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A Comprehensive Review on Biomarker and Its Role in Diseases

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Biomarkers are essential to clinical practice. Understanding the organized definition, types, and roles of biomarkers in various clinical phases and diseases is crucial for understanding the significance of biomarkers in healthcare and medical research. This data highlights the significance of biomarkers in prognosis prediction, therapeutic decision guidance, and the advancement of personalized medicine, in addition to their role in illness diagnosis.

The division of biomarkers into molecular, cellular, and imaging types offers a thorough summary of the various modalities that are employed in biomarker research. In addition, the segmentation according to clinical phases, which differentiates between prognostic, therapeutic, and diagnostic biomarkers, deepens the conversation by emphasizing the diverse functions that biomarkers fulfill in patient treatment.

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In the diagnosis, prognosis and treatment of a wide range of diseases, biomarkers are a component of a relatively new and perfect clinical instrument. Using biomarkers to research different aspects of diseases, develop new drugs, and track possible therapeutic intervention results has many advantages. They contribute to drug development, personalized medicine, and therapeutic interventions. The aim is to develop biomarkers with higher sensitivity and specificity to enhance decision-making and simplify the drug development process, add depth to the discussion, emphasizing the varied roles of biomarkers in patient care.

Keywords: Drug development; biomarkers; pharmaceutical discovery; pathogenic processes.

1. INTRODUCTION

“In recent years, biomarkers have gained significance in pharmaceutical discovery by playing a crucial role in understanding a drug's mechanism of action, assessing early-stage signals of toxicity and efficacy, and identifying patients likely to respond to therapy. The evolving tools in various scientific fields are enhancing our ability to decipher complex processes, contributing to the growing application of personalized medicine” [1]. In clinical practice, biomarkers are used to customize medication and healthcare, as well as to evaluate the safety of drugs. These markers are created by the body in reaction to different diseases or by organs impacted by an illness, including tumors. They are essential in assessing the safety profile of pharmaceuticals and customising treatment plans [2,3]. When effectively targeted, biomarkers have the potential to greatly improve prognosis, treatment, and diagnosis. Finding the best biomarkers is essential to the development of personalized medicine, which will eventually result in better clinical outcomes.

1.1 Definition

"Biomarker" is a shortened version of "biological marker." In 2000, the National Institutes of Health Biomarkers Definitions Working Group provided a formal definition for it [4]. “According to the definition, biomarkers are signs of pathogenic processes, normal biological processes, or reactions to therapeutic interventions. These indicators are frequently assessed in order to offer insights into different facets of health, illness and medical interventions. Undoubtedly, a biomarker, also known as a biological marker, is defined by the Food and Drug Administration (FDA) as a quantitative indicator that may prove useful at any point during the course of the disease. Biomarkers have a number of uses, including as research and treatment development, diagnosis complications, prognosis determination, illness progression tracking, and treatment response assessment” [5].

2. TYPES OF BIOMARKERS

Based on their properties, biomarkers can be divided into three main categories:

Molecular biomarkers: Substances that are found in biological systems at the molecular level, such as proteins, metabolites, DNA, or RNA. Molecular biomarkers include things like gene expression levels, genetic mutations, and certain proteins.

Cellular biomarkers: These biomarkers can reveal alterations in cellular structure or function and are linked to certain cells or cell types. Examples include modifications to the shape of cells or the identification of particular cell surface markers.

Imaging biomarkers: These come from different imaging modalities as PET, CT, and MRI scans. Imaging biomarkers contribute in the diagnosis and disease monitoring process by providing visible information about the composition or function of tissues and organs [6].

Biomarkers can be divided into three categories based on the clinical stages at which they are used: therapeutic, prognostic, and diagnostic.

Diagnostic biomarkers: These help determine whether an illness or condition is present or not. Diagnostic biomarkers, such as cardiac troponin for the diagnosis of cardiac muscle injury [7], as a set of glycans for cancer biomarkers [8], catestatin for the psychological stress response linked to an increased mortality rate among heart patients, cystatin-C for glomerular filtration, and liver-type fatty acid-binding protein (L-FABP) as a diagnostic biomarker for estimating the severity of renal injury or oxidative stress, aid in the early detection of diseases and enable prompt intervention and treatment [9,10].

Prognostic biomarkers: These predict how a disease will probably progress or turn out. Prognostic biomarkers offer insights into the course of the disease, the chance of recurrence, and the overall prognosis. They help in customising therapy regimens according to the anticipated progression of the illness. Prognostic biomarkers include, for instance, blood pressure, cholesterol [11], and N-acetyl-beta-D-glucosaminidase for cardiovascular disorders, D-serine for anti-depressant response to ketamine, and osteocalcin for bone and skeletal metastases [6].

Therapeutic biomarkers: These help identify the best course of action or forecast how a patient will react to a particular medication. Personalised medicine relies heavily on therapeutic biomarkers to help identify patients who are most likely to benefit from a given treatment [6].

Proteins like exosomes and miRNAs: These molecules have the ability to function as therapeutic biomarkers, suggesting that they may be useful in targeted treatments.

Low-density lipoprotein modified with malondialdehyde: Shows promise as a therapeutic biomarker by being used to predict clinical outcomes in patients undergoing endovascular therapy for peripheral artery disease.

d-Serine: Its potential use in the treatment of mental illness has been highlighted by research into its efficacy as a therapeutic biomarker in individuals with depression and schizophrenia.

CA15-3: A serum tumour biomarker that emphasises its usage in cancer care and is employed in monitoring therapy for breast cancer treatment.

Glycosylated haemoglobin A1c, or HbA1c: utilised to track the effectiveness of anti-diabetic medication, highlighting its function as a therapeutic biomarker in the treatment of diabetes [6].

3. ROLE OF BIOMARKERS IN VARIOUS DISEASES

3.1 Cancer

Cancer is the leading cause of mortality globally. It is a complex hereditary illness that spreads to major organs in the body. In clinical practise, cancer biomarkers are crucial in improving our comprehension of the disease process and enabling the creation of more precise diagnostics as well as the mitigation of undesirable systemic effects [12]. Many cancers can be diagnosed with a variety of biomarkers, such as procalcitonin for medullary thyroid cancer, serum microRNA-21 for breast cancer diagnosis, α-chain of haptoglobin (Hp-α) for ovarian cancer, and KRAS mutations for pancreatic cancer prognosis [13,14,15,16].

Procalcitonin for medullary thyroid cancer: "Medullary thyroid cancer (MTC) originates from parafollicular C-cells and represents 2% of all thyroid malignancies and 0.4–1.4% of all thyroid nodules" [17]. "MTC is sporadic in 75–80% of cases or manifests as a hereditary tumor in the remaining 25%, in the context of multiple endocrine neoplasia 2 (MEN2) syndrome, due to a germline rearranged during Transfection mutation. MTC is treated with a total thyroidectomy and a central lymph node dissection. More extensive surgery is necessary if there is lateral lymph node compartment involvement" [18].

"Detectable but ≤10 ng/L Ct and undetectable ProCt values, indicate no structural disease. The most accurate cut-off of ProCt to distinguish between the presence or absence of a structural disease is>0.12 ng/mL, with the following sensitivity, specificity, positive predictive value, and negative predictive value (NPV): 100%, 83.61%, 74.4%, and 100.0%" [19].

3.2 Heart Failure

Heart failure (HF) is a complex clinical condition with a wide range of phenotypes that is caused by a variety of cardiac and extracardiac pathophysiological causes. Because clinical signs are not always specific and hence have limited diagnostic value, diagnosing heart failure (HF) can be challenging. Developing specific and quick diagnostics to quickly "rule out" heart failure in the emergency room could be important. In order to provide an integrated approach to clinical care of cardiovascular disease, biomarkers play a variety of roles, including diagnosis, therapeutic monitoring, prognostic assessment, and risk stratification. The readout of imaging biomarkers is not able to detect subclinical or early stages of heart failure, but it does offer valuable information into the anatomical and functional abnormalities of the

heart. The protein biomarkers that are now being utilised to predict the prognosis of heart failure are either released from other cells in response to HF or from the heart itself, indicating the heart's value as a tissue-specific damage marker. Apart from tissue specificity, the half-life of protein biomarkers is often the most significant factor influencing their potential use as biomarkers. The American Heart Association and the European Society of Cardiology have added natriuretic peptides (NP), such as brain-type natriuretic peptide (BNP) and N-terminal prohormone of BNP, and cardiac troponin readings in their guidelines for the diagnosis and management of heart failure. Research has looked into the predictive power of NT-proBNP and BNP biomarkers in various HF conditions, such as acute or chronic HF [6].

NT-proBNP and BNP biomarkers in various HF conditions: "BNP is one of several proteins that help regulate blood circulation throughout your body. Even though your heart makes this protein, providers sometimes call it "brain" natriuretic peptide because it was first discovered in brain tissue. or NT-proBNP test helps your provider diagnose heart failure and rule out other health conditions". [20]

"For NT-proBNP, normal levels are less than 125 pg/mL for people under 75 years old and less than 450 pg/mL for people over age 75. NT-proBNP levels over 900 pg/mL may be a sign of heart failure"[20].

3.3 Neurological Diseases

Biomarkers have a significant role in the diagnosis, prognosis, therapy, and prevention of neurological and neuropsychiatric illnesses, including epilepsy, Parkinson's disease, Alzheimer's disease, stroke, and Huntington's disease. Angiogenin, Cystatin-C, and 4-hydroxy-2,3-noenal are potential protein biomarkers for the detection or advancement of motor neuron disease. Several additional metabolites that have been utilised to diagnose neurological disorders include clusterin, soluble glycoprotein V, myoinositol, and N-acetyl aspartate [6].

Cystatin-C for the detection of motor neuron disease: Cystatin C is a candidate diagnostic biomarker for Amyotrophic Lateral Sclerosis (ALS), a fatal neurologic disease characterized by progressive motor neuron degeneration.

Studies have shown that cystatin C protein levels are reduced in the cerebrospinal fluid (CSF) of ALS patients and increased in the plasma of ALS patients [21].

3.4 Lung Diseases

Clinical issues affecting the lungs include lung cancer, TB, chronic obstructive pulmonary disease, asthma, pleural effusion, pneumonia, and many other lung disorders. Lipid peroxidation product malondialdehyde is a dependable, affordable, and easy-to-use biomarker for lung disease diagnosis. It has been demonstrated that YKL-40, a glycoprotein with a molecular weight of 40 kDa and three amino acids in its N-terminal—tyrosine (Y), lysine (K), and leucine (L)—is a biomarker for pleural effusion detection [22].

YKL-40 for pleural effusion detection: "Median pleural fluid YKL-40 levels are higher in exudates than in transudates. High pleural YKL-40 levels, with a cutoff value of >215 ng/mL, is used for diagnosing exudate. Pleural YKL-40/serum YKL-40 ratio >1.5 is an indicator for diagnosing TBPE" [23].

3.5 Kidney Diseases

Renal disease biomarkers such as cysteine-rich proteins, fatty acid-binding proteins, N-acetyl-β-glucosaminidase, and microalbumin have been effectively employed. Serum and urine specimens are employed as a novel kidney biomarker for significant adverse kidney outcomes following heart surgery. Hepcidin-25 is an iron-binding protein linked to acute kidney injury [24].

Hepcidin-25 in acute kidney injury: Hepcidin-25 is an antimicrobial peptide that sequesters iron intracellularly, and its elevation following human ischemia reperfusion injury may represent a renoprotective response to minimize renal injury.

Elevated urinary hepcidin-25 is inversely and independently associated with the development of AKI in adult cardiac surgery patients [25].

3.6 Liver Diseases

Numerous ailments can affect the liver, including cirrhosis, hemochromatosis, hepatitis, fatty liver disease, cancer, fascioliasis, Wilson's disease, chronic liver failure, and autoimmune disorders. Alanine aminotransferase is a blood-based

surrogate biomarker that is highly specific for liver disorders [26].

Alanine aminotransferase for liver disorders: Alanine transaminase (ALT), also known as alanine aminotransferase, is an enzyme that's mainly found in your liver, though it exists in other parts of your body.

"The normal range for alanine transaminase (ALT) varies from laboratory to laboratory. One common reference range for an ALT blood test is 7 to 56 U/L (units per liter). High levels of ALT in your blood can be due to damage or injury to the cells in your liver" [27].

3.7 Gastrointestinal Diseases

Utilising non-invasive techniques, intermediate products of metabolism serve as useful indicators for the diagnosis of gastrointestinal disorders. Biomarkers include volatile organic molecules like acetone, ammonia, ethanol, indole, carbon disulfide, 2,3-butanedione, and acetic acid. These low-molecular-weight substances are made in the digestive system, can travel through the bloodstream, enter the lungs, and manifest as breath. GC-MS analysis was used to determine their ultimate composition. The main clinical applications for calcprotectin as a noninvasive biomarker are in the treatment of active inflammatory bowel disease (IBD) and digestive disorders. One biomarker used in the laboratory to diagnose clostridium difficile infections is lactoferrin. Gastrointestinal disorders have been identified by the use of microRNAs, electronic nose techniques such surface acoustic wave, carbon black polymer composite, and metal oxide semiconductors [6].

Calprotectin in IBD and digestive disorders: Calprotectin is an antimicrobial protein mainly secreted by neutrophils. This protein competes with bacteria over zinc, thus kills the bacteria.

"Serum calprotectin levels are increased in patients with bacterial sepsis, so it can be considered as a reliable biomarker. Values up to 112 µg/g in people over 60 years old and up to 186 µg/g in children aged between 2 and 9 years old, are the reference ranges of fecal calprotectin in healthy individuals" [28].

3.8 Skeletal Muscle and Bone Diseases

GNE myopathy is an uncommon degenerative skeletal muscle condition that has been studied and evaluated using MRI and proton magnetic resonance spectroscopy. Additionally, MRI can be used to assess changes in the amount of fat and fibrous tissue in muscles as it is a developing diagnostic technique and biomarker. By measuring osteocalcin, deoxypyridinolines, and pyridinolines, future bone illnesses were predicted based on clinical results. Growth failure, joint contractures, and hip dysplasia can all be predicted over the long term using plasma interleukin-6 as a sign of inflammation [6].

Osteocalcin: A protein hormone called osteocalcin is created in the bones and aids in bone growth and repair. It is commonly recognised as a marker of bone osteoblastic activity and is generated by osteoblasts. Widespread bone loss can raise blood levels of osteocalcin, which is a marker of decreased bone density and fracture risk, particularly hip fractures [6].

4. CONCLUSION

In the diagnosis, prognosis, and treatment of a wide range of diseases, biomarkers are a component of a relatively new and perfect clinical instrument. Using biomarkers to research different aspects of diseases, develop new drugs, and track possible therapeutic intervention results has many advantages. Biomarkers should give tests with higher sensitivity and specificity than existing assessments, enhance the decision-making process, and make the creation of medicines easier.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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