International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 4 July-Aug 2024, pp: 1438-1443 www.ijprajournal.com ISSN: 2456-4494

Evaluating Biomarkers significance to cardiovascular risk Prediction

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Date of Submission: 15-08-2024 Date of Acceptance: 25-08-2024

ABSTRACT:
Globally,cardiovascular disease (CVD) continues to be the main cause of morbidity and mortality. Reliable risk assessment is essential for successful management and preventive plans. Assessment of cardiovascular risk may be improved as a result of recent advances in biomarker research. Screening the biomarkers of cardiovascular risk prediction is one of the pivotal areas of study, enhancing our strategies to forecast cardiovascular events and tailored preventative techniques. Biomarkers, which encompass genetic, proteomic, and metabolic markers, offer important insights into a person's predisposition to cardiovascular ailments, such as heart failure, stroke, and coronary artery disease. The current status of biomarker evaluation is examined in this abstract, with a focus on important advances and the way these influence risk assessment. Advances in high-throughput technologies, namely in the areas of advanced genome sequencing have enhanced our understanding of the complex molecular processes underlying cardiovascular disorders. The potential for improving risk prediction models and clinical decision-making is also there when integrating these biomarkers with sophisticated data analytics and machine learning algorithms. The goal is to use these findings to inform tailored medications as scientific advances, offering more precise risk assessment and focused treatments. This emerging field seeks to support early diagnosis and preventative therapy while also helping to achieve the primary aim of reducing the worldwide cost of cardiovascular disorders.

KEYWORDS: Biomarkers, cardiovascular risk prediction, genetic markers, inflammatory markers, atherosclerosis, Mycocardial dysfunction, lipoprotien-associated, BNP(B-type natriuretic peptide)

I. INTRODUCTION

A significant burden on public health systems is borne by cardiovascular disease (CVD), which continues to be the world's leading cause of death. According to a report from WHO in 2019, an estimated 17.9 million individuals died from CVDs, accounting for 32% of all fatalities worldwide. Cardiovascular events were the cause of 85% of these fatalities.

More than 75% of deaths from CVD are found in countries with low or middle incomes.To determine a person's risk of getting CVD, conventional risk variables including age, gender, hyperlipidemia, blood pressure, and habit of smoking have long been employed. Even while these conventional measurements work well, they frequently fall short of capturing the entire range of risk, especially for people with unusual CVD presentations or those at intermediate risk. This restriction highlights the requirement for more accurate and tailored risk assessment instruments. Furthermore, the stage of the disease process determines which of these biomarkers provides the most information. It is now known that a protracted period of subclinical cardiovascular illness usually precedes over cardiovascular disease [1].

A broad array of substances, such as proteins, lipids, genetic markers, metabolites, and inflammatory markers, are referred to as biomarkers-quantifiable indicators of biological processes. Inflammation, oxidative stress, endothelial dysfunction, and thrombosis are some of the pathophysiological pathways of cardiovascular illnesses that these indicators provide important insights into. Biomarkers offer potential for improving risk classification beyond conventional clinical criteria by offering a more sophisticated comprehension of these processes [2].

These biomarkers are significant because they have a capacity to guide individualized preventative and treatment methods in addition to potentially increasing accuracy in cardiovascular risk prediction. The purpose of this study is to objectively assess the available data about the usefulness of different biomarkers in the prediction of cardiovascular risk, including lipoprotein(a), lipoprotein-associated phospholipase A2, troponins, natriuretic peptides, C-reactive protein

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(CRP), and novel genetic markers. Our goal is to present a thorough understanding of how these biomarkers might be incorporated into clinical practice to improve the management, prevention, and prediction of cardiovascular events by combining the results of previous studies [2].

II. ASSESSMENT FOR BIOMARKERS

For a biomarker to be considered unique, it must exhibit a robust and stable correlation with the illness and offer clinically significant and improving diagnostic or prognostic data to validated risk assessment systems [3]. An assessment of a biomarker test's accuracy is based on two factors: its specificity, which determines the identification of true-negatives at certain cutpoints, and its sensitivity, which detects illness when it is actually absent. There are several noteworthy outliers to the general distribution of several CVD biomarkers, which include genotypes, gender, race, diabetes, hypertension, and cardiovascular disease. For this reason, it is essential to assess a biomarker's information content across a range of values, frequently using receiver operating characteristic (ROC) curves [4]. Predicted risk and outcome relationships are quantified through calibration. Hence, in a correctly calibrated model, the observed proportion of patients displaying a given result should be close to this amount if we estimate a 15% probability of it [3].

Reclassification seeks to quantify the extent to which an extended model, as compared to a baseline model, accurately reclassifies individuals.[3] When biomarker levels are used clinically to detect illness, the ROC curves show the trade-off between sensitivity and specificity[4].

III. TYPES OF BIOMARKERS CARDIOVASCULAR RISK PREDICTION

Multiple types of biomarkers play a vital role in assessing and predicting various cardiovascular diseases offering multifarious insights on cardiovascular health. These biomarkers comprise those that indicate inflammatory and metabolic conditions as well as genetic predispositions. The broad spectrum of biomarkers makes it possible to forecast cardiovascular risk in a more precise and nuanced way, which enhances patient care on an individual level.

The biomarkers are as follows :-

3.1. Biomarkers for myocardial

3.1.1 Myoglobin

The protein called myoglobin can be found in blood, urine, skeletal muscle, and cardiac muscle. A myoglobin blood test can be used by medical professionals to determine injuries to muscles. Myoglobin is released into the bloodstream by the cells of muscle as a response to damage to the cardiovascular or skeletal muscles. Healthcare professionals usually monitor the blood's myoglobin level a few hours after an accident since it might rise rapidly in cases of serious muscle damage.

As early as one to three hours following ischemia insult, myoglobin is elevated, making it one of the first indicators to be released into the bloodstream following the commencement of myocardial necrosis. Then, six hours after the insult, it peaks, and 18 to 24 hours afterwards, it returns to normal. However, as myoglobin is also present in adult skeletal muscle, myoglobin is not unique to cardiac damage. Myoglobin testing is only advised for patients who report within 6 hours after the beginning of chest discomfort, according to current guidelines, because highly specific cardiac biomarkers like troponin I and T are easily available[5].

3.1.2 Cardiac Troponin

When it comes to myocyte damage, troponin I (cTnI) and troponin T (cTnT) are extremely sensitive and specific. Both of these are actin-binding subunits of the troponin regulatory complex[5]. cTnI levels are elevated in a number of cardiac and non-cardiac disorders, such as renal failure, myocardial infarction, HF, pulmonary embolism, myocarditis, and sepsis[6]. Elevated high-sensitivity cardiac troponin I (hs-cTnI) levels in HF patients have been linked to a worse prognosis and a higher chance of death, according to many studies [6][7] [8].

3.1.3 Heart type fatty acid binding protein (H-FABP)

Heart-type fatty acid binding protein, a low molecular weight protein present in cardiomyocytes, is produced by the metabolism of fatty acids in cardiac tissue. It possesses many qualities that make it a "perfect" ACS biomarker, including being stable and soluble, having a high concentration in the myocardium, being specific to heart tissue, and having a low molecular weight [9]. ROC evaluations from current studies have shown that H-FABP either adds extra value to

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Volume 9, Issue 4 July-Aug 2024, pp: 1438-1443 www.ijprajournal.com ISSN: 2456-4494

troponin or is superior to it in early detection of acute coronary syndrome (ACS) [10].

cTnI (18.8%) and CK-MB (12.5%) showed significantly lower sensitivity than H-FABP (60%) among AMI patients who presented within four hours of the onset of symptoms. However, the specificity was only 23.53%, which is lower than CK-MB's 100% and cTnI's 66.67%. H-FABP had a sensitivity of 86.96% within 4 and 12 hours after the beginning of symptoms, which was similar to that of cTnI (90.9%) and CK-MB (77.3%). The specificity of the 4–12 hour group was 60%, which was similar to that of cTnI (50%) and CK-MB (50%). Additionally, the H-FABP level was found to be an independent risk factor for both cardiovascular and mortality from all causes, and it increased in correlation with a higher number of cardiovascular risk factors [11].

3.2 Biomarkers in inflammation

3.2.1. High sensitivity c- reactive protein

A member of the pentraxin family of innate immune response proteins is C-Reactive Protein. Using HsCRP, which measures CRP at less than 5 mg/L, individuals are categorized as low, moderate, or high risk. Those who are classified as intermediate or high risk may benefit from more aggressive treatment.[22] Each standard deviation increase in hsCRP (log-normalized) was linked to a relative risk increase of 1.37 (95% CI: 1.27–1.48) for CAD and 1.55 (95% CI: 1.37–1.76) for cardiovascular mortality, according to a meta-analysis that included over 160,000 subjects, 1.3 million person-years of follow-up, and nearly 28,000 incidents of cardiovascular events [12]. Additionally, hsCRP is recommended as a Class IIb by the European Society of Cardiology (ESC) guidelines. This means that in patients with moderate or atypical cardiovascular risk profiles, hsCRP may be assessed as part of a refined risk assessment [13].

3.2.2. Growth-differential factor 15 (GDF-15)

GDF-15, formerly known as macrophage-inhibitory cytokine-1, is an expression-producing member of the transforming growth factor-β cytokine superfamily and a divergent member[12]

When juxtaposed with conventional indicators like C-reactive protein (CRP), serum MIC-1 / GDF15 is an independent predictor of death. Furthermore, the serum MIC-1 / GDF15 level is a predictor of potential myocardial infarction and pulmonary embolism mortality, and it is an independent risk factor for the development of cardiovascular events [14].

3.2.3. Fibrinogen

Acute phase proteins like fibrinogen are produced in the liver and can have circulation concentrations higher than 7 mg/mL when there is an acute inflammation. In addition, it contributes significantly to the development of thrombus and is implicated in endothelial damage, platelet aggregation, and plasma viscosity.

A higher chance of incident CVD is linked to elevated fibrinogen levels. Based on data from 31 prospective trials including 154,211 individual individuals without known CVD, the FSC analysis evaluated the association between fibrinogen concentrations and the risk of major vascular and non-vascular events[12].

Patients with an unusual or high risk of CVD can use fibrinogen testing as part of their risk assessment, according to ESC guidelines on CVD prevention in clinical practice. Not in asymptomatic individuals but at a moderate cardiovascular risk low-risk people[12].

3.3 Biomarkers for platelet activation

3.3.1 Lipoprotein-associated phospholipase A2 (Lp-PLA2)

One enzyme produced by inflammatory cells is called lipoprotein-associated phospholipase A2 (Lp-PLA2). As low-density lipoprotein (LDL) moves through the circulation, it breaks down the oxidized phospholipids inside the LDL. By degrading platelet-activating factor and eliminating certain phospholipids from modified low-density lipoprotein (LDL), Lp-PLA2 may offer protection against atherosclerosis, according to early research [15]. It usually builds up in atherosclerotic plaques, particularly in those that have ruptured or have a necrotic core. Rupture-prone plaques frequently exhibit elevated levels of Lp-PLA2, which seems to be secreted into the bloodstream by these plaques. This enzyme, which is mostly generated by macrophages, binds to several lipoproteins, such as lipoprotein(a) and the ApoB component of low-density lipoprotein (LDL) [16]. Kenneth J et al, concluded that Acute cardiovascular events are associated with a progressively increasing likelihood of having elevated blood levels of Lp-PLA2 [16].

3.4 Biomarkers for Myocardial dysfunction or stress

3.4.1 B-type Natriuretic Peptide (BNP)

B-type Natriuretic Peptide is one of the most well-known markers of biomechanical stress (BNP). When the heart's muscle cells are under stress, the ventricles produce this peptide[17].

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BNP binds to receptors that aid in diminishing central venous pressure, increasing sodium excretion (natriuresis), and lowering systemic vascular resistance. It is helpful in forecasting the course of events following a heart attack and has been thoroughly studied. Despite the brief half-life of BNP, it is released in conjunction with the pro-BNP peptide's N-terminal segment (NT-proBNP). It is easier to test and more stable in the blood than NT-proBNP[18].

According to research, BNP and NT-proBNP levels were higher in those who had cardiovascular events[19].

3.4.2 Galectin (Gal3)

The chromosome 14 LGALS3 gene, which comprises six segments (exons) and five non-coding sections (introns), produces the protein known as galectin-3. This protein consists of two distinct domains: a C-terminal domain that binds to carbohydrates and a unique N-terminal domain. A major player in the body's acute inflammatory response, galectin-3 is primarily produced when monocytes transform into macrophages. It draws monocytes, helps remove dead neutrophils, activates mast cells, and aids in the adhesion and activation of neutrophils. Chronic inflammation is linked to tissue scarring because it can cause fibrosis and tissue damage. For this reason, no matter heart-related stress, galectin-3 is a helpful marker for tissue injury[20].

In a recent study it shows that Galectin and cardiovascular events are closely linked. The predominant increase in Gal3 shows higher risk of cardiovascular stress and heart failure. This study also states that patients with elevated levels of Gal3 were twice as likely to develop heart failure[21].

3.5 Genetic biomarkers for cardiovascular risk prediction

Finding genetic markers associated with heart health offers crucial new information about the role that our genes play in cardiovascular diseases. Genes encoding Apolipoprotein, TTN, and Troponin, for instance, are essential for controlling cholesterol levels, cardiac muscle composition, and muscular contraction, respectively. The electrical activity of the heart is regulated by genes like KCNQ1 and KCNH2, which affects the heart's rhythm. PLIN1 influences the buildup of fat, which can have an effect on heart health, whereas MYBPC3 is essential for the integrity of the heart muscle. Blood pressure control has been linked with ACE genes, cholesterol processing is impacted by LDLR genes, and heart cell shape is preserved by LMNA genes. Developing an understanding of these genetic features allows us to establish more focused proactive and treatment approaches by better understanding the role that our genes play in heart health and illness[24]

There are two primary forms of lamins, Lamin A and Lamin C, which are proteins produced by the LMNA gene. These proteins are involved in several processes including cell division and DNA replication and are crucial to sustaining the stability of our cells' nuclei. These lamin proteins are created by the LMNA gene, and mutations in this gene can result in a variety of diseases referred to as laminopathies. Dilated cardiomyopathy is one of these ailments; it is a cardiac disease that impairs the heart's ability to pump blood efficiently[24].

IV. FUTURE DIRECTIONS TOWARDS THE BIOMARKERS FOR RISK PREDICTION

We anticipate significant developments in the assessment of biomarkers for cardiovascular risk prediction in the future. Advanced imaging methods and genetic sequencing are two examples of cutting-edge technology that will transform our understanding of cardiovascular health. Novel biomarkers that may offer greater insights into individual risk profiles and the causes of illness are the focus of emerging research. In addition, the development of more sophisticated algorithms and data analytics tools is projected to boost risk prediction accuracy. These developments will improve patient outcomes and revolutionize cardiovascular care by boosting our capacity to predict cardiovascular events and open the door for tailored proactive strategy as well as targeted treatments.

With the help of artificial intelligence and machine learning algorithms which can sort complex databases consisting of complex data of genetic information, biochemical and imaging data, can provide much higher precision of accuracy in predicting the new emerging biomarkers. Furthermore integration of large scale data with modern analytical risk models and improving the personalized strategies towards the therapeutic approach will help in management of cardiovascular disorders.

In addition, Metabolomics which is a study of metabolites. This might lead to identification of newly emerging biomarkers and can also provide huge insights in the field of cardiovascular risk

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prediction.Long-term patient monitoring studies, both now and in the future, will provide critical new insights into the relationship between the temporal changes in biomarkers and long-term cardiovascular health outcomes. Although there are many efforts from various parts of the world to reduce the prices of these biomarker testing but they still seem to be very pricey, getting these tests to a cost effective lane will help a huge array of crowds and it can also increase the morbidity of the population.

V. DO BIOMARKERS PROVIDE ADDITIONAL INSIGHTS BEYOND WHAT EXISTING CARDIOVASCULAR RISK SCORES OFFER?

This method has a few main arguments. Initially it has long been known that an amalgamation of risk factors, some of which can compound or even enhance the impact of one another, is typically the cause of cardiovascular disease (CVD). Consequently, the foundation of any preventive approach should be an individual's whole risk for CVD. The level of danger dictates how aggressively one should prevent it. When planning for CVD prevention, it's also critical to consider cost-effectiveness. This ensures that resources are used efficiently by matching the amount of prevention with the individual's total risk[22].

Many biomarkers have been advised from the field of lipid metabolism such as ApoB, ApoA1, ApoE, lipoprotein(a) (Lp(a)), particle size of low-density lipoprotein (LDL), oxidized LDL. Biomarkers related to inflammation such as high sensitivity C- reactive protein (hs CRP), growth differential factor-15 (GDF-15). Numerous key indicators, such as fibrinogen and plasminogen activator inhibitor-1, which are involved in blood clotting and breakdown, are vital to take into account while trying to comprehend thrombosis. Additionally, based on genetic studies, researchers are looking into additional markers, such as certain regions on chromosomes 9p21 and 12p13. N-terminal pro-B-type natriuretic peptide (N-BNP), homocysteine levels, and even indicators associated with air pollution are other variables that may be involved[22].

Through the SCORE project, scientists investigated several approaches to improve the model by adding elements including body mass index, homocysteine levels, and HDL cholesterol (HDL-C). Among these modifications, HDL-C turned out to be the most promising, exhibiting the most potential for enhancing risk assessment accuracy[23]. Although the BNP is said to be the golden biomarker for cardiovascular risk prediction [3].

VI. CONCLUSION

The biomarkers including B-type natriuretic peptide (BNP), lipoprotein(a), cardiac troponin, myoglobin, Growth-differential factor 15 (GDF-15), high-sensitivity C-reactive protein and other biomarkers showed significant associations with cardiovascular risk as revealed by the review. Other reported novel biomarkers include microRNAs and genetic variants. Some biomarkers have been shown to provide incremental risk stratification above and beyond standard methods, whereas the addition of these markers into current risk prediction models demonstrates variable accuracy enhancements in predictive performance

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International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 4 July-Aug 2024, pp: 1438-1443 www.ijprajournal.com ISSN: 2456-4494

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