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Surgery-induced immune modulation: a comprehensive review

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Surgical intervention induces profound and dynamic alterations in the body's immune reactivity. The postoperative period is typically characterized by an early hyperinflammatory response, followed by compensatory immunosuppression; however, in some cases, a maladaptive condition known as persistent inflammation, immunosuppression, and catabolism syndrome may develop. These immune disturbances are associated with an increased risk of infectious complications, impaired tissue repair, organ dysfunction, and potential tumor progression. Modulation of surgery-induced changes in immune responsiveness may represent a promising strategy for improving surgical outcomes. The aim of this review is to analyze and synthesize current literature on the mechanisms and key determinants of postoperative immunomodulation.

The review discusses the complex mechanisms underlying the initiation and progression of postoperative systemic hyperinflammation, as well as the triggers and pathways involved in compensatory anti-inflammatory response syndrome. Particular attention is given to the temporal dynamics and phase-dependent nature of postoperative immunomodulation. Key determinants shaping the intensity and trajectory of post-surgical immune responses are examined, including surgical factors such as the extent and duration of tissue injury, as well as anesthetic techniques and agents. In addition, patient-specific factors influencing postoperative immune modulation, such as age, sex, and preoperative immune status, are analyzed in detail.

Overall, the early postoperative period represents an underutilized window of therapeutic opportunity for improving surgical outcomes. However, its effective clinical exploitation requires a deeper understanding of the mechanisms underlying post-surgical immunomodulation, as well as the development and implementation of highly sensitive, dynamic biomarkers for continuous, real-time monitoring. Such advances would enable truly personalized, phase-adapted therapeutic strategies tailored to the patient's evolving immune state.

Keywords
post-surgical immunomodulation, systemic inflammatory response syndrome, compensatory anti-inflammatory response syndrome, persistent inflammation, immunosuppression, and catabolism syndrome.

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Surgical procedures profoundly impact the body's immune response. In most cases, the postoperative period is characterized by generalized immunosuppression [23, 74], although an alternative pattern may involve sustained inflammatory activation [6]. The magnitude and duration of these immune alterations are influenced, in part, by the extent of the surgical insult. Restoration of immune function may require several weeks to months.

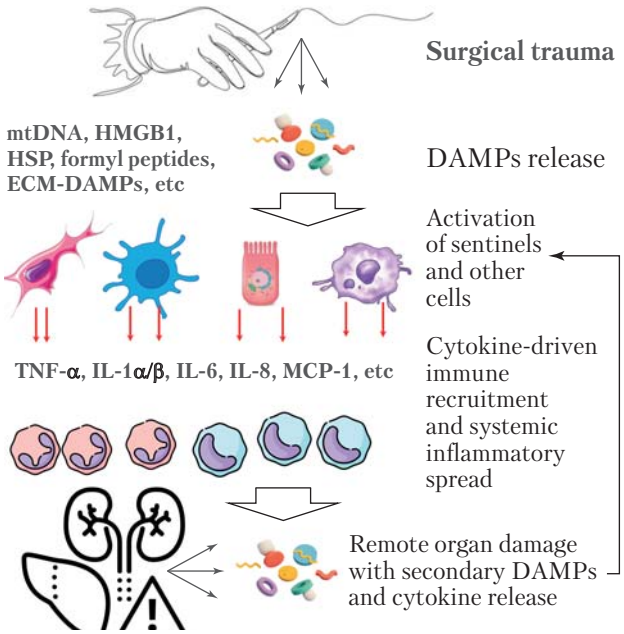
The clinical consequences of postoperative immune dysregulation remain incompletely defined. Nonetheless, accumulating evidence suggests that these changes are associated with an increased risk of postoperative complications. Immunosuppression in the postoperative setting is associated with increased susceptibility to infection and may also facilitate tumor development or progression [4]. In contrast, persistent postoperative inflammation can promote multiple organ dysfunction and exhaust the immune system's reparative capacity [46].

This review explores the factors and complex mechanisms driving post-surgical immunomodulation, highlighting its clinical relevance and discussing current and emerging strategies to mitigate associated immune disturbances.

Mechanisms, timeline, and surgery-associated determinants of post-surgery immunomodulation

It is well established that trauma profoundly alters immune function, and this response is both complex and highly dynamic. Extensive tissue injury associated with surgical trauma leads to the release of a wide array of endogenous antigens and mediators. Although this response is sterile, these factors engage cells of the innate immune system, triggering a local inflammatory reaction that can rapidly evolve into a systemic process, culminating in systemic inflammatory response syndrome (SIRS) [30, 66].

The primary aim of the inflammatory response is to contain further injury, facilitate the clearance of cellular debris, and promote tissue repair. The magnitude of immune activation during SIRS correlates with the extent of tissue damage and the concentration of inflammatory mediators produced at the site of injury. Almost concurrently, a crucial counter-regulatory mechanism is activated – the compensatory anti-inflammatory response syndrome (CARS) [38, 1]. This response reflects a state of global immunosuppression and is mediated predominantly by the adaptive immune system, particularly T lymphocytes. In addition, the dynamic, sequential metabolic polarization of innate immune cells is an important regulatory component of this process.



Mt-DNA – mitochondrial DNA; HMGB1 – high-mobility group box 1; HSP – heat shock protein; ECM-DAMPs – extracellular matrix Damage-Associated Molecular Patterns; IL – interleukin; TNF – tumor necrosis factor; MCP – monocyte chemoattractant protein

Figure 1. **Surgical-associated SIRS**

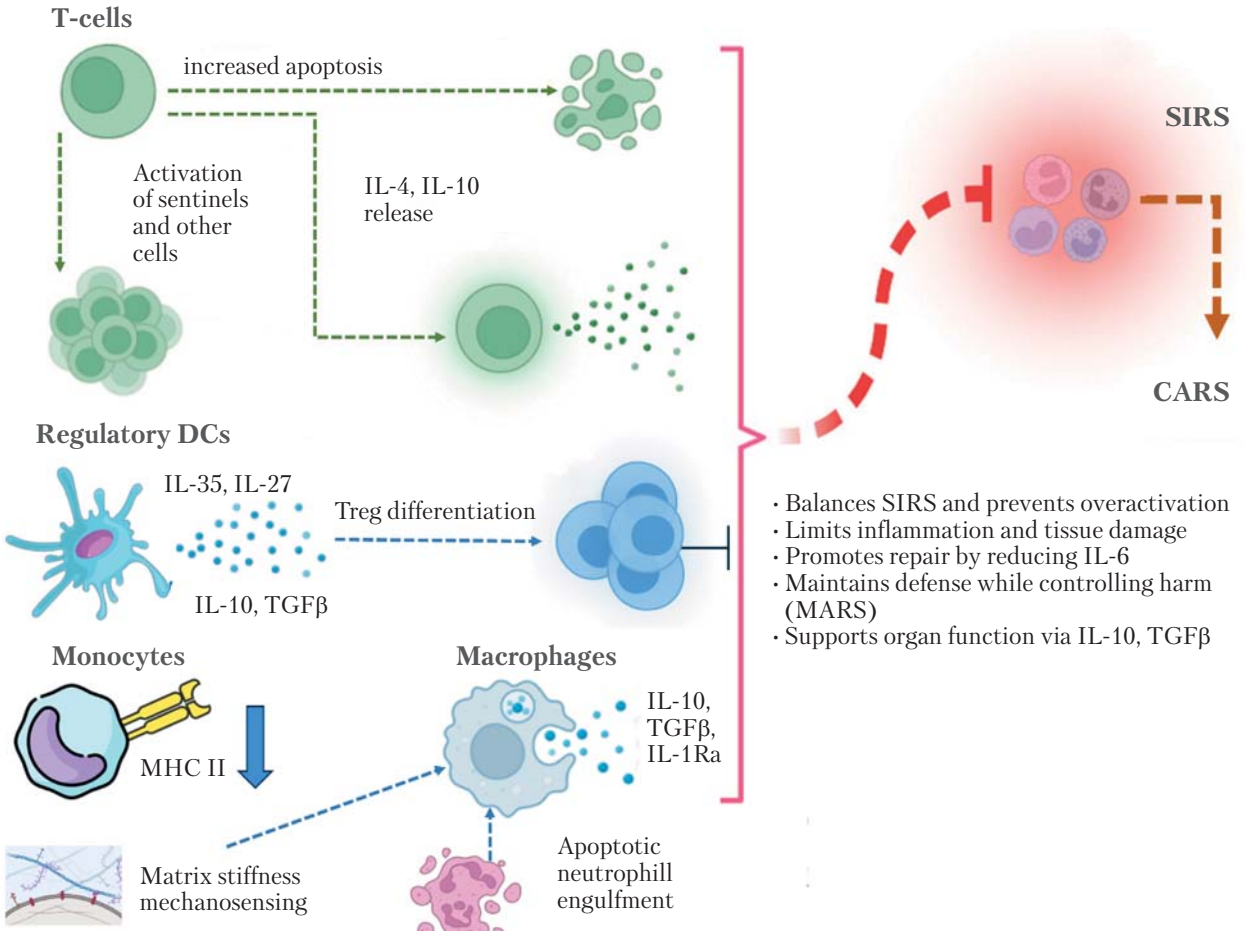
Post-surgical SIRS is initiated by the massive release of damage-associated molecular patterns (DAMPs) or alarmins (Fig. 1). These include intracellular alarmins released from injured or necrotic cells, such as high-mobility group box 1 (HMGB1), heat shock proteins (HSPs), nucleic acids (extracellular RNA and cell-free DNA), adenosine triphosphate (ATP), S100 proteins, etc. [32]. In addition, a distinct group of DAMPs arises from the degradation or remodeling of extracellular matrix (ECM) components – glycoproteins, proteoglycans, and glycosaminoglycans – during tissue injury. Examples include low-molecular-weight hyaluronic acid, biglycan, decorin, versican, fibronectin, and elastin fragments [25].

These DAMPs are recognized by pattern recognition receptors (PRRs) expressed on epithelial cells and innate immune sentinel cells, including macrophages (Mϕ) and dendritic cells (DCs), thereby initiating a local, noninfectious (sterile) inflammatory response [35]. Activation of PRRs leads to the production and systemic release of a broad spectrum of pro-inflammatory cytokines, chemokines, and other mediators, which promote the recruitment of circulating immune cells such as neutrophils and monocytes. This process drives the transition from localized inflammation to a systemic inflammatory response. Excessive systemic dissemination of pro-inflammatory mediators can result in multiple organ dysfunction, accompanied by secondary cell injury and further release of alarmins, thereby perpetuating a self-amplifying cycle of systemic inflammation.

In some cases, systemic inflammatory response syndrome can escalate into a harmful, dysregulated state of severe hyperinflammation, characterized by a cytokine storm [6, 13, 83]. This overwhelming and dysregulated immune activation markedly increases the risk of widespread tissue injury, progression to multiple organ dysfunction, and ultimately a significantly higher likelihood of mortality.

In response to excessive systemic inflammation, the body mounts a counter-regulatory, immunosuppressive state known as CARS, a concept introduced by Roger Bone in 1997 [1]. This response helps limit the potentially harmful effects of an uncontrolled proinflammatory reaction, such as that seen in sepsis, major trauma, or major surgical interventions (Fig. 2).

Importantly, CARS does not reflect a complete shutdown of the immune system. Rather, it represents a dynamic reprogramming of both circulating and tissue-resident immune cells. During this process, key proinflammatory pathways and destructive metabolic responses are downregulated, while essential antimicrobial and regulatory functions



DC – dendritic cell; Treg – regulatory T-cell; TGF – transforming growth factor; IL-1Ra – interleukin receptor antagonist; MARS – mixed antagonists response syndrome

Figure 2. **Surgical-associated CARS**

are preserved or selectively modulated [62, 77]. This allows the host to maintain a degree of defense against pathogens while reducing collateral tissue injury. The immune response in CARS is highly compartmentalized. Circulating leukocytes often exhibit functional impairment or altered signaling. Specifically, peripheral blood lymphocytes upregulate inhibitory receptors such as PD-1, CD47, and CTLA-4. This phenotypic shift is associated with reduced proliferative capacity and impaired responsiveness to stimulation, promoting cellular anergy and progressive dysfunction. As a result, the effectiveness of cell-mediated immunity declines, weakening the host's ability to control infections and maintain immune homeostasis [80]. In the context of CARS, naïve $CD4^+$ T helper cells are preferentially skewed toward a Th2 phenotype, accompanied by enhanced production of anti-inflammatory cytokines, including IL-4, IL-6, IL-10, IL-11, IL-13, and transforming growth factor-β (TGFβ). This shift reinforces an immunosuppressive milieu and dampens effective cell-mediated immune responses. Concurrently, there is a broad attenuation of cytokine signaling capacity, reflected by reduced expression of membrane-bound cytokine receptors and increased release of soluble receptor forms. These include soluble TNF receptors p55 (sTNFR I) and p75 (sTNFR II), soluble IL-1 receptor type II (sIL-1R II), and IL-18 binding protein (IL-18BP), all of which act as decoy molecules that sequester circulating cytokines. In parallel, the upregulation of endogenous receptor antagonists, such as the IL-1 receptor antagonist (IL-1Ra), further inhibits proinflammatory signaling. Together, these mechanisms contribute to a profound downregulation of immune activation and promote the development of functional immunoparalysis [37, 70].

Sustained inflammatory stimulation induces a process known as «emergency myelopoiesis», in which hematopoietic activity is shifted toward rapid production and release of myeloid-lineage cells. This response leads to the accumulation of immature myeloid-derived suppressor cells (MDSCs) in the circulation and tissues. Rather than enhancing host defense, these cells actively inhibit adaptive immunity by suppressing T-cell activation, proliferation,

and effector function, thereby reinforcing an immunosuppressive environment and potentially contributing to persistent immune dysfunction [5, 72].

Monocytes in CARS display reduced monocyte human leukocyte antigen-DR (mHLA-DR) expression and exhibit a blunted functional response, producing lower levels of key proinflammatory cytokines, such as TNF-α and IL-1, upon bacterial stimulation. Concurrently, monocyte-derived dendritic cells acquire a regulatory, tolerogenic phenotype, characterized by impaired antigen presentation and a bias toward immune suppression. These cells promote the differentiation of naïve T cells into regulatory T cells (Tregs), thereby reinforcing immunosuppressive pathways and further attenuating effective adaptive immune responses [3, 33, 43]. At the same time, immune cells within tissues may remain primed or even activated, ready to respond to local threats. Specifically, tissue-resident macrophages represent a highly heterogeneous population that includes sentinel cells of embryonic origin and monocyte-derived macrophages that appear during SIRS. Tissue-resident sentinels have an inherent M2-shifted phenotype, which obliges them to maintain tissue integrity and control inflammation. These cells are involved in reparative processes. Monocyte-derived macrophages initially focus on eliminating the threat and thereby shift to a proinflammatory M1 phenotype [41, 49]. These cells play a central role in sustaining local antimicrobial defense at the site of surgical injury. However, the microenvironment of damaged tissue provides multiple context-specific signals – such as the clearance of apoptotic neutrophils and other dying cells – that can drive their functional reprogramming toward an anti-inflammatory, pro-resolving phenotype. Moreover, both embryonically derived and monocyte-derived macrophages undergo metabolic polarization that is highly sensitive to mechanical cues, with mechanosensing pathways significantly shaping their activation state, functional profile, and contribution to tissue repair versus immune suppression [81]. After surgical injury, macrophages respond not only to biochemical mediators but also to profound changes in the tissue's physical microenvironment. Tissue damage and subsequent repair dynamically remodel the extracellular matrix, altering its stiffness, density, and structural organization. Both tissue-resident and recruited monocyte-derived macrophages sense these mechanical shifts and recalibrate their behavior accordingly. This mechanosensitive response is predominantly driven by cytoskeletal dynamics rather than by classical integrin-mediated adhesion, supporting a highly adaptable, amoeboid-like mode of migration and activation. Through this process, macrophages continuously adjust their functional state, integrating mechanical and molecular cues to coordinate migration, polarization, and tissue repair activities. In the early phase following surgical trauma, this results in a predominantly pro-inflammatory (M1-like) response that supports host defense and debris clearance. As healing progresses, macrophages progressively transition toward an anti-inflammatory, pro-reparative (M2-like) phenotype to promote tissue regeneration and resolution of inflammation. Importantly, the mechanical context critically shapes these outcomes: relatively compliant, low-stiffness environments tend to favor reparative and, in some cases, pro-fibrotic macrophage programs, whereas excessive matrix stiffening – such as that seen in chronic fibrosis or scar tissue – can impair macrophage function, disrupt proper polarization, and contribute to dysregulated healing [36]. This spatial and functional heterogeneity underscores the complexity of immune regulation in the perioperative period and helps explain why patients can exhibit simultaneous signs of inflammation and immunosuppression. Quite often, the coexistence or fluctuation between proinflammatory and anti-inflammatory processes can give rise to mixed antagonistic response syndrome (MARS), a complex and unstable immune state. Both CARS and MARS are governed by the dynamic interplay of multiple mediator systems, including humoral cascades such as coagulation and complement, as well as cellular and molecular effectors like cytokines, reactive oxygen species, arachidonic acid metabolites, and nitric oxide. Resolution of a generalized inflammatory response reflects effective engagement of immunoregulatory pathways. However, in MARS, this regulation becomes disordered, leading to immunological discordance characterized by alternating or overlapping phases of hyperinflammation (SIRS) and immunosuppression (CARS). These oscillations can intensify over time, ultimately contributing to the progression toward multiple organ dysfunction syndrome (MODS), septic shock, or a state of immune exhaustion and anergy [48, 45, 63].

Patients who survive initial surgical stress events, in which both inflammatory and immunosuppressive pathways are simultaneously activated, may follow two principal clinical trajectories. In some individuals, the immune system gradually re-establishes homeostasis, enabling effective tissue repair and relatively rapid recovery. In others, however, a maladaptive state develops, characterized by persistent inflammation, immunosuppression, and catabolism – known as PICS (persistent inflammation, immunosuppression, and catabolism

syndrome). This condition is marked by progressive protein depletion, severe muscle wasting and cachexia, ongoing organ dysfunction, and a high susceptibility to secondary infections [11, 82].

PICS is increasingly recognized as a major pathophysiological syndrome in critically ill surgical patients requiring prolonged intensive care unit (ICU) stays, often exceeding 10 days. These patients frequently survive the acute phase and are transferred from the ICU to long-term care facilities; however, they rarely regain full functional independence. Instead, they often experience recurrent hospital readmissions, including repeated ICU admissions due to infectious or organ-related complications. In a substantial proportion of cases, the condition progresses to profound physiological exhaustion and ultimately death, typically through a prolonged and debilitating clinical course [8, 52].

A central driver of this sustained inflammatory–immunosuppressive state is the expansion and activation of myeloid-derived suppressor cells (MDSCs). These cells exert broad regulatory effects across both innate and adaptive immune compartments, profoundly suppressing T-cell and other effector immune functions. Through these mechanisms, MDSCs contribute to immune dysregulation, impaired host defense, and the chronicity of the pathological process observed in PICS [79, 37].

Postoperative immunomodulation control requires a deep understanding and careful monitoring of its timeline. Dynamic changes in immune reactivity during the postoperative period can be conventionally divided into three phases. The initial hyperinflammatory phase lasts, on average, 0–3 days after surgical intervention and is characterized by elevated levels of proinflammatory cytokines, such as TNF-α and IL-6, as well as increased synthesis of acute-phase proteins, reflected by elevated C-reactive protein [10, 73, 17]. The level of proinflammatory mediator production during this period may, as noted above, reach the scale of a cytokine storm. Therapeutic interventions in this phase should focus on the precise use of anti-inflammatory agents to control hyperinflammation while avoiding premature CARS development [64, 14].

This is followed by a transitional phase of immune imbalance that may last 3–7 days. During this phase, the unfolding of the inflammation-resolution program and the reduction of destructive proinflammatory mediators may be accompanied by decreased efficiency of both innate and adaptive cellular immune defenses. This is associated with reduced antigen-presenting function of mononuclear phagocytes, the emergence of MDSCs, and the expansion of other regulatory cell populations. This is the most challenging period for planning therapeutic interventions and requires a highly personalized approach. In patients with signs of residual inflammatory processes during this period, continued use of anti-inflammatory agents may be appropriate. In contrast, in patients at risk of early CARS (with reduced absolute lymphocyte counts), low-dose administration of immunostimulatory agents is considered appropriate to prevent immune paralysis [60].

The third phase of postoperative immunomodulation is CARS, which is typically diagnosed 7–10 days after surgical intervention. During this phase, mechanisms of inflammation control by numerous regulatory cell populations may be combined with functional exhaustion of effector cell populations, significantly increasing the risk of infectious complications and justifying a shift in therapeutic focus toward restoring immune reactivity through the use of immunostimulatory agents and agents that inhibit lymphocyte apoptosis [78, 57, 24].

The proposed basic and advanced laboratory tests for stratifying patients after surgical intervention by postoperative immunomodulation phase, unfortunately, do not yet provide a comprehensive set of highly informative indicators. Clinical studies indicate that widely accepted markers of postoperative hyperinflammation (procalcitonin, C-reactive protein and IL-6) and CARS (reduced Human Leukocyte Antigen-DR (HLA-DR) and lymphopenia) have limited prognostic value. However, there is still no consensus on a unified set of alternative biomarkers. Instead, across different types of surgical interventions, various panels of biomarkers have demonstrated diagnostic and prognostic relevance, underscoring the need for a personalized approach to postoperative immunomodulation monitoring [69, 85]. Therefore, the search for reliable markers remains ongoing and represents a pressing challenge in surgical practice.

Promising candidates for such markers would include parameters derived from routine laboratory tests, such as WBC-derived indices (Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), etc.), which are robust, cost-effective, widely accessible in virtually any healthcare setting, and do not require expensive equipment [2, 44, 75]. Enhancing the diagnostic and prognostic value of proposed biomarkers requires their longitudinal assessment throughout the postoperative period. Such dynamic evaluation enables identification of phase transitions in postoperative immunomodulation at the individual patient level, while accounting for the inherent variability in the timing and progression of these processes.

The dynamics of postoperative immunomodulation exhibit substantial interindividual variability, driven by a wide range of contributing factors. In particular, the degree of postoperative hyperinflammation is not uniform but represents a predictable, scalable response to surgical injury: more extensive and invasive procedures are associated with a higher risk of systemic inflammatory dysregulation. In other words, the intensity of the inflammatory response is largely determined by the magnitude of the surgical intervention. Extensive tissue trauma leads to a more pronounced release of DAMPs, which act as triggers of persistent local and systemic inflammation, and to increased levels of inflammatory mediators in the systemic circulation. Additionally, it may induce prolonged ischemia–reperfusion injury, further amplifying the inflammatory cascade. While a moderate inflammatory response is essential for effective wound healing, excessive or dysregulated hyperinflammation – commonly observed after major surgery – can result in organ dysfunction, long-term disability, and increased mortality [16, 34].

By contrast, less invasive approaches, such as laparoscopic or robot-assisted surgery, are generally associated with a reduced systemic inflammatory response and better preservation of immune function compared to open procedures [7, 75]. Clinically significant hyperinflammation has been linked to a higher incidence of postoperative complications, including poorer quality of recovery and increased 90-day mortality.

Several procedural factors, such as duration of surgery, further modulate the severity of postoperative hyperinflammation. Specifically, a prolonged surgical procedure – commonly defined as one lasting more than 2–3 hours – is associated with a substantially increased risk of postoperative complications, with overall risk estimates roughly doubling compared to shorter operations. Moreover, even incremental increases in operative time appear to carry clinical significance: each additional 15 minutes of surgery has been linked to a proportional rise in the incidence of complications such as surgical site infections, impaired wound healing, and thrombotic events.

Several mechanisms may underlie this association. Longer procedures typically involve greater tissue exposure and manipulation, increased blood loss, and prolonged anesthesia, all of which can amplify the systemic inflammatory response and contribute to immune dysregulation. Extended operative duration may also increase the risk of microbial contamination and exacerbate metabolic stress, further compromising postoperative recovery. Taken together, these findings highlight the importance of optimizing surgical efficiency and minimizing unnecessary procedural delays as part of comprehensive risk-reduction strategies [39]. Important surgery-associated factors include the use of cardiopulmonary bypass, particularly when its duration exceeds 180 minutes. Similarly, circulatory arrest under deep hypothermia lasting more than 40 minutes is a critical contributor to the amplification of the postoperative inflammatory response. Collectively, these variables should be carefully considered when assessing patient risk and tailoring perioperative management strategies to maintain and/or restore immune homeostasis. This is critically important not only for preventing infectious complications but also for promoting effective tissue repair and the re-establishment of physiological homeostasis.

Additional determinants of post-surgery immunomodulation dynamics

The dynamics of postoperative immunomodulation are also strongly influenced by a broad range of additional factors that warrant careful consideration and further discussion in this review. These variables interact in complex, often patient-specific ways, shaping both the magnitude and the trajectory of the immune response following surgery.

The baseline state of immune reactivity, or an individual's immunophenotype, represents a critical determinant and starting point in the dynamics of postoperative immunomodulation. The pre-existing condition of the immune system largely defines the nature of its response to surgical injury, the magnitude of subsequent postoperative hyperinflammation, and the effectiveness of therapeutic strategies aimed at controlling SIRS. Within this framework, preoperative immune profiling emerges as a valuable tool for risk stratification. It may help predict the likelihood of postoperative complications – such as infections, sepsis, and organ dysfunction – and provide a rationale for tailoring and personalizing anti-inflammatory and immunomodulatory interventions. Incorporating baseline immunological assessment into perioperative care could therefore enhance clinical decision-making and improve patient outcomes by enabling more precise and targeted therapeutic approaches [22]. Specifically, a patient may exhibit a genetically determined hypo-responsive or hyper-responsive immunophenotype. A hypo-responsive immunophenotype is characterized by a relatively attenuated reaction of innate immune cells to inflammatory stimuli. This may be stipulated by variations in the expression levels of pattern-recognition receptors (PRRs) and key components of proinflammatory signaling pathways, which together shape the immune system's sensitivity to danger signals.

Additional contributors to a hypo-responsive immunophenotype may include an increased proportion or activity of regulatory cell populations, such as regulatory T cells and other immunosuppressive subsets [28]. Collectively, these features can dampen the initial inflammatory response, which may reduce the risk of excessive hyperinflammation, but may also impair effective pathogen clearance and increase susceptibility to infections in the postoperative period.

Surgical intervention itself may act as a trigger that unmasks or amplifies a genetically determined propensity for immune cell differentiation, particularly toward immunosuppressive subsets such as monocytic myeloid-derived suppressor cells (M-MDSCs). The expansion of these cells may increase the risk of oncologic progression, as they can suppress the functional activity of circulating natural killer (NK) cells – key effectors of innate antitumor immune surveillance [19].

Surgical stress has been shown to induce the systemic accumulation of M-MDSC–like cells, thereby creating a transiently immunosuppressive milieu. In this context, the diminished cytotoxic capacity of NK cells may facilitate the survival and dissemination of tumor cells, particularly those that are otherwise susceptible to NK cell–mediated lysis. Consequently, postoperative immune dysregulation of this type may increase the risk of tumor metastasis and highlights the importance of considering perioperative immune modulation in oncologic surgery.

An important determinant of post-surgical immunomodulation is preoperative immune exhaustion – pre-existing immune dysfunction characterized by T-cell senescence, chronic low-grade inflammation, and a loss of metabolic reserve in immune cells. Collectively, these alterations impair the patient's recovery capacity and increase susceptibility to postoperative complications [40].

As noted above, surgical intervention induces a profound systemic inflammatory response. When a patient undergoes surgery with an already weakened or «exhausted» immune system, their ability to cope with this physiological stress is significantly reduced [68]. This results in a markedly increased risk of infectious complications, largely due to impaired surveillance and effector functions of both tissue-resident and circulating sentinel immune cells, particularly mononuclear phagocytes. Uncontrolled and excessive pro-inflammatory polarization of mononuclear phagocytes – the principal tissue-resident sentinel cells – combined with depletion of the metabolic reserve required for effective phagocytic function, may represent a critical factor in increasing the risk of postoperative infectious complications of bacterial origin. Under physiological conditions, mononuclear phagocytes maintain a balanced functional state that enables both efficient pathogen clearance and controlled inflammation resolution. However, sustained hyperactivation and skewing toward a pro-inflammatory phenotype can lead to metabolic exhaustion, impairing key effector mechanisms such as phagocytosis, antigen processing, and microbial killing. As a result, despite an initially heightened inflammatory response, the host's ability to eliminate invading pathogens becomes compromised. This dysregulated immune state creates a permissive environment for bacterial infections in the postoperative period, highlighting the importance of maintaining functional and metabolic integrity of innate immune cells for optimal surgical outcomes [71, 67].

An equally important contributor to the weakening of anti-infective defense is the functional exhaustion of neutrophils. Neutrophils are key effector cells of the innate immune system and serve as the first line of defense against invading pathogens, particularly bacteria. However, under conditions of sustained preoperative inflammatory stress, their functional capacity can become compromised. Neutrophil exhaustion is characterized by impaired chemotaxis, reduced phagocytic activity, diminished reactive oxygen species production, and dysregulated formation of neutrophil extracellular traps (NETs). Assessing both the abundance and functional competence of this cell population prior to surgery enables early identification of patients at increased risk of impaired antimicrobial defense. Alterations in cell counts, activation status, phagocytic capacity, or effector functions may reflect underlying immune dysregulation, including exhaustion or maladaptive polarization. Incorporating such immunological profiling into preoperative evaluation protocols may improve risk stratification and support the development of personalized perioperative management strategies to reduce the incidence of postoperative bacterial infections [58, 71].

Preoperative immune exhaustion also predisposes patients to earlier onset of CARS and prolonged postoperative immunosuppression. These effects can severely disrupt tissue repair processes, contributing to delayed healing and, in some cases, the chronification of inflammatory and regenerative disturbances [59]. Furthermore, suppression of cellular immunity prior to surgery has been associated with prolonged postoperative fatigue and increased pain burden.

The preoperative detection and characterization of «immune exhaustion» represent a promising strategy for risk stratification and the development of personalized approaches to postoperative

immunomodulation. For instance, reduced functional capacity of T lymphocytes, along with an increased proportion of senescent T cells, is a strong indicator of diminished resilience to surgical trauma [74].

Addressing immune exhaustion before surgery – through targeted prehabilitation strategies – has the potential to significantly improve surgical outcomes. Such approaches may include optimizing nutritional status, physical conditioning, and interventions to restore immune competence, ultimately enhancing the patient's ability to withstand surgical stress and recover more effectively [29].

Patient age and sex are key determinants of both baseline immune reactivity in the preoperative period and the nature of the immune response to surgical intervention.

As people age, the immune system undergoes significant, gradual alterations in both its structure and function, influencing innate and adaptive immune responses. This phenomenon, known as immunosenescence, involves a decline in the body's ability to mount effective immune responses, leading to weaker protection against infections, reduced vaccine effectiveness, and a higher risk of developing cancer [18]. At the same time, aging is accompanied by a persistent, mild inflammatory condition called inflammaging, which occurs even in the absence of a clear infection and contributes to the deterioration of function in various tissues throughout the body [27].

Age-related changes in the immune system are accompanied by shifts in both the overall leukocyte population and specific subpopulations, disruptions in immune regulatory mechanisms, and the persistent production of pro-inflammatory mediators by senescent cells. Importantly, aging does not simply amplify inflammatory responses; rather, it alters their kinetics and the way they resolve over time.

The resolution of inflammation is an active, tightly controlled process that depends on the coordinated action of specialized pro-resolving lipid mediators (SPMs), the efficient clearance of apoptotic cells via efferocytosis, and the reprogramming of immune cells toward anti-inflammatory and tissue-repairing phenotypes. SPMs such as resolvins, protectins, maresins, and lipoxins are endogenously generated bioactive compounds derived from omega-3 and omega-6 polyunsaturated fatty acids. Rather than merely dampening inflammation, they actively orchestrate its resolution and help re-establish tissue homeostasis. These mediators reduce excessive neutrophil infiltration, enhance macrophage-driven clearance of apoptotic cells and debris through efferocytosis, and support tissue repair and regeneration. Importantly, they achieve these effects without broadly suppressing immune function, thereby preserving the host's ability to respond to pathogens while preventing prolonged or dysregulated inflammation [50]. With advancing age, multiple components of the inflammatory resolution pathways become dysregulated. Age-related alterations in both innate and adaptive immune functions often reduce resilience to surgical stress and impair recovery processes.

Despite the presence of chronic, low-grade systemic inflammation in older individuals, their acute inflammatory response to surgical injury can be unpredictable, manifesting as either attenuated or exaggerated compared with younger patients. This imbalance may contribute to poorer postoperative outcomes, delayed tissue repair, and an increased risk of complications [42].

Effective post-surgical immunomodulation in older patients requires age-adapted strategies to mitigate the effects of immunosenescence. Promising approaches with demonstrated efficacy include adoptive therapies using mesenchymal stem cells, as well as the administration of IL-7 and other growth and differentiation factors that help preserve the structural and functional integrity of the thymic epithelial compartment, thereby supporting the generation of naïve T cells [42].

An essential component in reducing the impact of immunosenescence on both systemic and local immune responsiveness is maintaining homeostasis within the symbiotic microbiota and the human phageome. The quantitative and functional characteristics of the microbiome and phageome play a critical role in regulating immune cell differentiation, tissue homing, and metabolic programming, thereby promoting a balanced, anti-inflammatory state.

Conversely, dysbiotic alterations can trigger or exacerbate ongoing inflammatory processes. In this context, strategies aimed at preserving or restoring microbial balance – such as prebiotics, probiotics, immunobiotics, and fecal microbiota transplantation – are increasingly viewed as promising therapeutic avenues for modulating immunosenescence [26]. This, in turn, may contribute to improved postoperative immunomodulation control in patients of this category.

The dynamics of perioperative immunomodulation also differ between male and female patients. This variation is largely driven by sex-based differences in immune reactivity, which are influenced by hormonal, genetic, and molecular factors. For example, sex hormones such as estrogens and androgens modulate immune cell function and cytokine production, leading to distinct inflammatory and immune response patterns in males and females. Across many infectious diseases, men tend to experience

more severe illness and have higher mortality rates, including in cases of acute viral and bacterial infections as well as cancers linked to infectious agents. In contrast, women often mount more effective protective responses against pathogens, which generally leads to better outcomes during infections. However, this heightened immune responsiveness comes with a trade-off: it is associated with an increased risk of developing autoimmune disorders and chronic inflammatory conditions. As a result, males and females differ not only in their vulnerability to infections but also in how their immune systems maintain balance, with important implications for disease susceptibility, progression, and therapeutic strategies [61]. These differences may affect susceptibility to surgical stress, the intensity of inflammatory responses, and the trajectory of postoperative recovery, highlighting the importance of considering sex as a biological variable in perioperative care and immunomodulatory strategies.

Although the overall intensity of the inflammatory response – particularly in the preoperative period – is generally higher in women than in men, accumulating evidence indicates that inflammation resolves more rapidly in females. This is largely attributable to more efficient, accelerated clearance of inflammatory cells, especially neutrophils, driven by enhanced phagocytic activity, including efferocytosis, carried out by professional phagocytes, such as macrophages. The faster resolution of inflammation in females is also partly explained by higher levels of SPMs, particularly D-resolvins, which actively promote the termination of inflammation and the restoration of tissue homeostasis [54, 76].

At the same time, despite a more rapid resolution of inflammation as a biological process, studies of inflammatory pain suggest that, in certain contexts, males may experience quicker pain relief. This phenomenon is likely associated with higher levels of monocytes producing the anti-inflammatory cytokine IL-10, which plays a key role in modulating pain perception and suppressing excessive inflammatory responses [65].

Thus, sex-based differences are reflected not only in the magnitude of immune responses but also in the kinetics of their resolution and in clinical manifestations such as pain. These distinctions underscore the importance of incorporating sex as a critical factor in personalized therapeutic strategies and postoperative patient management.

Anesthetic agents and techniques exert significant modulatory effects on the immune system at multiple levels, from local tissue immunity to systemic immune responsiveness. These effects involve both innate and adaptive immune components and may influence key processes, including cytokine production, leukocyte trafficking, antigen presentation, and cellular effector functions. Depending on the type of anesthetic and the method of administration, immune modulation can manifest as either immunosuppression or, less commonly, immune activation.

Overall, anesthesia exerts an immunosuppressive effect, further compounding the adverse impact of surgical stress on immune reactivity. Recent studies indicate that different anesthetic techniques are associated with varying degrees of immunosuppression. General anesthesia, particularly when inhalational agents are used, is often linked to the most pronounced suppression of immune function. In contrast, combining general anesthesia with regional techniques (such as epidural anesthesia) is associated with a less pronounced immunosuppressive effect than general anesthesia alone. This is largely due to the reduced requirement for intravenous opioids and inhalational agents. Regional anesthesia methods – including epidural, spinal, and peripheral nerve blocks – are generally considered the most protective of immune function. These approaches are associated with less inhibition of NK cell activity and a reduced negative impact on both the quantitative and functional characteristics of effector T-lymphocyte subpopulations ($CD4^+$ and $CD8^+$). This effect is primarily explained by regional anesthesia's ability to attenuate the surgical stress response, thereby limiting the release of immunosuppressive mediators, such as cortisol [21, 53].

As a result, the choice of anesthetic strategy may play an important role in preserving perioperative immune competence and could potentially influence postoperative recovery and complication rates.

The choice of anesthetic agents also plays a significant role in shaping postoperative immunomodulation. Volatile inhalational agents such as sevoflurane and isoflurane have been shown to enhance oxidative stress and promote macrophage polarization toward a pro-inflammatory M1 phenotype. In addition, they can impair neutrophil recruitment and phagocytic activity, as well as negatively affect macrophage-mediated phagocytosis. Sevoflurane and isoflurane (unlike desflurane) can also induce apoptosis in T cells, NK cells, and B cells. Furthermore, these agents may suppress NK cell cytotoxicity and reduce T-lymphocyte proliferation [9].

Total intravenous anesthesia with propofol is generally associated with better preservation of immune function than volatile inhalational agents. Propofol acts as an agonist of gamma-aminobutyric acid (GABA) receptors, which are widely expressed on cells of the immune system. Through interaction with these receptors on immune cells, propofol

suppresses the secretion of pro-inflammatory cytokines, inhibits cyclooxygenase-2 (COX-2) activity and prostaglandin E2 production, and reduces phagocytic activity, chemotaxis, and NET formation. Additionally, propofol can affect mitochondrial membrane polarization in macrophages, promoting apoptotic pathways. It also inhibits T-cell proliferation and may induce apoptosis in T lymphocytes by competitively interfering with the formation of immunological synapses. Importantly, however, propofol does not appear to suppress the cytotoxic activity of NK cells or cytotoxic T lymphocytes, nor does it significantly alter the immunoregulatory index [12]. Taken together, these properties suggest that propofol-based anesthesia may offer a more balanced immunomodulatory profile, attenuating excessive inflammation while preserving key components of anti-infective and antitumor immunity.

Dexmedetomidine, an α_2-adrenergic receptor agonist with sedative and mild analgesic properties, helps attenuate the degree of immunosuppression induced by surgical trauma and pain. It modulates immune reactivity, both directly and indirectly, by acting on central and peripheral α_2-adrenergic receptors, thereby reducing peripheral norepinephrine release, which, in turn, influences immune cell activity. At the molecular level, dexmedetomidine suppresses phosphorylation of nuclear factor kappa B (NF-κB), leading to decreased expression of pro-inflammatory cytokines and other inflammatory mediators produced by monocytes and macrophages. Concurrently, it enhances macrophage production of $TGF\beta_1$, which helps dampen excessive cytokine responses, limit hyperinflammation, and facilitate more efficient resolution of inflammation. Its analgesic effects also provide indirect immunoprotection during the perioperative period by reducing stress-induced cortisol release. In addition, dexmedetomidine helps prevent pain-associated overactivation of NK cells, reducing their cytotoxic activity while not significantly affecting overall lymphocyte proliferation [51, 12, 21].

Overall, these combined neuroimmune and anti-inflammatory effects make dexmedetomidine a valuable agent in perioperative care, supporting a more balanced immune response and potentially improving postoperative recovery outcomes.

Opioids are highly effective analgesics for severe pain but exert complex and often suppressive effects on the immune system. Although pain itself can contribute to immunosuppression, opioid analgesia does not fully counterbalance this effect and is frequently associated with direct impairment of immune function. Reported changes include reduced NK cell cytotoxicity, impaired T- and B-cell responses, decreased antibody production, diminished phagocytic activity of neutrophils and macrophages, altered cytokine secretion, increased macrophage apoptosis, and reduced TLR4 expression.

These effects result from both indirect neuroendocrine pathways – through activation of the hypothalamic–pituitary–adrenal (HPA) axis and stress hormone release – and direct action on opioid receptors on immune cells, particularly the μ-opioid receptor. The immunological impact varies between agents: morphine produces strong immunosuppression, affecting NK activity, antigen presentation, and T-cell differentiation; fentanyl and sufentanil suppress NK function but may increase regulatory T cells; remifentanil inhibits NK activity and lymphocyte proliferation, with minimal effects at low doses; and oxycodone induces relatively mild immune changes, mainly affecting cytokine production.

In contrast, tramadol demonstrates a more favorable profile, with evidence of preserved or even enhanced NK cell activity compared with morphine [31, 12, 21]. These differences emphasize the clinical relevance of opioid selection in perioperative immune regulation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered first-line agents for the management of pain of varying intensity and are recommended for acute perioperative analgesia in the absence of contraindications. Their incorporation into multimodal analgesic regimens improves pain control, reduces opioid requirements and opioid-related adverse effects, and lowers the risk of postoperative complications.

Unlike opioids, NSAIDs exert their effects primarily by inhibiting COX enzymes and reducing prostaglandin synthesis, particularly prostaglandin E2 (PGE2), which plays a central role in the development of postoperative immunosuppression. Decreasing PGE2 levels alleviates immune inhibition, helps restore the activity of NK cells and T lymphocytes, and enhances antitumor immune responses.

Clinical studies have demonstrated that agents such as parecoxib sodium can partially restore postoperative NK and $CD3^+$ T-cell levels, help maintain cytokine balance, and reduce excessive inflammatory responses. In addition, NSAIDs have been shown to attenuate postoperative increases in inflammatory markers, including the NLR, and may improve overall immune function in oncology patients [47, 84].

Overall, NSAIDs not only provide effective analgesia but also help mitigate surgery-induced immunosuppression, making them an important component of modern perioperative care strategies.

Lidocaine also has immunomodulatory properties and can influence immune cell activity. Clinical studies show that it reduces postoperative immunosuppression, lowers pro-inflammatory cytokine production, and enhances NK cell cytotoxicity at therapeutic doses. It has been associated with reduced neutrophil infiltration and lung injury in experimental models, as well as decreased formation of circulating NETs. In vitro data further indicate that lidocaine suppresses the release of inflammatory mediators from dendritic cells and macrophages, contributing to anti-inflammatory and potential antitumor effects. In patients, perioperative lidocaine has been linked to improved immune profiles, including increased levels of NK cells, T-cell subsets, and immunoglobulins, suggesting enhanced cellular and humoral immunity. These effects are thought to result from a combination of direct immune cell modulation, anti-inflammatory action, and regulation of the sympathetic nervous system and HPA axis, including reductions in serum cortisol levels [15].

The nocebo effect – a phenomenon in which a person experiences negative side effects from a treatment or procedure despite the absence of pharmacologically active or harmful ingredients– represents another important factor that can significantly influence post-surgical immunomodulation. Surgical interventions are often accompanied by considerable anxiety and fear in patients awaiting procedures. Research indicates that approximately 60–80 % of individuals experience preoperative anxiety, which can substantially affect postoperative outcomes [20].

Negative expectations, such as fear and anticipatory anxiety, activate the HPA axis, leading to elevated cortisol levels. Cortisol-mediated immunosuppression may slow wound healing and increase susceptibility to postoperative infections, thereby complicating recovery.

Nocebo-related responses can also engage specific brain networks involved in pain modulation, including the limbic system, the insular cortex, and the periaqueductal gray. Activation of these regions can amplify subjective pain perception, which, in turn, may further enhance stress-related immune dysregulation. In this way, psychological expectations and neurobiological responses interact to shape both pain experience and immune function [56].

Moreover, studies have shown that negative expectations during painful or stressful experiences can modulate levels of pro-inflammatory cytokines, thereby influencing the overall inflammatory response. This mechanism is particularly important in the immediate postoperative period, when immune balance and controlled inflammation are crucial for optimal recovery [20].

Importantly, psychological interventions such as patient education, anxiety reduction techniques, and coping strategy training may help mitigate nocebo effects. By reducing preoperative stress and negative expectations, such approaches can improve immune responses after surgery and support a faster, more stable overall recovery.

Conclusions

Post-surgical immunomodulation is a dynamic process shaped by the interplay between proinflammatory activation and compensatory immunosuppression. While essential for tissue repair and homeostasis, its dysregulation may result in infection, delayed healing, organ dysfunction, and prolonged recovery, underscoring the complexity of perioperative immune regulation and the limitations of uniform therapeutic approaches.

Postoperative immune responses evolve through distinct, time-dependent phases requiring tailored management: early hyperinflammation may necessitate controlled anti-inflammatory therapy, whereas later immunosuppression may require immunostimulatory interventions. Failure to recognize these phase-specific transitions can lead to persistent inflammation, immunosuppression, and catabolism syndrome.

The trajectory of immunomodulation is influenced by both surgical and patient-related factors, including the extent of tissue injury, operative duration, perioperative techniques, baseline immune status, age, sex, and pre-existing dysfunction. These variables highlight the need for personalized perioperative strategies supported by accurate immunological assessment. However, a major limitation remains the lack of reliable, universally applicable biomarkers capable of precisely identifying immunomodulatory phases and guiding clinical decision-making.

Thus, improving surgical outcomes depends not only on understanding immune mechanisms but also on developing and implementing sensitive, dynamic biomarkers for real-time monitoring, enabling truly individualized, phase-adapted therapeutic approaches.

Declaration of interests

The authors report no conflicts of interest. No financial assistance or funding was received for the conduct of this study.

Authors contributions

T. V. Babich and T. V. Bulyhina conducted the literature review, selected relevant publications, and analyzed the collected data. R. S. Dovhyi drafted the initial version of the manuscript. L. M. Skivka contributed to the final development of the review, critically evaluated the selected literature, revised the manuscript.

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Хірургічно індукована імуномодуляція: комплексний огляд

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Хірургічне втручання спричиняє глибокі та динамічні зміни імунної реактивності організму. Післяопераційний період зазвичай характеризується ранньою гіперзапальною відповіддю, пізніше — компенсаторною імуносупресією, але в деяких випадках може розвиватися дезадаптивний стан, відомий як синдром стійкого запалення, імуносупресії та катаболізму. Ці імунні порушення пов'язані з підвищеним ризиком інфекційних ускладнень, порушенням відновлення тканин, дисфункцією органів і потенційним прогресуванням пухлинного процесу. Модуляція хірургічно індукованих змін імунної реактивності може бути перспективною стратегією для поліпшення результатів оперативного лікування. Метою огляду є аналіз та узагальнення сучасної літератури щодо механізмів і ключових детермінант післяопераційної імуномодуляції.

Розглянуто складні механізми ініціації та прогресування післяопераційного системного гіперзапалення, а також тригери й шляхи розвитку компенсаторної протизапальної імунної відповіді. Особлива увага приділена часовій динаміці та фазовому характеру післяопераційної імуномодуляції. Детально проаналізовано ключові детермінанти, що визначають інтенсивність і траєкторію постхірургічної імунної відповіді, зокрема хірургічні чинники, такі як об'єм та тривалість ушкодження тканин, а також методи й засоби анестезії. Окремо розглянуто пацієнт-специфічні чинники, що впливають на післяопераційну імунну реактивність, зокрема вік, стать і передопераційний імунний статус.

Ранній післяопераційний період є недостатньо використовуваним «вікном терапевтичних можливостей» для поліпшення результатів хірургічного лікування. Однак його ефективна клінічна реалізація потребує глибшого розуміння механізмів постхірургічної імуномодуляції, а також розробки та впровадження високочутливих динамічних біомаркерів для безперервного моніторингу в режимі реального часу. Такі підходи дадуть змогу реалізувати персоналізовані, фазово-адаптовані терапевтичні стратегії, що враховують динамічні зміни імунного статусу пацієнта.

Ключові слова: постхірургічна імуномодуляція, синдром системної запальної відповіді, синдром компенсаторної протизапальної відповіді, синдром стійкого запалення, імуносупресії та катаболізму.

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