Review Article

Concrete Review on Cardiotoxicity Biomarkers

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ABSTRACT

Cardiovascular diseases (CVDs) are the major cause of mortality around the world. Modifiable risk factors concern lifestyle and individual behavior including smoking, obesity, stress, unhealthy diet, and underlying diseases such as hypertension, diabetes mellitus, and hypercholesterolemia. Cardiotoxicity from cytotoxic drug treatments is known to have a high prevalence. Cytotoxic drugs such as anthracyclines, 5-fluorouracil, cyclophosphamide are associated with serious cardiotoxicity effects. Different mechanisms of chemotherapy-induced cardiotoxicity are postulated including cellular damage due to the formation of free oxygen radicals and the induction of immunogenic reactions with the presence of antigen-presenting cells in the heart. Moreover, the influence of the cytotoxic agent on certain phospholipids, especially cardiolipin, may also explain the development of cardiotoxicity. This may cause apoptosis of cardiac cells and the induction of immunologic reactions. Recently, it has been stated that some novel cytotoxic drugs such as trastuzumab and cyclopentenyl cytosine are also known to induce serious cardiotoxic side effects. Biomarker is an entity that can be measured to predict diagnosis, onset, or progression of disease process. Various biomarkers used to analyze myocardial necrosis include troponin, creatinine kinase, myoglobin, C-reactive proteins, lactate dehydrogenase (LDH) isoforms, myeloperoxidase and interleukins. Various other biomarkers can be recommended as surrogate marker for forecasting clinical benefits in CVDs. Biomarkers have wide applications that can be used for identification of proteins, product of cellular and biological processes, and response of cells and tissues to therapeutic strategies. Certainly, biomarkers may assist in accelerating success rate of drug development and availability of new cardioprotective therapeutics.

Keywords: Biomarkers, cardiac damage, cardiac toxicity, creatinine kinase, myocardial infarction, myoglobin, troponin.

INTRODUCTION

CVDs are the major cause of mortality around the world. These diseases comprise a range of disorders within the heart and blood vessels, including coronary heart diseases, cerebrovascular diseases, peripheral arterial and rheumatic heart diseases, pulmonary embolism, deep vein thrombosis. Risk factors for CVDs can be classified into modifiable and non-modifiable risk factors. The modifiable risk factors concern the lifestyle and behavior of the individual, including smoking, obesity, stress, unhealthy diet, sedentary lifestyle, and diseases such as hypertension, dyslipidemias, diabetes mellitus, and hypercholesterolemia. [1, 2] Cardiotoxicity occurs during therapy with several cytotoxic drugs and maybe the dose-limiting factor in cancer treatment and hence tumor response. Furthermore, cardiotoxicity can also be responsible for long term side effects and may cause severe morbidity in surviving cancer patients, which may be relevant especially in pediatric oncology. Cardiotoxicity from cytotoxic treatment is known to have a high prevalence. Cardiotoxicity includes a wide range of potential effects from minor changes in blood pressure and arrhythmias to cardiomyopathy. In literature, different mechanisms of chemotherapy-induced cardiotoxicity are postulated including cellular damage due to the formation of free oxygen radicals and the induction of immunogenic reactions with the presence of antigen-presenting cells in the heart. Moreover, the influence of the cytotoxic agent on certain phospholipids, especially cardiolipin, may also explain the development of cardiotoxicity. [3]

Inducers of cardiotoxicity

1. Anthracyclines

Anthracyclines such as daunorubicin and doxorubicin have been reported to cause severe cardiotoxic disorders. The main mechanism behind the induction of toxicity by anthracycline is oxidative stress that is the formation of superoxide's and other free radicals. The reaction starts with the donation of one-electron by the doxorubicin to form a doxorubicin semiquinone radical with the help of the enzymes such as NADPH-cytochrome P450 reductase. [3] The complex formed by the semiquinone radical with iron is an anthracycline-iron free radical complex. The oxygen is

reduced by this complex to produce superoxide and to regenerate doxorubicin. The superoxide splits into oxygen and hydrogen peroxide. [4] The doxorubicin binds to the endothelial nitric oxide synthase causing a decrease in nitric oxide and an increase in superoxide formation. The formation of peroxynitrite could also play a role in the cardiotoxicity. From the combination of superoxide, free iron, and hydrogen peroxide, lipid peroxidation may be initiated of the cardiac cells to oxidative stress. [5]

2. Taxoids

The two anti-cancer drugs paclitaxel and docetaxel are important agents that are linked with cardiotoxicity. When the paclitaxel is administered in combination with cisplatin, the various cardiac disorders like cardiac ischemia, atrioventricular, bradycardia, and tachyarrhythmias are known to be reported. [6] The congestive heart failure in the patients is developed because of the prolonged use of toxoids. In order to improve the drug solubility of paclitaxel, it is formulated with the help of a vehicle cremophor EL. It has been reported that this vehicle, not just the paclitaxel alone, is associated with precipitating severe cardiac disorders. The main mechanism by which cremophor EL induces cardiotoxicity is that it causes the release of massive histamine. An alternative explanation for paclitaxel-induced cardiotoxicity could be the induction of cardiac muscle damage by affecting subcellular organelles. [7, 8, 9]

3. 5-Fluorouracil

The 5-Fluorouracil (5-FU) is antimetabolite with adverse effects like diarrhea, myelosuppression, dermatitis, and mucositis. High dose chemotherapy, age, and concomitant radiation therapy are major risk factors involved in inducing 5-FU related cardiotoxicity. [9] The mechanism behind the 5-FU related cardiotoxicity is not clear and it cannot be explained by the pharmacological action of 5-FU. The hypotheses postulated are vasospasms leading to activation of coagulation, ischemia, coronary artery thrombosis, direct toxicity on the myocardium, immuno-allergic phenomena, and cardiotoxic impurities in the 5-FU.[10-12]

4. Cyclophosphamide and ifosfamide

Cyclophosphamide is often used at a higher dose as transplant regimens which can cause acute cardiotoxicity such as cardiac failure or inherited cardiac muscle disease. Though the pathogenesis is not yet fully established it is believed that an increase in free oxygen radicles may cause oxazophosphorine induced cardiotoxicity that is mediated elevated intracellular levels of the actual cytotoxic metabolite phosphoramide mustard. [13]

5. Cisplatin

In the various treatments of cancers like testicular cancer, the cisplatin substance is used. Some factors have been recommended to be implicated such as hypomagnesemia, vascular damage, and platelet aggregation. [13] The platelet aggregation was trigger through the cisplatin and it also

responsible for the enhancement of the thromboxane formation by platelets when it's was an experiment on the human. [14, 15]

6. Isoproterenol (ISO)-induced myocardial damage

Subcutaneous administration of ISO produces significant biochemical and histological changes. Oxidative stress and lipid peroxidation (LPO) are amplified, resulting in significant increases in the level of malondialdehyde (MDA). The increase in oxidative stress corresponds to the elevated neutrophil count, which in turn, leads to increases in the release of leukotrienes, reactive oxygen species (ROS), and hydrolytic enzymes which further aggravate the myocardial injury. On the other hand, the levels of antioxidants, most notably catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), and glutathione peroxidase (GPx), are significantly reduced.[15] The levels of myocardial injury markers (aspartate transaminase [AST], troponin I [TnI], lactate dehydrogenase [LDH], creatine kinase [CK-MB], creatine phosphokinase [CPK-MB], serum glutamic-oxaloacetic transaminase [SGOT], and serum glutamic-pyruvic transaminase [SGPT]) and pro-inflammatory cytokines (C-reactive protein [CRP], interleukin-6 [IL-6], and tumor necrosis factor-alpha [TNF-a]) increase in response to ISO in proportion to the progression of necrosis. The lack of both oxygen and glucose results in disruption to the integrity of the cell membrane, with an increase in its permeability, allowing the enzymes SGOT, TnI, LDH, and CPK-MB to leak out. The concentration of urea was found to increase as well, and along with calcium phosphate complexes, which bind to intracellular proteins, creating inflammasomes. Inflammasomes are innate immune system receptors that regulate the activation of caspase-1 (Cas-1) and induce inflammation, thus increasing the secretion of IL-6 and nuclear factor-kappa B (NF-kB). The pathophysiological and morphological alterations produced by ISO in the heart are similar to those taking place in human MI. [16, 17, 18]

Biomarkers

The biomarkers are the quantifiable product in the biological samples for example urine, tissue, or blood that are related to the phenotype. The biomarkers have diagnostic, predictive, and beneficial values. For biological systems, a ''biomarker'' can consist of any entity that occurs in the body and that can be measured to predict the diagnosis, onset, or progression of a disease process. A biomarker is not confined to a single entity. As a result, the definition of a biomarker is intentionally broad and the application of biomarkers can be used for the determination of specific genes, proteins, and products of cellular and biological processes as well as the response of cells or tissues to therapeutic strategies. [19] The biomarkers are the deliberately wide applications which are used for the identification of proteins, a product of cellular and biological processes, and the response of cells and tissues to therapeutic strategies. There are various biomarkers which can recommend further benefit as a surrogate marker which is used to forecast clinical result in the various cases. An ideal

biomarker should be capable of anticipating the disease occurs most precisely in terms of both specificity and sensitivity as well as should be cost-effective, readily quantifiable, and corresponds to the clinically substantial phenotype portion. The utility of biomarkers can be further enhanced if the experimental data are presented to biologically support the connection between the biomarker and the phenotype.

Epidemiological research data that can predict the link of a particular biomarker with the interested phenotype may help to identify the biomarkers. Phenotypic expression of the ailment progression can also be employed as a biomarker. The idea was first presented by the Framingham Heart Study reports, which aided in the identification of conventional coronary atherosclerosis disease precipitating risk factors. Advancement in the field of molecular pharmacology and biochemistry has led to an upgraded group of CVD biomarkers that help to gain a better insight into the disease pathophysiology. Consequently, urine analysis or plasma estimation of the candidate proteins that are concerned with the CVD pathogenesis, are represented as the biomarkers for the disease. [19, 20]

Biomarkers are usually proteins like apolipoproteins, cytokines, C-reactive protein (CRP), or can be a single molecule like homocysteine and nitric oxide (NO). Till now, biomarkers identification for CVD was restricted to extraction and isolation of novel protein molecules such as estimation of troponin, CRP, creatinine kinase (CK) as the biomarkers for myocardial infarction. Recently, the field of genomics has emerged as an incredible method for identifying and isolating biomarkers. Numerous investigations have prompted to identify the genetic and molecular foundation of several CVD such as protein sequencing, expression profiling related to current strategies of hereditary linkage mapping, single nucleotide polymorphisms(SNPs), and haplotype affiliation and High-throughput DNA genotyping and sequencing. Likewise, as genetic expression at various protein levels can be analysed with the help of proteomics, the branch can serve as novel biomarkers by identifying new mediators or proteins associated with disease pathogenies. Proteomics, which empowers examination of gene expression at the protein level, can distinguish novel proteins engaged with the ailment and thus, new biomarkers. Human Genome Project as well as SNPs identification has introduced a novel succession of genetic biomarkers that can be utilized for pharmacogenetic preclinical analysis and risk evaluation. In the human genome, over 5,000,000 SNPs have been recognized that forms the foundation for the variation in disease susceptibility, treatment response as well as clinical outcome in the different individuals. Many functional SNPs are recognized as the major biomarker candidates for several forms of cardiovascular diseases (CVD) and many have been linked with cardiac phenotype. Also, several protein mediators of mapped genes are recognized as potent biomarkers. Conjugation of bioinformatics with proteomic and genomics has led to

enormous information and opportunity for detecting and characterizing novel biomarkers for CVD. [20, 21]

Biomarkers for myocardial infarction

Acute coronary syndrome (ACS) represents that the prototype phenotype for which biomarkers have been developed and utilized in the diagnosis, risk stratification, and treatment for several decades. The process of myocardial necrosis in ACS leads to the release of proteins from dead myocytes into circulation and hence, provides relatively accessible targets to identify biomarkers. The first biomarkers used to analyze myocardial necrosis integrated serum glutamate oxaloacetate transferase (otherwise called AST), consequently CK, lactate dehydrogenase (LDH) isoforms. Huge numbers of the previous biomarkers were not adequately sensitive or explicit for an early conclusion of MI and have in this way been replaced with the more current markers that have desirable recipient administrator trademark bends. [22, 23, 24] a few of these biomarkers are discussed below.

1. Creatinine kinase

The detection of creatininekinase (Creatine phosphokinase (CPK)) as the biomarker for analysis of MI has assumed an essential role in the contemporary analysis and the board of acute coronary syndrome. Creatinine kinase exists in three cytoplasmic (-MM, -MB and CK-BB) and the two mitochondrial (pervasive and sarcomeric) isoforms. At least the four different types of genes, CKMT1, CKB, CKMT2, and CKM encode for the creatinine kinase subunits M and B, and mitochondrial Creatinine kinase isoforms one and two, individually. Cytoplasmic Creatinine kinase subunits dimerize framing the –MB, CK-MM, and -BB isoforms. CK-MM is the main isoenzyme in both striated and vehicle and cardiac muscles. [25]

CK-MB cover most 15–20% of the entire CK in heart muscle while about 1–3% of the entire CK is present in striated muscle. Thus, both cardiovascular and striated muscle damage might lead to an expansion in the serum levels of complete Creatinine kinase. The damage to the cardiac muscle is characterized by a higher percentage of the CK-MB isoform in the serum in contrast to the striated muscle injury. Serum levels of total CK and CK-MB isoform increase 6–12 h after myocardial injury, peak in 12–24 h, and return to baseline levels in 48–72 h. The serum CK-MB levels stay outstanding amongst other biomarkers for MI, specifically reinfarction. CK-MB levels are routinely estimated in clinical practice related to more current biomarkers of MI, in particular cTnI. [26]

2. Myoglobin

Myoglobin is the low-atomic weight (17 kDa). The Myoglobin is expressed in skeletal and cardiovascular muscles and is discharged into plasma upon injury to both of these muscles. It is an early biomarker for the myocardial injury that can be distinguished inside 1–3 h after muscle injury, topping in 6–7 h. In any case, as it is plentifully expressed in skeletal muscles, it isn't adequately

explicit. Thus, while the negative analytical value, particularly when analyzed successively, is quite high, it has a moderately low specificity and positive predictive value. Therefore, it is employed in association with other biomarkers for the detection of ACS. [27, 28]

3. Troponins

Troponins are the anatomical parts of the sarcomeres in myocytes. Through the tropomyosin, they intercede the interface among actin and myosin during the heart cycle. The cTn complex comprises of three troponins, to be specific cTnI, - T and - C. cTnC involves fewer than 5% of the myofibrillar protein and it is the Ca2+-responsive segment of the troponin compound. The Human cTnC comprises of 161 amino acids deposits that are vastly conserved among species. The binding of Ca2+ to cTnC prompts a progression of allosteric changes in the troponin complex, which permits the cooperation of actin in the flimsy fibers with myosin heavy chain in the thick fibers of sarcomeres and resulting hydrolysis of ATP and displacement of action by the global head of the myosin heavy chain. cTnC has two distinct isoforms, referred to as slow and fast isoforms. Fast skeletal cTnC, is encoded by the TNNC2 and is expressed only in the quick jerk skeletal muscle. Conversely, the moderate isoform is expressed in both heart and moderate jerk skeletal muscle by the TNNC1 quality and is frequently referred to as the cardiovascular isoform. The cTnT contains around 5% of the all-out myofibrillar proteins and is responsible for the arrangement of the troponin compound over tropomyosin. [29] There are three isoforms encoded by three unique qualities:

•The moderate jerk skeletal muscle isoform encoded by TNNT1 on chromosome 19q34

•The quick jerk skeletal muscle isoform encoded by TNNT3 on chromosome 11p15.5 [29]

•The heart isoform (TNNT2) on the chromosome 1q32 [28]

The binding of the Ca2+ to the administrative site of cTnC evacuates the C-terminal bit of cTnI from the actin, allowing actin-myosin interaction. The three different qualities encode three significant isoforms of cTnI, in particularTNNI1, TNNI2, and TNNI3 that code for moderate jerk skeletal muscle, fast-twitch skeletal and heart muscle isoforms, individually. [29, 30] There is the 59% amino acid grouping homology between the moderate and quick skeletal isoforms and 57% amino acid homology between vehicle heart and skeletal isoforms. The cTnI is exclusively expressed only in the cardiac. [31]

Troponins exist as a complex with 1:1:1 stoichiometry and each comprises approximately 5% of the total myofibrillar proteins. Below the normal situation, the levels of the troponins in the blood are insignificant. The MI the heart injury the troponin unconfined from the cytosolic compartments and the sarcomeres into the systemic circulation and thus is detectable. Based on the identification of circulating troponin levels thus the different assays have been developed to

identify acute MI. The prominent levels of the troponins in the blood are identified within 3 to 4 hours after the acute MI and reach their peak in the 12 to 24 hours and remain elevated from up to 7 to 21 days. In general, the blood levels of the blood of cTns have become the ordinary biochemical assays for the analysis of the ACS. [29, 30]

4. C-Reactive Protein (CRP)

In the patient with ACS, the C-Reactive protein is the very predictive indicator, as the important CRP levels at the important self-regulating predictors of cardiovascular death, congestive cardiac failure, and AMI. Thus, this one is the most generally used inflammatory biomarkers in regular clinical practice. However, compared to the hs-cTn the C-Reactive protein are very much less sensitive and specific heart injury. Reynoso-Villalpando *et al*. establish that the C-Reactive protein levels are increased in the ACS patient's comparison to the patient having without a history of congestive heart failure. [32, 33]

5. LDH

In all the metabolically active cells the LDH is present and it is released into the serum in the response to the damage of the cell. In the heart tissue, there are at least five subunits of the LDH, So LDH-1, and LDH-2 is main. The myocardial necrosis caused the increase of LDH serum levels with the prevalence of the LDH-1 isoform. The LDH1/2 ratio is useful in the diagnosis of MI but not sufficiently specific since these subunits also exist in other tissues, such as the kidney, brain, and red blood cell. The LDH subunits are no longer usually used in the analysis of acute MI. [19]

6. Glycogen phosphorylase isoenzyme BB

The glycogen phosphorylase is the dimeric enzyme that catalyzes the first step in glycogenolysis, which is converting the glycogen to glucose 1- phosphate by utilizing inorganic phosphate. The glycogen phosphorylase has three homo dimeric iso-enzymes, LL, MM, and BB, in which the BB isoenzyme is expressed in the significant amounts in the heart and brain. With the onset of tissue hypoxia, glycogen phosphorylase isoenzyme BB (GPBB) is released from the sarcoplasmic reticulum glycogenolysis complex into the cytoplasm and mediates the breakdown of glycogen. [34] The GPBB is released in circulation within 1 to 4 hours after the myocardial injury, including congestive heart failure. This may provide as the useful biochemical assay for the analysis and the possibility of the patient with the ACS and all the forms of myocardial injury. The clinical efficacy of GPBB is limited due to the lack of specificity, thus it is also expressed in the other tissue and brain. [35]

7. Heart fatty acid-binding protein

The fatty acid-binding proteins are the low molecular weight protein with the elevated affinity for the noncovalent binding to the fatty acid and are circulated mainly in the fatty acid metabolizing tissue. The 15-kDa protein is the heart fatty acid-binding protein mainly expressed in the cardiac, approx. 5 to 15% of the total

amount of cytosolic protein group. Thus, it is accountable for the transportation and the release of the fatty acyl-coenzyme A for the oxidation within the mitochondria and thus the production of the energy. [36] The very low level of the H-FABP also originates in the kidney, brain, aorta, skeletal muscle, and some other organs. [20] The sensitivity of H-FABP for the analysis of acute MI within the first 4 h of onset of symptoms is greater than 80% and is equal if not superior to the most predictable biomarkers, such as CK-MB and cTnI. The renal failure and the skeletal muscle injury led to false-positive results and bound the efficacy of the test below such circumstances. [37]

8. Neopterin

The neopterin is the biomarker for the immune establishment formed by activated macrophages. Thus, one would expect an elevation of plasma levels of neopterin in atherosclerosis, which is considered an inflammatory disease. Certainly, recent studies have shown elevated circulating levels of neopterin in patients with ACS, compared with controls or patients with a history of MI and stable angina pectoris. Likewise, elevated neopterin levels are related with angiographically complex lesions in patients with unstable angina and the superior risk of the future cardiovascular measures in the women with the coronary artery disorders and in individuals without important disruptive coronary lesions. Treatment with statins is also associated with a significant reduction in plasma neopterin levels. [38, 39]

9. Myeloperoxidase

The reactive oxygen species (ROS) are implicated in the pathogenesis of the variety of human disorders as well as atherosclerosis. The ROS conveys the various array of the biologic property, partially straight and partly through the variation of the proteins and the lipids, that there are significant in the atherogenesis, as well as induction of the genetic material expression, support of the cell production and the apoptosis. The production ROS is regulated by the sequence of pro- and the antioxidant events and the enzymes as well as myeloperoxidase (MPO), superoxide dismutase glutathione peroxidase. The plasma levels of pro- and antioxidant enzymes and the proteins can provide as the biomarkers for atherosclerosis. The MPO is the lysosomal hemoprotein in the polymorphonuclear leukocytes and the monocytes, which is involved in the host and defense systems aligned with the wide range of the organisms. It promotes oxidative injure at the sites of the irritation as well as atherosclerotic plaque. The expression of the MPO has been detected in atherosclerotic plaques and have been linked with the angiographic coronary artery disorder. The Plasma MPO level has been exposed to been predictors of the main unpleasant cardiac measures, self-governing of the troponin level, in the person present with the chest ache to the urgent situation. The MPO levels also prominent even in the patient with the chest ache who presented with the primary normal level of the ordinary cardiac enzymes other than later developed prominent levels. The huge-scale experimental studies determination or enquire to the prospectively test the experimental implication of the plasma MPO level. [19]

10. Lipoprotein-associated phospholipase A$_2$

Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) also known as platelet-activating feature acetylhydrolase, is an enzyme that is connected primarily with the LDL-C, mainly with the undersized dense LDL-C. The Lp-PLA$_2$ have equally pro- and the anti-inflammatory property to stem from the hydrolysis of the oxidized phospholipids to the lysophosphatidic choline and the oxidized fatty acids and from the hydrolysis of the platelet-activating factor and the other phospholipids, correspondingly. [40]

The emerging biomarkers

1. Inflammation Biomarkers

Interleukin-6 (IL-6): The IL-6, is a serious irritation biomarker that might be concerned in the analysis, risk stratification, and the prognosis of the person with the AMI. The IL-6 appearance is revealed to be elevated in induce myocardial infarction by the Trans coronary ablation of septal hypertrophy, signifying its analytical role. As well as, CRP and the IL-6 are both considerably upregulated in the acute coronary condition. [41] The coronary syndrome IL-6 concentration, independent of the already established predictors is too linked to the adverse cardiac actions, behind its impending beneficial target in the unbalanced congestive heart failure. The IL-6 receptor antagonist could improve the inflammatory response and the percutaneous coronary intervention- (PCI-) treated cTn release in NSTEMI, and this improvement is independent of the inhibition of the endothelial cell activation. [42]

Soluble CD40 Ligand (sCD40L)

The sCD40L is the molecule that is involved in the mutual inflammation and the thrombosis method, and the study has revealed that it mediates the interface of the platelets and the neutrophils. Besides, one more study confirms that the sCD40L plays the responsibility in the vascular and endothelial dysfunction seen in the AMI development. It has been demonstrated that the sCD40L concentration is up-regulated in AMI patients, accompanied by the rise of the inflammatory markers IL-6 and the two adhesion molecules, sVCAM-1 and sICAM-1. nevertheless, there are debates over the analytical performance in the patients with the ST rise who have to undergo PCI. While one study shows that the person with the lower sCD40L concentration present with the unpleasant outcome, the one more study indicate that the elevated sCD40L level is the cause of increased in-hospital and one-year all-cause mortality rate. [43]

Galectin-3 (Gal-3)

The Gal-3 is the member of the inflammation mediators and is linked to the amount of the myocardial inflammation and the fibrosis, which is also negatively linked with the ventricular expulsion fraction. Moreover,

the Gal-3 is attention to be concerned in development, damage, and the rupture of the plaques. The Serum Gal-3 is associated with left ventricular dilation and is a contributory factor in predicting the outcome and guiding the monitoring of patients with both acute heart failure and chronic heart failure. [44]

2. The Cardiomyocytes Injury Markers

Cardiac Myosin-Binding Protein C (cMyC)

cMyC is one of the three isoforms of myosin-binding protein C expressed in the cardiac tissue whereas the other two isoforms are expressed in the skeletal muscle. Following cardiomyocyte necrosis, cMyC appears in the circulation earlier compared to hs-cTn. Notably, the cMyC has a higher efficacy for ruling out (safe) and ruling in patients than hs-cTn, while the diagnostic accuracy is similar. Another study also demonstrates that cMyC has discriminatory power comparable to hs-cTn and may perform favorably early after symptom onset. [45]

3. The endothelial cell-associated biomarkers

The endothelial cell precise molecule, also called as endocan, is the marker for the endothelial dysfunction and may serve as the novel assessment methods for the risk stratification of the persons with the acute STEMI. Another study also demonstrated that high endocan level at presentation was an independent predictor for adverse cardiac events. [46]

4. The Platelet Related Biomarkers

The Mean platelet volume (MPV) and the beta-thromboglobulin are the two significant platelet markers that could amplify during the platelet establishment and has an elevated appearance in the patients with congestive heart failure diseases. [45, 46]

5. Other biomarkers

Cystatin C (cys-C)

The cystatin is generated in almost all the human nucleated cells and serve as the marker for the early on renal impairment. An important cystatin level is related to the impaired coronary perfusion and the unwanted improvement of the heart function in STEMI patients undergo PCI and predict adverse outcome. The meta-analysis is also established that the improved cystatin absorption is completely correlated with the readmission rates and the all-cause mortality in the Heart failure patients. [47]

miRNAs

The miRNA-499 and miRNA-208 are exclusively expressed in the cardiomyocytes. The acute myocardial infarction (AMI) patients display an important increase in the concentration of the circulating miRNA-208b and the miRNA-499 compare with health control grouping. In terms of conclusion, there is an association between microRNA-208b and the plasma cTnT concentration. However, miR-208b provides lower diagnostic accuracy

than miR-499 and hs-cTnT. miR-208b and miR-499 are inversely proportional to ejection fraction and can be used as a prognostic biomarker for left ventricular dysfunction after MI. The miRNA-133a and miRNA-1 are the influence-specific microRNAs that regulate cardiomyocyte growth and discrimination. They both are in abundance expressed in both skeletal and the cardiac muscles and the human cardiomyocytes and have been shown too implicated in the instruction of the cardiac hypertrophy. Serum miRNA-133a and mi-RNA1 levels were extensively prominent in the group of the person with the unselected AMI. [48]

Long Noncoding RNAs (lncRNAs).

The lncRNAs, as well as the miRNAs, are observed to change in the patients with the myocardial infarction and might be valuable for the analysis of the myocardial infarction. In addition, plasma levels of the lncRNAs are established to provide the predictive in sequence for the myocardial infarction and predict potential death in the patients with cardiac failure. [48]

Sirtuin (SIRT)

The SIRT family, comprise 7 proteins (SIRT1–SIRT7), involved as the stress adaptors and the epigenetic enzymes occupied in the cellular events involving age-related disorder and heart disease. Along with sirtuins, SIRT1 is the greatest characterized protein for its defensive roles besides the vascular aging, inflammation, atherosclerotic, plaque development, and heart disease. [49]

Triggering Receptor Expressed on Myeloid Cells (TREML).

The TREMLs are the most significant effectors of the innate immune system, and the polymorphisms within genes encoding them may increase the risk of occurrence of various pathologies including cardiovascular disorders. The 2e investigation of the whole genomic appearance in the marginal blood cell model showed that the TREML4 was up-regulated in the early stage of the acute coronary disease, which may be indicated that the TREML4 may be used as the marker in early on stage of the ACS and check the improvement of the early myocardial ischemia. The TREML1 expression is up-regulated in the ischemic myocardium. The 2e activate form of TREML1 can detect in plasma of the patients with the acute myocardial infarction, thus the concentration of which is a self-governing predictor of the death. The TREML1 genetic and pharmacological inhibition dampens myocardial irritation and improves left ventricular utility and survival. [47, 48]

Growth-Differentiation Factor-15 (GDF-15)

The GDF-15 is associate with the transforming growth factor-β cytokine superfamily which is extensively expressed and might be induced in the response to tissue damage. Under the pathological circumstances, the GDF-15 can be formed by numerous hearts and non-cardiovascular cell types. [48]

The elevated circulating GDF-15 level is connected with the rising cardiometabolic risk factor in the individual exclusive

of the overt heart disease. The GDF-15 expression is considerably upregulated in heart disease, and the incidence of cardiovascular events is positively associated with the attention of the GDF-15, signifying its potential value and as the disease marker. [49]

Pregnancy-Associated Plasma Protein-A (PAPP-A).

The PAPP-A is an elevated molecular weight and the zinc-binding metalloproteinase, and some studies have been demonstrated that the PAPP-A plays a vital role in heart diseases. The PAPP-A are the responsive, precise, and the untimely biomarker for the ACS analysis. The Coronary PAPP-A levels were considered important among patients at the risk of heart diseases. In the early stage of the STEMI, the compassion of PAPP-A was superior to that of CK-MB and the troponin T. Even in the cTnI-negative patients among the acute coronary disorder, the important PAPPA has to be used as an autonomous predictor of the unfavorable outcome. [50, 51, 52]

CONCLUSION

The biomarkers are deliberately wide applications that are used for the identification of proteins, the product of cellular and biological processes, and the response of cells and tissues to therapeutic strategies. There are various biomarkers which can recommend further benefit as a surrogate marker which is used to forecast clinical result in the various cases. The first biomarkers used to analyze myocardial necrosis integrated serum glutamate oxaloacetate transferase, consequently CK, lactate dehydrogenase (LDH) isoforms. Cardiotoxicity can occur as acute or as a long-term side effect. With increasing, survival rates interest is also focused on avoiding the late-onset and chronically effects.

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