI may be diminished owing to their elevation in other myocardial conditions, emphasizing the need for further investigation to distinguish the types of troponins found in different clinical scenarios [57].

Emerging Biomarkers

Novel biomarkers, such as growth differentiation factor-15 (GDF-15), soluble ST2, and galectin-3, exhibit significant potential in predicting risks and diagnosing various diseases early. GDF-15, a cytokine involved in inflammation and tissue damage response, has been extensively studied and found to be elevated in numerous conditions, including non-communicable diseases, rheumatoid arthritis, juvenile dermatomyositis, and cardiovascular diseases. For example, levels of GDF-15 are notably higher in patients with rheumatoid arthritis, correlating with disease severity and cardiovascular risk, underscoring its role in inflammation and lipid metabolism [65]. Similarly, in juvenile dermatomyositis, GDF-15 levels strongly correlate with disease activity scores and functional measures, making it a valuable biomarker for

evaluating disease activity and guiding treatment decisions [66]. Moreover, GDF-15 has been associated with the coronary slow flow phenomenon, where elevated levels can predict the presence and severity of the condition, highlighting its usefulness in cardiovascular diagnostics [67]. Galectin-3, an emerging biomarker, plays a critical role in inflammation, immunity, and fibrosis. It has been linked to reduced eGFR in chronic kidney disease and is implicated in renal fibrosis, making it a reliable biomarker for early detection and monitoring of kidney disease progression [68]. Galectin-3 also has potential in cardiovascular diseases as its levels can predict the severity of coronary slow flow phenomenon in conjunction with GDF-15 [65]. The use of GDF-15, soluble ST2, and galectin-3 as diagnostic tools presents a promising strategy for the early detection of diseases, categorizing risk, and enhancing patient outcomes in various medical conditions, including cardiovascular diseases.

Epigenetic Biomarkers

Epigenetic biomarkers have become a promising asset in the realm of cardiovascular disease (CVD) diagnosis, prognosis, and treatment, utilizing mechanisms such as DNA methylation, histone modifications, and non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) [16,22,28,59]. Differential DNA methylation, particularly in repetitive elements and specific genomic regions, has been linked to CVD-related traits such as inflammation, dyslipidemia, hypertension, and obesity [13,17-19]. Drugs targeting DNA methyltransferases, such as hydralazine and procainamide, are being explored for their potential to hinder abnormal methylation patterns seen in CVDs [69]. Histone modifications also play a vital role in various cardiovascular conditions such as atherosclerosis, hypertension, and heart failure. Histone deacetylase inhibitors have displayed anti-proliferative and anti-inflammatory characteristics, with preclinical research affirming their cardioprotective effects [70-72]. miRNAs, which are small non-coding RNAs involved in gene regulation, have been recognized as significant contributors to the pathophysiology of several cardiovascular ailments, including myocardial infarction, coronary heart disease, and heart failure. Their presence in extracellular fluids makes them appealing circulating biomarkers with enhanced properties compared to traditional protein markers. For example, miRNAs have been suggested as diagnostic and prognostic indicators of acute coronary syndrome and other heart conditions [8,13,22].

Nonetheless, the clinical implementation of these biomarkers requires further validation through extensive multicenter studies to ensure their dependability and practicality in everyday medical practice. Progression in big data analysis and personalized epigenetic mapping is paving the way for individualized diagnosis and treatment, under the field known as pharmaco-epigenetics, which considers each patient's epigenetic foundation to forecast drug reactions and formulate personalized therapies [13, 22]. Despite the encouraging potential of epigenetic biomarkers, the transition from research to clinical use has been gradual, with ongoing trials and investigations crucial for establishing their effectiveness and safety [8,13,22]. For instance, the Bromodomain and Extra-Terminal motif inhibitor, RVX-208, demonstrated varied outcomes in trials about blood lipids, atherosclerosis, and major adverse cardiovascular events [73].

Metabolic Biomarkers

Metabolomic biomarkers have become an asset in the detection, prediction, and management of cardiovascular diseases (CVDs), providing thorough insight into the underlying mechanisms of the disease and assisting in tailored medical care. Essential biomarkers include natriuretic peptides (BNP/NT-proBNP) for heart failure diagnosis and prognosis evaluation and troponins for myocardial infarction diagnosis and other heart injury assessments [28,29,34,74]. Moreover, C-reactive protein is commonly used to gauge the inflammation levels linked to CVDs [75]. Lipid metabolites, such as phospholipids, sphingolipids/ceramides, glycolipids, cholesterol esters, fatty acids, and acylcarnitines, have been recognized as significant biomarkers through metabolomic profiling, with sphingolipids/ceramides displaying potential in CVD diagnosis and prognosis [76]. The amalgamation of metabolomics with genomic and proteomic information can offer a comprehensive outlook on the disease, uncovering new biochemical pathways and potential treatment targets. For example, metabolomic research has emphasized the impact of redox and nitrosative reactions on CVD progression, indicating that imbalances in these reactions can lead to disease progression. Additionally, metabolomics has played a vital role in comprehending the systemic nature of CVDs, pinpointing metabolic pathways, such as gut microbial co-metabolism, branched-chain amino acids, glycerophospholipids, cholesterol metabolism, and inflammatory processes [77]. This detailed metabolic analysis can enhance risk assessment and direct personalized therapeutic approaches, especially in complex conditions, such as coronary artery disease. Advanced technologies, such as nuclear magnetic resonance spectroscopy and liquid chromatography-mass spectrometry, have allowed the exploration of numerous metabolites, unveiling new biological pathways, and enriching our knowledge of disease development [78]. Furthermore, metabolomics has been employed to identify biomarkers linked to wholesome dietary habits that are inversely associated with CVD risk, suggesting that diet-related metabolites could function as preventive indicators [79]. Despite these encouraging prospects, challenges persist in standardizing methodologies and merging metabolomic data from various studies and platforms to ascertain clinical effectiveness. Nevertheless, continuous research and technological progress in metabolomics offers substantial potential for enhancing CVD

management, ranging from early detection to individualized treatment and prevention strategies.

Challenges and Future Directions

The complexity of cardiovascular diseases (CVDs) requires unbiased approaches and incorporation of biological knowledge into computational models to improve early detection and prevention strategies. Traditional methods of detection, such as invasive angiography, have limitations that necessitate more precise and reliable solutions through machine learning and intelligent automation [42]. Progress in genomics, including whole-genome sequencing and gene-editing techniques, has created new opportunities for understanding the genetic mechanisms underlying CVDs, enabling the creation of predictive genomic models and facilitating advancements in life-course treatment and prevention. Nevertheless, the incorporation of genomics into economic health models for CVD prevention has not been fully utilized. By integrating Mendelian randomization analyses into these models, a strong economic case can be made to incorporate genomics into clinical practice, shifting our approach from reactive to preventive healthcare [80].

Machine learning models, such as neural networks, decision trees, and support vector machines, have demonstrated potential for improving the accuracy of CVD detection by analyzing diverse and complex data sources, including clinical records and omics data [38-44]. Tackling issues, such as imbalanced datasets, is crucial, as evidenced by the enhancement of the XGBoost model, which notably increased the diagnostic accuracy for heart disease [55]. Future efforts should concentrate on developing more precise and cost-efficient biomarkers for early prevention of heart disease. This entails utilizing feature selection methods, such as the relief technique, which has been proven to enhance accuracy when paired with effective classification algorithms such as the Random Forest and Extra Trees classifiers [81]. Collaborative efforts among medical professionals, data scientists, and subject matter experts are vital to guarantee the smooth integration of these innovative technologies into clinical practice, ultimately leading to a more precise, timely, and personalized diagnosis and management of CVDs [82].

Summary and Conclusion

Biomarkers play a crucial role in the early detection, diagnosis, and management of cardiovascular diseases. They provide valuable insights into the normal and abnormal conditions of the heart and vascular system, enabling timely and precise medical interventions. Commonly used biomarkers, such as high-sensitivity troponin, C-reactive protein, troponin I or troponin T, creatine kinase, B-type natriuretic peptide, and myoglobin, are essential for monitoring and treating cardiovascular diseases. Additionally, emerging biomarkers like extracellular vesicles and circular RNAs are gaining recognition for their potential in early diagnosis and treatment. Also, they play a pivotal role in understanding the pathophysiology of CVDs, risk stratification, and therapeutic decision-making. Computational biology, an interdisciplinary field, integrates various scientific disciplines to identify and validate biological markers for disease diagnosis, prognosis, and drug response prediction, thereby enhancing the diagnosis and prevention of CVDs. The integration of 'omic' data, including genomics, proteomics, and metabolomics, enables a comprehensive understanding of the molecular mechanisms underlying CVDs and facilitates the discovery of new biomarkers and treatments. Furthermore, incorporating artificial intelligence and machine learning techniques in these interdisciplinary fields is expected to enhance further our ability to analyze complex biological data and develop more accurate diagnostic and therapeutic strategies for CVDs.

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