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REVIEW

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Understanding integrative approach of translational bioinformatics on cardiovascular disease: Myocardial Ischemia

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Abstract

Background Myocardial ischemia is a significant problem in cardiovascular health caused by the obstruction or constriction of coronary arteries, resulting in diminished blood supply to the heart muscle. Translational bioinformatics bridges the gap between biological discoveries and clinical applications, enabling early disease identification, therapy response confirmation, and prognosis prediction. It facilitates the integration and analysis of vast amounts of clinical data, hence advancing clinical research and enhancing therapeutic approaches.

Main body This review explores the role of translational bioinformatics in understanding and treating cardiovascular disease, specifically Myocardial Ischemia. It covers the discovery of novel biomarkers (miRNA, lncRNA, and tsRNA), analysis of genes and proteins, and integrated bioinformatics to identify differentially expressed genes. The study highlights the impact of personalized medicine, drug discovery, and repurposing through bioinformatics. Additionally, it examines the application of systems biology and network analysis to understand biological networks, and the use of clinical decision support systems to enhance patient care. This integrative approach demonstrates the potential of bioinformatics to improve cardiovascular health outcomes.

Conclusions Combining clinical and omics data using translational bioinformatics is critical for refining treatment regimens and speeding up medication repurposing. This comprehensive study emphasizes the necessity of combining interdisciplinary data to enhance patient outcomes in myocardial ischemia, minimize the global burden of cardiovascular-related deaths, and improve cardiovascular disease management.

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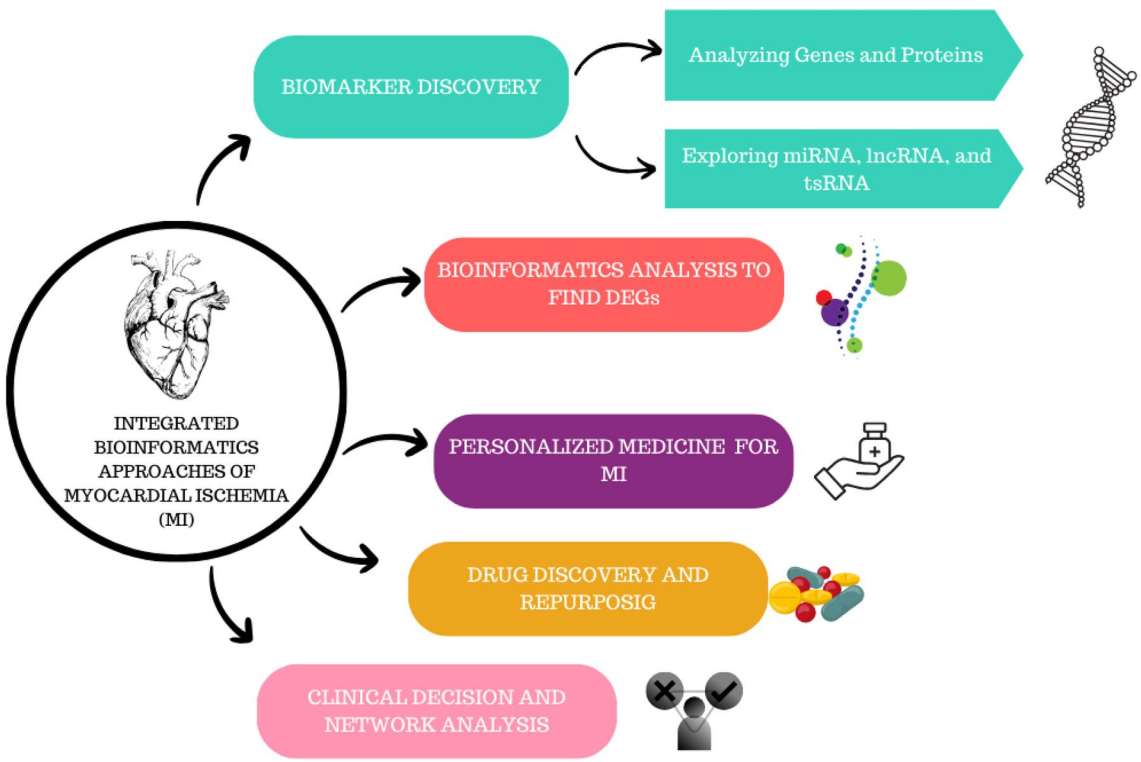
Graphical abstract



Background

Myocardial Ischemia is a condition that arises due to blockage or contraction of coronary arteries, resulting in diminished blood supply to heart muscles. It is characterized by the accumulation of plaque (lipids, cholesterol, etc.) on the inner walls of the artery or by the formation of blood clots in the coronary artery [1]. Prolonged oxygen deficiency in the myocardium leads to cell death, plaque rupture, and heart attack, causing abnormal heart rhythms, arrhythmia, and chest pain. Translational bioinformatics (TBI) in healthcare plays an important role by accelerating the translational and computational methods and connecting the gap between biological findings and clinical applications [2]. Translational bioinformatics involves the collection of literature data and clinical trial data from various databases and integrates them to improve the prognosis, diagnosis, and treatment of disease [3]. Additionally, it helps identify and validate biomarkers, enabling early disease detection, treatment response validation, and prognosis prediction [4]. Translational bioinformatics enables the integration and analysis of large-scale clinical data from Electronic Health Records (EHR) and other healthcare databases, supporting clinical research, population health studies, and patient outcome patterns [5]. It contributes to drug discovery and repurposing by identifying potential targets, predicting efficacy, and optimizing the drug design. The investigation of gene expression patterns in cardiac tissue or blood samples from people with myocardial ischemia is made possible by translational bioinformatics.

Researchers can find differentially expressed genes, signaling networks, and molecular mechanisms underlying myocardial ischemia by comparing the transcriptomes of healthy and sick hearts [6]. To fully comprehend cardiac ischemia, translational bioinformatics enables the combination of multi-omics data, such as genomics, transcriptomics, proteomics, and metabolomics [7]. The formation and progression of myocardial ischemia result from complex interactions and pathways, which can be uncovered by evaluating and integrating data from these various omics layers [8]. Collaboration and data sharing across academic institutions and research in studying myocardial ischemia encourages translational bioinformatics. Researchers can share datasets, resources, and tools by setting up data repositories, and standardized formats, and encouraging interdisciplinary partnerships.

This review overviewed the importance of Translational bioinformatics in the treatment of Myocardial Ischemia which is yet to be developed and highlights the identification of biomarkers for the diagnosis and treatment of Myocardial Ischemia using Bioinformatics techniques.

An overview of translational bioinformatics in cardiovascular disease

Translational Bioinformatics (TBI) aims to convert data processing findings into clinical practice, becoming a significant field in personalized medicine. It is an interdisciplinary field that combines scientific and clinical research, with other disciplines like imaging, clinical, and public health informatics. Cardiovascular disease accounts for the predominant causes of death in the globe [9]. By determining the risk factors of cardiovascular disease, the use of bioinformatics methods and computational analysis for the invention of novel biomarkers may enhance clinical decision-making as well as therapeutic approaches [10]. Programming requirements for the bioinformatics benchmarking and knowledge of cutting-edge instruments for conducting CVD research will cross multiple fields of expertise (for example single cell sequencing technologies, a truly multidisciplinary initiative for analyzing the molecular mechanisms underlying complex CVD traits) [11, 12]. Advances in clinical and molecular phenotyping, along with recent improvements in bioinformatics techniques for combining multidimensional high-content and throughput databases with clinical data will ignite the spark [13]. In the field of drug discovery, predicting the preferred orientation between a small molecule ligand and a target receptor to form a stable complex can be studied by well-liked and helpful technology called molecular docking which gives a better knowledge of the molecular mechanisms that underpin myocardial ischemia and the significance of certain proteins in the illness process [14]. Molecular docking enables the development of personalized medicine techniques by discovering medicines that specifically target molecular anomalies in individual patients.

With the use of high-throughput techniques and bioinformatics, it is now possible to comprehend the molecular mechanisms behind the development of many diseases, including myocardial ischemia [15, 16] Microarray and RNA-seq gene expression data bioinformatics analysis has been widely used to study diagnostic and prognostic biomarkers and important genes and biological processes in various disorders [17]. The Robust Rank Aggregation (RRA) technique helps in solving this issue by integrating the findings of several gene expression data sets. It employs a statistical model that naturally allows for the evaluation of the efficiency of the results [18]. The data of gene expression profiles were subjected to several analyses using bioinformatics techniques, and the analysis results were employed in order to expand the research on genes for the molecular pathogenesis of Coronary Artery Disease (CAD) and Ischemic Cardiomyopathy (ICM) [15]. To analyze the difference between CAD patients and healthy individuals, and to investigate the molecular pathogenesis of CAD and ICM, bioinformatics techniques such as PPI, enrichment analysis, network analysis, and gene expression profile data are used [19]. The Gene Expression Omnibus (GEO) database's original data from microarray analyses and RNA sequences performed on heart samples from ICM patients were obtained, and a detailed study was carried out [20]. After that, research was conducted to identify the important genes and molecular pathways underlying the pathophysiology of clinical ICM that provide new pharmaceutical targets. Globally, cardiovascular diseases (CVDs) comprise the primary cause of mortality [21, 22]. Estimates indicate that 17.9 million deaths globally in 2019 (32%) were related to CVDs, where heart attacks, heart imbalances, and strokes were the leading causes of death. Non-communicable diseases caused 17 million premature deaths, and 38% of those deaths were attributable to CVD recorded during 2019 [23]. The rise in the cardiovascular death rate from 1990 to 2023 is shown in Fig. 1 which represents the severity of the disease, which is more prone to adverse effects and increases the death rate. Currently, there is no proven treatment for myocardial ischemia/reperfusion damage, which is brought on by a stoppage of the blood flow. Combining the clinical data from previous cases of TBI with the molecular mechanism of the degenerative processes of cardiac I/R injury is critical from a clinical perspective to develop novel medications to treat patients more effectively [24].

Biomarker discovery with knowledge of bioinformatics for myocardial ischemia

Identification of molecular markers or biomarkers linked to myocardial ischemia is made possible by bioinformatics. By examining large-scale omics data, researchers can pinpoint specific genes, proteins, or metabolites that are changed or differently expressed in individuals with myocardial ischemia. These biomarkers can help with early identification of diseases, risk assessment, and disease progression monitoring.

Exploring miRNA, lncRNA, and tsRNA: a novel biomarker for acute myocardial ischemia

MicroRNAs (miRNAs) are a novel class of gene regulators that are endogenous, noncoding, single-stranded RNAs with about 22 nucleotides. The fully formed miRNAs impede translation or degrade the 3'-UTRs (untranslated region) of their mRNA targets, which has

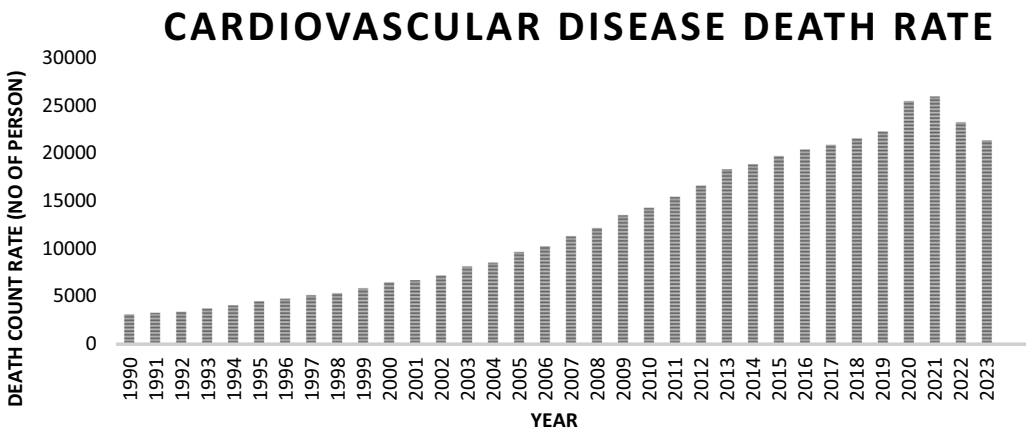


Fig. 1 Death rate of cardiovascular disease between the years 1990 and 2023 from PubMed data (This bar chart depicts the death rate from cardiovascular disease (measured by the number of people) from 1990 to 2023. The *x*-axis represents years, and the *y*-axis shows the death count rate. The graphic indicates a constant increase in the death rate over time, with a noteworthy spike beginning around 2005 and continuing until 2023. The highest death count rates were recorded in 2019, 2020, and 2021, with a modest drop in 2022 and 2023. This pattern indicates that cardiovascular health outcomes have deteriorated over time)

a detrimental effect on gene expression. In certain tissues or cells, a miRNA may express itself very strongly, while showing little to no expression in other tissues or cells. One such miRNA is miR-1, which is said to be specific to the cardiac and skeletal muscles. The precise concentration of miRNA in blood and the potential applications of circulating cell-free microRNA-1 (miR-1) in acute myocardial infarction (AMI) were investigated by Cheng et al. [25]. They utilized qRT-PCR technology to establish a quantitative method for assessing serum miR-1 levels, demonstrating its potential as a new biomarker for AMI in rat serum. Through in vitro experiments, they demonstrated that injured cardiac cells are capable of releasing miR-1 into the culture media. The amount of miR-1 released is directly correlated with the degree of cell damage, and it stays constant for a full day. They showed that serum miR-1 increases rapidly with a peak at 6 h following AMI in a rat model of coronary ligation-induced AMI, and showing an increase in miR-1 of over 200 times. Their findings also showed that miR-1 is the most prevalent miRNA in the heart and can be employed as a very accurate early biomarker for AMI may result in a new era in contemporary cardiology [26, 27].

Endogenous molecules with no ability to encode proteins are known as long noncoding RNAs, or lncRNAs are important in various diseases, including cardiovascular ones. It has been imposed as a potential biomarker or therapeutic target. In molecular biology, lncRNA competes through miRNA response elements with other RNAs**.** Ying Han et al. [28] sought to learn more about the molecular mechanism behind the lncRNA-mediated MI/R competing endogenous RNA (ceRNA) network. To find important lncRNAs connected to MI/R, the goal was to build the lncRNA-mediated ceRNA network. Gene Omnibus database(GEO) was used to obtain two datasets (GSE130217 and GSE124176) of MI/R and normal tissues. Using integrated bioinformatics, differentially expressed genes (DEGs) were identified and the starBase database was then used to construct an lncRNA-mediated ceRNA network. KEGG pathway analysis and GO annotations were used to look into the action mechanism and related pathways of DEGs in MI/R. The STRING internet database was utilized to import DEGs to create a network of interactions between proteins and they also screened the foremost 100 amplified genes in the network using Cytoscape v3.6.0. As a result, they obtained 156 DE-miRNAs, 70 DE-lncRNAs, and 2406 differentially expressed DE-mRNAs [29]. By using functional enrichment analysis, it is demonstrated that the lncRNAs in the ceRNA network may have roles in the oxidative stress and calcium signaling pathway. Under Hypoxia/Reoxygenation (H/R) conditions, the expression of the lncRNA Xist is downregulated, which is followed by an increase in the level of the miRNA-133c. The lncRNA Xist/miR-133c/Slc309 axis was part of the found ceRNA network, which may help us understand the etiology and course of MI/R damage and offer a fresh strategy for targeted therapy [30]. Transfer RNA-derived small RNAs (tsRNAs), a distinct class of short noncoding RNAs, have the potential to control an array of physiological and pathological processes. Calorific Restriction (CR), a special dietary treatment, aids in

preventing myocardial ischemia. Liu et al. [31] investigated the expression levels of tsRNAs in rats that experienced cardiac ischemia brought on by isoproterenol (ISO) with or without CR pretreatment using high-throughput RNA sequencing technology. Five tsRNAs were examined for their biological roles to identify possible CR therapeutic strategies for reducing myocardial ischemia. In their study, biological processes, cellular components, and molecular function domains are all covered by the analysis of biological functional connections among target genes using Gene Ontology (GO). The overlap between the DE and GO annotation lists was determined using the Fisher exact test in Bioconductor's topGO. They used tsRNA sequencing to investigate potential novel CR treatment targets. According to predictions made about the target genes and tsRNA sequencing bioinformatics study, these tsRNAs might act as therapeutic agents by regulating their metabolism of macromolecules. The ncRNAs have recently been demonstrated to be unique biomarkers in the processes of cardiovascular illness as they are stable in blood and other bodily fluids. In light of the cardioprotective effects of CR during myocardial ischemia processes, they therefore predicted that CR may have therapeutic effects via tsRNAs [32]. This is because tsRNAs are members of the noncoding RNA (ncRNA) class, which is essential for prokaryotic and eukaryotic cells to produce proteins [33, 34].

Analyzing genes and proteins involved in myocardial ischemia

Gene expression profile data for important genes implicated in cardiac I/R injury was found using bioinformatics databases like the Gene Expression Omnibus (GEO) database, Kegg Pathways (KEGG), STRING database, PANTHER database, and Gene Ontology (GO) in many studies and there are many software for interconnecting genes involved in Myocardial Ischemia. Similarly, in Fig. 2, interconnection of biomarker genes of Myocardial ischemia with heart disease is represented.

According to Wang et al. [35] the interleukin-8 receptors CXCR1 and CXCR2 were expressed more in obstructive coronary artery disease patients and less in patients with improved perfusion, suggesting that these genes could serve as markers for the severity and course of the condition. Interferons (IFNs), which are cytokines, are released in response to deadly viral infections by mammalian cells. Examining interferon-stimulated genes more closely using bioinformatics techniques like identification of DEGs, recent studies showed three interferon-stimulated genes (IFIT2, IFI44L, and IFIT3) as potential biomarkers [36]. Cardiac diseases have been closely related to changes or mutations in these DEGs and are used in ischemic cardiomyopathy as therapeutic targets and biomarkers, together [37] with significant pathways that could be applied to accurately diagnose and treat ischemic cardiomyopathy clinically [38, 39].

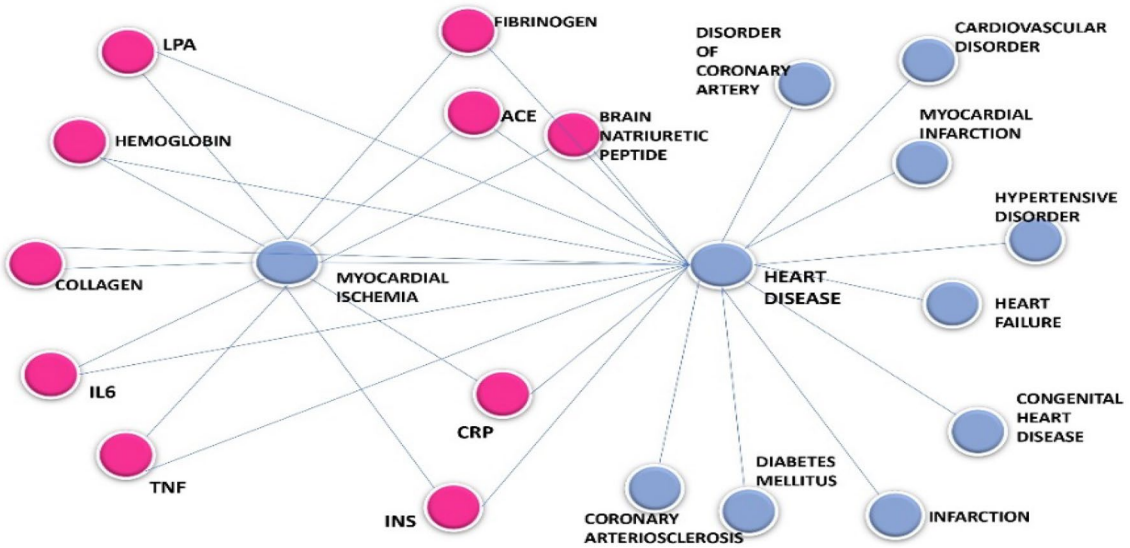


Fig. 2 The interconnection of biomarker genes involved in myocardial ischemia with heart disease using Laverne Tool (This network diagram depicts the links between different factors, biomarkers, and medical problems related to heart disease. The key nodes, "Heart Disease" and "Myocardial Ischemia," are linked to a variety of factors and illnesses. Pink nodes show biomarkers and factors including fibrinogen, ACE, and CRP, whereas blue nodes reflect linked medical problems. This graphic depicts the intricate relationship between biological markers and cardiovascular health issues, illustrating the multifaceted nature of heart disease)

One of the most efficient techniques to recognize functional characteristics based on gene co-expression networks is the Weighted Gene Co-Expression Network Analysis (WGCNA). However, it is important to first perform Differentially Expressed Genes (DEG) analysis, which serves as a preliminary step before applying WGCNA. IFIT2, IFIT3, and IFI44L have strong correlations with myocardial infarction and heart disease, according to data from cardiovascular disease knowledge. This provides strong evidence that IFIT2 and IFIT3 are the genes most frequently expressed in MI or cardiovascular disease. It was previously believed that IFIT 2/3 was secreted in the infarcted region of the heart by conventional macrophages, supporting or sustaining the process of reverse cardiac tissue repair. Other than genes and interleukin, proteins also play a major role as a biomarker for Myocardial disease. The String is one among the many bioinformatics tools which is used for representing protein–protein interaction. Here, in Fig. 3, the interaction between the proteins involved in myocardial ischemia was shown, where the protein IL-6 and CRP play a crucial role in inflammation and tissue response to injury when it comes to myocardial ischemia. Their levels can offer important details for cardiovascular disease diagnosis, risk assessment, prognosis, and therapy plans. Basalay et al. [40] conducted research that remote ischemic conditioning mediated cardioprotection by glucagon-like peptide-1 (GLP1). The findings by DeNicola et al. [41] say that exendin-4-stimulated glp-1r functions as a unique method for promoting cardioprotection and minimizing damage brought on by oxidative stress.

According to Cervia et al. [42] somatostatin analogs that target G protein-coupled receptor kinase 1 (GRK1) modulate the neuronal response to ischemia. When Nihei et al. [43] looked at the Rho-kinase function of circulating leukocytes, they discovered that it varied clearly throughout the day and was related to changes in coronary vasomotor responses and autonomic activity in visual analog scale (VAS) patients. One of the polypeptide proteins, vascular endothelial growth factor-A (VEGF-A), is a validated member of the VEGF family and a predictive biomarker for coronary heart disease. The primary enzyme in prostaglandin biosynthesis is prostaglandin-endoperoxide synthase (PTGS), and it has been established that PTGS inhibitors have adverse effects on the cardiovascular systems. When analyzing these biomarkers specific biological information is collected and stored in the database and those will be helpful in the

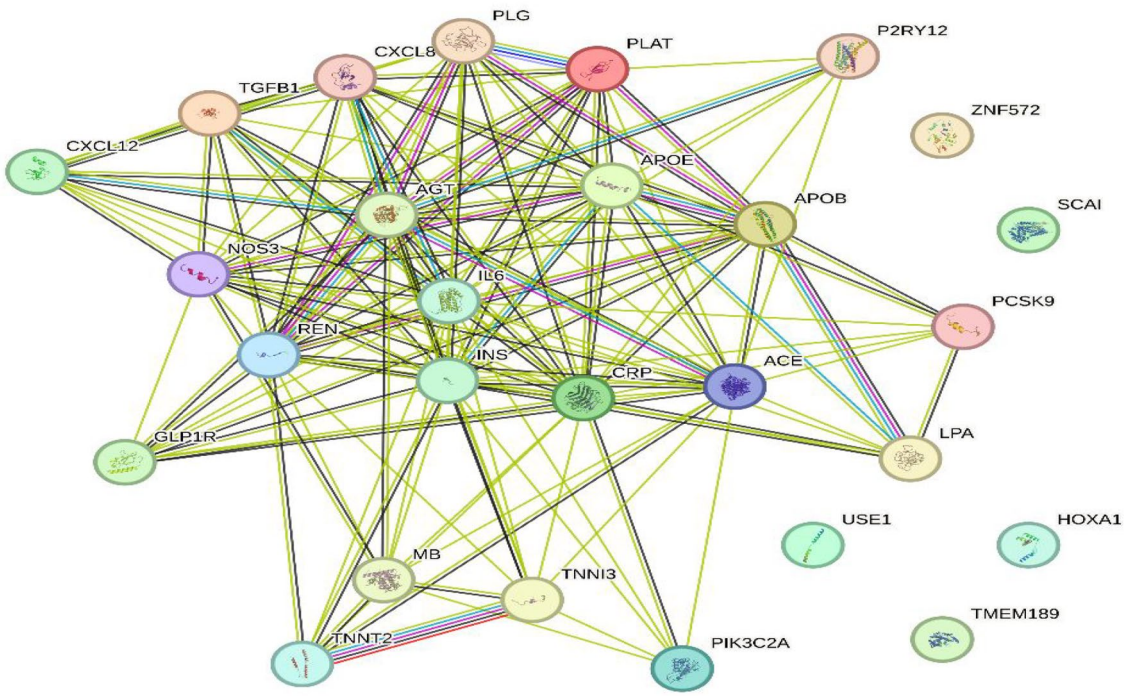


Fig. 3 Representation of protein–protein interaction between the proteins of myocardial ischemia using the STRING database (This figure depicts a complicated protein–protein interaction (PPI) network, illustrating the interactions between numerous proteins implicated in cardiovascular disorders. Each node represents a protein, and the lines (edges) that connect them show known or expected interactions. The core cluster has a high level of connectedness, indicating a densely interconnected network of proteins. Key proteins such as INS (Insulin), ACE (Angiotensin-Converting Enzyme), CRP (C-Reactive Protein), and PLAT (Tissue Plasminogen Activator) have several interactions, indicating their importance in the network)

clinical or medical sector to give a better understanding of cardiovascular medical conditions.

Integrated bioinformatics analysis to find differentially expressed genes

The differentially expressed genes (DEGs), might serve as fresh biomarkers or potential Acute Myocardial Infarction treatment targets. The DEGs were discovered using robust rank aggregation (RRA) and integrated bioinformatics analysis [44]. With the advancement of gene chip technology, an increasing number of genetic expression spectra were evaluated in cardiovascular research and clinical contexts. Consequently, reliable molecular biomarkers are provided for the diagnosis, prognosis, and screening of AMI. Usually in research, Mouse myocardium and blood arteries from myocardial infarction patients were subjected to extensive microarray analysis. The use of microarray analysis will enable the identification of any potential genes connected to AMI. It was found that the DEGs from the analysis were more common in pathways and activities associated with AMI, particularly that its expression levels are reliably altered in a particular state when compared with control or reference samples, it is commonly utilized as a biomarker in cardiovascular ischemic illness [45].

In a study by Zhang et al. [46], the "MetaOmics" package was utilized to perform a comprehensive meta-analysis of gene expression data to identify potential therapeutic targets in heart failure which includes the unified R packages MetaQC, MetaPath, and MetaDE for meta-analysis. The MetaQC package provides a quantitative and unbiased technique for selecting the inclusion/exclusion criteria for meta-analyses. Modern genomic meta-analysis techniques are included in MetaDE to find differentially expressed genes [47]. Finally, a cohesive meta-analysis methodology and inference are provided by the MetaPath software for identifying improved routes linked to outcomes. [Fisher], [adaptively weighted statistic (AW)], [minimum *p*-value (minP)], [maximum *P*-value (maxP)], [stouffer], [random effects model (REM)], [rank product (rankProd)], [rank sum (rankSum)], [naive sum of ranks], [rth ordered *P*-value (rOP)], [fixed effects model (FEM)] and also [naive products of ranks] are 12 significant meta-analysis pathway for differential expression (DE) analysis that are carried out by the MetaDE package. The findings demonstrated the effectiveness of "MetaOmics" in uncovering key biomarkers and pathways associated with heart failure, thus providing a robust framework for further research and therapeutic development. There is a high correlation between cardiovascular disease and markers including fibrinogen, vitamin D, and cystatin C [48, 49].

Personalized medicine

The development of individualized treatment plans for myocardial ischemia is made easier by translational bioinformatics. Bioinformatics can identify patient-specific characteristics and predict treatment outcomes by combining data from individual patients, such as genetic profiles, clinical information, and imaging data, with large-scale datasets and computational models. Such understanding can aid medical professionals in selecting medications, invasive procedures, or lifestyle interventions that are suitable for each patient's needs. CVD accounts for the major cause of death in women. The high incidence of nonobstructive coronary artery disease makes it challenging to diagnose cardiovascular disease (CVD) in women, and a history of pre-eclampsia (PE) is consistently associated with an elevated risk of developing CVD [50]. Pre-eclampsia, a maladaptation to hemodynamic and metabolic stress brought on by pregnancy, may also be viewed as a "precision" test result that forecasts future cardiovascular risk. Therefore, the emergence of PE offers a fantastic, early opportunity that may alter the future well-being of both the mother and child. To establish a more precise definition and reclassification, precise medicine-based approaches are required because the underlying pathogenesis of PE is not well understood [51]. Zhou et al. [52] suggested a stage-specific, PE-targeted (Predictive and Preventive) algorithm would combine a variety of data, including clinical, genetic, and lifestyle information provides a novel theory to close the gap between clinical translational research and large data-generating methods for long-term CVD management, clinical therapy, and PE prediction and prevention.

According to Garrie et al. [53] it is now crucial to identify the underlying cause of dilated cardiomyopathy (DCM). Hence this Late Gadolinium Enhancement (LGE) with cardiovascular magnetic resonance (CMR) has emerged as a technique for locating myocardial scars to determine the cause. Patients with idiopathic DCM and their families were to be included in the DCM Precision Medicine project to participate in genetic research. Other recognized forms of cardiomyopathy, such as ischemic DCM, valvular and structural heart disease, history of cardiotoxic exposure, and illnesses like iron overload or thyroid disease, were not included in the study. Clinical history, echocardiography, and coronary angiography have historically been used as clinical trials to support and confirm DCM diagnoses. 156 (93.3%) of the 327 patients that were involved in the study revealed an LGE pattern that is typically seen in idiopathic DCM. Of the 327 patients, 178 (54.4%) showed evidence of LGE [54]. Their results show that Idiopathic DCM exhibits left ventricular (LV) hypertrophy and systolic dysfunction

despite having no sign of ischemia injury or other obvious cause. In many cases, the cause of idiopathic DCM is unknown. To conduct a genetic inquiry, the DCM precision medicine investigation aimed to enlist a cohort of patients (probands) with idiopathic DCM and their relatives. Those who fulfilled strict idiopathic DCM criteria that is, those who excluded all other clinically detectable causes of DCM except genetics were included in the study, which was an important component. They ruled out any other known cardiomyopathy conditions. The study explores the causes of myocardial ischemic injury in idiopathic diastolic cardiomyopathy (DCM) and the potential impact of genetic disease on LGE. One mechanism is coronary artery embolus from left ventricular or left atrial thrombus, which is a common cause of myocardial infarctions [55]. Ten individuals in the study showed ischemia-pattern LGE, indicating that the cardiomyopathy was most likely not ischemic in origin. Accurate phenotyping and potential prognostic value can be obtained by detecting ischemic-pattern LGE in idiopathic DCM. The cause of idiopathic DCM and myocardial scars, which develop after the damage caused by some traumatic events, can thus be found using LDE in conjunction with coronary magnetic resonance imaging.

Barua et al. [1] in their research used System biology and bioinformatics methods for identifying genetic risk factors in the development of cardiovascular disease. To reveal the association between CVD and risk factors, they followed an analytical strategy such as GEO microarray datasets for study analysis. Further several analyses namely gene expression analysis, diseasome analysis, Protein–Protein Interaction (PPI) analysis, and pathways analysis with the aid of the gold benchmark databases like OMIM, dbGAP, and DisGENET were employed to resolve the connection between CVD and its risk factors, in addition to validity of their research [56]. It has been observed that Type 2 Diabetes (T2D), Hypercholesterolemia (HCL), obesity, Hypertension (HTN), and aging–risk factors of CVD overlap with one another. About 12 considerable functional pathways, 11 gene ontological pathways, and ten major hub proteins (CXCL1, CYBB, PTGS2, ITGAX FPR2, TNF, CXCL8, and CCR5, IL1B, VEGFA) that are associated with CVD and its risk variables were found in the gold benchmark datasets. Their research findings show a strong correlation between CVD risk factors like T2D, HCL, obesity, HTN, and aging. They added that their computational method recognized significant DEGs, hub proteins, signaling, and ontological pathways to explore the genetic relationship between CVD and its risk factors. With the findings of hub proteins and treatments to individual genetic profiles, precision medicine helps minimize adverse drug reactions, ensuring safer therapeutic options for patients with myocardial ischemia. Some of the applications of the translation bioinformatics approaches in the diagnosis and treatment of Myocardial Ischemia are shown in Table 1

Drug discovery and repurposing

Drug for myocardial ischemia is discovered and repurposed more quickly by translational bioinformatics. TBI can analyze tremendous quantities of biological

Table 1 Relation of translational bioinformatics approaches in myocardial ischemia and application in the diagnosis and treatment

S.No	Translational approach	Description	Example application
1	Genomic analysis [57]	Identification of associated genetic variants with Myocardial Ischemia	Whole exome sequencing—to identify unusual and potentially harmful genetic variations within the genome's protein-coding regions (exons) that relate to the risk and severity of myocardial ischemia
2	Transcriptomics [58]	Analysis of Gene expression profiles to better understand illness mechanisms	Identification of Differentially expressed genes as potential therapeutic targets for Myocardial Ischemia
3	Proteomics and Metabolomics [59, 60]	Studying the protein expression and metabolic changes associated with Myocardial Ischemia	Mass spectrometry and NMR to identify changed proteins and metabolites during ischemia, helping in early diagnosis and treatment
4	System biology [61]	Integrating multi-omics data to understand disease pathways	Network analysis used to map interaction in myocardial ischemia helps in understanding complex disease mechanism
5	Drug repositioning [62]	Repurposing of the existing drugs to treat myocardial ischemia	Identification of potential repurposed drugs like metformin for reducing heart damage
6	Functional genomics [63]	Using CRISPR and other gene-editing tools to investigate gene function in ischemia	CRISPR-Cas9 screens have identified critical regulatory genes involved in myocardial ischemia as prospective targets for gene therapy

This table summarizes various translational research approaches and provides a complete overview of the Current methodology used in the study of myocardial ischemia, emphasizing their importance and practical implications in furthering understanding and treatment of the illness

and chemical data using computational methods to pinpoint potential drug targets and forecast how well currently available medications will work to treat myocardial ischemia. The time and expense involved in conventional drug development procedures can be significantly decreased with this approach. Sabatine et al. [64] in their study aimed to demonstrate the robustness of current technologies in identifying circulating metabolites, characterize metabolic pathways and metabolites influenced by myocardial ischemia and investigate the potential of metabolic profiling in identifying patients with acute myocardial ischemia [65]. Discordant regulation of various metabolites increased or decreased in cases but remained stable in controls in a study of 36 patients with inducible ischemia. Lactic acid and skeletal muscle AMP catabolism increased during exercise. Six metabolite changes, including citric acid changes, were able to distinguish patients from controls with accuracy. For their investigation of the metabolomic discovery of novel biomarkers of myocardial ischemia, they developed algorithms to find trends in pathways in high-throughput mRNA expression data. This software was based on FunAssociated and with this strategy, the time and cost associated with traditional drug development processes can be greatly reduced. It will be a simple strategy in the area of drug discovery. They used the KEGG database's a priori annotation of metabolites by the disease, pathways, and reactions they were linked.

Lu et al. [66], in their investigation, used a network pharmacology technique to determine the herb pair FCNs (*Fructus Choerospondiatis* and *Nutmeg*), potentially active components, and synergistic effects as traditional Mongolian medicine. In traditional medicine, one of the most common plant pairings is GuangZao and RouDouKou. The protective effect of FCN is supported by some evidence, but the exact mechanism by which it works is still unknown [67]. Using SWISS, PharmMapper, and SuperPred Server, they clustered CHD-related targets from the DrugBank and OMIM databases and predicted the targets of all available FCN constituents. Additionally, they evaluated the relationships between the pharmacological effects and herbal constituents to explore the possible mechanism of FCN. They discovered that a network of crucial biological functions, such as cell apoptosis cell adhesion and connections, stress reaction, inflammatory and immune responses, angiogenesis, necrosis, the endocrine system, and other biological functions, are all targeted by FCN [68].

They looked into FCN's protective effect on Isoproterenol (ISO)-Induced Myocardial Ischemia in rats to see if the results supported the predictions. According to a pathological analysis, FCN suppresses the myocardium's inflammatory and apoptotic responses. Western blotting analysis and quantitative real-time Polymerase Chain Reaction (qrt-PCR) were used to show that FCN had positive effects on rats with ISO-induced myocardial ischemia. Restricting inflammatory responses and stress may have led to these effects, which in turn limited the apoptosis of cardiomyocytes. According to the results, explaining the complex multitarget mechanism of action of FC through the use of bioinformatics in conjunction with experimental verification provides a trustworthy and objective method.

System biology and network analysis

System biology techniques are used in translational bioinformatics to examine the intricate molecular networks underlying myocardial ischemia. Researchers can develop a comprehensive understanding of the disease mechanisms by integrating various biological data types, including protein–protein interactions, signaling pathways, and gene regulatory networks. This data can point out important pathways or nodes that can be the focus of therapeutic interventions. Nguyen et al. examine the question of how, after a myocardial infarction, the left ventricle (LV) repairs itself at the molecular and cellular levels and used integrative statistical and experimental methods to identify a post-myocardial infarction(MI) understanding map [69]. They put forth a framework that integrates computational methods with experimental information. They created a protein–protein interaction network (MIPIN) that is specific to MI by choosing a starting set of proteins associated with MI from published human studies. The extracellular matrix (ECM) remodeling, inflammatory response, and transcriptional activity proteins were more prevalent in the post–MI LV, according to structural and functional investigation of the MIPIN [70].

By data mining the PubMed and UniProt knowledgebases, it was possible to identify known changes in the MIPIN protein expression in plasma or serum in MI patients. These data served as a training set for the prediction of unlabeled MIPIN protein changes following MI. They presented an integrative computational approach that involved building a knowledge map that examines the regulator relationship between ECM, cellular responses, and biological pathways post-MI as well as an MI-specific PPI database created by mining PubMed and Uniprot. This biological pathway, cellular reaction, and molecular interaction data map is the first significant step toward improving our comprehension of molecular interactions specific to MI [71]. Myocardial Infarction was used as the search term to find MI-related proteins in the PubMed, Online Mendelian Inheritance in Man (OMIM) database, and PubMed protein database [72].

Clinical decision and support system

The design and development of clinical decision support systems (CDSS) for myocardial ischemia is aided by translational bioinformatics. To analyze patient data, medical literature, and recommended courses of treatment, these systems make use of computational algorithms and machine learning techniques. CDSS can help medical professionals make decisions about patient management and better patient outcomes. In general, translational bioinformatics is essential for advancing our knowledge of myocardial ischemia and enhancing therapeutic approaches [73]. By using computational techniques and combining multiple data sets, this field helps bridge the gap between basic research and clinical practice, leading to more tailored and effective ways to treat cardiovascular problems.

According to Villanueva et al. [74] study, adhesion molecules that are acutely expressed during ischemia can be targeted by microbubbles to identify post ischemic myocardium using ultrasound. Specifically, they showed that inflammatory endothelium adheres to an ultrasonic contrast agent that targets the selectin family of adhesion molecules. They also demonstrated how echocardiographic identification of the post ischemic region is made possible by selectin-targeted microbubbles. In this study, they used the Kruskal–Wallis test for nonparametric comparisons during intravital microscopy and linear regression analysis that assessed the relationship between risk area size and post ischemic contrast enhancement region size. Using ultrasonography to map the location and magnitude of recent myocardial ischemia and detect the expression of acute adhesion molecules on post ischemic endothelium may be possible [75]. They demonstrated that selectin-targeted micro bubbles enable the post ischemic zone to be identified, localized, and spatially quantified using echocardiography [76, 77]. These imaging techniques are used in the understanding of the disease for physicians to make better clinical decisions.

Limitation

Due to the limited availability of large-scale data for myocardial ischemia, integrating heterogeneous data from many sources can hinder a complete understanding. Myocardial ischemia is caused by a complicated combination of biological mechanisms and current bioinformatics models can overgeneralize these pathways, resulting in inadequate or inaccurate interpretations. Computational predictions for drug repurposing require rigorous experimental and clinical validation, where the high cost and time necessary to evaluate repurposed medicines may delay their clinical application for myocardial ischemia.

Conclusion

This review highlights the crucial role of translational bioinformatics in understanding and treating myocardial ischemia. By identifying novel biomarkers, analyzing gene and protein expressions, and emphasizing personalized medicine and drug repurposing, the study underscores the potential of bioinformatics to improve cardiovascular health outcomes. The integrative approach enriches current knowledge and paves the way for targeted interventions.

Future research should expand datasets and tools, integrate multi-omics data for a comprehensive understanding, and utilize AI and machine learning to refine predictive models. Collaborative efforts will be essential in translating these discoveries into clinical practice, enhancing patient outcomes, and driving innovations in cardiovascular disease management.

Author contributions

Yeswanth Ranganathan was involved in methodology, investigation, and writing. Saayaa Nazar was involved in methodology, writing, and investigation. Ravi Shankar Krishnan was involved in conceptualization, validation, and supervision. Yuvaraj Dinakarkumar was involved in review & editing. Vijayalakshmi Varadarajan was involved in writing, and editing. Lenita Sebastian was involved in writing, editing. Brindha Rethinam was involved in review & editing, validation, and supervision.

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Availability of data and materials

All data and materials supporting the findings of this study are available within the manuscript.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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