World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

A Systematic review of Inflammatory biomarkers, Clinical significance, Detection, and their therapeutic agents

Varahalarao Vadlapudi * and Sandeep Kulkarni

Diabetomics Medical Private Limited, Muppireddypally Village, Medak - 502336, Telangana, India.

World Journal of Biology Pharmacy and Health Sciences, 2024, 17(03), 242–251

Publication history: Received on 09 February 2024; revised on 16 March 2024; accepted on 19 March 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.17.3.0137

Abstract

Biomarkers in inflammation are measurable and valuable biological indicators that can be used to assess the severity, presence, progression of inflammatory processes within the body. Inflammation is a complex physiological response that occurs in response to various stimuli, such as tissue damage, infections, and autoimmune reactions. There are several types of biomarkers Cytokines, Eicosanoids, Calprotectin, E-selectin, P-selectin, Fibrinogen, C-reactive protein (CRP), Exosomes, Myeloperoxidase (MPO), Chemokines , Neurofilament light chain (NfL), MMPs, 8-isoPGF2α, TIMPs, cell NO2-, adhesion molecules, PTX3, autoantibodies, complements, sRAGE, NT-proBNP, acute-phase and immunology-related proteins, thrombogenicity markers, ghrelin, leptin and adipokines, Presepsin, p75ECD, phosphorylated neurofilament heavy (pNfH), IDO1 and TARC, SCCA2, CTACK, EDN, MDC, LDH, and commonly used in the context of inflammation. We analysed the literature through online databases such as PubMed ScienceDirect and Google Scholar were used to search for journals and studies published. In this review, we discuss about different types of biomarkers involved in inflammation and their levels of elevation in various disease conditions. Quantified inflammatory biomarkers are effective clinical strategy for correct and reasonable drug treatment. There may have been advancements in the development of new treatments or therapies since my last update. Therapeutic agents like colchicine can modulate the immune response to reduce inflammation.

Keywords: Biomarkers; Inflammation; Exosomes; Cytokines; Interleukin

1. Introduction

Biomarkers are usually used in disease screening, diagnosis, and monitoring [1]. A biomarker used to detect or confirm presence of a disease or condition. Biomarkers provide valuable information to healthcare professionals for diagnosing and managing inflammatory conditions, monitoring treatment effectiveness, and predicting disease outcomes. Biomarkers in inflammation are measurable and valuable biological indicators that can be used to assess the severity, presence, progression of inflammatory processes within the body. In the recent years biomarkers in inflammation are gaining increasing interest given their clinical benefits [2].

Inflammation is a complex physiological response that occurs in response to various stimuli, such as tissue damage, infections, and autoimmune reactions. Inflammation can be created by infections by viral, bacterial, fungal, and protozoan pathogens[3] and causes including blood clot that induces an ischaemic stroke; a physical injury including trauma or a haemorrhagic stroke; an immune system disorder; dioxin, a cancer; Alzheimer's disease, a chemical exposure from polycyclic aromatic hydrocarbons, smoking, etc; or a neurological condition, and depression[4-6]. Inflammation is mainly divided into two types acute and chronic inflammation. The inflammatory response in the body's causes cellular changes and immune responses that result in repair of the damaged tissue and cellular proliferation (growth) at the site of the injured tissue. Inflammatory reactions involve a series of cellular and biochemical changes.

* Corresponding author: Varahalarao Vadlapudi

Inflammation can be visualized using imaging techniques like magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound. These techniques can reveal inflamed tissues and help monitor the response to treatment. Inflammatory biomarkers are used to monitor the progression of the many diseases like cardiovascular diseases, diabetes cancer, autoimmune diseases, arthritis, Alzheimer's disease, and pulmonary diseases [7]. Biomarkers like rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies are elevated levels in Specific Inflammatory Conditions like rheumatoid arthritis (RA). Elevated MPO levels can be found in conditions like rheumatoid arthritis, vasculitis, and lupus. Scientists reported that the combination of three or six pro-inflammatory biomarkers more accurately identified patients with bacterial infection than any one biomarker alone [8].

1.1. Types of biomarkers commonly used in the context of inflammation

Cytokines are signalling molecules that play a crucial role in immune responses and inflammation and they include interleukins (IL-1, IL-6, IL-10), tumor necrosis factor-alpha (TNF-α), and interferons. At present, there are very less or no specific markers available for identification of inflammation; but some broad- spectrum inflammatory biomarkers were routinely investigated in hospitals. IL-1α, IL-1β, IL-6, and TNF-α biomarkers are the major pro-inflammatory cytokines responsible for early responses. TNF-α, IL-1β and IL-6, are relatively upstream biomarkers of inflammation [9].

Interleukin 6 (IL-6) is a critical cytokine involved in the pathogenesis of several chronic inflammatory diseases. It is one of the hallmarks of cancer [10] IL-6 plays major immunomodulatory agent, playing active roles in activation of T helper cells, acute phase reactions, inhibition of T regulatory (Tregs) cells and differentiation of B cells by orchestrating innate and adaptive immune response IL-6 family of cytokines include IL-11, oncostatin M (OSM), ciliary inhibitory factor (CNTF), IL-31.IL-6, leukemia inhibitory factor (LIF), cardiotropin-1 (CT-1), IL-27, cardiotrophin-like related cytokine and stimulating neurotrophin-1/B-cell stimulating factor 3 (NNT-1), and neuropoietin (NPN) [11].Serum levels of IL-6 can be useful as diagnostic biomarker and this cytokine has also been implicated in the progression of this type of tumor [12]. Measuring IL-6 and IL-1β as upstream of inflammation compared to downstream of inflammation, such as C-reactive protein, an acute-phase protein produced in the liver under the influence of IL-6. IL-1β levels are a major inducer for the synthesis and expression of several secondary inflammatory biomarker IL-6 [13]. Inflammatory biomarkers will be elevated on different disease conditions like in immune system disorder TNF-α, IL-6, IL-8 and IL-12,[14] in bacterial infection IL-1β, TNF-α, IL-6 and IL-8, in colon cancer IL-1β, TNF-α, IL-6, IL-8 and interferon-α, IL-1β, TNF-α, IL-8 and interferon-γ,[15] by exposure to polycyclic aromatic hydrocarbons levels of IL-6, IL-8 ; [16] depress IL-12, but IL-1β, TNF-α, interferon-α and interferon-γ levels in trauma,[17] TNF-α and IL-6 in Alzheimer's disease, TNF-α and IL-6 levels in Depression [18]. Eicosanoids are lipid signalling molecules that include prostaglandins, leukotrienes, and thromboxanes involved in the regulation of inflammation and can serve as biomarkers. Calprotectin is a protein found in neutrophils and is released during inflammation. It is often measured in stool samples and is used as a biomarker for intestinal inflammation, such as in inflammatory bowel disease (IBD). E-selectin and P-selectin are adhesion molecules expressed on the surface of endothelial cells. They play a role in recruiting immune cells to sites of inflammation. Fibrinogen is a protein involved in blood clotting, but it also increases during acute-phase responses to inflammation. It is one of the key components of the blood clotting system, and it becomes directly involved in the inflammatory process through several mechanisms like blood clot formation, immune response, tissue repair and remodelling and modulation of inflammation.

2. Biomarkers involvement in inflammation of various diseases

CRP is a well-established acute-Phase biomarker of inflammation, and the levels will rise much more significantly during acute inflammation [19] and other one is serum amyloid A (SAA). Measurement of C-reactive protein (hs-CRP), serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule type 1 (sICAM-1) levels may provide in identifying persons at risk for cardiovascular events [20]. The association between inflammation and change in nature or expression level of some exosomal cargos is the fundamental step for identifying possible novel biomarkers of inflammatory-based diseases [21]. Myeloperoxidase (MPO) is an enzyme that is primarily found in neutrophil granulocytes, is involved in the process of inflammation [22-23]. MPO's main function is to generate hypochlorous acid (HOCl)[24] by catalyzing the reaction between hydrogen peroxide (H_2O_2) and chloride ions (Cl-) within neutrophils used to kill bacteria and fungi. MPO can generate reactive oxygen species (ROS) and other reactive intermediates that have the potential to cause oxidative stress and damage to nearby tissues and causes the inflammation. MPO is often considered a biomarker for inflammation and elevated levels indicate inflammatory response. Elevated MPO levels have been associated with increased risk of cardiovascular diseases, such as atherosclerosis, myocardial infarction (heart attack), and stroke and Crohn's disease and ulcerative colitis involve chronic inflammation of the gastrointestinal tract.[25] MPO levels can reflect the degree of inflammation in the airways. It is important to note that while MPO can serve as a valuable biomarker for inflammation, its measurement should be considered alongside other clinical and

diagnostic factors to obtain a comprehensive understanding of a patient's condition. Inflammation plays a significant role in respiratory diseases like asthma and chronic obstructive pulmonary disease (COPD).

A major reactive by-product of lipid peroxidation is malondialdehyde (MDA) [26- 28]. MDA is also produced in the process of prostaglandin synthesis [29]. MDA as a sensitive marker of inflammation in patients with rheumatoid arthritis [30]. Chemokines are a type of cytokine that specifically attract immune cells to sites of inflammation. They play a role in coordinating the immune response include CXCL8 [IL-8] and CCL2 [monocyte chemoattractant protein-1). Inflammatory responses play a pivotal role in COVID-19 pathogenesis of coronavirus disease 2019 (COVID-19) pandemic. tumor necrosis factor (TNF), CXC-chemokine ligand 10 (CXCL10), Interleukin 6 (IL-6), C-reactive protein (CRP), and CC-chemokine ligand 2 (CCL2), contributed to hyperinflammatory reactions to SARS-CoV-2, leading to a "cytokine storm" increases disease severity and death. [31- 33]. Multiple sclerosis (MS) is an autoimmune disorder. At present, there is a lack of effective treatment for the progressive form of MS, neurofilament light chain (NfL) found to be a potential new biomarker in predicting disease activity and progression of MS [34]. Cardiovascular disease (CVD) or heart diseases affects the total cardiovascular system, the heart or blood vessels (like arteries, capillaries, and veins), vascular system of the brain and kidney, and peripheral arterial disease. Heart Failure (HF) remains a major health problem, with both increasing incidence and prevalence over the past decades. Seven groups of biomarkers associated to HF are neurohumoral activation [adrenomedullin, MR-proADM; copeptin), myocyte injury [high-sensitive troponins, hs-cTn; heart-type fatty acid-binding protein, H-FABP; myocardial stretch [mid-regional proatrial natriuretic peptide, MR-proANP), glutathione transferase P1, GSTP1), matrix remodeling (galectin-3; soluble isoform of suppression of tumorigenicity 2, sST2), inflammation (growth differentiation factor-15, GDF-15), renal dysfunction [neutrophil gelatinase-associated lipocalin, NGAL; kidney injury molecule-1, KIM-1), and oxidative stress (ceruloplasmin; myeloperoxidase, MPO; 8-hydroxy-2'-deoxyguanosine, 8-OHdG; thioredoxin 1, Trx1) [35].

Congestion is the main driver behind symptoms of heart failure (HF), and associated with inflammatory biomarkers FGF-21, FGF-23, soluble ST2, CA-125, IL-6, FABP4, GDF-15, and BNP were the strongest up-regulated and KITLG, EGF, and PON3 were the strongest down-regulated in the study [36]. CD163 130-kDa membrane protein is a potential inflammation biomarker. Now evidenced that the level of soluble CD163 increases in several acute and chronic inflammatory disorders [37]. One of the leading causes of death worldwide is coronary heart disease (CHD) and it is characterized by formation of arterial plaques which are mainly comprised inflammatory cells, lipids and calcium. CHD is assessed by the levels of inflammatory biomarkers, CD40, C-reactive protein (CRP) and interleukin-6), complement, and myeloperoxidase (MPO). CRP levels being a more reliable biomarker of cardiovascular disease than LDL cholesterol [38]. Oxidative stress is considered as a key factor involved in the pathology of ophthalmic complication and inflammatory process and whereas Oxidative stress and inflammation are closely related pathophysiological process [39]. Inflammatory changes include activation of microglia and astrocytes, with increased levels of proinflammatory cytokines [40]. Increasing evidence has highlighted the roles of oxidative stress and inflammation in the promotion of atherosclerotic cardiovascular disease [41].

Chronic neurodegenerative disease Alzheimer's disease (AD) is a characterized by the accumulation of neurofibrillary tangles and amyloid plaques in the brain [42]. Oxidative damage and inflammation are important features of the brain pathology of AD. AD pathogenesis is associated neuroinflammation [43] and abnormal levels in different brain regions. Neuroinflammation may be an early event and plays a critical role in tau pathology, characterized by microglial activation preceding tau tangle formation [44].

Systemic chronic inflammation (SCI) is low-grade inflammation that plays a major role in immune senescence and in development and progression of many diseases [45].

Chronic inflammation arising in a diverse range of non-cancerous and cancerous diseases and related immunosuppression, directly support tumor growth. Monitoring such biomarkers is expected to have a major clinical impact. Newly discovered biomarkers and those are projected to open a new era towards combating the silent damage induced by chronic inflammation.[46]

Takayasu arteritis (TA) is a rare large vasculitis with unknown etiology, which affects the aorta and its primary branches, as well as the pulmonary and coronary arteries. Chronic inflammation involved into TA pathogenesis. Biomarkers, such as, have revealed great values in early diagnosis, evaluating disease activity.[47] MMPs, 8-isoPGF2α, TIMPs, cytokines, cell NO2-, adhesion molecules, PTX3, autoantibodies, complements, sRAGE, NT-proBNP, acute-phase and immunology-related proteins, thrombogenicity markers, ghrelin, leptin and adipokines.

Inflammation is the key driver of liver fibrosis progression in non-alcoholic fatty liver disease (NAFLD). There are challenges to assess the inflammation in NAFLD due to its dynamic nature and poor correlation with liver biochemical

markers. Cytokeratin-18, are well-studied in NAFLD [48].Study of Systemic immune-inflammation biomarkers in psoriasis patients under interleukin 17A-inhibitor treatment [49].

Sepsis is caused by a dysregulated host response to infection. The role and the discriminating potency of host-derived inflammatory biomarkers are the main etiological types of sepsis [50]. In the early sepsis macrophages produce tumor necrosis factor (TNF), interleukin-1β (IL-1β) and IL-6 in response to bacterial ligands. Out of three major pro-inflammatory cytokines, IL-6 has received the most attention in sepsis Chemokines is another group of pro-inflammatory biomarkers which have been investigated in sepsis [51]. Numerous studies shown mortality increases with elevated levels of IL-6 in septic patients [52-53]. Inflammatory biomarkers may have prognostic value for predicting cardiovascular risk in high-risk patients. A combination of biomarkers is utilized in clinical diagnosis. Microarray and immunohistochemistry analysis of IL-6 in human cervical cancer tissues suggest its usefulness as prognostic biomarker [54].

Atherosclerosis is a systemic inflammatory disease leading to lipid-laden inflammatory lesions in the arterial walls that may destabilize and rupture. hsCRP, fibrinogen and IL-6 are novel biomarkers to be used in high throughput assays are necessary for diagnosis [55]. MPO and its oxidative products react with various lipids, proteins, and nucleic acids causing atherosclerosis [56]. Biomarkers can be defined as characteristics which are measured and evaluated as indicators of a normal biologic, or pathologic process, or pharmacologic responses towards a therapeutic intervention [57]. Plasma levels of several inflammatory biomarkers are elevated in patients with Atrial Fibrillation. Inflammation is a key component of the pathophysiological processes that lead to the development of AF [58]. Novel inflammatory biomarkers are also used to better rest ratify patients in risk groups but their potential to guide treatment decisions and management of patients [59]. Presepsin is a 13 kDa fragment derived from plasmatic cleavage of CD14, a toll-like receptor family molecule, stimulates the inflammatory response. This molecule has recently been used in diagnostic biomarker or prognostic biomarker for bacterial infection in cirrhosis [60- 64].

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease in which many processes are detected including neuroinflammation. Biomarker research in ALS has led to the identification of p75ECD from urine,[65] phosphorylated neurofilament heavy (pNfH) in cerebrospinal fluid (CSF),[66] and neurofilament light (NfL) in serum [67] as diagnostic, prognostic, and pharmacodynamic biomarkers. In the CNS Inflammation occurs during ALS, and is also detected released factors [68- 69].

The detection of peripheral inflammation in blood samples of ALS patients led to the assessment of these blood-based markers [70]. Urinary neurotrophin receptor extracellular domain p75NTRECD increases over time as disease progresses.[71] The translocator protein (TSPO), is highly expressed in activated astrocytes and microglia and it serves as marker of neuroinflammation [72- 73]. Sarcoidosis is a systemic inflammatory disorder which affects the lungs and intrathoracic lymph nodes. Diagnostic of sarcoidosis is long and complicated. The discovery of a specific biomarker for this disease would help. At present biomarkers like Serum angiotensin-converting enzyme (sACE), Neopterin,[74] YKL-40, CD163, C-C motive chemokine ligand 18 (CCL18), Serum amyloid A (SAA), Serum soluble interleukin 2 receptor 9sIL-2R), B-cell activating factor (BAFF), IL-10,[75] IFN-γ, IL-12, CXCL9, CXCL10, CXCL11 [76, 77,78, 79] and IL-18 are important biomarkers for finding Sarcoidosis [80, 81] in molecular diagnosis.

Colorectal cancer (CRC) is the leading cause of cancer deaths around the world. Here inflammation-related prognostic biomarkers have been reported [82].

Several studies published on Low back pain (LBP) [83], and looked at the relationship between inflammatory biomarkers and symptoms, clinical presentation, and outcomes in patients with NSLBP [84, 85]. Three studies compared CRP levels in acute (1 study in 2 publications) and chronic NSLBP patients with healthy controls [86] and found a significant difference in CRP levels in the acute NSLBP group compared to healthy controls at baseline. One previous systematic review has been published examining the relationship between inflammatory biomarkers and NSLBP which found moderate evidence for the relationship between CPR and IL-6 and the NSLBP pain levels, as well as the presence of TNF-α and NSLB [87]. Atopic dermatitis (Ads) is a complex, chronic, with a highly heterogeneous inflammatory skin disease [88].The intense itching, accompanied by psychological pressure greatly affects people's quality of life [89]. In recent decades, several candidate biomarkers related to ADs have been proposed [90]. Expression levels of both serum IL-36γ and skin IL-36γ increased in Ads [91]. To date, there are no data demonstrating that endotypes respond differently to different therapies, compared with patients in the other 2 clusters, patients stratified into the "TH2 cell/TH22 cell/PARC–dominant" and "TH1 cell/TH2 cell/TH17 cell–dominant" clusters in representing about 40% of the included patients, showed particularly high levels of type 2 cytokines (including IL-4, IL-5, and IL-13) [92-93]. Chemokines CXCL10 and CCL17 express high levels in the epidermis of allergic contact dermatitis (ACD). Serum TARC/CCL17, an important chemoattractant of T cells, is considered a biomarker for monitoring the severity of AD in

adults in daily practice,[94] Predictive biomarkers like IL-17, IL23, IL-33, and IDO1 and TARC, SCCA2, CTACK, EDN, MDC, LDH, and IL-18 are used for monitoring the severity of for Ads [95]. In Dandruff/seborrhoeic dermatitis (D/SD) cathepsin S could be used as a biomarker to objectify itching sensations [96]. Biomarkers IL-1β, IL-6, IL-12, and IL-18 with IFN-γ and TNF-α are found during Depression [97].

3. Detection of Inflammatory biomarkers

Inflammatory biomarkers are measurable indicators in the body that can signal the presence and severity of inflammation.

Novel method triple lateral flow immunoassay (triple LFIA) had firstly been developed for specific and simultaneous detection of three inflammatory biomarkers like procalcitonin (PCT), C-reactive protein (CRP), and serum amyloid A (SAA) via biotin-streptavidin-phycoerythrin signal amplification system in one strip [98].

Another method called aptamer-based graphene affinity nanobiosensor is used to detect and measure the biomarkers in undiluted physiological fluids [99]. Recent years have shown that the diagnosis and monitoring of biomarkers involved in inflammatory-associated medical conditions such as cancer, neurological disorders, viral infections, The development of low-cost, miniaturized, and portable, user-friendly devices that provide an answer in a timely manner, such as electrochemical sensors, is relevant for the elaboration of point-of-care testing devices [100]. Quantified inflammatory biomarkers are effective clinical strategy for correct and reasonable drug treatment. Detection inflammatory biomarkers can also be done by using novel methods like proteomic profiling [101] and analysis [102] Commercial tapes (Sebutapes) coated for measuring IL-1α, IL-6, IL-8, INF-γ, TNF-α, and IL-1 [103], CRP was detected by using a Novel Nanoplasmonic Immunoturbidimetry Assay (NanoPITA)[104] and other methods Multiplexing Biosensor[105], Multiplexed protein analysis[106], Multiomics Analysis[107], In- Silico Analysis [108].

4. Common Drugs Used to Target Inflammation

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): NSAIDs like ibuprofen and naproxen are commonly used to relieve pain and reduce inflammation. They work by inhibiting enzymes called cyclooxygenases (COX), which are involved in the production of inflammatory prostaglandins. Drugs used against cyclooxygenases (COX) inflammation are typically nonsteroidal anti-inflammatory drugs (NSAIDs). These medications work by inhibiting the activity of cyclooxygenase enzymes, specifically COX-1 and COX-2. These enzymes are involved in the production of prostaglandins, which play a key role in the inflammatory response and pain sensation. By blocking COX enzymes, NSAIDs can reduce inflammation and alleviate pain. Aspirin is an NSAID that inhibits both COX-1 and COX-2. It is used for pain relief, reducing fever, and preventing blood clots. Celecoxib is a prescription NSAID that specifically targets COX-2, which can reduce the risk of gastrointestinal side effects compared to non-selective NSAIDs. It is used for conditions such as osteoarthritis, rheumatoid arthritis, and acute pain. Interleukin inhibitors are a class of drugs used to treat inflammatory conditions by targeting specific cytokines called interleukins. Interleukin inhibitors work by blocking the action of specific interleukins, thus modulating the immune response and reducing inflammation.

5. Conclusion

Biomarkers are of crucial importance in modern medicine for early diagnosis, risk-assessment, drug target identification, disease prevention, drug response and monitoring of disease activity. It is important to note that while biomarkers are valuable tools, they are often used in conjunction with other clinical assessments to make accurate diagnoses and treatment decisions. Additionally, biomarker levels can vary based on individual differences, the stage of inflammation, and other factors, so their interpretation should be done by healthcare professionals familiar with the specific context. Inflammation has the physiological purpose of restoring tissue homeostasis. Systemic inflammation has been recognized as essential components in the pathogenesis of several diseases such as rheumatoid arthritis, cancer, type 2 diabetes, inflammatory bowel diseases, obesity, and neurodegenerative diseases. Inflammatory biomarkers are measurable indicators in the body that can signal the presence and severity of inflammation. Therefore, their use is closely monitored by health care providers, and patients receiving these treatments often require regular check-ups and laboratory tests to assess their safety and effectiveness. Always consult with a healthcare professional for proper diagnosis and guidance on the most appropriate treatment for a specific inflammatory condition.

Compliance with ethical standards

Acknowledgments

We would like to thank and acknowledge, team members of our organization.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Ansar W, Ghosh S. Inflammation and inflammatory diseases, markers, and mediators: role of CRP in some inflammatory diseases. Biology of C Reactive Protein in Health and Disease. 2016; 4:67-107.

[2] Aronson JK, Ferner RE. Biomarkers-A general review. Curr Protoc Pharmacol. 2017; 76:9.23.1-9.23.17.

[3] Prasad S, Tyagi AK, Aggarwal BB. Detection of inflammatory biomarkers in saliva and urine: potential in diagnosis, prevention, and treatment for chronic diseases. Exp Biol Med (Maywood). 2016;241(8):783-99

[4] Doll DN, Barr TL, Simpkins JW. Cytokines: their role in stroke and potential use as biomarkers and therapeutic targets. Aging Dis. 2014;5(5):294-306.

[5] Humphreys J, Valdés Hernández MDC. Impact of polycyclic aromatic hydrocarbon exposure on cognitive function and neurodegeneration in humans: A systematic review and meta-analysis. Front Neurol. 2023; 13:1052333.

[6] Reikeras O, Borgen P, Reseland JE, Lyngstadaas SP. Changes in serum cytokines in response to musculoskeletal surgical trauma. BMC Res Notes. 2014; 7:128.

[7] Aggarwal BB. Nuclear factor-kappaB: the enemy within. Cancer Cell. 2004;6(3):203-8.

[8] Shapiro NI, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM, et al. A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. Crit Care Med. 2009;37(1):96-104.

[9] Roe K. An inflammation classification system using cytokine parameters. Scand J Immunol. 2021;93(2):e12970.

[10] Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30(7):1073-81.

[11] Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta. 2011;1813(5):878-88..

[12] Kim HW, Lee JC, Paik KH, Kang J, Kim J, Hwang JH. Serum interleukin-6 is associated with pancreatic ductal adenocarcinoma progression pattern. Medicine (Baltimore). 2017;96(5): e5926.

[13] Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res. 2016;118(1):145-56.

[14] Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. Int J Mol Sci. 2019;20(23): 6008..

[15] Francescone R, Hou V, Grivennikov SI. Cytokines, IBD, and colitis-associated cancer. Inflam Bowel Dis. 2015;21(2):409-18.

[16] Lecureur V, Ferrec EL, N'diaye M, Vee ML, Gardyn C, Gilot D, et al. ERK-dependent induction of TNFalpha expression by the environmental contaminant benzo(a)pyrene in primary human macrophages. FEBS Lett. 2005;579(9):1904-10.

[17] Sercombe R, Dinh YR, Gomis P. Cerebrovascular inflammation following subarachnoid hemorrhage. Jpn J Pharmacol. 2002;88(3):227-49.

[18] Banerjee A, Khemka VK, Roy D, Dhar A, Sinha Roy TK, Biswas A, et al. Role of pro-inflammatory cytokines and vitamin D in probable Alzheimer's disease with depression. Aging Dis. 2017;8(3):267-76.

[19] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999 Feb 11;340(6):448-54.

[20] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342(12):836-43.

[21] Console L, Scalise M, Indiveri C. Exosomes in inflammation and role as biomarkers. Clin Chim Acta. 2019; 488:165-171.

[22] Zamocky M, Jakopitsch C, Furtmüller PG, Dunand C, Obinger C. The peroxidase-cyclooxygenase superfamily: reconstructed evolution of critical enzymes of the innate immune system. Proteins. 2008;72(2):589-605.

[23] Arnhold J. The dual role of myeloperoxidase in immune response. Int J Mol Sci. 2020;21(21):8057.

[24] 24. Aratani Y. Myeloperoxidase: its role for host defense, inflammation, and neutrophil function. Arch Biochem Biophys. 2018; 640:47-52.

[25] Vanhamme L, Zouaoui Boudjeltia K, Van Antwerpen P, Delporte C. The other myeloperoxidase: emerging functions. Arch Biochem Biophys. 2018; 649:1-14.

[26] 26. Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid. Med. Cell Longev. 2014; 2014:360438.

[27] Esterbauer H, Schaur RJ, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free Radic. Biol. Med. 1991;11(1):81-128.

[28] Gaschler MM, Stockwell BR. Lipid peroxidation in cell death. Biochem Biophy. Re. Commun. 2017;482(3):419-25.

[29] Raghavan S, Subramaniyam G, Shanmugam N. Proinflammatory effects of malondialdehyde in lymphocytes. J Leukoc Biol. 2012;92(5):1055-67.

[30] Kalavacherla US, Ishaq M, Rao UR, Sachindranath A, Hepsiba T. Malondialdehyde as a sensitive marker of inflammation in patients with rheumatoid arthritis. J Assoc Physicians India. 1994;42(10):775-6.

[31] Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J Med Virol. 2020;92(11):2409-11.

[32] Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26(10):1636-43.

[33] Zhao J, Schank M, Wang L, Dang X, Cao D, Khanal S, et al. Plasma biomarkers for systemic inflammation in COVID-19 survivors. Proteomics Clin Appl. 2022;16(5):e2200031.

[34] Yang J, Hamade M, Wu Q, Wang Q, Axtell R, Giri S, et al. Current and future biomarkers in multiple sclerosis. Int J Mol Sci. 2022;23(11):5877.

[35] Savic-Radojevic A, Pljesa-Ercegovac M, Matic M, Simic D, Radovanovic S, Simic T. Novel biomarkers of heart failure. Adv Clin Chem. 2017; 79:93-152

[36] Pandhi P, Ter Maaten JM, Anker SD, Ng LL, Metra M, Samani NJ, et al. Pathophysiologic processes and novel biomarkers associated with congestion in heart failure. JACC Heart Fail. 2022;10(9):623-32.

[37] Etzerodt A, Moestrup SK. CD163 and inflammation: biological, diagnostic, and therapeutic aspects. Antioxid Redox Signal. 2013;18(17):2352-63.

[38] Ridker PM, Koenig W, Fuster V. C-reactive protein and coronary heart disease. N Engl J Med. 2004;351(3):295-8; author reply 295.

[39] Ahmad A, Ahsan H. Biomarkers of inflammation and oxidative stress in ophthalmic disorders. J Immunoassay Immunochem 2020;41(3):257-71.

[40] Galasko D, Montine TJ. Biomarkers of oxidative damage and inflammation in Alzheimer's disease. Biomark Med. 2010;4(1):27-36.

[41] Uno K, Nicholls SJ. Biomarkers of inflammation and oxidative stress in atherosclerosis. Biomark Med. 2010;4(3):361-73.

[42] Park JC, Han SH, Mook-Jung I. Peripheral inflammatory biomarkers in Alzheimer's disease: a brief review. BMB Rep. 2020;53(1):10-9.

[43] Heneka MT, Carson MJ, El Khoury JE, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14(4):388-405.

[44] Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. Neurobiol Aging. 2000;21(3):383-421.

[45] Rasmussen LJH, Petersen JEV, Eugen-Olsen J. Soluble urokinase plasminogen activator receptor (suPAR) as a biomarker of systemic chronic inflammation. Front Immunol. 2021; 12:780641.

[46] Meirow Y, Baniyash M. Immune biomarkers for chronic inflammation related complications in non-cancerous and cancerous diseases. Cancer Immunol Immunother. 2017;66(8):1089-101.

[47] Wen D, Feng L, Du X, Dong JZ, Ma CS. Biomarkers in Takayasu arteritis. Int J Cardiol. 2023; 371:413-17.

[48] Yip TC, Lyu F, Lin H, Li G, Yuen PC, Wong VW, et al. Non-invasive biomarkers for liver inflammation in non-alcoholic fatty liver disease: present and future. Clin Mol Hepatol. 2023; 29;Suppl:S171-83.

[49] Gambichler T, Würfel L, Abu Rached N, Mansour R, Bechara FG, Scheel CH. Systemic immune-inflammation biomarkers in psoriasis patients under interleukin 17A-inhibitor treatment. J Eur Acad Dermatol Venereol. 2023;37(7):e837-9.

[50] Grondman I, Pirvu A, Riza A, Ioana M, Netea MG. Biomarkers of inflammation and the etiology of sepsis. Biochem Soc Trans. 2020;48(1):1-14.

[51] Faix JD. Biomarkers of sepsis. Crit Rev Clin Lab Sci. 2013 ;50(1):23-36.

[52] Patel RT, Deen KI, Youngs D, Warwick J, Keighley MR. Interleukin 6 is a prognostic indicator of outcome in severe intra-abdominal sepsis. Br J Surg. 1994;81(9):1306-8.

[53] Pettilä V, Hynninen M, Takkunen O, Kuusela P, Valtonen M. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive Care Med. 2002;28(9):1220-5.

[54] Song Z, Lin Y, Ye X, Feng C, Lu Y, Yang G, Dong C, et al. Expression of IL-1α and IL-6 is Aassociated with Pprogression and Pprognosis of Hhuman cervical cancer. Med Sci Monit. 2016; 22:4475-4481.

[55] Kozarov E, Huber K, Wojta J. Infection-associated biomarkers of inflammation in atherosclerosis. Curr Pharm Des.2015;21(13):1776-82.

[56] Frangie C, Daher J. Role of myeloperoxidase in inflammation and atherosclerosis (Review) Biomed Rep. 2022;16(6):53.

[57] Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89-95.

[58] Zacharia E, Papageorgiou N, Ioannou A, Siasos G, Papaioannou S, Vavuranakis M, Latsios G, et al. Inflammatory Bbiomarkers in Aatrial Ffibrillation. Curr Med Chem. 2019;26(5):837-854.

[59] Tsigkou V, Siasos G, Oikonomou E, Zaromitidou M, Latsios G, Vavuranakis M, Deftereos S, Cleman MW, Kokkou E, Limberi M, Dimitropoulos S, Zografos T, Marinaki S, Stefanadis C, Tousoulis D, et al. Novel Iinflammatory Bbiomarkers in Ccardiovascular Ttherapeutics. Curr Med Chem. 2015;22(23):2773-85.

[60] Ferrarese A, Frigo AC, Mion MM, Plebani M, Russo FP, Germani G, Gambato M, Cillo U, Cattelan A, Burra P, Senzolo M, et al. Diagnostic and prognostic role of presepsin in patients with cirrhosis and bacterial infection. Clin Chem Lab Med. 20202021;59(4):775-782.

[61] Ferrarese A, Plebani M, Frigo AC, Burra P, Senzolo M. Presepsin as a biomarker of inflammation and prognosis in decompensated liver disease. J Hepatol. 2021;75(1):232-234.

[62] Papp M, Tornai T, Vitalis Z, Tornai I, Tornai D, Dinya T, Sumegi A, Antal-Szalmas P, et al. Presepsin teardown - pitfalls of biomarkers in the diagnosis and prognosis of bacterial infection in cirrhosis. World J Gastroenterol. 2016;22(41):9172-9185.

[63] Elefsiniotis I, Tsakiris SA, Barla G, Tasovasili A, Vrachatis D, Mavrogiannis C. Presepsin levels in cirrhotic patients with bacterial infections and/or portal hypertension-related bleeding, presenting with or without acute kidney injury. Ann Gastroenterol. 2018;31(5):604-612.

[64] Fischer P, Grigoras C, Bugariu A, Nicoara-Farcau O, Stefanescu H, Benea A, Hadade A, Margarit S, Sparchez Z, Tantau M, Ionescu D, Procopet B et al. Are presepsin and resistin better markers for bacterial infection in patients with decompensated liver cirrhosis? Dig Liver Dis. 2019;51(12):1685-1691.

[65] Shepheard SR, Wuu J, Cardoso M, Wiklendt L, Dinning PG, Chataway T, et al. Urinary p75ECD: a prognostic, disease progression, and pharmacodynamic biomarker in ALS. Neurology. 2017;88(12):1137-43.

[66] Rossi D, Volanti P, Brambilla L, Colletti T, Spataro R, La Bella V. CSF neurofilament proteins as diagnostic and prognostic biomarkers for amyotrophic lateral sclerosis. J Neurol. 2018;265(3):510-21.

[67] Verde F, Steinacker P, Weishaupt JH, Kassubek J, Oeckl P, Halbgebauer S, et al. Neurofilament light chain in serum for the diagnosis of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2019;90(2):157-64.

[68] McCombe PA, Lee JD, Woodruff TM, Henderson RD. The peripheral immune system and amyotrophic lateral sclerosis. Front Neurol. 2020; 11:279.

[69] Philips T, Robberecht W. Neuroinflammation in amyotrophic lateral sclerosis: role of glial activation in motor neuron disease. Lancet Neurol. 2011;10(3):253-63.

[70] Beers DR, Appel SH. Immune dysregulation in amyotrophic lateral sclerosis: mechanisms and emerging therapies. Lancet Neurol. 2019;18(2):211-20.

[71] Benatar M, Boylan K, Jeromin A, Rutkove SB, Berry J, Atassi N, Bruijn L, et al. ALS biomarkers for therapy development: Sstate of the field and future directions. Muscle Nerve. 2016;53(2):169-82. doi: 10.1002/mus.24979, PMID 26574709.

[72] Brown AK, Fujita M, Fujimura Y, Liow JS, Stabin M, Ryu YH, et al. Radiation dosimetry and biodistribution in monkey and man of 11C-PBR28: a PET radioligand to image inflammation. J Nucl Med. 200748. 2007;(12)12(12):2072-9.

[73] Lavisse S, Guillermier M, Hérard AS, Petit F, Delahaye M, Van Camp N, Ben Haim L, et al. Reactive astrocytes overexpress TSPO and are detected by TSPO positron emission tomography imaging. J Neurosci. 2012;32(32):10809-18.

[74] Hoffmann G, Wirleitner B, Fuchs D. Potential role of immune system activation-associated production of neopterin derivatives in humans. Inflamm Res. 2003; 52(8):313 -21.

[75] Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat Immunol. 2002;3(10):944-50.

[76] Arger NK, Ho ME, Allen IE, Benn BS, Woodruff PG, Koth LL. CXCL9 and CXCL10 are differentially associated with systemic organ involvement and pulmonary disease severity in sarcoidosis. Respir Med. 2020; 161:105822

[77] Arger NK, Ho M, Woodruff PG, Koth LL. Serum CXCL11 correlates with pulmonary outcomes and disease burden in sarcoidosis. Respir Med. 2019; 152:89-96.

[78] Lee K, Chung W, Jung Y, Kim Y, Park J, Sheen S, et al. CXCR3 ligands as clinical markers for pulmonary tuberculosis. Int J Tuberc Lung Dis. 2015;19(2):191––9.

[79] Chung W, Lee K, Jung Y, Kim Y, Park J, Sheen S, et al. Serum CXCR3 ligands as biomarkers for the diagnosis and treatment monitoring of tuberculosis. Int J Tuberc Lung Dis. 2015; 19(12):1476––84.

[80] Kraaijvanger R, Janssen Bonás M, Vorselaars ADM, Veltkamp M. Biomarkers in the Ddiagnosis and Pprognosis of Ssarcoidosis: Ccurrent Uuse and Ffuture Pprospects. Front Immunol. 2020; 11:1443.

[81] Majcherczyk PA, Langen H, Heumann D, Fountoulakis M, Glauser MP, Moreillon P. Digestion of Streptococcus pneumoniae cell walls with its major peptidoglycan hydrolase releases branched stem peptides carrying proinflammatory activity. J Biol Chem. 1999; 274(18):12537-43.

[82] Yamamoto T, Kawada K, Obama K. Inflammation-Rrelated Bbiomarkers for the Pprediction of Pprognosis in Ccolorectal Ccancer Ppatients. Int J Mol Sci. 2021 ;22(15):8002.

[83] Morris P, Ali K, Merritt M, Pelletier J, Macedo LG. A systematic review of the role of inflammatory biomarkers in acute, subacute and chronic non-specific low back pain. BMC Musculoskelet Disord. 2020;21(1):142.

[84] Heffner KL, France CR, Trost Z, Ng HM, Pigeon WR. Chronic low back pain, sleep disturbance, and interleukin-6. Clin J Pain. 2011;27(1):35-41.

[85] Klyne DM, Barbe MF, Hodges PW. Systemic inflammatory profiles and their relationships with demographic, behavioural and clinical features in acute low back pain. Brain Behav Immun. 2017; 60:84-92.

[86] Stürmer T, Raum E, Buchner M, Gebhardt K, Schiltenwolf M, Richter W, Brenner H, et al. Pain and high sensitivity C reactive protein in patients with chronic low back pain and acute sciatic pain. Ann Rheum Dis. 2005;64(6):921-5.

[87] van den Berg R, Jongbloed EM, de Schepper EIT, Bierma-Zeinstra SMA, Koes BW, Luijsterburg PAJvan den Berg R, et al. The association between pro-inflammatory biomarkers and nonspecific low back pain: a systematic review. Spine J. 2018;18(11):2140-2151.

[88] Glickman JW, Han J, Garcet S, Krueger JG, Pavel AB, Guttman-Yassky E. Improving evaluation of drugs in atopic dermatitis by combining clinical and molecular measures. J Allergy Clin Immunol Pract. 2020; N;8(10):3622-3625.e19.

[89] Filanovsky MG, Pootongkam S, Tamburro JE, Smith MC, Ganocy SJ, Nedorost ST. The financial and emotional impact of atopic dermatitis on children and their families. J Pediatr. 2016; 169:284-90.e5–90.e5.

[90] Broderick C, Ziehfreund S, van Bart K, Arents B, Eyerich K, Weidinger S, Rastrick J, Zink A, Flohr C, et al. BIOMAP Consortium Biomarkers associated with the development of comorbidities in patients with atopic dermatitis: A systematic review. Allergy. 2023 ;78(1):84-120.

[91] Otobe S, Sugaya M, Nakajima R, Oka T, Takahashi N, Kabasawa M, et al. Increased interleukin-36γ expression in skin and sera of patients with atopic dermatitis and mycosis fungoides/Sézary syndrome. J Dermatol. 2018; 45(4):468–-71.

[92] Bakker D, de Bruin-Weller M, Drylewicz J, van Wijk F, Thijs J. Biomarkers in atopic dermatitis. J Allergy Clin Immunol. 2023;151(5):1163-1168.

[93] Thijs JL, Strickland I, Bruijnzeel-Koomen CAFM, Nierkens S, Giovannone B, Csomor E, Sellman BR, Mustelin T, Sleeman MA, de Bruin-Weller MS, Herath A, Drylewicz J, May RD, Hijnen D, et al. Moving toward endotypes in atopic dermatitis: Iidentification of patient clusters based on serum biomarker analysis. J Allergy Clin Immunol. 2017;140(3):730-737. Epub 2017 Apr 13. Erratum in: J Allergy Clin Immunol. 2018 ;142(2):714

[94] Landheer J, de Bruin-Weller M, Boonacker C, Hijnen D, Bruijnzeel-Koomen C, Röckmann H. Utility of serum thymus and activation-regulated chemokine as a biomarker for monitoring of atopic dermatitis severity. J Am Acad Dermatol. 2014;71(6):1160-6.

[95] Yu L, Li L. Potential biomarkers of atopic dermatitis. Front Med (Lausanne). 2022; 9:1028694.

[96] Viodé C, Lejeune O, Turlier V, Rouquier A, Casas C, Mengeaud V, Redoulès D, et al, Schmitt AM. Cathepsin S, a new pruritus biomarker in clinical dandruff/seborrhoeic dermatitis evaluation. Exp Dermatol. 2014;23(4):274-5.

[97] Harsanyi S, Kupcova I, Danisovic L, Klein M. Selected Bbiomarkers of depression: what Aare the Eeffects of Ccytokines and Iinflammation? Int J Mol Sci. 2022;24(1):578.

[98] Wang XM, Li S, Li LH, Song JX, Lu YH, Zhou ZW, Zhang L. Triple quantitative detection of three inflammatory biomarkers with a biotin-streptavidin-phycoerythrin based lateral flow immunoassay. Anal Biochem. 2022 ;657:114915.

[99] Wang Z, Dai W, Yu S, Hao Z, Pei R, De Moraes CG, Suh LH, *et al.* Towards detection of biomarkers in the eye using an aptamer-based graphene affinity nanobiosensor. Talanta. 2022; 250:123697.

[100] Macovei DG, Irimes MB, Hosu O, Cristea C, Tertis M. Point-of-care electrochemical testing of biomarkers involved in inflammatory and inflammatory-associated medical conditions. Anal Bioanal Chem. 2023; 415(6):1033-1063.

[101] Sîrbe C, Badii M, Crişan TO, Benţa G, Grama A, Joosten LAB, Rednic S, Pop TL. Detection of Novel Biomarkers in Pediatric Autoimmune Hepatitis by Proteomic Profiling. Int J Mol Sci. 2023;24(8):7479,

[102] Vitali R, Palone F, Armuzzi A, Fulci V, Negroni A, Carissimi C, Cucchiara S. Proteomic Analysis Identifies Three Reliable Biomarkers of Intestinal Inflammation in the Stools of Patients with Inflammatory Bowel Disease. J Crohns Colitis. 2023 ;17(1):92-102.

[103] Jayabal H, Bader DL, Worsley P. Development of an Efficient Extraction Methodology to Analyse Potential Inflammatory Biomarkers from Sebum. Skin Pharmacol Physiol. 2023;36(1):38-50.

[104] Dang T, Li Z, Zhao L, Zhang W, Huang L, Meng F, Liu GL, *et al.* Ultrasensitive Detection of C-Reactive Protein by a Novel Nanoplasmonic Immunoturbidimetry Assay. Biosensors (Basel). 2022;12(11):958,

[105] Picciolini S, Mangolini V, Rodà F, Montesano A, Arnaboldi F, Liuzzi P, Mannini A, et *al*. Multiplexing Biosensor for the Detection of Extracellular Vesicles as Biomarkers of Tissue Damage and Recovery after Ischemic Stroke. Int J Mol Sci. 2023;24(9):7937.

[106] Zetlen HL, Cao KT, Schichlein KD, Knight N, Maecker HT, Nadeau KC, Rebuli ME, et al. Comparison of multiplexed protein analysis platforms for the detection of biomarkers in the nasal epithelial lining fluid of healthy subjects. J Immunol Methods. 2023 ;517:113473.

[107] Xing L, Wu T, Yu L, Zhou N, Zhang Z, Pu Y, Wu J, et al. Exploration of Biomarkers of Psoriasis through Combined Multiomics Analysis. Mediators Inflamm. 2022 ;2022:7731082.

[108] Kaddoura R, Ghelani H, Alqutami F, Altaher H, Hachim M, Jan RK. Identification of Specific Biomarkers and Pathways in the Treatment Response of Infliximab for Inflammatory Bowel Disease: In-Silico Analysis. Life (Basel). 2023 ;13(3):680.