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# Tracking inflammation status for improving patient prognosis: A review of current methods, unmet clinical needs and opportunities

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ABSTRACT

Inflammation is the body's response to infection, trauma or injury and is activated in a coordinated fashion to ensure the restoration of tissue homeostasis and healthy physiology. This process requires communication between stromal cells resident to the tissue compartment and infiltrating immune cells which is dysregulated in disease. Clinical innovations in patient diagnosis and stratification include measures of inflammatory activation that support the assessment of patient prognosis and response to therapy. We propose that (i) the recent advances in fast, dynamic monitoring of inflammatory markers (e.g., cytokines) and (ii) data-dependent theoretical and computational modeling of inflammatory marker dynamics will enable the quantification of the inflammatory response, identification of optimal, disease-specific biomarkers and the design of personalized interventions to improve patient outcomes - multidisciplinary efforts in which biomedical engineers may potentially contribute. To illustrate these ideas, we describe the actions of cytokines, acute phase proteins and hormones in the inflammatory response and discuss their role in local wounds, COVID-19, cancer, autoimmune diseases, neurodegenerative diseases and aging, with a central focus on cardiac surgery. We also discuss the challenges and opportunities involved in tracking and modulating inflammation in clinical settings.

## 1. Introduction

Physiological processes required for human health are maintained by multiple levels and rely on complex regulatory signaling mechanisms that control normal cellular biochemistry Pocock et al. (2013). During injury, infection, surgery, or disease, inflammatory markers play an important role in communicating this disturbance to the cells of the immune system, brain, and other physiological systems Thomson and Lotze (2003). This involves interactions between immunoregulatory proteins, such as cytokines, acute phase proteins, hormones and bioactive lipids, to ensure this response is effective and is not detrimental to the host Turnbull and Rivier (1999). When appropriately regulated, this network of inflammatory regulators support competent host defense and restoration of normal physiology. However, any loss of this control

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contributes to chronic inflammation and transition towards pathophysiology. In this regard, adverse inflammatory processes play pivotal roles in the development of cancers, infectious diseases, autoimmune diseases typified by immune-mediated inflammatory diseases and autoinflammatory disorders.

In the past decades, significant efforts have been directed towards measuring inflammatory markers to improve medical outcomes for patients. Recent technological and computational advancements make the unmet clinical need of continuous tracking, quantification and treatment of inflammation by dynamically monitoring biomarker levels in response to various inflammatory stimuli possible, all of which are areas of potential interest to biomedical engineers Leonard and Lin (2023); Liu et al. (2021); Chakraborty and Burns (2019); Alex et al. (2007). In this review, we provide a conceptual overview of the physiology underlying the inflammatory response across timescales from acute to chronic, including local wounds, COVID-19, cancer, autoimmune diseases, neurodegenerative diseases and aging, with an exemplar focus on the inflammatory response to cardiac surgery as (i) the initiation of inflammation is known precisely unlike in cancers or other diseases and (ii) the timeline of recovery is of the order of days, making longitudinal studies from inflammation onset to resolution viable. We especially emphasize the need for cytokine sensing, modeling and analysis as they are more specific markers of inflammation in comparison to other biochemicals. We review recent advances in inflammatory marker sensing and discuss the role of modeling and computational analysis in solving complex, multidisciplinary research problems of significance: understanding new aspects of inflammatory marker biology, identification of optimal, inflammatory stimuli-specific biomarkers, providing insights for individual-specific therapeutic interventions and finally, improvement of patient outcomes.

## 2. The inflammatory response

The inflammatory response is mediated by stimuli-driven secretion of signaling biochemicals such as cytokines, hormones and acute phase proteins which we describe below (see Fig. 1 for an overview).

### 2.1. Cytokine signaling and actions during inflammation

#### 2.1.1. Cytokines and their properties

Cytokines are soluble proteins produced by white blood cells and many other nucleated cell types that allow cellular communication via actions transmitted by specific receptor systems. Cytokines are of many types such as interleukins (IL), interferons (IFN), chemokines (chemotactic cytokines), tumor necrosis factors (TNF), hematopoietins, growth factors (GF), neurotrophic factors etc. They often display pleiotropic properties, but typically control responses essential for cellular proliferation, differentiation, survival (or death) and functional identity. Cytokines are produced in small quantities under normal physiology in a circadian manner, are susceptible to seasonal changes and their levels remain low in subjects without inflammatory disorders Li et al. (2021); Waggoner (2020). These rhythms are disrupted in acute and chronic disease, further contributing to the progression or resolution of illness Waggoner (2020); Hand et al. (2016); Coiffard et al. (2019). Plasma cytokine concentrations rise by a few orders of magnitude greater than the nominal resting levels during inflammation Gibbison et al. (2015, 2020) and cytokine activities have widespread actions on the cells local to the site of disease by regulating stromal tissue responses that shape the recruitment, involvement (e.g., effector properties), and maintenance of immune cells. However, they equally contribute to systemic immune activation, impacting processes linked with the regulation of body temperature, metabolism, pain, neuroendocrine function and in some instances, psychological well-being Thomson and Lotze (2003); Turnbull and Rivier (1999). Abnormal cytokine levels have been associated with pathophysiology including autoimmune disorders, immunoparalysis, adverse surgery outcomes, etc. Tønnesen et al. (1996); McGuinness et al. (2008); McBride et al. (1995). While we focus on a few cytokines in this work, in lieu of the vastness of this topic, we refer the reader to *The Cytokine Handbook* Thomson and Lotze (2003) for a comprehensive discussion.

#### 2.1.2. Cytokine levels in health and disease

Cytokine levels are low in healthy adults. Recently it has been reported that in a group of 126 healthy adults aged 18–64 years, cytokine

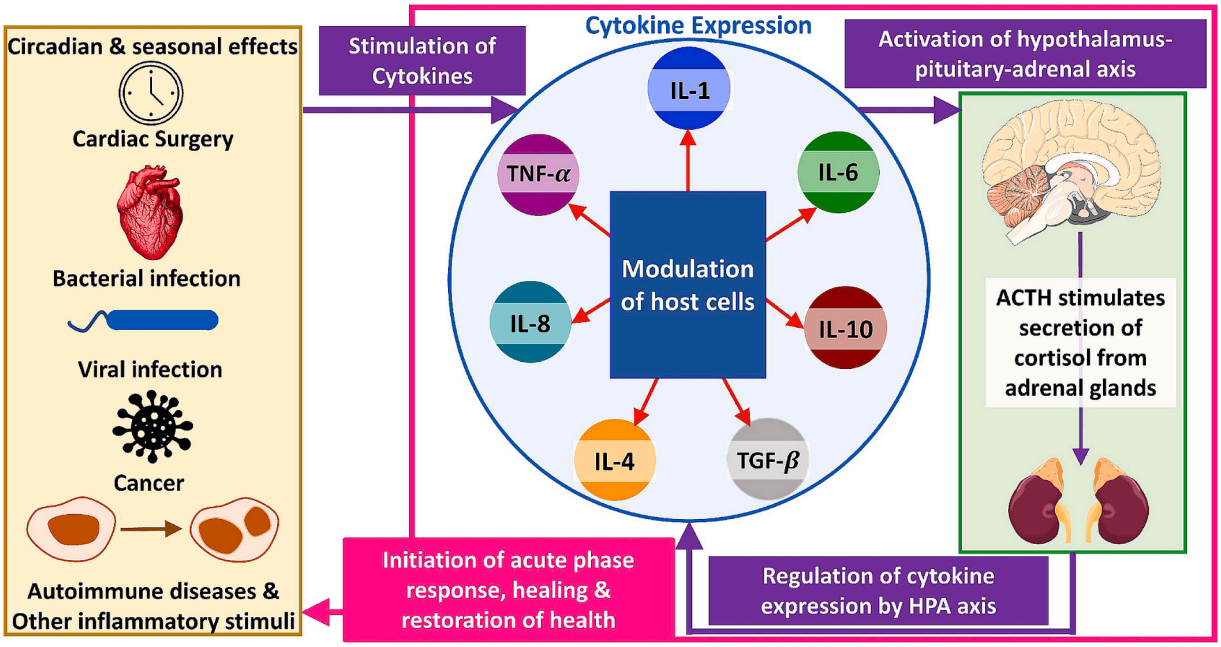


**Fig. 1.** Overview of the inflammatory response. Immune threats (injury, surgery, bacterial or viral infections, cancer, autoimmune diseases etc.) stimulate the secretion of cytokines from various host cells. Beyond the control of local inflammation, cytokines control various physiological processes, including activation of the HPA axis to produce ACTH and cortisol. Cortisol dampens cytokine activities through its anti-inflammatory action on cytokine production, and the inflammatory response is a result of the combined cytokine-HPA axis actions, which sequence the required repair and restorative mechanisms in the body.

levels averaged less than 100 pg/mL, if at all above the detectable minimum limit Li et al. (2021). Particularly, IL-6 was not detected in this group. The levels of IL-6, IL-8, IL-10 and TNF-$\alpha$ rise as high as 1000 pg/mL due to the surgery Galvis et al. (2022). A maladaptive inflammatory response has been implicated in critical illness, morbidity, and mortality of patients post-cardiac surgery Cappabianca et al. (2011); Graham et al. (2014). In the case of injury from surgery for example, excessive loss of blood due to lack of clotting and excessive clotting can both be fatal McGuinness et al. (2008); McBride et al. (1995); Graham et al. (2014); Wan et al. (1996); Wan and Yim (1999); Brix-Christensen et al. (1998). Further, the effect of the same cytokine secretion levels is different in the presence of confounding factors including pre-existing conditions such as diabetes and hypertension, or age-related propensity for organ damage due to chronic inflammation Graham et al. (2014); Pahwa et al. (2022). This was particularly noted following acute infection with SARS-CoV-2 during the COVID-19 pandemic Pettit et al. (2020). In tissue injury, several cytokines are involved in the ultimate healing and return to homeostasis. During severe injuries such as those due to hemorrhagic trauma or surgery, a dysfunctional cytokine response (Cytokine Release Syndrome CRS or cytokine storm) may potentially cause multiple organ failures Carden and Granger (2000); Algoet et al. (2023) immunoparalysis Allen et al. (2006), post pericardiotomy syndrome Lehto and Kiviniemi (2020); Maranta et al. (2022) or even death Zhang et al. (2015).

### 2.1.3. Types of signaling

The complexity of cytokine signaling such as the type of target cell whose function is enhanced and their stimulatory/inhibitory effect on the secretion of other cytokines by the target cells ensures the specificity of their action Turnbull and Rivier (1999). The number, types, levels, and nature of the inflammatory action of cytokines involved altogether determine their collective effect Leonard and Lin (2023). Cytokines signal the inflammatory stimulus by binding to receptors in the target cells and act locally in four ways Thomson and Lotze (2003), as shown in Fig. 2 and listed below.

(a) *Autocrine signaling* involves action of the cytokine on the source cell(s) that produced it. In local wounds, the autocrine action of some interleukins produced from white blood cells or leukocytes (macrophages, monocytes, lymphocytes, neutrophils etc.), endothelial cells (cells lining blood vessels) and skin cells (keratinocytes) act to proliferate the source cell type Werner and Grose (2003).

(b) *Paracrine signaling* involves the action of the cytokine on nearby cells. The paracrine action involves the production of growth factors, and results in the cell growth, proliferation and directed migration of keratinocytes and endothelial cells to facilitate wound repair and closure Werner and Grose (2003); Barrientos et al. (2008); Nurkesh et al. (2020).

(c) *Juxtacrine signaling* between adjacent cells is caused by cytokines bound onto the plasma membrane of one. Juxtacrine signaling is exhibited by IL-15 and IL-6 Tsukamoto et al. (2006); Millrine et al. (2022).

(d) *Transsignaling* is caused by alterations of the sensitivity of receptors to other cytokines. This is observed in IL-6 actions as part of IL-6-soluble IL-6 receptor (IL-6/sIL-6R) complex which may not be observed purely via IL-6 stimulating target cells Jones et al. (2005).

### 2.1.4. Inflammatory effects of cytokine signaling

Cytokine signaling actions may have proinflammatory or anti-inflammatory effects depending on the inflammatory context, the cell type they act upon and the stage of disease in which they function. The feedback interactions between cytokines such as the interleukins IL-1, IL-8 (a chemokine also known as CXCL8), and tumor necrosis factor TNF-$\alpha$ enhance their production and execution of inflammatory function, while other cytokines such as interleukins IL-4 and IL-10 act in negative feedback on these cytokines having an anti-inflammatory effect Thomson and Lotze (2003). IL-6 action is proinflammatory in cardiac surgery Galvis et al. (2022) while it is anti-inflammatory on macrophages in tuberculosis Linge et al. (2022) or may downregulate other proinflammatory cytokines Opal and DePalo (2000) in other contexts. Although IL-4 and IL-13 are typically considered anti-inflammatory Weiss et al. (1997), IL-4 may be pro-inflammatory in allergy or parasitic infections, and together with IL-13 it also contributes to fibrosis (e.g., in the lung) Shankar et al. (2022).

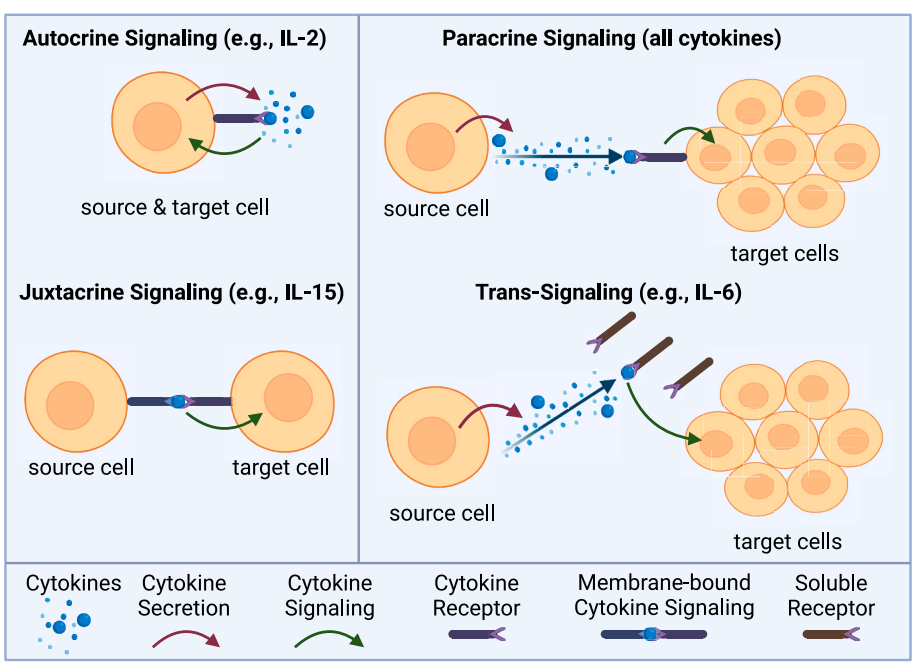


**Fig. 2.** Conceptual depiction of cytokine signaling mechanisms (autocrine, juxtacrine, paracrine and transsignaling) and examples of cytokines exhibiting them. *Created with BioRender.com.*

#### 2.1.5. Global actions and interactions with hormones

Cytokines may also act globally. High circulating levels of cytokines may bind to receptors in the hypothalamus-pituitary-adrenal (HPA) glands and organs such as liver, resulting in the synthesis of HPA axis hormones and acute phase proteins (APP), respectively Turnbull and Rivier (1999). When the inflammatory stimulus is localized and less severe in origin (e.g., small wounds), it results in a local inflammation at the site of injury, while major injuries such as surgery or bacterial/viral infections and sepsis induce a systemic inflammatory response Turnbull and Rivier (1999). Cardiac surgery, being hemorrhagic trauma, is superposed on the pathology that necessitated the surgical intervention and causes a systemic inflammatory response, which involves the secretion of HPA axis hormones such as adrenocorticotropic hormone (ACTH) and cortisol and initiates the acute phase response resulting in the synthesis of acute phase proteins in the liver Turnbull and Rivier (1999); Tønnesen et al. (1996). We refer the reader to Fig. 1 for a schematic on the role of cytokines in the inflammatory response.

### 2.2. Hormone secretion during inflammation

While cytokine actions are typically autocrine and paracrine, high levels of circulating cytokines can activate the hypothalamus-pituitary-adrenal axis resulting in the secretion of adrenocorticotropic hormone (ACTH) and cortisol. Normally, neuronal stimuli in the hypothalamus stimulate the secretion of corticotropin-releasing hormone (CRH), which then travels to the anterior pituitary gland inducing ACTH secretion. Then, via systemic circulation, ACTH stimulates cortisol secretion from the adrenal glands. The secreted cortisol further inhibits the CRH and ACTH secretion, thereby ensuring that cortisol levels are always within a desired range Faghih et al. (2014, 2015). For normal, healthy individuals, cortisol secretion has pulsatile, diurnal secretory patterns with 15–22 pulses per day Brown et al. (2001). A high amplitude secretory event in the morning enables awakening Fries et al. (2009), and circadian and ultradian patterns in the levels and timings of secretory events throughout the day sustain the cortisol level Brown et al. (2001). Deviations from normality due to hypercortisolism, hypocortisolism or other cortisol disorders such as Addison's disease caused by autoimmune destruction of the adrenal gland are pathological, causing a significant increase in ACTH and cortisol secretion, and many studies have investigated the associated changes in their pulsatility Turnbull and Rivier (1999); Galvis et al. (2022); Raju et al. (2023b). The cytokine response is downregulated by the anti-inflammatory action of the HPA axis hormones Silverman et al. (2005). Other than the HPA axis hormones, growth hormone (secreted in anterior pituitary gland) and leptin (secreted by adipose tissues in the body) are involved in the inflammatory processes of wound-healing and muscle and bone repair, and regeneration Werner and Grose (2003); Thomson and Lotze (2003).

#### 2.2.1. Hormone-cytokine interactions

There are instances in which cytokines may act like hormones and vice versa. For example, IL-6, a major source of which is the adrenal cortex Turnbull and Rivier (1999); Päth et al. (1997); Yavropoulou et al. (2022), has been reported to increase cortisol levels by stimulating CRH secretion at the hypothalamus, and potentially by stimulating the production of ACTH at the pituitary Turnbull and Rivier (1999). Hormone-like action of IL-6 produced in adipose tissue to regulate body fat and its ability to correlate with body mass index (like leptin) has been reported Stanford et al. (2012). Further, IL-6 is known to affect insulin sensitivity, and enhance other metabolic markers such as glucose and triglycerides, suggesting its role in chronic diseases like atherosclerosis, diabetes and obesity Stanford et al. (2012). On the other hand, leptin, a hormone, has been shown to accelerate wound healing by promoting re-epithelialization Werner and Grose (2003); Lee et al. (2018); Tadokoro et al. (2015).

### 2.3. Acute phase response and the role of acute phase proteins

Acute phase proteins (APPs) such as C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, $\alpha$2-macroglobulin, hepcidin and ferritin are synthesized in liver hepatocytes by stimulation from circulating cytokines (e.g., IL-1, IL-6, and TNF-$\alpha$)Turnbull and Rivier (1999); Heinrich et al. (1990). The timing and type of APP stimulation are dependent on the inflammatory stimuli and result in the acute phase response comprising fever, alterations in plasma cation concentrations and other physiological changes meant to promote the restoration of healthy homeostasis. CRP's potential to indicate chronic inflammation in many diseases has motivated the development of a novel, wearable sensor Tu et al. (2023). High levels of APPs have been shown to correlate with altered lipid profiles in those with rheumatoid arthritis Singh et al. (2013) and indicative of outcomes in acute coronary syndrome patients Sim and Ahn (2013); Harb et al. (2002). APPs constitute clinically significant non-specific biomarkers in many pathologies such as community acquired pneumonia, cardiovascular diseases, liver disease, graft versus host disease, autoimmune diseases such as systemic lupus erythematosus (SLE), cancer, infection and critical illness Lobo (2012). Additional information on cytokine actions, hormone-cytokine interactions and the role of APPs as potential biomarkers is in Table 1.

#### 2.3.1. Acute phase proteins as biomarkers

In a study of 1045 patients, serum amyloid A and CRP were shown to be biomarkers for ACS but not independently prognostic of long-term recurrence of cardiac events Harb et al. (2002). In another cross-sectional study comprising 2925 patients Zamani et al. (2013), CRP, SAA and IL-6 were shown to be indicative of risk of death but not of recurrent ACS. High CRP with high IL-6 correlated with high rate of readmission and mortality after 1 year Barichello et al. (2022). Fibrinogen levels are estimated from the erythrocyte sedimentation rate (ESR) and are indicative of blood coagulation, but its long half-life and minimal variations during the acute phase response have limited its use as a biomarker in ACS Abbate et al. (2003). Ferritin levels are known to be elevated due to inflammation and a range between 20 and 100 ng/mL is

**Table 1**
Acute phase proteins (APPs) and hormones in inflammatory response.

| Inflammatory Marker | Properties and temporal behavior in diseases |
|---|---|
| CRP (APP) | Stimulated by IL-6; increased levels after acute coronary syndrome and myocardial infarction indicate inflammation level Abbate et al. (2003); Tousoulis et al. (2011); associated with risk of death and not recurring myocardial infarction Zamani et al. (2013); diagnostic and prognostic biomarker in pneumonia Chalmers et al. (2019), sepsis Barichello et al. (2022), post-pericardiotomy syndrome Tamarappoo and Klein (2016); marker of disease severity in COVID-19 García (2020), HD Rocha et al. (2016); diagnostic indicator in osteomyelitis Dartnell et al. (2012). |
| ESR (APP) | Associated with patient prognosis in short and long term Abbate et al. (2003), e.g., cardiovascular diseases Barichello et al. (2022), diagnostic indicator in osteomyelitis Dartnell et al. (2012). |
| Ferritin (APP) | Very high levels are associated with inflammatory events in patients DePalma et al. (2021). |
| Hepcidin (APP) | Production stimulated by IL-6 and blocked by tocilizumab, hepcidin is a biomarker for sepsis and inflammatory diseases such as Crohn's disease Kali et al. (2015). |
| SAA (APP) | Increased levels after acute coronary syndrome and myocardial infarction indicate inflammation level Sim and Ahn (2013), elevated after acute coronary syndrome (ACS); increased risk in hospitalized patients Abbate et al. (2003). |
| Leptin (hormone) | Anti-inflammatory in wound healing Werner and Grose (2003); Lee et al. (2018); Tadokoro et al. (2015); stimulates IL-6, TNF-$\alpha$ and IL-10 secretion Procaccini et al. (2017). |
| Cortisol (hormone) | Controls overall inflammatory response Turnbull and Rivier (1999), downregulates proinflammatory cytokines with IL-4, IL-10 Turnbull and Rivier (1999). |

denoted as the range suitable for reduced mortality, with values greater than 194 ng/mL indicating mortality risk, while lower values are a diagnostic criterion for iron deficiency anemia DePalma et al. (2021). CRP and ESR are used to determine the severity of infection and determine the clinical intervention in osteomyelitis Dartnell et al. (2012). Moreover, drugs such as tocilizumab that target IL-6 or its receptor act in part via control of acute phase reactants Sebba (2008). The potential use of APPs as non-specific indicator of inflammation in various diseases is evident and their prognostic value can be further investigated with longitudinal data Lobo (2012).

## 3. Inflammatory marker sensing

### 3.1. Cytokine sensing

Since cytokines provide more specific information on inflammation in comparison to hormones or APPs, the development of cytokine sensors that sample multiple cytokines in parallel with fast assay times using low sample volumes enabling near-real time data collection will enable longitudinal inflammation monitoring and interventions, an unmet clinical need. Some examples where such sensors will help track the progression of inflammation and healing and improve outcomes through early interventions are: (i) cardiac surgery, where inflammation monitoring can help determine prognosis, recovery and development of adverse outcomes such as septic shock or organ failures for which the underlying mechanism is still unclear Galvis et al. (2022); Kurabayashi and Park (2023) and (ii) vascularized composite allografts (VGA), which are complex transplants comprising various cell types, extracellular matrix and vasculature Aggas et al. (2023).

Cytokines range in MW from 7 to 70 kDa and in homeostasis are detected at low pg/mL concentrations. While elevations in cytokine production in response to inflammation often correlate with disease activity scores, the clinical value of these measures as diagnostic or prognostic markers is difficult to judge. In terms of biology, genetic polymorphisms affecting the expression or activity of cytokines have profound influences on their bioactivity Masuda et al. (2013); Viswanathan et al. (2009); Garbers et al. (2014), and current measures typically monitor cytokine levels in snapshots that fail to consider the circadian/temporal control of their expression. These include changes over the course of the day and seasonal variations in cytokine expression that alter between summer and winter months Sugimoto et al. (2014); Lissoni et al. (1998); Fernandes et al. (2017); Dopico et al. (2015). Moreover, the accuracy of cytokine level measurements is sensitive to the (i) methods of sample collection and storage, (ii) the source, temperature and timing of sampling and (iii) the duration required to isolate the cytokines Liu et al. (2021); Thavasu et al. (1992); Stenken and Poschenrieder (2015).

Previous efforts to relate observed disease states to cytokine signaling have motivated the development of cytokine sensors over the past decades. Longitudinal cytokine monitoring provides a less specific sensing of inflammation pathology in comparison with computationally intensive clinical diagnostic methods such as biomedical imaging to determine severity of disease or disability in cancer or neurodegenerative diseases respectively, but more specific sensing than hormones or APPs. Longitudinal cytokine sensing and other inflammation monitoring methods such as bio-imaging represent two diverse diagnostic modes: (i) portable or point-of-care cytokines monitoring, if successfully achieved, may be relatively cheaper and offer high temporal resolution data with fewer side effects, while (ii) precise diagnostics via specialized methods including biomedical imaging may be more expensive, less accessible or portable and may have adverse side effects.

Cytokine sensors may be of many types based on the mode of sensing. They may be mechanical, electrochemical, optical, colorimetric, fluorescence immunoassays or plasmonic sensors Liu et al. (2021); Chen et al. (2015). Methods to measure, store and process peripheral blood samples to obtain reliably the levels of multiple cytokines in parallel have been studied for decades and include enzyme-linked immunosorbent assays (ELISA), polymerase chain reaction (PCR), multi-array sensors and magnetic multiplex arrays Liu et al. (2021); Li et al. (2022); Quinn et al. (2018); Bouquet et al. (2020); Yang et al. (2022); Ungaro et al. (2020); Leng et al. (2008); Osuchowski et al. (2005); Moody et al. (2001). Recently, sweat-based sensors for detection of cytokines have been developed Hirten et al. (2024), offering promising real-world cytokine sensing. Multiomics cytokine datasets on the other hand, offer rich information on the cellular-level cytokine signaling. 'CytoSig' Jiang et al. (2021) comprising a database of genes targeted by cytokine signaling and a predictive statistical model, has addressed single-cell and tissue level cytokine signaling effects on gene expression in target cells from in-vivo studies. 'CytoSig' has been validated for inferring cytokine signaling pathways in various datasets including cytokine-blocking clinical response, tumor and cancer therapy response and severe COVID-19 disease Jiang et al. (2021).

In Kurabayashi and Park (2023), the potential of nanoplasmonic sensors in clinically monitoring the levels of IL-2, IL-4, IL-6, IL-10, IFN-$\gamma$ and TNF-$\alpha$ by detecting altered peaks in the refracted light spectrum due to cytokine molecules binding to antibodies at the sensor surface has been demonstrated with a significantly smaller assay duration (less than 40 min). These sensors have been utilized to monitor (i) incidence of cytokine storm in SARS-CoV-2, (ii) state of inflammation due to cardiac surgery and (iii) septic shock, by enabling accurate, fast, sensitive and cost-effective, point-of-care testing (POCT) in critical care Kurabayashi and Park (2023). Such sensors may enable the early detection and tracking of acute and chronic inflammatory disorders or disease flare ups involving pathological cytokine expression via near real-time monitoring Liu et al. (2021); Chen et al. (2015); Kurabayashi and Park (2023).

### 3.2. Hormones and acute phase proteins sensing

Previous efforts to study 24-h hormone dynamics involved blood sampling every 10 min through venous sampling in a clinical setting Kok et al. (2006a, 2006b, 2008) allowing for the study of interactions between hormones in women with premenopausal obesity Vis et al. (2014). The cardiac surgery dataset Galvis et al. (2022) also contained the 10-min sampling of ACTH and cortisol from patients. The recently developed invasive, portable hormone sampling device termed "U-RHYTHM" has offered a novel paradigm to perform HPA axis hormone sensing every 20 min Upton et al. (2023). Here, hormone concentrations are determined by 20-min subcutaneous biosampling through the infusion of a perfusion fluid via a catheter inserted in the abdominal fat tissue in subjects. In this work, free hormone concentrations of several adrenal steroids including cortisol were recovered from 24-h samples in 214 healthy subjects Upton et al. (2023). A wearable, active patch sensor termed "InflaStat" has been developed for monitoring CRP from sweat Tu et al. (2023). While U-Rhythm is invasive and requires lab assaying to determine the hormone concentrations, Inflastat is non-invasive, offers in-situ analysis and is equipped with wireless communication to relay CRP information in real-time.

## 4. Modeling inflammatory marker dynamics

While cytokine actions are predominantly local, the emanation of the systemic inflammatory response in relation to the local and circulating cytokines due to inflammatory stimuli such as surgery remains to be quantitatively investigated (e.g., see Raju et al. (2023a)). The inference of the relationship between the local and systemic inflammatory marker expression may help assess disease severity by estimating patient-specific cytokine secretory rate parameters and feedback cascades in cytokine signaling inferred from longitudinal data. We note that many studies reported in this review involve one of (i) animal models, (ii) tightly controlled settings in non-clinical, laboratory settings or (iii) healthy people subject to interventions, while there is a dearth of data

from very young or old people, the predominant population of patients in hospitals who are ill, or ill people in general.

Minimally descriptive secretion models can help quantify useful metrics of physiological signals and help assess various prognostic scenarios Faghih (2018). Previously, such models have helped understand the secretory characteristics of hormones such as ACTH with cortisol, growth hormone, leptin etc. from plasma concentrations of these hormones Faghih et al. (2015); Genty et al. (2021); Amin et al. (2022). Similarly, quantitative modeling of plasma cytokine levels can be used to determine the inflammation characteristics Raju et al. (2023a). More generally, differential equation models of the form:

$$\dot{x}_i = f_i(x_i) + g_i(x_1, , x_n) + u_{i,act.} + u_{i,inhib.} \tag{1}$$

for $i = 1, \ldots, n$ can capture the systemic dynamics of a collection of $n$ cytokines, hormones and APPs. Here, the change in the concentration $x_i$ of the $i^{th}$ inflammatory marker depends on (i) its instantaneous concentration, modeling its net expression or clearance, (ii) feedback interactions that depend on the instantaneous marker profile $(x_1, \ldots, x_n)$, i.e., the concentrations of all the cytokines, hormones and APPs under consideration, inferred from single-cell or tissue-level signaling studies for various cell types Jiang et al. (2021) and (iii) exogenous or endogenous inputs that may be activating ($u_{i,\mathbf{act.}}$) or inhibitory ($u_{i,\mathbf{inhib.}}$). This can be extended to include cytokine-hormone interactions, time-varying systemic inflammatory response parameters or to account for spatial dynamics by using partial differential equation models Ghosh et al. (2020). Such models have been employed to study (i) pancreatic cancer dynamics by modeling interleukins and growth factors and additionally incorporating the densities of pancreatic, cancerous and immune cells Louzoun et al. (2014), (ii) bone fractures by modeling the density of bone cells, debris and cytokines Trejo and Kojouharov (2020), (iii) endotoxin-driven inflammatory response of IL-6, TNF-$\alpha$, ACTH and cortisol to study the signaling between the cytokines and HPA axis hormones Malek et al. (2015); Clodi et al. (2008) and (iv) the role of IL-2, IL-10 and TGF-$\beta$ in tumorigenesis in Robertson-Tessi et al. (2012). We note that evolutionary dynamical models have a rich history in mathematical biology and the framework above is analogous to propagation of phenotypes in population genetics Svirezhev and Passekov (2012); Hofbauer and Sigmund (2003); Sandholm (2010); Weibull (1997). There too, microscopic interactions between alleles (treated as replicators) is aggregated into the macroscopic dynamics (replicator dynamics) governing the propagation of types.

In contrast to physiological models intended to capture temporal behavior of inflammatory markers, data-driven approaches have the potential to reveal insights on the biomarkers associated with disease from high dimensional gene expression datasets Jiang et al. (2021). Machine learning-based approaches have been applied on datasets comprising complex sensory information with large number of features in the data (e.g., bio-imaging) or in transciptomics studies to infer cytokine signaling Dzau et al. (2023); Bertagnolli (2023). Such model-free frameworks may be successful in identifying and predicting the salient features of an ensuing inflammatory response, including biomarker identification (e.g., Jiang et al. (2021) identified IL-8 as a COVID-19 biomarker). Effective utilization of these methods requires (i) the generation of large datasets and their curation to avoid introduction of sampling bias in the training datasets, (ii) interpretive learning to justify outcomes such as clinical decisions and (iii) accommodation of experts' insights and non-structured clinical data e.g., inclusion of doctors' notes via large language models (LLM) framework into the algorithm for validation and trustworthy deployment Singhal et al. (2023); Whitney et al. (2025). Fig. 3 shows the proposed pipeline for computational analysis.

Wider application of these modeling and inference approaches to inflammatory markers is limited by (i) lack of explicit inclusion of feedback pathways in inflammatory marker signaling in the prevailing

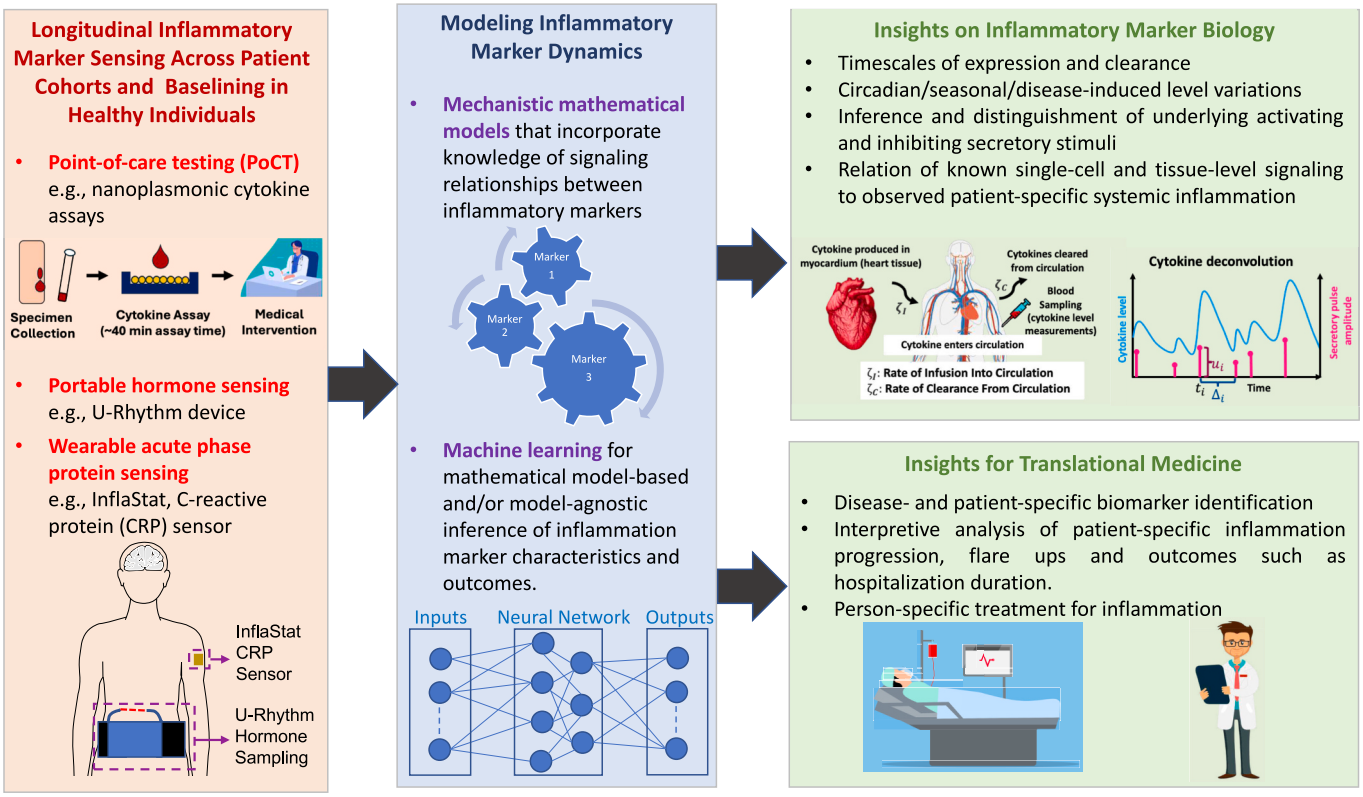


**Fig. 3.** Proposed pipeline for longitudinal inflammatory marker data collection using novel wearable, portable and point of care testing devices Kurabayashi and Park (2023); Upton et al. (2023); Tu et al. (2023) and computational modeling and analysis e.g., Raju et al. (2023a, 2023b) for providing insights on the biological and clinical aspects of systemic inflammation.

models and (ii) the absence of longitudinal measurements of the cytokine levels that may potentially help estimate inflammation progression. For example, Clodi et al. (2008) reports the inflammatory marker levels every 30 or 60 min, with a total of 10 data points and may not offer rich temporal information on the transients in cytokine actions necessary to capture the dynamics of the inflammatory markers. Another study Puchinger et al. (2022) considered 9 measurements in 6 h post-surgery, followed by one measurement per day for 10 days, totaling 19 measurements to assess IL-6 dynamics in response to cardiac surgery. In recent works Raju et al. (2023a, 2023b), the 10-min sampling of cytokines and cortisol in cardiac surgery over a 12-h duration was used to infer the secretory rate constants and stimuli governing the circulating cytokine and cortisol levels, and to determine the dyadic causal relationships between them, providing insight into the patient-specific nature of inflammation in these patients by employing a compressed-sensing based approach Faghih (2018). We note that solutions to these biochemical deconvolution problems are in general non-unique, and physiological constraints on the rate constants and the total number of underlying stimuli (sparsity constraints) are used to arrive at a physiologically feasible solution Faghih (2018). Since inflammation onset is precisely known and the resulting inflammation typically subsides in the order of days, cardiac surgery provides a unique setting in which to study inflammation and apply many of the methods described in this review, and is detailed in the next section.

## 5. Inflammatory response to cardiac surgery

Coronary artery bypass grafting (CABG) is an operative procedure to treat blockages of coronary arteries which involves use of a graft of artery from the patients' body to bypass the blocked blood vessel L. Melly et al. (2018). It involves incision in the sternum (sternotomy) and is accompanied by administration of anti-inflammatory and pain medications Galvis et al. (2022). When the procedure involves cardiopulmonary bypass (CPB), the blood is rerouted through a mechanical device. The blocked section of the aorta is then clamped off, and a bypass graft is placed to restore uninhibited blood flow to the heart. After declamping, blood flow is subsequently restored to the heart and its function is reinstated. There are inflammatory triggers from the start of surgery due to tissue injury from surgical incision, trauma and interaction of the human tissue and blood with CPB device surfaces. Failure of oxygen delivery to meet the metabolic requirements of heart tissue (ischemia) and resumption of blood supply after surgery (reperfusion) both cause additional injury due to release of cytokines Carden and Granger (2000); Wan et al. (1996); Cowled and Fitridge (2020); Algoet et al. (2023); Uyar et al. (2014). Cardiac surgery offers an important clinical context in which to study correlations and causations underlying patient-specific inflammatory marker expressions since (i) it is possible to precisely define the initiation point triggering the host's inflammatory response unlike in infections, and (ii) the temporal modulations of the inflammatory markers occur and terminate at an expedited rate in comparison to chronic immune conditions. Mathematical inference of the parameters governing the inflammatory marker expression and clearance may be viewed analogous to system identification of dynamical systems from input perturbations. Fig. 4 describes the various factors that influence the inflammatory response to cardiac surgery and Fig. 5 tabulates the physiological factors involved.

IL-6, IL-8, IL-10 and TNF-$\alpha$ have been identified as among the key indicators of inflammatory response to cardiac surgery McBride et al. (1995); McBride and McBride (1998); Wan et al. (1996); Wan and Yim (1999); McGuinness et al. (2008); Mahle et al. (2014). Tissue injury caused by sternotomy results in the local production of IL-6 and TNF-$\alpha$ at the incision site Wan et al. (1996); Wan and Yim (1999). In addition, CPB causes the production of IL-6 due to blood circulation via bypass devices Wan et al. (1996). IL-6 increases the permeability of endothelial monolayer that serves to maintain the tissue fluid balance Puchinger et al. (2022). IL-10 is capable of auto-regulation and is known to suppress production of proinflammatory cytokines by stimulation of cortisol secretion Thomson and Lotze (2003); Turnbull and Rivier (1999); McBride et al. (1995). Cytokine actions can be direct or indirect. Direct actions of TNF-$\alpha$ (and IL-1) to enable phagocytosis of dead cells and other functions is accompanied by their indirect action involving the expression of other proinflammatory cytokines such as IL-6 and IL-8 in other cells Wan et al. (1996); Thomson and Lotze (2003). TNF-$\alpha$ is also thought to influence the production of IL-10 which in turn is reported to downregulate TNF-$\alpha$ in many in-vivo and in-vitro studies Thomson and Lotze (2003); Turnbull and Rivier (1999); Wan et al. (1996). IL-6 signaling also results in the onset of the acute phase response, causing APP synthesis in the liver Wan et al. (1996); Mahle et al. (2014);

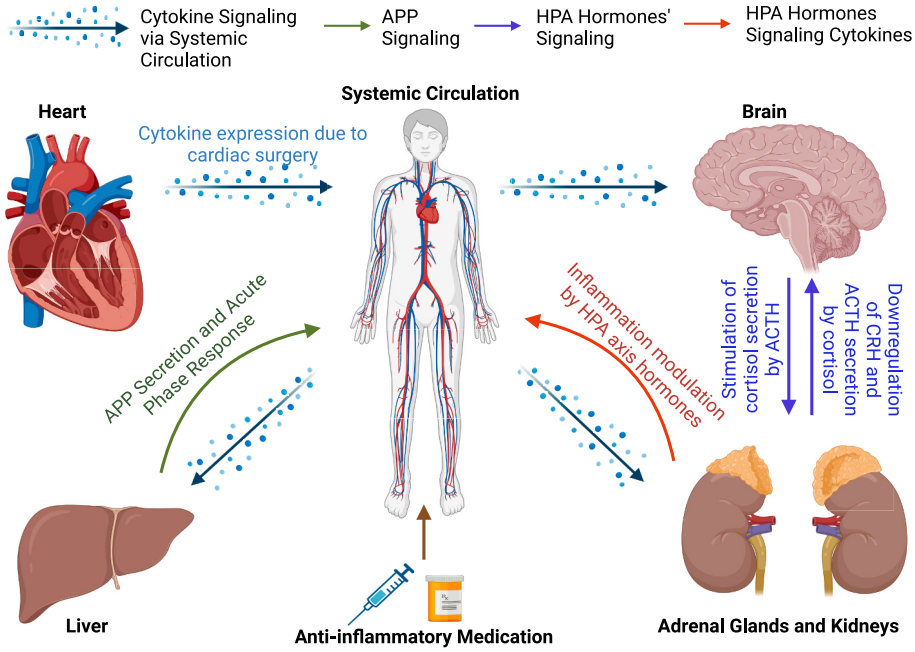


**Fig. 4.** System-level description of inflammatory response to cardiac surgery. The signaling effects between the inflammatory markers and the effect of medication need to be mathematically quantified in a patient-specific manner through mechanistic modeling. *Created with BioRender.com.*

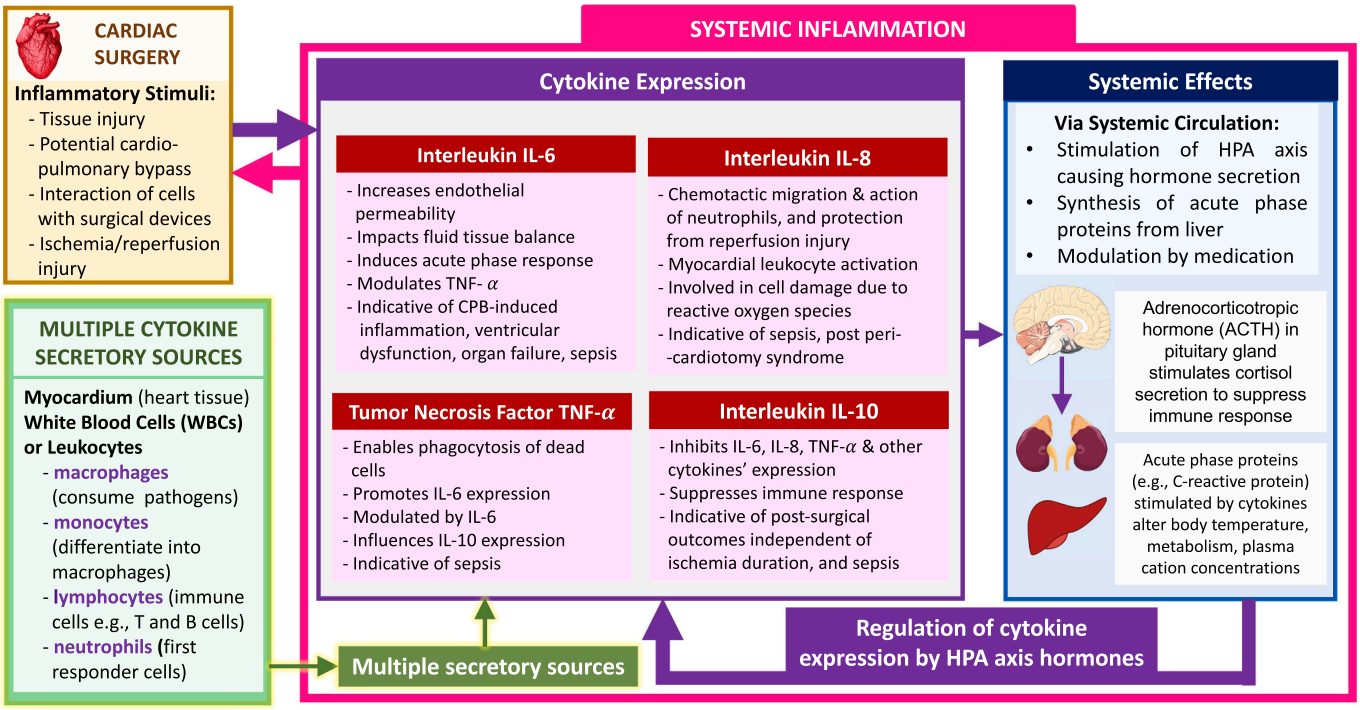


**Fig. 5.** Overview of the inflammatory response to cardiac surgery with a focus on the role of most commonly studied cytokines and their observed relation to patient outcomes, and the systemic inflammation response involving hormone and acute phase protein secretion McGuinness et al. (2008); McBride et al. (1995); Tønnesen et al. (1996); Galvis et al. (2022); Mahle et al. (2014).

Thomson and Lotze (2003), while IL-8 causes activation of leukocytes Wan et al. (1996).

### 5.1. Cytokines as indicators of patient prognosis

Cytokine levels have been known to correlate with inflammation and post-surgical outcomes McGuinness et al. (2008); McBride et al. (1995); McBride and McBride (1998); Tønnesen et al. (1996); Mahle et al. (2014); Galvis et al. (2022). In a study Wan et al. (1996) of eight patients (average age greater than 61) who underwent CABG with the cytokine levels tracked at various time points during and post-surgery, the response of TNF-$\alpha$ was observed foremost during cross-clamping, followed by IL-6 immediately after declamping, and subsequently IL-8 20 min after surgery, while IL-10 rose from the time of administration of heparin, while IL-6 and IL-8 were found to correlate with the duration and extent of ischemia, with IL-10 not having any such effect Wan et al. (1996); Wan and Yim (1999). TNF-$\alpha$ exhibited a response with multiple peaks, the second occurring post-surgery. IL-6 peaked much later in this study. Another study performed during cardiac surgery on the unpredictable activation of immune system due to surgical trauma Puchinger et al. (2022) emphasized that the degree to which cytokines (particularly IL-6) are activated differs across patients and their ability to result in complications is more pronounced in patients undergoing CPB.

The elevated levels of TNF-$\alpha$, IL-6, IL-8 and IL-10 are respectively implicated in sepsis Wan et al. (1996), and while release of IL-10 has been shown to be independent of the duration of ischemia and implicated in post-surgical complications Allen et al. (2006). IL-6 and IL-8 are potent indicators of systemic inflammatory response syndrome which increases the risk of multiorgan failure Uyar et al. (2014), although its biological action may provide protection from reperfusion injury Wan et al. (1996). In Lehto and Kiviniemi (2020); Maranta et al. (2022); Tamarappoo and Klein (2016), chemotactic signaling by IL-8 is implicated in the incidence of post-pericardiotomy syndrome in which pleural and pericardial effusion may present health complications resulting in unexplained fever, prolonged hospitalization, and increased post-surgical mortality rate, extending over a period of two years, with its prevalence recently reported to be ranging between 21 and 29 % of post-surgery patients Lehto and Kiviniemi (2020). Although it is known that the immune dysfunction plays a major role in causing this syndrome, little is known about the progression of the condition to make the diagnostics standardized, or to enable standardized interventions and enable preventative care.

### 5.2. Anti-inflammation strategies

Steroidal and non-steroidal anti-inflammatory treatments are administered during surgery (e.g., heparin, methylprednisolone, colcichine, baricitinib etc. on patient prognosis). The efficacy of treatments depends on the age, sex, health and other confounding factors of individual patients. The alterations in HPA axis hormone secretion physiology due to treatments e.g., altered sensitivity of adrenal glands to ACTH and cortisol insufficiency) and their effect on systemic inflammation is an important area of ongoing research Galvis et al. (2022). Sparsely sampled hormones and cytokines in many studies e.g., 5 samples with the intervals between successive measurements increasing from 6 to 48 h after end of surgery over a total 72-h duration in Puchinger et al. (2022); Graham et al. (2014); Lehto and Kiviniemi (2020) offer limited insight and motivate the need for dynamic inflammatory marker monitoring accompanied by mathematical modeling incorporating the effect of medication on inflammatory marker expression in each individual patient.

### 5.3. Anti-inflammatory treatments for cardiac surgery

As coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CBP) involves interaction of the patient's blood with extracorporeal devices, an activator of the inflammatory response, the surfaces of devices are coated with heparin or other anti-clotting agents to prevent adverse reactions Cappabianca et al. (2011). Moreover, the patient's inflammatory response is triggered systemically, rather than

locally, by surgical trauma. To counteract the immune response, the patient undergoing surgery is also administered pain medication, anesthesia and anti-inflammatory medication to minimize the possibility of a dysfunctional, potentially fatal inflammatory response Cappabianca et al. (2011); Graham et al. (2014).

In a prior study of the effect of dosage of anesthesia on patient prognosis, it was found that neither high nor low doses of opioid anesthesia caused significant changes in the inflammatory response Brix-Christensen et al. (1998), despite lack of control for confounding factors. Treatment with glucocorticoids such as methylprednisolone has been shown to have the anti-inflammatory effect of reducing the proinflammatory cytokine concentrations in patients undergoing cardiac surgery with CPB Paparella et al. (2002). Glucocorticoid administration has been shown to mitigate the proinflammatory cytokine action, caused potentially by an increase in IL-10 expression Paparella et al. (2002). For example, dexamethasone was shown to suppress TNF-$\alpha$ without any post-operative negative side effects Paparella et al. (2002), while its effects in younger patients remain inconclusive Graham et al. (2014). It is reported that such drug administration may have the benefit of reduced mortality rate in patient cohorts, improvement of patients' health post-operatively and a reduced risk of post-operative complications such as myocardial infarction. Methylprednisolone reportedly reduces TNF-$\alpha$ and IL-8 in injury, and may cause a potential reduction of reperfusion injury Paparella et al. (2002); Liakopoulos et al. (2007).

Heparin has been used during cardiopulmonary bypass to prevent blood clotting in bypass devices and is shown to prevent the expression of proinflammatory cytokines IL-6, IL-8 and TNF-$\alpha$ Paparella et al. (2002). Further, it is reported that the chemotactic action of IL-8 was reduced due to heparin administration, and that myocardial function was preserved post-surgery Paparella et al. (2002). Other drugs such as sodium nitroprusside combined with aprotinin have been indicated to be anti-inflammatory, reducing the local and systemic levels of IL-6 and IL-8, with lessened coagulative effects of leukocyte accumulation Paparella et al. (2002). The efficacy of monoclonal antibodies as an alternative solution is inconclusive Paparella et al. (2002). Non-steroidal anti-inflammatory drugs (NSAIDs) may have potential side effects such as renal failure which makes the study of optimal dosages that do not cause post-operative increase of serum creatinine, which is indicative of renal failure, vital Acharya and Dunning (2010).

Inflammation plays a significant role in the incidence of post-operative atrial fibrillation (POAF) post-cardiac surgery Echahidi et al. (2008) and other complications which have been linked to proinflammatory cytokines in Zakkar et al. (2015). In Zakkar et al. (2015), it is reported that statins administered at 40 mg/day from seven days prior to surgery caused a significant reduction in POAF. Corticosteroids have been shown to reduce POAF as well as being associated with lowered post-operative hospitalization duration in ICU, bleeding and infection, while the results from studies involving polyunsaturated fatty acids were not conclusive Zakkar et al. (2015). Colchicine was shown to decrease IL-6 levels Zakkar et al. (2015). Non-steroidal anti-inflammatory treatment such as intravenous administration of ketorolac every six hours followed by oral administration of 600 mg ibuprofen three times a day was shown to reduce post-surgical risk of POAF and other complications Echahidi et al. (2008). Dexmedetomidine administered at dosages depending on patients' weight resulted in a reduction of inflammation, sympathetic stimulation and oxidative stress, all potential causes of POAF, by downregulating the proinflammatory cytokine response Boons et al. (2021).

We also considered meta-analyses on anti-inflammatory medication and their effect on patient outcomes including length of stay (LoS), mortality etc. A meta-analysis involving patients with septic shock has shown that administration of corticosteroids such as hydrocortisone, methylprednisolone, dexamethasone or prednisolone as bolus or infusion were similarly effective in reducing incidence of mortality, gastrointestinal bleeding or superinfection Gibbison et al. (2017). In patients with COVID-19, the administration of an inhibitor of cytokine signaling, baricitinib, which reduces the ability of cytokines to potentiate target cell functions was studied, and it was shown to reduce the risk of death in patients Abani et al. (2022). In a study comprising 138 patients divided into an experimental and a control group Martínez-Comendador et al. (2009), pre-operative administration of statins over a three-week period was found to be effective in lowering the levels of IL-6, without significant effect on IL-8 or TNF-$\alpha$. It is worth noting that the cytokine levels were sparsely sampled, with the intervals between successive measurements increasing from 6 to 48 h after end of surgery. Measurements at six time points are used to make these conclusions over the 72-h duration. The anti-inflammatory effect of 2 different dosages of pre-operatively administered 2-dexamethylprednisolone was studied in two neonatal population of subjects, a total comprising 68 neonates Graham et al. (2014). It was shown that the steroidal drug did not have an anti-inflammatory effect into the recovery period, and pre-medication baseline levels of IL-6, IL-8, IL-10, and TNF-$\alpha$ were predictive of longer periods of ICU and hospital stays, while only postoperative IL-8 levels indicated these factors Graham et al. (2014). The effect of medications such as aspirin, statins or metformin is not included in their analysis. Similar anti-inflammatory treatment strategies have been used to treat post-pericardiotomy syndrome for which dysfunctional inflammation plays a crucial role Lehto and Kiviniemi (2020).

### 5.4. Shortcomings and clinically unmet needs

Studies involving measurements of cytokine, hormone and APP concentrations to determine medical outcomes often involve a small sample size and sparse sampling. Hence, we also considered systematic reviews and meta-analyses on critical illness, anti-inflammatory medication and their outcomes. A meta-analysis involving patients with septic shock has shown that administration of corticosteroids such as hydrocortisone, methylprednisolone, dexamethasone or prednisolone as bolus or infusion were similarly effective in reducing incidence of mortality, gastrointestinal bleeding, or superinfection Gibbison et al. (2017). In patients with COVID-19, the administration of an inhibitor of cytokine signaling, baricitinib was shown to reduce the risk of death in patients Abani et al. (2022). Still, these studies are often cross-sectional, or contain too few measurements of inflammatory markers and provide little insight into the temporal progression of inflammation. Understanding the mechanisms underlying cytokine secretion and early indications of poor outcomes is a clinically unmet need motivated by (i) the incidence of dysfunctional systemic inflammation post-surgery, especially in vulnerable populations often underrepresented in clinical studies, (ii) the need for personalized treatments based on the temporal course of the inflammatory response and (iii) the need for preventative care and effective treatments, to minimize the downstream need for complex, potentially invasive interventions Lehto and Kiviniemi (2020). The incorporation of temporal dynamics of inflammatory markers and inclusion of diverse patient populations will enable effective determination of patient outcomes.

## 6. Cytokine response in other diseases

Cytokines are more specific inflammatory markers than hormones or APPs, as they directly mediate the physiological processes for restoration of healthy homeostasis. For this reason, they have been extensively studied to identify disease-specific biomarkers. In the following section, we describe the cytokine response to other acute and chronic inflammatory stimuli to highlight (i) the identified biomarkers in various diseases and (ii) which cytokines' longitudinal data may further inform disease-specific insights due to the complexity of their actions. A detailed list can be found in Table 2. We note that this summary of relevant inflammatory responses and markers is meant to motivate the importance of mechanistic, longitudinal study of inflammation, and is not an exhaustive study of the inflammatory markers or the underlying medical conditions. We refer the interested reader to the cited studies for

**Table 2**
Major cytokines involved in inflammatory response.

| Inflammatory Marker | Properties and temporal behavior in diseases |
|---|---|
| IL-1 | Activation of HPA axis, initiation of acute phase response Turnbull and Rivier (1999); stimulates IL-6, IL-8 production Turnbull and Rivier (1999) and is synergistic with TNF Lin et al. (2000); blocking IL-1 successfully treated rheumatoid arthritis, inflammatory bowel disease, but not sepsis Dinarello (2000); early responder in wound healing Fahey III et al. (1990); Nurkesh et al. (2020); Eming et al. (2014); implicated in ischemia and reperfusion injury post cardiac surgery Zakkar et al. (2015); elevated in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS) Paul et al. (2021); IL-1$\alpha$ is elevated in neuroinflammation Samudyata et al. (2022); IL-1 is elevated in cytokine storm in COVID-19 Fara et al. (2020); IL-1$\beta$ in involved in joint inflammation (osteoarthritis) Rahman et al. (2023); IL-1 is an early marker of Alzheimer's disease (AD) Akiyama et al. (2000) and particularly, IL-1$\beta$ is elevated in AD Wang et al. (2015), Parkinson's disease (PD) Nagatsu et al. (2000); Roy et al. (2021) and Huntington's disease (HD) Rocha et al. (2016). |
| IL-4 | Downregulates inflammation Turnbull and Rivier (1999); diminishes proinflammatory cytokine levels Turnbull and Rivier (1999); elevated during cytokine storm in SARS-CoV-2 Hu et al. (2021); elevated in PD Nagatsu et al. (2000); Roy et al. (2021). |
| IL-6 | Activation of HPA axis, mediation of acute phase response Turnbull and Rivier (1999); high levels associated with severity of inflammation, ischemia and tissue damage in cardiac surgery McGuinness et al. (2008); Wan and Yim (1999); Lin et al. (2000); Zakkar et al. (2015); modulates IL-1 and TNF activity Lin et al. (2000); indicator of length of stay post-surgery in neonates Mahle et al. (2014); elevated during cytokine storm Hu et al. (2021) and redox imbalance in SARS-CoV-2 Paul et al. (2021) and an indicator of poor patient prognosis and risk of death García (2020); e Silva et al. (2022), and disease severity Fara et al. (2020); Han et al. (2020); biomarker for increased risk of psychosis in schizophrenia Gracias et al. (2022); early marker and indicative of shorter survival in lung cancer Li et al. (2022); elevated and therapeutic target in cancer Kumari et al. (2016); Barton (2001); Jones and Jenkins (2018); elevated after muscle injury Blau et al. (2015); marker for mortality rate in adults, sarcopenia and with TNF-$\alpha$, a marker for physical disability in women Lee et al. (2007); elevated in AD Akiyama et al. (2000); Wang et al. (2015), decreased in severe dementia Sala et al. (2003); Park et al. (2020), elevated in PD Nagatsu et al. (2000); Roy et al. (2021), HD Rocha et al. (2016) and early marker of severity of symptoms Green et al. (2019). |
| IL-8 | Chemokine action, directs chemotactic transport of cellular active matter Thomson and Lotze (2003); correlated with ventricular dysfunction post-cardiac surgery McGuinness et al. (2008); biomarker for risk of multiple organ failure Rocha et al. (2016), acute myocardial infarction after CPB Wan and Yim (1999); associated with prolonged stay in intensive care unit in neonates Mahle et al. (2014); indicator of risk of post-pericardiotomy syndrome Tamarappoo and Klein (2016); elevated during cytokine storm in SARS-CoV-2 Hu et al. (2021); early marker and indicative of shorter survival in lung cancer Li et al. (2022); increased in AD Akiyama et al. (2000), HD Rocha et al. (2016). |
| IL-10 | Downregulates inflammation Turnbull and Rivier (1999); diminishes proinflammatory cytokine levels Thomson and Lotze (2003); Turnbull and Rivier (1999); high levels may be beneficial for ischemia/reperfusion injury but is a risk factor for immunoparalysis in children Allen et al. (2006); indicated in Opal and DePalo (2000) to be clinically investigated for therapeutic use in acute lung injury, gut injury, inflammatory bowel disease, psoriasis and multiple sclerosis; modulator of TNF Lin et al. (2000); excess in Systemic Lupus Erythematosus (SLE) Elenkov and Chrousos (2002) and deficient in rheumatoid arthritis, multiple sclerosis (MS), type 1 diabetes mellitus, autoimmune thyroid disease Elenkov and Chrousos (2002); protective during and after cardiac surgery Wan and Yim (1999); indicative of disease severity Fara et al. (2020); Han et al. (2020) and cytokine storm in COVID-19 Hu et al. (2021); early marker for lung cancer Li et al. (2022); elevated in autoimmune diseases O'Shea et al. (2002), elevated in PD Nagatsu et al. (2000), HD Rocha et al. (2016); enhanced wound healing Nurkesh et al. (2020); Eming et al. (2014). |
| IL-12 | Elevated in those who were responsive to therapy for psoriasis Magee et al. (2021); stimulates protective immune cell proliferation and activation, and stimulates production of IFN-$\gamma$ but its toxicity has required variations in drug combinations with IL-12 administration to mitigate these effects and promote anti-cancer actions of immune cells via IL-12 and IL-12 - IL-23 signaling Propper and Balkwill (2022); Weiss et al. (2007); Verstockt et al. (2023); Berraondo et al. (2019); Lippitz (2013); elevated in patients with response to psoriasis therapy Magee et al. (2021); with IL-23, it's expression is elevated and IL-12 - IL-23 signaling promotes neurodegenerative diseases such as AD via amyloidosis Vom Berg et al. (2012) |
| IL-17 | IL-17 dysregulation is noted in autoimmune and inflammatory diseases such as inflammatory bowel disease, tumorigenesis and malignancy Berry et al. e Silva et al. (2022); Fabre et al. (2016); elevated and mediates development of autoimmune diseases (e.g., RA, inflammatory bowel disease IBD, type 1 diabetes mellitus T1DM, Celiac disease etc.) and is stimulated by IL-23 expression Costa et al. (2010); Zhu and Qian (2012); Kuwabara et al. (2017); elevated and protective action in response to bacterial and viral infections Mills (2023). |
| IFN-$\gamma$ | Involved in wound-healing response with chemokines to induce immune cell activation and migration Werner and Grose (2003); promotes macrophage proliferation in COVID-19 Zhang et al. (2021) and is a marker of hospitalization duration and mortality Cremoni et al. (2022); Gadotti et al. (2020); pleiotropic role in tumor microenvironments, and influence on progression of cancer and immunotherapy outcomes via environment-specific signaling effects on immune cells Gocher et al. (2022); Magee et al. (2021); Propper and Balkwill (2022); protective role in fungal and bacterial infections Mills (2023); possibly involved in occurrence of T1DM Zhu and Qian (2012); De George et al. (2023); involved in acceleration of neurodegeneration and cognitive dysfunction in AD via activation of microglia Kann et al. (2022); effect in reducing hospitalization duration when used a recombinant therapy for immunosuppression in sepsis, and Delano and Ward (2016); elevated in immune aging without telomere shortening Lustig et al. (2017). |
| TGF-$\beta$ | Cell proliferation, differentiation, tissue regeneration Turnbull and Rivier (1999); modulated by proinflammatory cytokines Roman-Blas et al. (2007); enable wound healing Werner and Grose (2003); Barrientos et al. (2008); Nurkesh et al. (2020); Eming et al. (2014); together with IL-1 and TNF-$\alpha$, implicated in osteoarthritis Roman-Blas et al. (2007); elevated in PD Nagatsu et al. (2000). |
| TNF-$\alpha$ | Cytotoxic to tumors Thomson and Lotze (2003); stimulates IL-1, IL-6, IL-8 production Turnbull and Rivier (1999); Cowled and Fitridge (2020); early responder in wound healing Fahey III et al. (1990); Nurkesh et al. (2020); Eming et al. (2014); post-cardiac surgery, associated with ventricular dysfunction, ischemia and reperfusion McGuinness et al. (2008); Wan and Yim (1999); deficient in SLE Elenkov and Chrousos (2002) and excess in rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus, autoimmune thyroid disease Elenkov and Chrousos (2002); causes myocardial apoptosis Wan and Yim (1999); elevated during cytokine storm in SARS-CoV-2 Hu et al. (2021) and marker for disease severity Fara et al. (2020) and death e Silva et al. (2022); elevated in neuroinflammation and acute respiratory distress syndrome (ARDS) in COVID-19 Samudyata et al. (2022); Fara et al. (2020); with IL-6, a marker for physical disability in women Lee et al. (2007); key in joint inflammation (osteoarthritis) Rahman et al. (2023); elevated in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS) Paul et al. (2021); involved in AD Akiyama et al. (2000); Wang et al. (2015), elevated in PD Nagatsu et al. (2000); Roy et al. (2021), HD Rocha et al. (2016); therapeutic target in HD Hsiao et al. (2014), PD McCoy et al. (2006) and cancer van Horssen et al. (2006). |

further disease-specific insights.

### 6.1. Local wounds

Localized injury involving tissue damage causes the transport of immune cells (leukocytes such as macrophages) to the injury site Werner and Grose (2003). They initiate phagocytosis to clear the damaged cells, prevent wound contamination, secrete cytokines, and deliver growth factors, all crucial functions for wound repair Fahey III et al. (1990). Broken blood vessels at the site of injury initiate blood clotting; the cytokines such as IL-1, IL-6, TNF-$\alpha$ and IL-8 (a neutrophil-activating chemokine) and IL-10, and growth factors (such as platelet-derived growth factor (PGDF), fibroblast growth factor (FGF), epidermal growth factor (EGF) etc.) act to help rebuild the blood vessels (angiogenesis), proliferate new cells, perform chemotactic cellular migration and thereby rebuild the tissue (re-epithelialization) and form the extracellular matrix Barrientos et al. (2008). Elevated levels of the proinflammatory cytokines IL-1, IL-6 and TNF-$\alpha$ are known to enable wound healing by inducing growth factor production in autocrine and paracrine actions. However, their actions to enhance or inhibit healing is dependent on the prevalent cytokine profile Barrientos et al. (2008). For example, it has been shown that in small amounts, TNF-$\alpha$ promotes wound healing, while in large amounts, it can be inhibiting Barrientos et al. (2008). IL-10 is involved in the downregulation of the proinflammatory cytokines as healing progresses and termination after completion of repair Werner and Grose (2003). The direct action of exogenous (systemic or local administration) of leptin on the wound site accelerates healing through enhanced keratinocyte mitogenesis Werner and Grose (2003).

### 6.2. COVID-19

In severe COVID-19 disease, the cytokine storm caused by SARS-CoV-2 infection has been shown to result in acute respiratory distress syndrome (ARDS) in some patients, increasing their length of hospitalization and potentially causing mortality Hu et al. (2021); Fajgenbaum and June (2020). IL-6 and IL-10 have been identified as predictors of disease severity and may be potential dynamic biomarkers for disease progression and mortality Han et al. (2020); Liu et al., Liu et al. (2020b); Ciotti et al. (2020). IL-10 has been found to be a marker for increased T cells (immune cells) and consequently, a predictor of severity of illness in those infected Neumann et al. (2020). These observations have motivated the use of cytokine blockade as a potential therapy sin COVID-19 (e.g., IL-6 blockade Liu et al. (2020a)). Symptoms of COVID-19 as well as post-acute sequelae of SARS-CoV-2 infection or 'long COVID' span multiple organ systems Davis et al. (2023); Reese et al. (2023), including neurological symptoms such as parosmia, anosmia, brain fog or executive dysfunction Melamed et al. (2023); Graham et al. (2021); Watson et al. (2021); Jaywant et al. (2021); Fine et al. (2022); Hugon et al. (2022), cardiovascular symptoms such as postural orthostatic tachycardia syndrome (POTS) Whiteson et al. (2022); Davis et al. (2023), gastrointestinal symptoms Elbeltagi et al. (2023), pulmonary symptoms Maley et al. (2022), chronic fatigue syndrome Paul et al. (2021); Herrera et al. (2021), and mental health disorders such as depression, anxiety and post-traumatic stress disorder Cheng et al. (2023). Abnormalities of cytokines such as IL-6, IL-10 have been shown to correlate with long COVID disease De Luca et al. (2022); Carlini et al. (2023). Cytokines have been linked to neuroinflammation and persistence of neurological symptoms often present in long COVID De Luca et al. (2022); Meyer et al. (2022); Boldrini et al. (2021). Since neuroinflammation can also result in psychiatric symptoms like schizophrenia, the behavior of proinflammatory cytokines has been investigated Samudyata et al. (2022); Gracias et al. (2022), and such effects were partially attributed to changes in brain connectivity caused by the disease Samudyata et al. (2022).

### 6.3. Cancer

The study of inflammatory response in patients with cancer Li et al. (2022); Ness and Modugno (2006) has enabled development of immunotherapeutic interventions via characterization of the role of cytokines in health, disease, and post-treatment. For instance, recently it has been shown that targeted cytokine signaling by administration of inducing agents can enable selective phagocytosis of cancer cells, without any side effects to the host Turco et al. (2023); Leonard and Lin (2023). Higher IL-6 levels in many cancers have been shown to accelerate disease progression through changes to the ability of cells to curb tumor growth and decrease of efficacy of treatments Kumari et al. (2016); Barton (2001); Ness and Modugno (2006); Lee and Margolin (2011); Jones and Jenkins (2018). Besides IL-6, many other cytokines such as IL-1$\beta$, IL-2, IL-7, IL-8, IL-10, IL-12, IL-15, IL-17, IL-21, IL-23, TNF-$\alpha$ and TGF-$\beta$ have been identified to have significant roles in the pathogenesis and malignancy of cancers and are of therapeutic interest in immunotherapy Koch et al. (2020); Berraondo et al. (2019); Berry et al. (2022); Propper and Balkwill (2022); Waldmann (2018); Conlon et al. (2019).

#### 6.3.1. CAR-T therapy side effects

Chimeric antigen receptor T-cell (CAR-T) therapies have exhibited highly effective anti-tumor responses and are undergoing rapid development to encompass various cancer types Maude et al. (2014b); Grupp et al. (2013); June et al. (2014). However, it is noteworthy that approximately 70 % of individuals receiving CAR-T therapy encounter potentially life-threatening side effects, with Cytokine Release Syndrome (CRS) emerging as the most prevalent among those complications Maude et al. (2014a). CRS entails an overwhelming immune response, characterized by symptoms such as lowered blood pressure, fever, increased capillary permeability, failure of multiple organ systems, which accompany heightened concentrations of serum cytokines, including IL-6 (for which tocilizumab is used to control CRS in CAR-T-cell therapy Si and Teachey (2020); Jones and Jenkins (2018)) and IFN-$\gamma$, among others Maude et al. (2014b); Teachey et al. (2016); Hay et al. (2017); Fitzgerald et al. (2017). The occurrence of severe CRS and its precise timing cannot be accurately predicted. The progression to severe CRS can be rapid, with mild initial symptoms escalating to unstable vital signs and necessitating ICU admission within a span of 6–48 h. Regrettably, it poses a constraint on the broader adoption of CAR-T therapies across diverse patient populations and cancer categories. Monitoring those serum cytokines in patients on an ongoing basis could provide early warning of impeding severe CRS, enabling earlier intervention and leveraging the potential of personalized medicine (i.e., using cytokine profiles to direct therapy).

### 6.4. Autoimmune diseases

Autoimmune disorders constitute a major class of diseases caused due to a chronically malfunctioning or overactive inflammatory response where the immune system is unable to distinguish the host from an inflammatory stimulus Gulati et al. (2016). Autoimmune diseases such as Systemic Lupus Erythematosus (SLE), the symptoms of which can vary from mild muscle pain and fatigue to debilitating conditions involving arthritis and organ dysfunction, have a higher incidence rate in women Elenkov and Chrousos (2002); Raphael et al. (2015); Rosenblum et al. (2015). Elevated IL-10 and IL-17, and deficient TNF-$\alpha$ are associated with SLE, while in autoimmune thyroid disease, a deficiency of IL-10 is noted Elenkov and Chrousos (2002); Raphael et al. (2015); Rosenblum et al. (2015); Zhu and Qian (2012). In rheumatoid arthritis, elevation of TNF-$\alpha$, and deficiency of IL-10 are indicated Dinarello (2000); Elenkov and Chrousos (2002). IL-17 and IL-23 expression, and the stimulatory effect of IL-23 on IL-17 expression are also implicated in autoimmune diseases such as rheumatoid arthritis, type 1 diabetes mellitus, psoriasis and inflammatory bowel disease (IBD) Zhu and Qian (2012); Kuwabara et al. (2017), making them viable

therapeutic targets Mills (2023). Additionally, IL-12 - IL-23 interactions are also involved in psoriasis and IBD Magee et al. (2021); Verstockt et al. (2023).

### 6.5. Neurodegenerative diseases

Alzheimer's Disease (AD) is a common cause of dementia associated with memory loss and degradation of mental function Galimberti et al. (2008). The pathogenesis of AD is related to the deposition of Amyloid Beta(A$\beta$)-42, a protein associated with lesions in the brain, which causes an inflammatory response and a localized upregulation of cytokines Mahle et al. (2014); Rubio-Perez and Morillas-Ruiz (2012), eventually leading to permanent and irreversible neuronal damage Wang et al. (2015); Galimberti et al. (2008). Recent research has suggested that this relationship may be reversed and that the observed cytokine expression may be a protective response to neuronal damage Decourt et al. (2022). Elevated levels of cytokines such as IL-6 and TNF-$\alpha$ in cerebrospinal fluid have been associated with neural inflammation, the buildup of A$\beta$-42 plaque, and the eventual progression of AD Akiyama et al. (2000); Sala et al. (2003); Galimberti et al. (2008); Park et al. (2020). There is a lack of consensus on the temporal and causal variations of these cytokines and the disease progression Sala et al. (2003); Decourt et al. (2022); Park et al. (2020). Parkinson's Disease (PD) is a neurodegenerative disease associated with loss of muscle control, including tremors, slow movement, and instability due to degeneration of dopamine neurons in the brain Nagatsu et al. (2000); Roy et al. (2021); X. Qin et al. (2016). Increased levels of IL-6, TNF-$\alpha$, and IL-1$\beta$ have all been observed in cerebrospinal fluid of patients with PD and this is further exacerbated by stimulatory interactions between them Rocha et al. (2016); X. Qin et al. (2016). Unlike AD and PD, Huntington's disease (HD) is hereditary, caused by a defect in the huntingtin gene Frank (2014), and involves upregulated cytokine expression Green et al. (2019); Menza et al. (2010) (with IL-1 being a potential early marker of disease Politis et al. (2015).

### 6.6. Immune aging

The effectiveness of inflammatory response to exogenous bodily threats declines with age and can affect the proper execution of regenerative cellular processes, further accelerating aging. Cytokines help repair imperceptible, daily wears and tears of muscles, and eventually influence their mass and function in aging people Liu et al. (2021); Blau et al. (2015); Cannon (1995); Pellegrino et al. (2024). Cytokines, especially IL-1 and TNF-$\alpha$, play an important role in repairing such injuries and have the ability to influence muscular mass and function in the older population Blau et al. (2015); Cannon (1995); Pellegrino et al. (2024). Further, the presence of IL-6 is another important determinant of loss of muscle regeneration Lee et al. (2007). A study of 465 subjects, aged 21 to 88 years, showed significant increases with age in IFN-$\gamma$, IL-6, and IL-10 confirm immune aging, however, these increases were not correlated with telomere shortening Lustig et al. (2017). Cytokines have also been studied in the context of pain in inflammatory response Zhang and An (2007); Cook et al. (2018); Schaible et al. (2010) and is also influential in the progression of osteoarthritis with age Rahman et al. (2023).

### 6.7. Other diseases and disorders

Anti-inflammatory actions of IL-10 and TNF-$\beta$ may improve immune tolerance in allergies, suggesting a potential mechanism of immunotherapy, with the optimal treatment imposing a significant clinical challenge Głobińska et al. (2018). Blocking of IL-1 action is known to successfully treat inflammatory bowel disease Dinarello (2000). A recent meta-study has shown that inflammatory biomarkers such as IL-6, IL-12, TNF-$\alpha$, CRP were elevated in depression based on a study of more than 5000 patients and controls each, with CRP and IL-12 showing lower variability, while the variability of others remained similar Osimo et al. (2020). IL-1$\beta$, TNF-$\alpha$ and IL-8 may be potentially indicative of depressive and suicidal episodes in pregnant women Szpunar et al. (2021). In critical care, the cause of septic shock which is associated with a high mortality risk in some patients is still unclear, motivating the need for cytokine monitoring Kurabayashi and Park (2023). Systemic inflammation modulation (e.g., in central nervous system) due to a novel drug comprising a microbial metabolite (butyrate) found in gut bacteria is being studied in experimental models of rheumatoid arthritis and multiple sclerosis Cao et al. (2024).

## 7. Challenges and opportunities

The generation of extensive inflammatory marker datasets may enable the improvement of healthcare and patient outcomes in the following ways. *(i) Diagnostics:* Recently, there is a move to understand how cytokine systems contribute not only to cancer, but also to diseases like rheumatoid arthritis, where joint inflammation is often heterogeneous, through holistic Next Generation Sequencing (NGS) methods (e.g., RNA-seq, ATAC-seq) to record how biological medicines or targeted therapies alter disease pathways and processes. Such methods are being used to work backwards to define the signals that might be relevant as diagnostic indicators. *(ii) Person-specificity:* The pathophysiology of inflammatory disorders varies with age, sex, and other confounding factors. For instance, the criteria used to determine sepsis, septic shock and eventual multiorgan failure in the critically ill are not effective for the very young or old populations Chakraborty and Burns (2019). Some autoimmune disorders such as SLE are disproportionately prevalent in women O'Shea et al. (2002), while osteomyelitis is more commonly diagnosed in children Dartnell et al. (2012). *(iii) Novel dynamic biomarker identification:* Identification of disease-specific optimal set of biomarkers is a dire need to enable clinical diagnostics and devise intervention Bray et al. (2016). The foregoing suggest the need for adequate individual and population baselining such as in Li et al. (2021). *(iv) Effects of systemic inflammation:* Data-driven modeling of cytokines in conjunction with the HPA axis hormones and APPs will help infer the mechanisms underlying systemic inflammation and alterations in HPA hormone secretory characteristics Galvis et al. (2022).

Factors that influence the choice of biomarkers associated with an inflammatory stimulus include the underlying cause of inflammation, ease of measurements, specificity, predictive ability, indifference to daily activities or medications, and whether directly modulating inflammation may help improve patient prognosis. The rise of CRP and ESR levels above certain thresholds have successfully helped determine treatments and interventions for osteomyelitis in children Dartnell et al. (2012). For CABG, cytokines such as IL-6, IL-8, IL-10, and TNF-$\alpha$ are most often studied along with HPA axis hormones Galvis et al. (2022), while IL-6 and TNF-$\alpha$ are both indicative for heart failure Swirski and Nahrendorf (2013). However, the response of acute phase proteins is patient-dependent (CRP is shown to vary with age, sex, health status of patients Woloshin and Schwartz (2005), may be affected by daily activities such as the drinking of coffee and exercise De Maat and Kluft (2001); Allen et al. (2015), health factors such as liver disease, pregnancy, iron deficiency anemia and kidney diseases, and are also sensitive to temperature and duration after which the samples are processed to obtain their levels, due to blood clotting Gulhar et al. (2018). Still, CRP is unaffected by the circadian phase or intake of corticosteroids and remains a potent biomarker of chronic inflammation Tu et al. (2023).

APPs alone may not suffice to infer the temporal evolution of systemic inflammatory response syndrome where the imbalance between the proinflammatory and anti-inflammatory cytokine expression may significantly alter the medical outcome. In Zairis et al. (2007), leukocyte count was shown to be more informative over CRP in relation to long-term mortality in patients with ACS, while SAA, fibrinogen or IL-6 did not have this additional predictive value. Moreover, while IL-6 predominantly causes CRP synthesis in the liver, the levels of IL-10 are crucial to determining the overall anti-inflammatory action Chalmers et al. (2019). Novel cytokine sensing paradigms Tu et al. (2023);

Kurabayashi and Park (2023); Lu et al. (2021), principled modeling approaches Faghih (2018) and clinical insights from experts Whitney et al. (2025), research and quantification of inflammation and prognosis from longitudinal inflammatory marker datasets for various diseases considered in this review may help reveal additional insight. Longitudinal data collection using such novel sensors will help minimize blood draws, enable point-of-care testing with near real-time monitoring of physiology and health, and inform personalized interventions by enabling large-scale studies of inflammation.

Wearables-based monitoring of physiological signals have been increasingly garnering interest both in the research community as well as the broader public. Commercial non-invasive sensors as part of smart watches that enable health monitoring by measuring heart activity and motion are commonplace today Tettey et al. (2024). However, wearables-based data collection involving non-invasive electrophysiology sensors Tettey et al. (2024); Wang et al. (2021) or minimally invasive hormone sampling Upton et al. (2023); Tu et al. (2023); Hirten et al. (2024) involve additional regulations required to guarantee patient privacy, confidentiality and safety in both clinical and real-world settings, and extensive validation against existing detection methods. In the United States, such sampling devices must undergo the approval of the institute's Institutional Review Board to commence any research data collection, and the eventual approval of the Food and Drug Administration for broader public and clinical adoption. While remote health monitoring using such devices can greatly improve healthcare during pandemic conditions by helping discern in-patient visits from patients for whom health can be managed remotely, even minimally invasive dynamic, near real-time measurements of inflammatory biochemical or bio-electrical markers that provide rich information regarding the one's health can disrupt one's activities of daily living. For example, wearing portable hormone sampling devices that involve catheter insertion to sample tissue biofluids may restrict one's ability to bathe, sleep freely or perform activities at work or home involving physical exertion. Therefore, these constraints must be addressed to the extent possible in the design of wearable or portable health sensors and the benefits to participants must be weighed against the minimal risk during inclusion of participants for studies and eventually to enable their approval, commercialization and broader use a reality Wang et al. (2021).

*Potential Solutions:* There is an increasing clinical need for dynamic cytokine monitoring and computational modeling to enable real-time detection of inflammatory events from inflammatory marker profiles, their integration into clinical scoring systems (algorithms designed to predict outcomes, aid decision making, support treatment options, manage clinical risk, or improve efficiency), and design of optimized, patient-specific treatments for cancer and other diseases Leonard and Lin (2023); Liu et al. (2021); Alex et al. (2007); Millán and Brunet (2016); McDonald et al. (2023); Margraf et al. (2020). Mathematical modeling has found success in characterizing hormone secretion using physiologically plausible, minimal finite order secretory dynamics to find the infusion and clearance rate constants, and quantify pulsatility Brown et al. (2001); R. Faghih et al. (2011); Faghih et al. (2014); Amin et al. (2022); Raju et al. (2023b,a) and can enable the joint system identification of cytokines and hormone response in inflammation. The development of novel wearable or portable sensors or point-of-care devices Aggas et al. (2023); Kurabayashi and Park (2023); Tu et al. (2023) that enable continuous monitoring of inflammatory marker levels similar to the recently developed automated hormone sampling devices Upton et al. (2023) will empower these computational modeling efforts within and outside clinical settings.

Data-driven computational modeling can help by: (i) characterization of temporal and causal response of inflammatory markers (ii) identification of cascaded feedback interactions governing inflammatory marker response, (iii) resolution of inflammatory marker signaling to separate exogenous secretory influences from endogenous or secondary secretory events, (iv) separation of the influence of each marker when redundancy is involved to determine key biomarkers, (v) early detection of flare ups in chronic inflammatory diseases such as SLE, rheumatoid arthritis, multiple sclerosis, or poor patient prognosis in systemic inflammatory response syndrome and other inflammatory diseases via identification of the optimal, disease-specific set of inflammatory biomarkers, and (vi) determination and continuous evaluation of targeted, patient-specific interventions. These clinical investigations will generate enough data over which machine learning and AI tools may be then leveraged for biomarker identification and inflammation scoring, similar to their profound success in predicting risk of cancer Yala et al. (2019) and in many other clinical applications Rajpurkar et al. (2022); Haug and Drazen (2023); Mueller et al. (2022); Varoquaux and Cheplygina (2022).

### 7.1. Interventions

In acute inflammatory conditions such as the inflammatory response due to cardiac surgery, cytokine monitoring can enable early detection and progression of a dysregulated inflammatory response. Acute phase proteins can indicate the initiation, progression and termination of the inflammatory response. For example, IL-6 and CRP can act via multiple pathways and in addition to being indicators of maladaptive inflammatory response also elicit protective daily repair and regeneration which may be misinterpreted as adverse low-grade inflammation without additional context of their actions Del Giudice and Gangestad (2018). Since the acute phase response is activated by cytokines, and it is the imbalance between proinflammatory and anti-inflammatory actions of cytokines which directs the course of the systemic inflammation and its timely termination, tracking and modulating cytokine actions may be beneficial to determine therapy Chakraborty and Burns (2019).

*Potential Solutions:* For neurodegenerative diseases, there is evidence that inhibiting the activity of certain cytokines, specifically TNF-$\alpha$, improved symptoms and increased neuronal density in patients, suggesting the potential to slow the progression of the disease by controlling the cytokine activity Hsiao et al. (2014); McCoy et al. (2006). Blocking the pathways of proinflammatory cytokine signaling has proved to be useful for treating autoinflammatory diseases de Jesus et al. (2023); Lin and Goldbach-Mansky (2022). Recently, many therapeutic strategies to enhance or inhibit cytokine actions indicate the applications of inflammation modulation via stimulation or inhibition of cytokine actions in many clinical settings Jones and Jenkins (2018); Leonard and Lin (2023); Cao et al. (2024). Wearable/out-patient monitoring may help manage chronic inflammatory conditions such as autoimmune disorders, migraine etc. by a reduction of blood draws. For example, biomarkers to predict multiple sclerosis relapses, Crohn's flares, or migraine headaches before symptoms manifest may serve clinically pressing needs pertaining to chronic inflammation monitoring similar to glucose monitoring for type II diabetes mellitus Skyler (2000); Hoeks et al. (2011). Here, the ability to distinguish elevated inflammatory marker levels due to an inflammatory stimulus from other influences such as daily activities (e.g., exercise) requires careful characterization of their behavior from exploratory studies. We emphasize what we have presented here is a first step for exploring various clinical applications.

Tracking of cytokine levels and system identification of inflammatory response in a patient-specific manner could help identify disease onset when intervention could have the greatest benefit to patients in cancer and other chronic diseases while addressing health disparities Louzoun et al. (2014). Currently, the systemic inflammation index (SII) and systemic inflammatory response index (SIRI) are used to evaluate the propensity of patients to develop cardiovascular disease and to assess the risk associated with re-occurrence of cardiac events and as indicators of patient's poor prognosis Dziedzic et al. (2022). Recently developed systemic organ failure assessment criteria have been shown to be more predictive of patients' mortality and organ dysfunction due to septic shock Chakraborty and Burns (2019). Similar to the estimation of hidden, internal cognitive and physiological states such as cognitive

arousal Wickramasuriya and Faghih (2020) and performance Khazaei et al. (2021); Amin et al. (2021), it may be possible to statistically infer the states of inflammation, pain, and healing together with the propensity for prolonged hospitalization or mortality Wickramasuriya and Faghih (2024). The role of cytokines as mediators of active transport of cellular matter in wound healing processes including during surgery has garnered interest in exploring active matter therapeutic strategies Ghosh et al. (2020).

### 7.2. Limitations

The list of inflammatory markers and diseases discussed here is incomplete, and many studies involving the tracking of cytokine levels referenced here involve animal models or single tissue models, minimal temporal sampling, and limited representation of various patient demographics based on age, sex, health status etc., which may limit the extrapolation of findings to human subjects across inflammatory diseases and timescales. The peripheral cytokine levels may have profound inter-individual differences due to confounding factors that influence (i) the underlying pathology that necessitated medical intervention (e.g., CABG or CPB surgery Galvis et al. (2022)) or (ii) the optimal dosage of TNF-$\alpha$ for treating cancer van Horssen et al. (2006) that provides beneficial health effects without adverse side effects Thomson and Lotze (2003). Moreover, systemic markers of disease activity (e.g., CRP) do not adequately reflect the nature of the local pathology, which may explain why some patients with the same condition respond differently to different classes of biological or targeted medicine.

The effect of local inflammations (e.g., neuroinflammation) on peripheral cytokine levels, and vice versa, can also adversely impact the progression of inflammatory diseases such as PD Ferrari and Tarelli (2011). However, the inverse problem of identifying how peripheral cytokine levels may provide additional local inflammatory stimuli-specific information is ill-posed. In physiological modeling, the inclusion of known mechanisms of hormone signaling along with secretory parameter estimates from experimental studies (including the pulsatile and circadian rhythmic properties, and the nature of secretory pulses) have allowed for development of computational methods that offer physiologically plausible inference of the underlying hormone secretion Faghih (2018). Expansion of such methods to cytokine inferencing may be a first step towards understanding the impact of tracking and modulating inflammatory markers in health and disease and warrants extensive testing and validation of the developed computational methods to draw physiologically meaningful conclusions.

## 8. Conclusion

The goal of this review was to inspire longitudinal studies of cytokines, hormones and APPs for tracking inflammation and informing treatment to improve medical outcomes in acute and chronic inflammation. We discussed their specific roles in inflammation and their potential as prognostic markers (see Table 3 for a summary of their clinical significance). Due to their specificity, we described the major cytokine expressions in acute and chronic inflammations including cardiac surgery, COVID-19, cancer, autoimmune diseases, neurodegenerative diseases and in aging. We described the state-of-the-art approaches for dynamic inflammatory marker sensing and anti-inflammatory treatment in cardiac surgery, where the timescale of inflammation onset and resolution makes it viable for clinical investigations. We highlighted the need for (i) the generation of longitudinal inflammatory marker datasets for biomarker identification, motivating especially the longitudinal study of cytokines that have the potential to reveal mechanisms that drive pathophysiology and offer disease-specific therapeutic insights, (ii) wearable or portable sensor development to generate such datasets via near real-time sensing, and (iii) modeling and computational analysis and data-driven approaches for a systematic study of the temporal evolution of inflammatory markers and the intricacies of their collective action, including the potential for the stimulation of specific markers as corrective effect responses in therapy and not just treating them as adverse responses. We call for inflammatory cytokine baselining, useful for epidemiological studies of pandemics and environmental exposures. Specifically, the development of novel biomedical instrumentation, together with computational methods for (i) early detection of inflammatory diseases, disorders or flare-ups, (ii) determination of causality relationships underlying the inflammatory marker response and (iii) investigation of person-specific medical interventions for patients are areas in which biomedical engineers may make scientific contributions. Such work may also have the peripheral benefit of relieving the cognitive burden of healthcare professionals providing critical care by providing key biomarkers for clinical decision-making, potentially improving medical outcomes, all exciting avenues for future research.

**Table 3**
Summary of detection methods and clinical significance of inflammatory markers.

| Inflammatory Marker | Detection methods | Clinical Significance |
|---|---|---|
| Hormones | Immunoassays (e.g., fluoroimmunoassay for growth hormone Kok et al. (2008), hemo-luminescent enzyme linked immunoassay (ECLIA) for detecting cortisol and adrenocorticotropic hormone (ACTH) Galvis et al. (2022)), liquid chromatography-tandem spectrometry Vignesh et al. (2024); Upton et al. (2023), tissue sampling of free hormone concentrations via portable devices (e.g., U-RHYTHM device where tissue sampling is followed by liquid chromatography and mass spectroscopy to determine concentrations Upton et al. (2023)) | Hormonal disorders indicate deviation from bodily homeostasis which may be of metabolic, inflammatory or neuroendocrine origins, and are non-specific (e.g., cortisol may be elevated in metabolic as well as inflammatory disorders Walker (2006)). The circadian and ultradian secretory patterns captured by dynamic monitoring can help quantify deviation from homeostasis Faghih et al. (2014, 2015); Pednekar et al. (2019). |
| Acute phase proteins | Immunoassays (e,g., enzyme-linked immunosorbent assay (ELISA), immunochemiluminometric assay (ICMA) or immunoturbidimetric assay) from blood sampling Guo et al. (2018), wearable sweat-based sensing Guo et al. (2018) | Used as non-specific indicators of inflammation due to hepatocyte stimulation by cytokines e.g., high sensitivity CRP is a biomarker for risk and outcomes associated with cardiovascular disease (see Table 1). |
| Cytokines | Immunosorbent assays such as ELISA Galvis et al. (2022), nano-plasmonic multiplex sensing Kurabayashi and Park (2023), sweat-based sensing Hirten et al. (2024) | Very low in health and more specific indicators of pro-inflammatory and anti-inflammatory mechanisms driving disease via disease-specific biomarkers Li et al. (2021). Their direct actions on immune cells makes them a viable therapeutic target for many diseases Liu et al. (2021). |

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## Declaration of competing interest

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