Chapter

Perspective Chapter: Inflammatory Cytokines and Postoperative Complications – Mechanistic Pathways and Therapeutic Targets

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Abstract

Surgical trauma induces a sterile inflammatory response characterized by the release of damage-associated molecular patterns (DAMPs) and activation of innate immune signaling pathways. While this response is essential for tissue repair and host defense, dysregulated cytokine activity can amplify endothelial dysfunction, microcirculatory impairment, and organ-specific injury. The clinical phenotype following surgery is not determined by a single mediator but by a dynamic balance between early hyperinflammation and subsequent compensatory immunosuppression. This shifting immune landscape contributes to postoperative pulmonary complications, acute kidney injury, myocardial dysfunction, neurocognitive impairment, and, in severe cases, multiorgan dysfunction. Emerging concepts such as immunoparalysis and persistent inflammation, immunosuppression, and catabolism syndrome (PICS) highlight the importance of temporal immune profiling. Integrating mechanistic insights with perioperative strategies, including protective ventilation, hemodynamic optimization, multimodal analgesia, and early rehabilitation, may enable phase-appropriate interventions. Understanding the endothelial-centered and time-dependent nature of cytokine responses is essential for translating immunobiology into rational postoperative care.

Keywords: cytokine signaling pathways, immunomodulation, inflammatory cytokines, postoperative complications, surgical stress response

1. Introduction

Postoperative complications remain a major global health challenge despite advances in surgical and anesthetic care. Major inpatient surgical procedures are associated with complication rates approaching 22% and mortality rates of up to 0.8%. Globally, an estimated 7 million patients experience serious postoperative complications each year, resulting in approximately 1 million deaths [1]. In some

settings, the burden is even greater; for example, gastrointestinal surgeries in Ethiopia report a 30-day complication rate of 30.5% and a mortality rate of 14.3% [2].

Beyond their clinical consequences, postoperative complications impose a substantial economic burden. They significantly increase hospitalization costs, rehospitalization rates, and outpatient utilization across diverse healthcare systems. In Kenya, hospitalization costs were 77% higher among patients with complications [3]. In Vietnam, respiratory complications added an average of 1,053 USD per procedure, corresponding to approximately 41% of Vietnam's GDP per capita in 2018, indicating a considerable economic burden in resource-limited settings [4].

These clinical and economic consequences ultimately reflect biological processes initiated at the time of surgical injury. At the biological level, many postoperative complications originate from dysregulated inflammatory and immune responses triggered by surgical trauma. Even in the absence of infection, tissue injury initiates a sterile inflammatory response characterized by the release of damage-associated molecular patterns (DAMPs) and the rapid activation of the innate immune system [5, 6]. While this response is essential for clearing damaged cells and promoting tissue repair, excessive or prolonged activation may propagate systemic inflammation and organ dysfunction.

Damage-associated molecular patterns, including high-mobility group box protein 1 (HMGB1), interleukin-1α (IL-1α), interleukin-33 (IL-33), and mitochondrial DNA, activate pattern recognition receptors (PRRs) and trigger intracellular signaling pathways that culminate in cytokine production [7–9]. Among innate immune cells, macrophages play a pivotal role as both sensors of tissue injury and regulators of inflammatory resolution. Their functional plasticity allows adaptation to evolving microenvironmental cues; however, an imbalance in cytokine production may shift this response from protective to maladaptive [10, 11].

In severe cases, uncontrolled cytokine amplification may progress to systemic inflammatory response syndrome (SIRS), characterized by widespread endothelial activation, capillary leak, and microcirculatory dysfunction [5, 12]. Importantly, endothelial dysregulation represents a central mechanistic link between molecular inflammation and organ-specific injury, contributing to postoperative pulmonary complications (PPCs), acute kidney injury, myocardial dysfunction, and neurocognitive impairment [5, 10]. Conversely, an exaggerated compensatory antiinflammatory response (CARS) may lead to immune suppression, increasing vulnerability to secondary infections and delayed recovery [5, 10].

Despite recognition of these clinical syndromes, postoperative complications often reflect an incomplete integration of molecular immunology into perioperative practice [5, 10]. Clinical manifestations, such as respiratory failure or acute kidney injury, are downstream expressions of complex cytokine-mediated signaling networks initiated at the cellular level [6, 7, 10, 13]. A coherent framework that connects early inflammatory signaling, endothelial dysfunction, immune phenotypes, and organ injury is, therefore, essential for risk stratification and targeted intervention [5, 10, 13].

This chapter adopts a translational perspective, tracing the continuum from DAMP release and intracellular signaling pathways to systemic immune dysregulation and organ-specific complications. By integrating mechanistic insights with clinical evidence, it aims to clarify how the dynamic balance between hyperinflammation and immunosuppression shapes postoperative outcomes.

Furthermore, it explores phase-appropriate therapeutic strategies, including anesthetic modulation, hemodynamic optimization, and emerging immunomodulatory approaches to support a shift from reactive management toward mechanism-based, personalized perioperative care.

2. Pathophysiology of sterile inflammation in surgery

Surgical trauma triggers a sterile inflammatory response, defined as inflammation that occurs in the absence of external pathogens or infection. This response is essential for clearing damaged cells and initiating tissue repair [5, 13, 14]. However, when excessive or dysregulated, it may progress to systemic inflammation and organ dysfunction. The transition from localized protective inflammation to maladaptive systemic injury represents a critical turning point in postoperative outcomes [5, 10, 15] (see **Figure 1**).

The primary drivers of sterile inflammation are endogenous molecules released from injured or necrotic cells, collectively known as DAMPs [7–9]. These molecules act as internal alarm signals that activate the innate immune system.

High-mobility group box 1 (HMGB1), a nuclear protein, is released into the extracellular space following cellular injury [7–9]. Once outside the cell, HMGB1 functions as a potent danger signal that amplifies inflammatory signaling cascades. Alarmins, including interleukin-1α (IL-1α) and interleukin-33 (IL-33), represent a subset of DAMPs capable of signaling tissue injury even in the absence of overt cell death. They play a crucial role in initiating the early inflammatory response [8, 12].

In addition, mitochondrial DAMPs (mDAMPs), such as mitochondrial DNA and other mitochondrial components released into the circulation after trauma, are

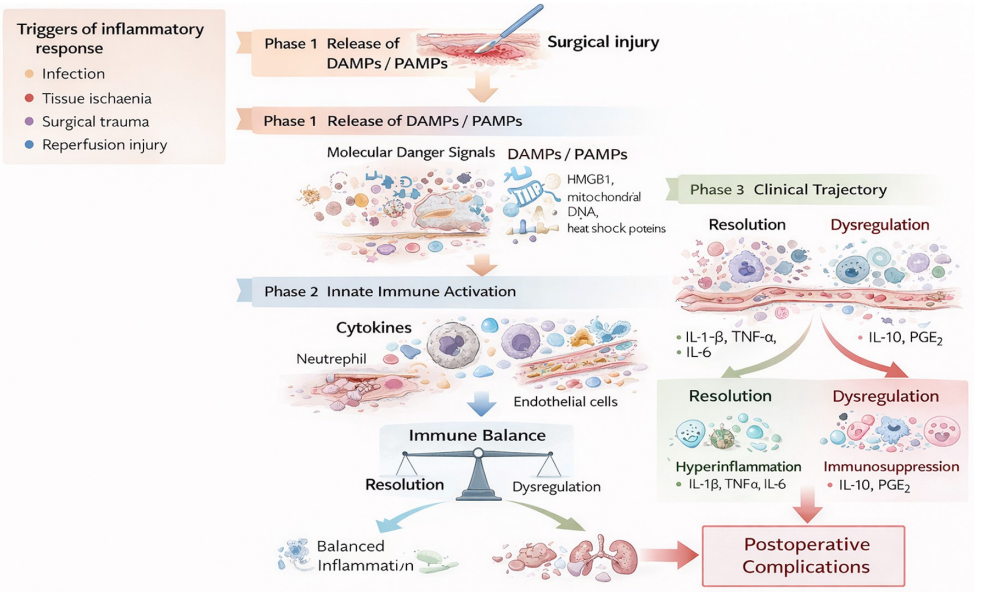

Figure 1.
Overview of the inflammatory and immune response to surgical injury, from DAMP release and innate immune activation to cytokine amplification and systemic organ dysfunction.

powerful activators of the innate immune system. Due to their bacterial ancestry, mitochondrial molecules are recognized as foreign by immune receptors, thereby intensifying systemic inflammatory propagation [9].

The innate immune system serves as the first responder to tissue injury through the recognition of danger signals. DAMPs bind to PRRs, including Toll-like receptors (TLRs), expressed on immune cells. This interaction activates intracellular signaling pathways that culminate in the production of proinflammatory mediators [5, 6, 11].

Macrophages occupy a central role in this process, acting both as sensors of tissue damage and regulators of inflammation [11]. Owing to their remarkable plasticity, macrophages can dynamically shift their phenotype in response to the microenvironment. Initially, they adopt a proinflammatory profile to contain injury and recruit additional immune cells. As healing progresses, they transition toward a reparative phenotype that promotes tissue resolution and the restoration of homeostasis.

Cytokines function as key orchestrators of the inflammatory response, coordinating immune cell recruitment, activation, and eventual resolution. Rapid cytokine release following surgical injury ensures an efficient local immune response necessary for repair [10, 11, 15].

However, when cytokine production becomes excessive or imbalanced, localized inflammation may escalate into SIRS [5, 7, 12]. This condition mimics sepsis despite the absence of infection and is characterized by widespread endothelial dysfunction, capillary leakage, and organ injury. In severe cases, sustained cytokine dysregulation may lead to multiple organ dysfunction syndrome (MODS) [5].

Clinically, the balance of cytokine production during this phase represents a decisive determinant of the postoperative trajectory. A well-regulated response supports recovery, whereas uncontrolled inflammation predisposes patients to adverse surgical complications [15–17].

3. Molecular orchestrators: Intracellular signaling pathways

The translation of extracellular stimuli, such as pathogen-associated molecular patterns (PAMPs) or cytokines, into coordinated cellular responses is governed by a sophisticated network of intracellular signaling cascades [7, 8, 13, 18]. These pathways do not act in isolation; rather, they form a complex regulatory "crosstalk" that determines the magnitude, duration, and specificity of the inflammatory response [13, 18].

The nuclear factor-kappa B (NF-κB) family of transcription factors is the central hub for innate and adaptive immunity. In its canonical form, it regulates the rapid expression of cytokines such as IL-1β, TNF-α, and IL-6 [18]. Under basal conditions, NF-κB dimers (typically p50/p65) are sequestered in the cytoplasm by IκB (Inhibitor of κB) proteins. Upon stimulation of receptors like TLR4 or TNFR, the IκB kinase (IKK) complex is activated. IKK phosphorylates IκB, marking it for ubiquitination and proteasomal degradation [19]. Once released, the NF-κB dimers translocate into the nucleus, binding to specific DNA sequences (κB sites) to initiate the transcription of over 200 genes involved in inflammation and cell survival [20].

Persistent NF-κB activation is a hallmark of chronic inflammatory diseases and serves as a key driver of the "cytokine storm" observed in severe viral infections.

While NF-κB initiates the "first wave" of cytokines, the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway is the primary mechanism through which these cytokines exert their downstream effects on other cells [21]. Upon cytokine binding to transmembrane receptors, receptor-associated JAKs (JAK1, JAK2, JAK3, or TYK2) undergo transphosphorylation. These activated kinases then create docking sites for STAT proteins [22]. Recruited STATs are phosphorylated, allowing them to form homodimers or heterodimers. These dimers enter the nucleus to regulate genes critical for immune polarization (e.g., Th1, Th2, Th17 differentiation) and the interferon (IFN) response [23].

The specificity of this pathway, where different cytokine receptors recruit distinct STAT combinations, has made it a high-value target for "jakinibs" (JAK inhibitors) in treating autoimmune disorders. The mitogen-activated protein kinase (MAPK) pathways are evolutionarily conserved kinase chains that integrate physical and chemical stress signals into biological outputs [24].

Three major MAPK branches are particularly relevant. ERK1/2 is activated primarily by growth factors; it regulates cell differentiation and survival. JNK (c-Jun N-terminal Kinase) is activated by environmental stress and proinflammatory cytokines; it is a key player in apoptosis and the T-cell response. p38 MAPK, often termed the "stress-activated protein kinase," is crucial for the production of inflammatory mediators and the stabilization of mRNA for cytokines like TNF-α [25].

Mitogen-activated protein kinase also phosphorylate and activate the activator protein-1 (AP-1) transcription factor. The AP-1 frequently works in tandem with NF-κB to achieve maximal induction of inflammatory genes, representing a critical integration point for cellular "danger" signals [24].

3.1 Signaling crosstalk in postoperative inflammation

In addition to individual pathway activation, inflammatory signaling after surgical injury is governed by an integrated network in which NF-κB, JAK/STAT, and MAPK pathways interact dynamically. Danger signals, such as DAMPs and PAMPs, activate pattern-recognition receptors, including Toll-like receptors, leading to rapid NF-κB activation and early transcription of proinflammatory mediators such as TNF-α, IL-1β, and IL-6. These cytokines subsequently amplify signaling through cytokine receptors and the JAK/STAT pathway, extending the inflammatory response to endothelial, immune, and parenchymal cells [18–23].

Crosstalk occurs at multiple levels. NF-κB signaling primes cytokine production, while MAPK pathways, particularly JNK and p38, enhance inflammatory gene expression via AP-1 and regulate cytokine mRNA stability. In parallel, cytokine-driven JAK/STAT activation modulates immune cell polarization and may either reinforce proinflammatory signaling or contribute to counter-regulatory responses, depending on temporal and cellular context [19, 21–25]. (see **Figure 2**).

This signaling convergence provides a mechanistic explanation for the transition from localized protective inflammation to systemic endothelial dysfunction and organ injury. It also underpins phase-specific perioperative modulation, in which early hyperinflammatory states may require attenuation of excessive pathway activation, whereas later stages characterized by immune exhaustion may benefit from supportive rather than suppressive strategies [26–28].

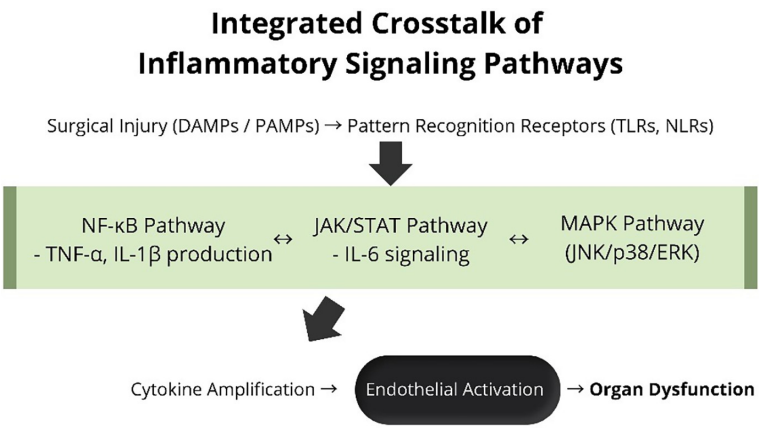

Figure 2.
Integrated crosstalk among major inflammatory signaling pathways in postoperative inflammation. Surgical injury induces the release of DAMPs and PAMPs, activating pattern-recognition receptors. This leads to activation of NF-κB, JAK/STAT, and MAPK signaling pathways, which interact through dynamic crosstalk to amplify cytokine production. The convergence of these pathways drives endothelial activation, resulting in microcirculatory dysfunction and subsequent organ injury. Source: From literature [18–25].

4. The dynamic balance: From SIRS to immunoparalysis

Major surgery produces a sterile inflammatory response that is initially adaptive, mobilizing innate immunity, recruiting leukocytes, and supporting tissue repair [26, 27]. However, when the early response becomes excessive, patients may enter a state resembling SIRS, driven by high circulating proinflammatory mediators (e.g., IL-1β, IL-6, TNF-α) and amplified intracellular signaling (notably NF-κB and MAPK) [26–28]. This "hyperinflammatory" phase can rapidly translate into endothelial activation and injury, with glycocalyx disruption, increased permeability, microcirculatory impairment, and tissue hypoxia. Clinically, the consequence is early postoperative organ dysfunction (e.g., hypoxemia/ARDS physiology, AKI, shock), and the severity of the inflammatory surge often correlates with the outcome. In trauma and critical illness models that closely mirror major surgery, proinflammatory cytokine excess is repeatedly linked to endothelial damage and systemic deterioration, illustrating how an initially local response becomes systemic and organ-threatening [26, 29–32].

4.1 Hyperinflammation (SIRS): When "necessary inflammation" becomes harmful

Hyperinflammation reflects a feed-forward loop: The DAMP-driven innate immune activation increases cytokine release; cytokines then further damage the endothelium and activate immune cells, perpetuating inflammation [33–35]. This phase is clinically "visible" as early tachycardia, fever/hypothermia, leukocytosis/leukopenia, rising lactate, escalating oxygen requirements, and increasing vasopressor need – features that may occur even without infection. Importantly, endothelial dysfunction is not just a marker of severity; it is a mechanistic hub that helps explain why cytokine surges can produce multiorgan dysfunction through

barrier failure, dysregulated coagulation, and impaired oxygen delivery at the microvascular level [34, 36–38].

4.2 Compensatory antiinflammatory response: Protection that may overshoot

In parallel with SIRS, the host activates counter-regulatory pathways, often described as a CARS, to limit collateral tissue damage. Antiinflammatory cytokines (classically IL-10 and TGF-β), neuroendocrine stress responses, and cellular reprogramming collectively "apply the brakes" to inflammation [33, 39]. In the perioperative context, this is protective when appropriately timed and proportionate. The problem is that CARS may overshoot, tipping patients into immune dysfunction characterized by impaired antigen presentation, reduced T-cell function, and diminished innate effector capacity. Contemporary trauma–immunity syntheses emphasize that SIRS and CARS are not strictly sequential; they can occur simultaneously, producing a mixed phenotype where patients exhibit ongoing inflammation while becoming increasingly vulnerable to infection [39–41].

5. Emerging concept 1: Immunoparalysis and vulnerability to secondary infection

Immunoparalysis refers to a state of profound immune suppression that follows an initial hyperinflammatory insult. While early surgical trauma and sepsis are characterized by a cytokine surge and innate immune activation, a subset of patients subsequently transitions into a phase of functional immune exhaustion. Mechanistically, this process involves lymphocyte apoptosis and exhaustion, expansion of suppressor cell populations, dysregulated cytokine signaling, and increased expression of inhibitory immune checkpoints [33, 42, 43].

Clinically, immunoparalysis is particularly concerning in postoperative and critically ill patients because it predisposes them to secondary infections, impaired source control, tolerance, delayed recovery, and prolonged ICU stay [40, 44]. Importantly, the transition toward immune suppression may occur even as classical inflammatory markers decline. Thus, decreasing fever curves or falling C-reactive protein (CRP) levels do not necessarily indicate immune recovery.

Contemporary research increasingly emphasizes measurable immune "signatures" rather than relying solely on static inflammatory markers. Multiplex immune mediator profiling and dynamic biomarker trajectories have demonstrated that immune suppression can coexist with or follow systemic inflammatory responses, particularly in patients with complicated postoperative courses [45, 46]. In both sepsis and surgical critical illness literature, late morbidity is strongly associated with persistent immune dysfunction and susceptibility to secondary infections [36, 40].

Perioperative management should extend beyond assessing "how inflamed" a patient is. An equally critical question is whether the patient is transitioning into functional immunosuppression. In high-risk surgical populations, this perspective supports earlier diagnostic vigilance for occult infection and a more cautious approach to therapies that may further suppress immune competence [44, 45].

6. Emerging concept 2: Persistent inflammation, immunosuppression, and catabolism syndrome

For some patients, particularly older, frail individuals or those experiencing complicated ICU trajectories, the immune response does not resolve toward homeostasis. Instead, it evolves into a chronic critical illness endotype known as PICS [26, 40].

Persistent inflammation, immunosuppression, and catabolism syndrome is characterized by a self-perpetuating triad: ongoing low-grade inflammation, sustained immune suppression, and progressive catabolic metabolism [40, 44]. Unlike early SIRS, which reflects excessive acute inflammation, PICS represents the maladaptive persistence of immune dysregulation coupled with metabolic breakdown. Endothelial dysfunction, impaired organ perfusion, and sustained inflammatory signaling contribute to multiorgan vulnerability [34, 40].

Clinically, PICS manifests as persistent organ dysfunction, recurrent nosocomial infections, poor wound healing, prolonged ventilator dependence, sarcopenia, and failure to rehabilitate [34, 40]. Importantly, the syndrome reframes postoperative complications: The problem is not merely excessive early inflammation but the failure of immune resolution. Chronic immune exhaustion, cytokine dysregulation, and impaired host defense create a state of reduced immune fitness, increasing late morbidity and healthcare burden [33, 46].

Although definitional heterogeneity persists across studies, there is convergence around the concept that PICS represents sustained immune imbalance with major downstream functional consequences [40, 43]. For anesthesiologists and perioperative teams, recognizing this trajectory is crucial in patients who deviate from expected recovery patterns, particularly those with prolonged ICU courses [27, 40, 43].

Practical implication for anesthesiologists: Prevention begins early, minimizing iatrogenic contributors (over-sedation, immobility, avoidable transfusion burden, prolonged mechanical ventilation) and supporting recovery pathways (early nutrition and mobilization where feasible). Once established, PICS highlights the need for multidisciplinary, recovery-oriented ICU strategies rather than repeated reactive escalation [26, 27, 40, 43].

7. Applying the inflammatory homeostasis model to perioperative care

Conceptually, the dynamic balance between hyperinflammation and immunosuppression reflects the principle of inflammatory homeostasis after surgical injury (see **Figure 3**). The continuum from SIRS to CARS, and, in some patients, to immunoparalysis or PICS, provides a mechanistic framework for perioperative clinical decision-making [26, 27].

During the early hyperinflammatory phase, strategies that preserve inflammatory homeostasis may help prevent excessive cytokine amplification and endothelial injury. These include lung-protective ventilation, avoidance of excessive hyperoxia, maintenance of normothermia, and careful hemodynamic optimization. Such interventions aim to attenuate the magnitude of the inflammatory response while maintaining physiological stability [47, 48].

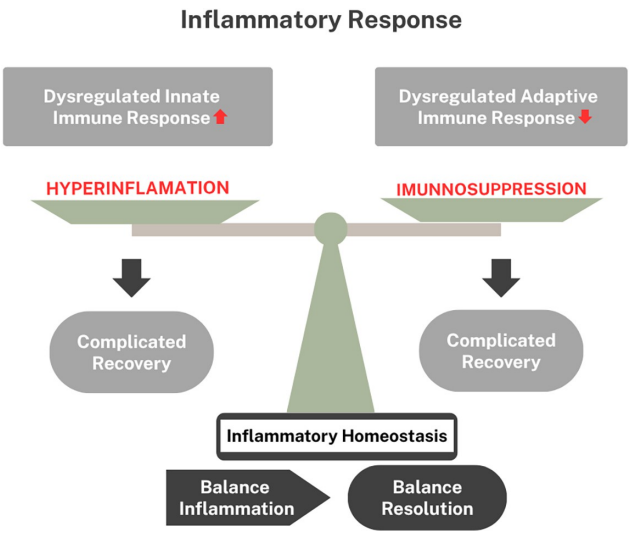

Figure 3.
Dynamic balance between hyperinflammation and immunosuppression in postoperative immune homeostasis.

In later phases, particularly when patients develop recurrent infections or prolonged dependence on intensive care support, clinicians should consider the possibility that the immune response has shifted away from inflammatory homeostasis toward an immunosuppressed state. In this context, heightened vigilance for secondary infections and cautious use of therapies that may further suppress immune function become essential [40, 43, 44].

Overall, maintaining inflammatory homeostasis should be viewed as a central objective of perioperative management. Recognizing the dynamic trajectory of the immune response allows clinicians to move beyond static diagnostic labels and toward mechanism-informed strategies that balance necessary inflammation with the preservation of immune competence [26, 27, 43, 49].

8. Cytokine-mediated organ dysfunction after surgery: Organ-specific

Systemic inflammatory response after major surgery can progress into a cytokine storm that injures the endothelium, causes capillary leak and microcirculatory failure, culminating in multiorgan dysfunction. Surgical trauma releases DAMPs that activate PRRs (TLR, NLRP3, cGAS–STING), driving NF-κB/MAPK and high output of IL-6, IL-1β, TNF-α, and other mediators, which link the different organ complications [27, 28, 49].

8.1 Pulmonary: ALI and ARDS

In the lung, circulating cytokines and activated neutrophils damage the alveolar–capillary barrier, with endothelial activation, glycocalyx shedding, and leukocyte adhesion [30, 49]. This leads to protein-rich edema, impaired gas exchange, and clinically manifests as ALI/ARDS in the postoperative/SIRS setting [30, 37, 49].

8.2 Renal: Inflammatory AKI

Kidneys are highly vulnerable to hypoperfusion and endothelial dysfunction. Systemic inflammation and tubular PRR activation amplify IL-6, TNF-α, and chemokine production, promoting tubular injury and microvascular congestion, manifesting as AKI after major surgery, sepsis, or shock [30, 49, 50].

8.3 Cardiovascular: Myocardial injury and hemodynamic instability

Cytokine-driven endothelial injury causes vasoplegia, capillary leak, and reduced vascular responsiveness to vasopressors, producing hypotension and shock [30, 49]. At the heart, hyperinflammation and microcirculatory dysfunction lead to myocardial injury and global systolic impairment, similar to what is seen in other hyperinflammatory states such as MIS-C and COVID-19, where IL-6/IL-8-skewed responses correlate with dysfunction [37, 51].

8.4 Neurological: Neuroinflammation and POCD

Surgery-induced systemic inflammation propagates to the brain, activating microglia and astroglia, disrupting the blood–brain barrier, and sustaining neuroinflammation [29, 52]. This is linked to postoperative delirium and postoperative cognitive dysfunction (POCD), especially in older patients, with a long-term risk of persistent cognitive decline or dementia [29].

8.5 Tissue repair: Wound healing and fibrosis

Cytokines orchestrate normal wound healing, but sustained IL-1β, IL-6, TNF-α, and profibrotic mediators (e.g., TGF-β) prolong the inflammatory phase, impair reepithelialization, and drive fibroblast activation and extracellular matrix deposition [28, 49, 53]. Clinically, this manifests as delayed wound healing, excessive scarring, and organ fibrosis following ischemia–reperfusion or burns [53, 54].

The clinical manifestations summarized in **Table 1** underscore that the endothelium functions as a central mechanistic hub linking cytokine signaling to organ dysfunction. Regardless of the initial trigger, whether IL-6–dominant hyperinflammation or IL-10–mediated compensatory suppression, cytokine-driven endothelial activation governs vascular permeability, leukocyte trafficking, coagulation balance, and microcirculatory integrity [10, 34, 37]. Consequently, postoperative organ injury often represents a downstream expression of endothelial dysregulation rather than the isolated effect of a single mediator [34, 49]. Importantly, clinical phenotypes are not determined by one cytokine in isolation but by the dynamic interplay between proinflammatory amplification (SIRS-like responses) and counter-regulatory antiinflammatory pathways (CARS, immunoparalysis) [41, 43, 49]. The relative dominance of these pathways shifts over time, creating heterogeneous and evolving immune endotypes. Timing is critical: Interventions that attenuate excessive inflammation may be appropriate in the early hyperinflammatory phase, whereas later stages characterized by immune exhaustion and catabolism require strategies focused on immune support, infection vigilance, metabolic optimization, and rehabilitation [26, 40, 43, 49].

Dominant cytokines/Immune pattern	Target organ/ system	Pathophysiologic mechanism	Clinical phenotype	Practical perioperative implication	Reference
IL-6, TNF-α, IL-1β (early hyperinflammatory response)	Lung	Endothelial activation, increased vascular permeability, neutrophil infiltration, alveolar–capillary barrier disruption	Postoperative pulmonary complications (PPC), hypoxemia, ARDS-like physiology	Lung-protective ventilation, avoiding hyperoxia, early mobilization, and opioid-sparing analgesia	[10, 37, 49]
IL-6, TNF-α, HMGB1	Kidney	Renal microvascular dysfunction, tubular apoptosis, inflammatory infiltration	Acute kidney injury (AKI)	Goal-directed fluid therapy, avoid nephrotoxins, optimize perfusion pressure	[5, 10, 34]
TNF-α, IL-1β, IL-6	Cardiovascular system	Myocardial depression, nitric oxide–mediated vasodilation, endothelial dysfunction	Vasoplegia, perioperative hypotension, myocardial injury	Vasopressor titration: avoid excessive inflammatory amplification and maintain hemodynamic stability	[13, 34, 49]
IL-6, IL-1β, microglial activation	Brain (CNS)	Blood–brain barrier permeability, neuroinflammation, neurotransmitter imbalance	Postoperative delirium (POD), cognitive dysfunction (POCD)	Delirium prevention bundle, minimize deep sedation, maintain oxygenation, and normocapnia	[29, 52]
IL-10, TGF-β (antiinflammatory dominance/CARS)	Systemic immune function	Lymphocyte exhaustion, reduced antigen presentation, immune checkpoint upregulation	Immunoparalysis, secondary infection, delayed recovery	Infection surveillance, avoiding unnecessary immunosuppression, and phenotype-aware management	[41, 43]
Persistent IL-6 + catabolic cytokine milieu	Whole-body metabolism	Sustained low-grade inflammation, muscle proteolysis, impaired anabolism	Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS)	Early nutrition, protein optimization, rehabilitation	[40, 43]
IL-1β, TNF-α (excessive early response)	Endothelium (cross-organ hub)	Glycocalyx shedding, capillary leak, microthrombosis	Multiorgan dysfunction syndrome (MODS) phenotype	Hemodynamic optimization, avoiding fluid overload, and employing endothelial-protective strategies	[32, 34, 35, 49]
TGF-β (late phase)	Wound/tissue repair	Fibroblast activation, extracellular matrix deposition	Delayed healing or fibrosis	Glycemic control, adequate perfusion, and avoiding prolonged inflammatory stress	[14, 15]

Table 1.
Interaction between cytokines, organ systems, and clinical phenotypes in the postoperative period.

Recognizing this temporal and endothelial-centered framework is essential for translating cytokine biology into rational, phase-appropriate perioperative management [26, 27, 49].

9. Perioperative cytokine risk stratification

9.1 Populations at risk and inflammatory dysregulation

Major surgery can trigger SIRS, leading to organ dysfunction via proinflammatory cytokines, endothelial injury, and glycocalyx damage [49]. Surgical trauma–induced inflammation is closely linked to postoperative immunosuppression and cancer progression, especially after extensive oncologic surgery [43]. Advanced age, comorbidities (diabetes, obesity, cancer), and baseline immune alterations shape a "high postoperative inflammatory dysregulation–risk phenotype" that should be specifically targeted and phenotyped in future trials [26, 43, 49].

9.2 Role of IL-6, CRP, and procalcitonin in infection discrimination

IL-6 is a key early cytokine driving the acute-phase response; it rises rapidly after tissue injury and precedes the increase in CRP and body temperature [55, 56]. IL-6 peaks within hours after pulmonary cancer surgery, whereas CRP peaks days later; both are associated with postoperative infection risk but add only modest predictive value beyond clinical factors [44]. In vascular surgery patients, dynamic perioperative IL-6 and CRP trajectories helped identify those prone to complications and prolonged hospitalization [57].

C-reactive protein is a widely used, sensitive but nonspecific marker of postoperative inflammation; elevated values on postoperative days 3–4 predict complications in abdominal surgery [9] and poorer long-term prognosis after various cancers [43].

Procalcitonin and CRP help differentiate sepsis from noninfectious SIRS in ICU patients, with CRP being useful for inflammation tracking but having limited specificity [14]. Large hospital data show frequent discordance between CRP, PCT, and IL-6, and emphasize combined interpretation rather than reliance on a single marker [58].

9.3 Integration with clinical scores and management implications

American Society of Anesthesiologists (ASA) physical status and related models strongly predict postoperative mortality and correlate with comorbidity burden [59–61]. Combining ASA or other scores with additional objective data improves risk prediction compared with either alone [61, 62].

Protective perioperative strategies, such as lung-protective ventilation, goal-directed hemodynamic therapy, enhanced recovery after surgery (ERAS) pathways, and multimodal analgesia, reduce PPCs and stress-response–related morbidity [47, 48, 56, 63, 64].

10. Therapeutic modulation of postsurgical inflammation

After major surgery, immune modulation aims to blunt the harmful "cytokine storm" while preserving host defense and wound healing. Strategies span anesthetic choices, drugs, perioperative pathways, and, in the future, phenotype-guided immunotherapy [27, 38, 44, 56, 57].

10.1 Anesthetic techniques: General anesthesia alone versus combined regional–general anesthesia

The choice of anesthetic technique may influence the magnitude of the perioperative inflammatory response and subsequent postoperative outcomes [10, 27, 56]. General anesthesia alone provides adequate hypnosis and immobility but may not sufficiently attenuate surgical stress and nociceptive signaling, potentially contributing to increased sympathetic activation, opioid requirements, and systemic inflammatory responses [26, 27, 56].

In contrast, combining regional anesthesia techniques, such as epidural, paravertebral, or fascial plane blocks, with general anesthesia can modulate the surgical stress response by reducing nociceptive input, opioid consumption, and neuroendocrine activation [27, 47, 56, 63]. These regional techniques are key components of ERAS pathways and have been associated with reduced PPCs, improved analgesia, and a decreased incidence of organ dysfunction [47, 48, 64].

Thoracic epidural or chest wall regional analgesia, when incorporated into multimodal perioperative strategies, has been linked to improved respiratory mechanics, reduced respiratory depression, shorter durations of mechanical ventilation, and a lower incidence of arrhythmias following major surgery [47, 48, 63]. Beyond its analgesic effects, regional anesthesia may also contribute to improved immune and inflammatory regulation by attenuating neuroendocrine stress responses [27, 56].

Regarding anesthetic agents, volatile anesthetics such as desflurane and sevoflurane have been reported to attenuate local pulmonary inflammatory markers compared with propofol-based total intravenous anesthesia (TIVA) [10, 26]. However, evidence demonstrating clear differences in clinical outcomes between these approaches in noncardiac surgery remains limited [27, 56]. Overall, a strategy combining regional anesthesia with light general anesthesia appears to provide beneficial immunomodulatory effects, largely through opioid-sparing analgesia and improved physiological stability rather than through a single molecular pathway [47, 48, 64].

10.2 Pharmacologic interventions

Classical corticosteroids provide broad antiinflammatory effects and are embedded in several ERAS protocols (e.g., for nausea prevention and inflammation attenuation), but must be balanced against infection and glycemic risk [47, 48]. Targeted cytokine antagonists (e.g., IL-6 or IL-1 blockade) and other novel antiinflammatory agents are conceptually attractive for cytokine-storm–like states, but high-quality perioperative trials are sparse; use remains experimental and outside routine ERAS recommendations [28, 30, 49].

10.2.1 Clinical pathways: ERAS, protective ventilation, GDFT

The ERAS bundles for thoracic and cardiac surgery emphasize prehabilitation, minimal fasting, regional analgesia, opioid-sparing multimodal analgesia, normothermia, euvolemic or goal-directed fluid therapy (GDFT), and early mobilization, all aimed at limiting surgical stress and organ dysfunction. In noncardiac surgery, a metaanalysis shows that enhanced recovery pathways, lung-protective ventilation, epidural analgesia, and GDFT each probably reduce PPCs; enhanced recovery and GDFT reached trial-sequential thresholds for approximately 25% PPC risk reduction. Protective ventilation and postoperative CPAP/NIV also likely mitigate lung injury in high-risk patients [47, 48, 64].

10.2.2 Toward personalized immunotherapy

Future directions point to tailoring modulation to patient immune phenotypes: Frail or chronically inflamed patients may benefit from stronger dampening of innate responses; immunosuppressed or septic phenotypes may need immune stimulation rather than suppression [26, 40, 43]. Integrating biomarkers (e.g., IL-6 trajectories, endothelial injury markers), genomics, and dynamic risk scores into ERAS and anesthetic choices could enable precision "immuno-ERAS," but this remains largely conceptual, with little prospective validation to date [27, 44, 55–57].

11. Conclusion(s)

Postoperative complications reflect the biological consequences of the host response to surgical injury. Sterile inflammation, initiated by the release of damage-associated molecular patterns, activates innate immune pathways and intracellular signaling networks that drive cytokine production and systemic immune activation. When this response remains proportionate, it supports tissue repair and recovery. When dysregulated, it promotes endothelial dysfunction, microcirculatory disturbance, and organ-specific injury involving the lungs, kidneys, cardiovascular system, and brain. The postoperative clinical trajectory is therefore shaped by the dynamic balance between early hyperinflammation and counter-regulatory immune suppression, which in some patients may progress toward immunoparalysis or PICS.

A mechanistic understanding of inflammatory homeostasis provides a useful framework for translating molecular immunology into perioperative practice. Recognizing how cytokine signaling, endothelial biology, and immune phenotypes interact over time allows clinicians to better interpret postoperative deterioration and tailor supportive strategies accordingly. Perioperative management should therefore aim to preserve physiological stability, limit excessive inflammatory amplification, and maintain immune competence. Future progress in perioperative medicine will likely depend on improved integration of clinical risk stratification, biomarker trajectories, and phenotype-guided therapeutic strategies that support more precise and mechanism-informed care.

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Conflict of Interest

The authors declare no conflict of interest.

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