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REVIEW

Effects of anesthesia and other perioperative factors on immune function: a narrative review

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Abstract

This study investigates the impact of perioperative factors on patients' immune functions including physiological condition, surgical strategy, anesthesia methodology, intraoperative usage of anesthetics, blood transfusion, intraoperative body temperature, and inspired oxygen concentration. Results demonstrate that the individual perioperative factors have varying degree of impact, while their combined effect may cause changes in patients' immune function. The study outcomes suggest that patient's immune function must be assessed prior to the surgery based on individual characteristics. The surgical and anesthetic methods are accordingly selected. During the surgery, prudent usage and monitoring of factors like anesthesia techniques, anesthetics, inhaled oxygen concentration, blood transfusion, and patient's body temperature are vital for minimizing the immune system disruptions. These findings practically guide regarding the optimization of perioperative care strategies and mitigation of immunosuppression risks.

Keywords

Immune function; Perioperative factors; Anesthesia

1. Introduction

Multiple perioperative factors alter the patient's immune function. They subsequently have an impact on perioperative infections and surgical outcomes.

The immune system is divided into innate and adaptive immunity. Innate immunity involves the evolutionarily conserved host defense systems which rapidly respond to the pathogens without specific antigenic stimuli. Contrarily, adaptive immunity recognizes antigens and maintains antigen-specific immune "memory" to protect the host from forthcoming attacks by the same pathogen.

Several factors may influence innate and adaptive immunity prior to and during surgery. Sometimes, relationship between the two types of immunity is also affected. However, the changes in immune function are not completely understood because of the immune system's complexity, patient's pathophysiological state, and impacts of surgery and anesthesia on organ systems. The impact of perioperative factors on patient's immune function cannot thus be described by terms like "immunosuppression" or "immune activation".

The perioperative management and patients' prognosis can be improved by understanding the influence of perioperative factors on immune function of surgical patients.

In this review, the common perioperative factors affecting the immune function of patients are summarized.

2. Characteristics related to the patient

2.1 Age

World is facing an exacerbation in population aging. Body's immune function declines with the age, known as immune aging. It increases the susceptibility to infectious diseases, cancers, autoimmune disorders, and other chronic illnesses [1].

Immune aging in innate immunity is depicted through changes in skin and mucosal barriers, macrophages, neutrophils, dendritic cells (DCs), and natural killer (NK) cells. With the age, turnover of skin cells decreases, sweat and sebum secretions diminish, and structural changes occur to damage the skin and mucosal barriers. Macrophages function is affected by the aging which include phagocytic activity, secretions of cytokines and chemokines, antimicrobial defense, infiltration, wound healing, and antigen presentation [2]. An animal model study has revealed that the expression of Toll-like receptors (TLRs) on macrophages decreases with the age [3]. TLRs have role in recognizing pathogen-specific molecular patterns, activating innate immune responses, and consequently regulating the adaptive immunity. The number, adhesion, and migration functions of neutrophils are unaffected by aging [4], however, their potential regarding phagocytosis, reactive oxygen species (ROS) production, and intracellular killing decreases [5, 6]. DCs' overall number is not affected by aging, yet the specific subpopulations (such as Langerhans cells in skin [7], and plasmacytoid DCs [8]) decrease in number. Furthermore, aging affects the

functionality of pattern recognition receptors, phagocytosis and migration [9, 10]. The number of NK cells increases in elderly individuals possibly because of mature cells accumulation, however, there is decrease in target cell cytotoxicity and cytokine secretion [11]. Mouse models [12] study has shown that aging affects NK cells migration. The cytokine secretion function declines [11], and proliferation response to Interleukin-2 (IL-2) stimulation decreases [13].

Adaptive immune response is affected more by the age-related changes in immune system [14]. Aging affects T and B cells number. T cells absolute values decrease during aging [15]. The activity and proliferative capacity also decline, which reduce the function of immune response [16]. Animal model and human studies have found that T cell function declines with age [17, 18]. It is discovered in mouse models that aging leads to functional defects in T cells because of changes in quantity or function of T cell surface glycoproteins. This may hinder T cell signal transduction and function [19]. Aging reduces B cell repertoire diversity as characterized by the decrease in naive B cells, increase in memory B cells [20], and reduction in clonal expansion capacity of memory B cells [21], which ultimately decrease the antibody production by B cells.

Older patients compared to younger ones are thus more prone to immune dysfunction during the perioperative period. This increases the challenges of postoperative recovery (Fig. 1).

2.2 Alcohol

Excessive alcohol consumption is linked to immunosuppression [22], which affects the innate and adaptive immune cells regarding quantity, phenotype and function.

The impact of alcohol on innate immune function depends on exposure pattern. Production of inflammation mediators decreases with acute drinking and enhances with chronic drinking [23]. Alcohol misuse may deplete NK cells, impair its cytotoxicity [22], and affect antigen presentation of Kupffer cells [24]. Alcohol misuse affects the activation, recruitment, phagocytosis, and killing functions of neutrophils [25].

Alcohol also impacts adaptive immune function. Acute alcohol exposure may reduce inflammation and increase number of peripheral blood B and T cells [26]. On the contrary, chronic alcohol consumption suppresses T cells proliferation and induces apoptosis [27], which decreases the number of Cluster of Differentiation 4^+ T ($CD4^+$ T) and $CD8^+$ T cells, and inhibits T cell activation and function [26]. It also reduces B cell count [26] and differentiation [28], and decreases protective antibodies production [29].

Alcohol-induced immune dysfunction and suppression may be caused by the inhibition of thymus and spleen growth, which damages intestinal barriers [30]. Resultantly, nutrients are difficult to absorb and cause nutritional immunosuppression [31]. It also harms the bone marrow by affecting granulocytes function [32]. Liver damage by alcohol consumption can compromise the immune function [33]. Alcohol misuse disrupts hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system, which cause higher baseline cortisol levels [34] to further impair the immune function via neuroendocrine system.

2.3 Diabetes

Diabetes mellitus type 2 (T2DM) is a low-grade chronic inflammatory condition affecting the entire body. These inflammatory responses are linked to the activation of innate immunity. Immune function dysregulation in diabetic individuals is interlinked with metabolic disruptions to create cause-and-effect relationship. Immune dysfunction worsens the metabolic disturbances, and consequently metabolic byproducts adversely affect the immune system. Immune dysfunction contributes toward the complications of heart, brain, kidney, *etc*. and the infections in diabetic patients [35].

Neutrophils and monocytes in diabetics show reduced phagocytic and chemotactic functions, which decrease the antigen presentation [36]. DCs create a link between innate and adaptive immune responses, and this link is reduced in diabetic people [37].

The humoral and cellular immune functions are compromised in diabetic patients. Elevated blood glucose can modify the structure and thus functions of immunoglobulins to weaken the humoral immunity. Glycation lowers the antibody affinity for antigens, and increases the dissociation rates of antigen-antibody complex [38]. The susceptibility to infections is thus increased. Several studies have demonstrated the elevated levels of activated $CD4^+$ $CD278^+$ T helper cells, cytotoxic T cells, and Th17 cells [39, 40], while the decreased levels of $CD4^+$ T-cells [40], naive T-cells [41], and Tregs [42]. Cytokine production like that of IL-2 is crucial for antibody production and lymphocyte function, and its imbalance further inhibits the humoral immune function.

Several factors during perioperative period such as the stress, anxiety, surgical trauma, pain, and anesthesia can trigger body's stress response which increase the synthesis and release of stress hormones through HPA axis. This causes metabolic changes including the increased glucose levels, decreased insulin production, and reduced sensitivity to insulin. Resultantly, stress-induced hyper-glycemia occurs during the perioperative period. Intraoperative elevated blood glucose is an independent risk factor for postoperative complications and mortality in patients [43]. Controlling blood glucose during surgery can thus protect the body's immune function, reduce complications, and improve prognosis.

Insulin therapy can control the blood glucose and thus alleviate its inhibitory impact on immune function. Insulin is also an immune-regulating hormone which modulates the differentiation and effector functions of immune cells. It induces T cells to differentiate into Th2 subtype, regulate neutrophil migration, and enhance prostaglandin E2 production. Consequently, immune function is protected directly and indirectly to reduce the risk of associated complications and mortality [44]. However, recent studies have demonstrated that severe hypoglycemic events are increased during the insulin-intensive therapy [45–47]. A study compared the impact of IIT (intensive insulin therapy; maintaining blood glucose between 4.4 and 6.1 mmol/L) and CIT (conventional insulin therapy; blood glucose $<$11.1 mmol/L) on postoperative immune function of diabetic patients undergoing radical gastrectomy. It was found

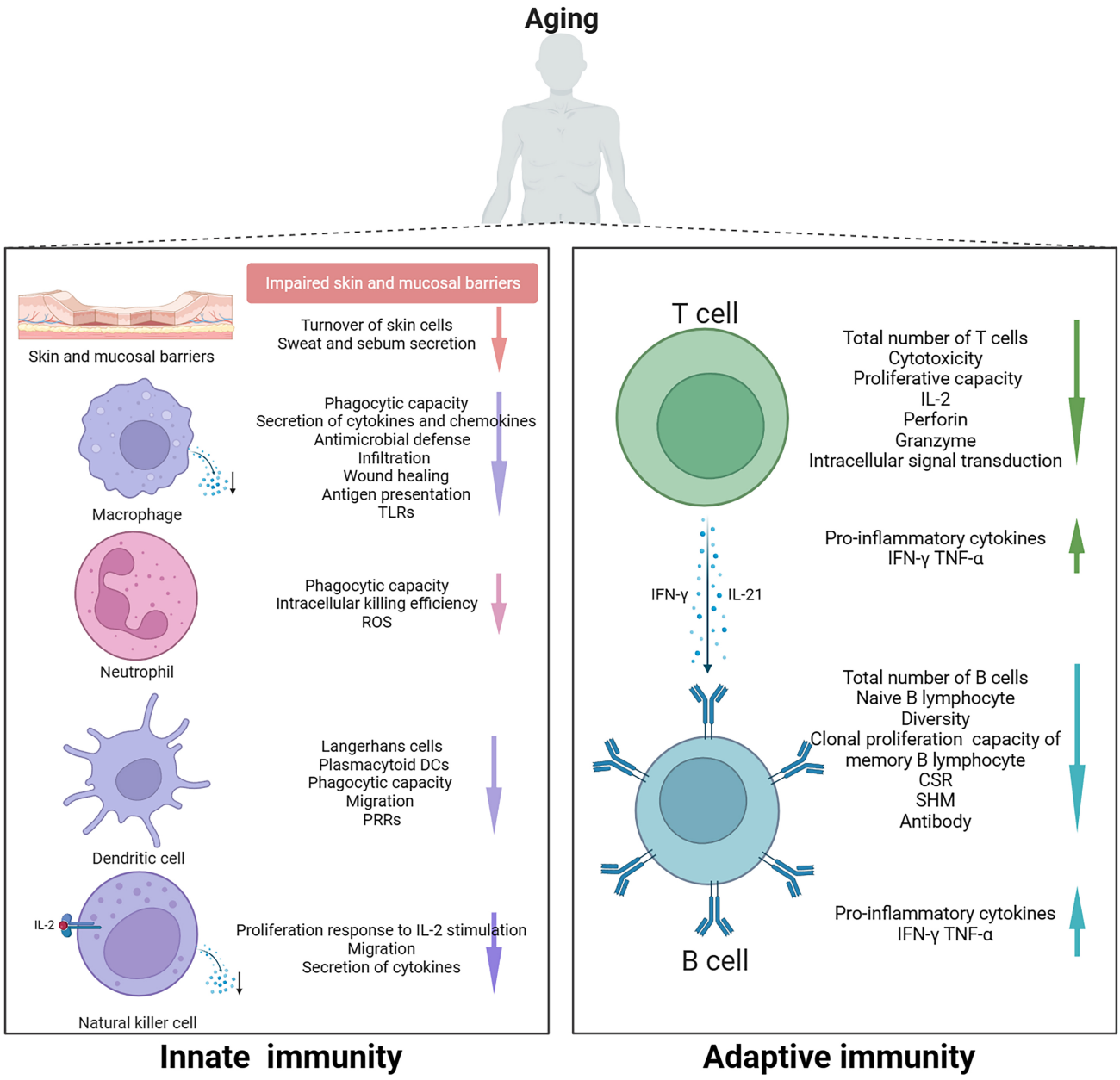

FIGURE 1. The aging impact on innate and adaptive immunity. TLRs: Toll-Like Receptors; ROS: Reactive Oxygen Species; DCs: Dendritic Cells; PRRs: Pattern Recognition Receptors; IL-2: Interleukin-2; IFN-γ: Interferon-γ; TNF-α: Tumor Necrosis Factor; CSR: Class-switch recombination; SHM: Somatic Hypermutation.

that IIT group had higher human leukocyte antigen (HLA)-DR expression on postoperative days 3 and 5. Moreover, low HLA-DR expression was associated with the impairment of monocytic functions. IIT thus improved the postoperative immune-suppressed condition and enhanced monocytic function [48]. In a study on patients undergoing coronary artery bypass grafting, moderate blood glucose control reduced the hypoglycemic events, complications, and mortality compared to the strict blood glucose control [49]. Hypoglycemia is a complication of strict blood glucose control and its relationship with immune function and clinical relevance is unclear.

2.4 Obesity

Obese patients have chronic inflammation throughout the bodies. Their immune function is impaired which exacerbate immune dysfunction in perioperative period. Clinical studies demonstrate that increased body mass index (BMI) may disrupt the immune function during perioperative period in patients of hip and knee replacement surgeries, which causes delayed wound healing [50].

Obesity triggers chronic inflammation in adipose tissue. It is marked by the infiltration and activation of immune cells and leads to cytokines and chemokines production. Obesity also disrupts the functions of innate and adaptive immune cells [51–53]. The innate immune cells are reprogrammed in obese individuals, especially the mononuclear phagocytes to cause inflammation [54]. A shift toward pro-inflammatory phenotype is indicated by the increase of pro-inflammatory T cells (Th1 and Th17), and decrease of anti-inflammatory T cells (Treg and Th2) in adipose tissue and circulation [53, 55].

B cells also adopt the pro-inflammatory phenotype [56]. T cells and B cells differentiation, function and survival are affected in obese individuals [53, 57, 58].

Obesity leads to abnormal release of pro-inflammatory cytokines and adipokines (such as leptin) from adipose tissue to cause local and systemic inflammation [59, 60]. This disrupts immune cells' function, and promotes transition of T and B cells toward pro-inflammatory cell subtypes [55]. It also triggers immune cells' proliferation and enhances cytokine secretion [61]. Circulating lipids like the free fatty acids activate pro-inflammatory pathways in immune cells [62]. Obesity increases fat deposition in immune tissues, disrupts tissue integrity, and impairs the production and maturation of white blood cells to negatively impact the immunity.

3. Intraoperative factors

3.1 Blood transfusion

Studies have revealed that perioperative blood transfusion suppresses patient's immune function, known as transfusion-related immunomodulation (TRIM) [63, 64]. TRIM mechanisms include the inhibition of NK cells, monocytes and macrophage activity, release of immunosuppressive prostaglandins, inhibition of IL-2 production, increase in number of inhibitory T cells, and activity enhancement. Reduced recipient immune function increases postoperative infections and tumor recurrence, and affects the patient prognosis [63, 65].

Blood transfusion methods (allogeneic and autologous) have different effects on recipient immune function and outcomes. Perioperative allogeneic blood transfusion decreases T cell subpopulations and NK cells in malignant tumor patients, increases inhibitory cytokine secretion, and decreases stimulatory cytokine secretion. They all lead to Th1/Th2 imbalance and transient decrease in plasma immunoglobulin levels. On the contrary, autologous blood transfusion has less inhibitory impact on immune function in malignant tumor patients and may improve postoperative immune function [66]. A study compared the effects of two blood transfusion methods on immune function of patients receiving total hip replacement. It was found that autologous blood transfusion had minor impact on postoperative immune function compared to that of allogeneic [67]. It even improved the immune function and recurrence survival of liver cancer patients [68].

The storage time of suspended red blood cells (RBCs) also affects patient's immune function. The storage time impact of transfused suspended RBCs on immune function of gastrointestinal cancer patients was studied. It was depicted that storage of suspended RBCs for less than two weeks resulted in higher levels of $CD4^+$ T cells and CD4/CD8 ratio in patients after transfusion as compared to those stored for more than 2 weeks. Shorter storage period had lower adverse reactions [69]. In another study, effects of RBCs transfusion on immune function in critically ill children were investigated [70]. Longer storage times of RBCs were associated with congenital immunosuppression. They sustained systemic inflammation, which was not the case in fresh RBCs transfusions.

The volume of transfused suspended RBCs also affects patient's immune function. Aguilar-Nascimento JE suggested that the low survival rate related to TRIM in colorectal cancer might be because of the increase in quantity of allogeneic blood transfusions and/or prolonged blood storage time [71]. The impact of perioperative blood transfusion on immune function and prognosis in colorectal cancer patients was studied. It was exhibited that the mortality rate was higher in patients receiving $\geq$3 Units of blood compared to those with <3 Units. The survival rate was negatively correlated to transfusion volume [72].

Does reducing the white blood cell (WBC) count mitigate TRIM? Decreasing WBCs can be beneficial for specific patients. The effect of leukodepleted RBCs transfusion on immune function in bladder cancer patients was evaluated [73]. It was revealed that perioperative RBCs transfusion reduced immune function, and decreased T cell subpopulations, NK cells, and immunosuppressive acidic protein (IAP) levels. In contrast, leukodepleted RBCs transfusion improved the immune function.

Studies on pancreatic [74], ovarian (cytoreductive surgery) [75], and colon cancers have found associations between perioperative allogeneic blood transfusion and the cancer recurrence risk, however, this relationship is controversial. A definitive conclusion is yet not reached despite several mechanistic studies to elucidate this relationship.

3.2 Hypothermia

Intraoperative hypothermia is caused by large volume of rapid fluid infusion, blood transfusion, abdominal lavage fluid, excessive surgical exposure, and the anesthesia state. Anesthetic drugs inhibit the regulation of body temperature by affecting central and peripheral nervous systems. Some anesthetic drugs cause vasodilation which increases heat dissipation. Muscle relaxants reduce muscle activity to decrease heat production [76]. Intraoperative hypothermia is caused after the spinal-epidural anesthesia in cesarean delivery [77]. It results from core-to-peripheral redistribution of body heat [78]. Perioperative hypothermia prolongs anesthesia recovery time and affects patient coagulation function to cause cardiovascular abnormalities. It also suppresses immune function, increases postoperative infections, and affects patient prognosis.

It was found in animal models that hypothermia exposure suppressed innate immunity of freshwater drum and led to oxidative stress and immunosuppression [79]. An *in vitro* human study found that hypothermia reduced the HLA-DR expression, delayed Tumor Necrosis Factor-α (TNF-α) clearance, and increased IL-10 release compared to control. Perioperative hypothermia thus reduced the cell-mediated immunity [80]. Recent clinical trials demonstrated that Tregs had strong immunosuppressive potential and anti-inflammatory phenotype. Another study found that mild hypothermia of 33 °C preserved Tregs stability and function, and accelerated their proliferation to suppress the deleterious immune response [81].

Hypothermia's inhibition regarding body immune function may be related to following factors. Low temperatures trigger stress response in the body, activate HPA axis, and increase cortisol and catecholamine concentrations in circulation. These factors inhibit T cells activity and synthesis of

Th1-type cytokines, IL-2 and Interferon- γ (IFN- γ). Furthermore, low body temperatures lead to increased intraoperative blood loss and the need for blood transfusion, which increases immunosuppression risk.

3.3 Oxygen inhalation concentration

Most patients receive routine oxygen supplements during anesthesia and surgery. These oxygen inhalation concentrations range from 30% to 100%. There is no consensus on the optimal oxygen concentration. Prolonged exposure to high oxygen concentrations leads to cough, tachypnea, reduced lung capacity, and increased alveolar-capillary permeability, which result in pulmonary edema and fibrosis [82]. These timeframes are beyond the duration of oxygen inhalation during surgery. A meta-analysis of 17 randomized controlled trials found no evidence that oxygen inhalation concentration of 80% is associated with increased risk of perioperative harm compared to 30% to 35%. Oxygen inhalation concentration of 80% had no safety issues in adult surgical patients receiving general anesthesia [83]. High oxygen concentrations like 80% are beneficial to the patients without associated risks. The World Health Organization's evidence-based guidelines recommend high-concentration (80%) oxygen inhalation to reduce surgical site infections in adult patients undergoing tracheal intubation for general anesthesia [84].

Studies show that perioperative high-concentration oxygen supplementation improves inflammation and immune function. Studies on laparoscopic Nissen fundoplication surgery [85] and laparoscopic cholecystectomy surgery [86] exhibited that low-concentration (Fraction of Inspired Oxygen (FIO_2) 30%) oxygen supplementation decreased the expression of monocyte HLA-DR and increased the plasma elastase concentrations after surgery. On the contrary, no significant differences were observed in patients receiving high-concentration (FIO_2 80%) oxygen supplement. Monocyte HLA-DR expression is an indicator for innate immunity and its expression is clinically significant in postoperative patient assessments. Patients with persistently low HLA-DR expression are in immunosuppressed state. High-concentration oxygen supplementation (FIO_2 80%) reduces postoperative increase in pro-inflammatory cytokines, *i.e.*, IL-1, IL-6, C-Reactive Protein (CRP). The perioperative high-concentration oxygen thus reduces postoperative inflammatory responses and prevents immunosuppression. However, studies are limited on whether immune function differences affect the clinical outcomes. Further research is required to determine the correlation between clinical outcomes and immunological changes.

3.4 Surgical approach

Surgical trauma and stress suppress body's immune function. The suppression extent is related to surgical trauma level. Studies show that laparoscopic surgery has less stress and immunosuppression compared to open surgery, which helps in postoperative recovery [87, 88]. Moreover, laparoscopic surgery allows higher levels of B cells and NK cells [89], and shorter immunosuppression duration.

Nevertheless, research has found that pneumoperitoneum during the laparoscopic surgery has dual effect on peritoneal defense system which involves changes in peritoneal morphology and metabolism [90]. Peritoneal changes are influenced by the gas type, pressure applied, and pneumoperitoneum duration. Regarding the local peritoneal immune function, CO_2 pneumoperitoneum in laparoscopic surgery induces more immunosuppression compared to open surgery. CO_2 pneumoperitoneum leads to local peritoneal hypoxia, and decreased intraperitoneal pH to result in peritoneal acidosis. CO_2 absorption through peritoneum affects systemic acid-base balance. These factors alter the cytokine production and phagocytic function of peritoneal macrophages [91]. Animal studies indicate that Secretory Immunoglobulin A (sIgA) levels in pneumoperitoneum group are increased compared to the open surgery group. This may be because of CO_2 pneumoperitoneum which reduces visceral and portal blood flow and leads to intestinal ischemia. This temporarily impairs mucosal barrier function and causes mucosal damage [92]. Pneumoperitoneum pressure also affects patient recovery and innate immune homeostasis. Low-pressure pneumoperitoneum improves postoperative recovery, maintains innate immune homeostasis, and reduces postoperative inflammation markers and damage-associated molecular patterns linked to tissue ischemia [93]. Reducing pneumoperitoneum pressure to 6–8 mmHg during laparoscopic surgery decreases postoperative inflammation and prevents postoperative immunosuppression [94].

3.5 Anesthesia techniques

Volatile anesthetics and opioid drugs in the perioperative period are associated with immunosuppression. Regional anesthesia like the epidural anesthesia provides effective pain relief in perioperative period. Combining epidural anesthesia with general anesthesia reduces the extent of postoperative immune suppression caused by surgery and pain and improves body's immune function during perioperative period [95]. An animal study demonstrated that propofol general anesthesia combined with lidocaine epidural anesthesia increased the number and percentage of cells and monocytes postoperatively compared to propofol general anesthesia alone. Cortisol levels were also lower than those in control group to suggest that epidural anesthesia had protective effect on innate and cellular immunity [96]. Clinical studies have also shown that epidural anesthesia combined with general anesthesia can alleviate immunosuppression after the surgeries pertaining to gastric cancer [97], esophageal cancer [98, 99], and orthopedic [100]. Tumor recurrence is reduced after the surgery.

The immune-enhancing impact of epidural anesthesia after surgery can be attributed to three mechanisms: reducing opioid drugs and general anesthetics usage during general anesthesia; combined epidural anesthesia blocking the harmful signaling from surgical area; and blocking surgical stimulation from being transmitted to central nervous system. Both incoming and outgoing harmful pathways are thus blocked. The general anesthesia drugs have inhibitory effect on patient's cerebral cortex system. They cannot block the HPA axis activation, and synthesis and release of catecholamines caused by surgical stimulation. They possess direct immunosuppressive effect [101]. Combined epidural anesthesia provides effective pain

relief as the pain itself causes immunosuppression. Epidural anesthesia also acts as the postoperative epidural analgesia, which is more effective than patient-controlled intravenous analgesia. Epidural analgesia combined with general anesthesia prevents surgery-induced hyperglycemia by reducing endogenous glucose production [102]. Excluding contraindications related to epidural anesthesia and employing epidural anesthesia combined with general anesthesia provides more effective perioperative pain relief and alleviates postoperative immunosuppression.

3.6 Anesthetics

3.6.1 Opioid drugs

Opioid drugs are among the most effective analgesics in treating severe pain. Studies suggest that opioids may indirectly influence the immune system by affecting pain pathways. Pain itself can lead to immunosuppression. Opioids relieve pain and alleviate this immunosuppression. However, most *in vitro* and *in vivo* studies suggest that opioids suppress the body immune function [103]. It is manifested via the decreased cytotoxic activity of NK cells [104], reduced T cells and B cells response to mitogens, inhibition of *in vivo* and *in vitro* antibody formation, suppression of neutrophil and macrophage phagocytic activity and cytokine production [105], promotion of macrophage apoptosis, and reduced macrophage TLR4 expression [106, 107].

The immunosuppressive impact of opioid drugs on immune system includes direct and indirect actions. Previous views have focused on opioids activating the HPA axis, which leads to increased stress hormones release, and results in immunosuppression. However, it is discovered that opioid receptors are distributed outside the central nervous system in tissues and organ systems (such as immune system cells). More studies suggest that opioid drugs interact with innate and adaptive immune systems and impact the opioid receptors on immune cells. The μ-opioid receptor is specifically involved in opioid-induced immunosuppression [108]. Opioid drugs induce apoptosis of immune-active cells expressed with opioid receptors. However, the same immune-suppressive effects are not induced by all opioid drugs. Different opioid drugs show varying effects on immune system including immunosuppression, immune stimulation, or dual actions [109].

Morphine suppresses NK cells activity and lymphocyte differentiation, promotes lymphocyte apoptosis, lowers TLR4 expression on macrophages [110, 111], and mediates neutrophil infiltration [112]. It hampers dendritic cells maturation, diminishes antigen-presenting potential, and restrains antigen-specific $CD8^+$ T cells activation [113]. Th1/Th2 ratio is decreased after administering morphine via Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT) pathway [114]. Both morphine and fentanyl reduce humoral response because of reduced phagocytosis by macrophages [115].

Fentanyl and sufentanil also reduce NK cells activity, however they increase regulatory T cells count [116, 117]. Cataldo analyzed fentanyl effect on splenic cellular immune response in mouse. It was found that 24 h of fentanyl administration reduced lymphoproliferation, and natural killer cell activity [115].

Remifentanil inhibits NK cells activity [104] and lymphocyte proliferation [118]. In a rat study, it reduced the activation and cytokine secretion from bronchoalveolar neutrophils and macrophages in Lipopolysaccharide (LPS)-induced lung injury [119]. Low-dose remifentanil infusion in healthy volunteers did not alter the number or NK cells cytotoxicity after 8-h infusion [120].

Oxycodone did not affect the monocyte and neutrophil phagocytosis or NK activity, however it decreased IL-6 production by T cells [121]. Oxycodone compared to morphine slightly suppressed the effector phase of cell-mediated immune response both in mice and clinical study [122, 123].

Tramadol is an atypical opioid analgesic. It was compared with morphine regarding the postoperative immune response and pain in uterine cancer patients. It was suggested that tramadol attenuated the postoperative immunosuppression and enhanced NK cells activity compared to morphine [124, 125]. Furthermore, in a study on gastric cancer surgery patients, tramadol reduced T cell subpopulations and NK cells to improve perioperative cellular immune function [126].

Evaluating the extent of immunosuppression by opioid drugs is thus essential for selecting appropriate analgesics.

Opioid receptor antagonists reverse the respiratory depression caused by opioid drugs. Studies indicated that low-dose opioid receptor antagonists improved the immune function. Postoperative infusion of low-dose naloxone increased NK cells and CD4/CD8 T cells in sufentanil-controlled analgesia patients undergoing thoracoscopic surgery. The immunosuppression caused by opioid drugs was mitigated [127]. Low-dose naltrexone (LDN) also increased M1-type macrophages to inhibit colorectal cancer progression [128]. The surgery-induced natural killer cell cytotoxicity, B and T cell proliferation, and IFN- γ production were reduced in animal experiments. They were alleviated by naltrexone [129], along with the increase in Th1 and decrease in Th2 cytokine production [130]. LDN might thus be an immunomodulatory agent in therapies for cancer and immune-related diseases [131].

3.6.2 Volatile anesthetics

Some volatile anesthetics induce apoptosis of immune cells (T cells and NK cells) and inhibit lymphocytes proliferation and function to reduce adaptive immune responses. An animal study found that isoflurane decreased T cell and monocyte infiltration in murine model [132]. Isoflurane and sevoflurane triggered apoptosis in human T cells and B cells [133, 134], while desflurane did not induce apoptosis [134]. A clinical trial on 40 breast cancer surgery cases showed that desflurane maintained the Th1/Th2 and IL2/IL4 ratios [135]. Isoflurane and sevoflurane decreased Th1/Th2 ratio in patients [133, 134]. Moreover, isoflurane, sevoflurane and desflurane caused B cell damage due to endoplasmic reticulum calcium release [136].

Volatile anesthetics also inhibit the body innate immune function. Sevoflurane and isoflurane increase oxidative stress (OS), and lead to M1 macrophage polarization [137], attenuates recruitment and phagocytosis of neutrophils [138], weakens macrophage phagocytosis [139], reduces number of circulating NK cell, and suppresses cytotoxicity [104].

Volatile anesthetics indirectly affect the immune system via

hormone levels. Volatile anesthesia patients have enhanced stress responses, pronounced surgical-induced inflammatory reactions, and altered cell-mediated immunity compared to the total intravenous anesthesia [140]. Volatile anesthetics also affect immune function by influencing blood glucose levels. Patients undergoing anesthesia with sevoflurane in combination with fentanyl have higher blood glucose compared to those with propofol in combination with fentanyl [141]. Possible mechanisms include volatile anesthetics promoting the opening of Adenosine Triphosphate (ATP)-sensitive potassium channels in pancreatic β cells to reduce insulin secretion [142]. Propofol inhibits the opening of these channels and thus promote insulin secretion [143]. Sevoflurane and isoflurane also impair glucose-stimulated insulin secretion to cause hyperglycemia [144].

3.6.3 Propofol

Propofol is a common intravenous anesthetic and a gamma-aminobutyric acid (GABA) receptor agonist. Propofol not only enhances the activity of central GABA receptors, producing rapid hypnotic and sedative effects, but also has anti-inflammatory and antioxidant properties. It has role in immune regulation with complex impact on immune system. Propofol inhibits the neutrophil extracellular traps (NET) [145]. It also inhibits the activation and function of macrophage [146]. They all reduce pro-inflammatory cytokines release to reduce inflammatory response and tissue damage. *In vitro* and *in vivo* studies demonstrated that propofol did not impair NK cell-mediated cytotoxicity [147–149]. Propofol impact on adaptive immune function includes enhancing Cytotoxic T Lymphocyte (CTL) activity, reducing pro-inflammatory cytokines, and inhibiting Cyclooxygenase-2 (COX2) and Prostaglandin E2 (PGE2) functions [150]. It inhibits T cells proliferation without affecting Th1/Th2 ratio [151]. A mice study showed that propofol and dexmedetomidine reduced $CD4^+$ T cells expression by increasing their apoptosis [152].

The mechanism of propofol's impact on immune function is proposed as follows. Immune cells such as neutrophils, monocytes, macrophages, and T cells contain GABA receptors. Propofol acts on GABA receptors of immune cells, and inhibits cytokine secretion, cell proliferation, phagocytic activity, and chemotaxis [153, 154]. It also induces apoptosis. Propofol competes for binding near Intercellular Adhesion Molecule-1 (ICAM-1) contact zones to inhibit the binding of Lymphocyte Function-Associated Antigen-1 (LFA-1) to ICAM-1 on T cells, and suppress T cell proliferation and IL-2 production [155]. Mitochondrial dysfunction is the key reason for propofol-induced immunosuppression in macrophages. Clinical concentrations of propofol inhibit mitochondrial membrane potential and adenosine triphosphate (ATP) synthesis to impair the macrophage function (mitochondrial integrity is vital for macrophage chemotaxis, migration and phagocytosis) [156]. Propofol also induces the mitochondrial reactive oxygen species (ROS) production to trigger the NOD-like Receptor Family, Pyrin Domain Containing 3 (NLRP3) inflammasome activation, which in turn activates caspase-1 to cause macrophage apoptosis [157].

Compared to volatile anesthetics, propofol does not affect Th1/Th2 balance [151, 153], and reduces perioperative stress responses [158]. Propofol has protective impact on body's immune function to promote better patient outcomes.

3.6.4 Dexmedetomidine

It is an α_2 adrenergic receptor agonist with sedative and mild analgesic effects. It activates presynaptic α_2 receptors on spinal cord dorsal horn neurons to reduce excitatory nerve transmission. Its action on spinal cord relates to primary nociceptive neurons. It also affects the locus coeruleus above the spinal cord to achieve analgesic effects.

Dexmedetomidine reduces the immunosuppression caused by surgery and pain. In cancer patients undergoing surgery, it maintains CD3 cells proportion, number of NK cells, CD4/CD8 ratio, and Th1/Th2 balance, while decreasing pro-inflammatory cytokines levels like those of IL-6 and TNF-α [159]. Dexmedetomidine regulates immune system through its direct impact on immune cells and indirectly by acting on α_2 adrenergic receptors to inhibit norepinephrine release in periphery, which indirectly affects immune cells. Dexmedetomidine reduces IL-6 and TNF-α levels in rat splenocytes and lymphocytes as stimulated by LPS. This effect is blocked by α_2 adrenergic receptor antagonist (yohimbine) to indicate that dexmedetomidine inhibits inflammatory responses by acting on α_2 adrenergic receptors. This experiment also shows that dexmedetomidine does not affect the immune cells activity in spleen and lymph nodes [160].

Dexmedetomidine directly affects the function of monocytes and macrophages. Li *et al.* [161] reported that dexmedetomidine reduced Nuclear Factor kappa B (NF-κB)-p65 phosphorylation to minimize TNF-α production in mouse BV-2 microglial cells and RAW264.7 macrophages as stimulated by LPS. It led to the decreased levels of pro-inflammatory cytokines. Dexmedetomidine increased $F4/80^+Ly6G^+$ macrophages in Dex-treated mice. It enhanced Transforming Growth Factor Beta 1 (TGF-β1) production secreted by macrophage, and led to attenuated cytokine storm and accelerated inflammation resolving [152]. Dexmedetomidine also regulated sympathetic nervous system (SNS) and HPA axis to reduce Adrenocorticotropic Hormone (ACTH) secretion and cortisol levels. Consequently, it alleviated the inflammation induced by surgical stress and immunosuppression [162].

Analgesic effects of dexmedetomidine protect immune function during perioperative period. Pain activates the SNS through neuroendocrine pathways to promote the plasma catecholamines and immune responses, induce redistribution of immune cells (*e.g.*, neutrophils, monocytes and T cells), enhance NK cell cytotoxic activity, lymphocytes proliferation, and cytokine production [163]. Reducing pain or SNS activation by tissue damage can thus modulate the immune activity. In formalin pain mouse model, dexmedetomidine prevented pain-induced activation of NK cells, and reduced the NK cell cytotoxicity without affecting lymphocytes proliferation [164]. Furthermore, dexmedetomidine reduces early postoperative pain severity and alleviates immunosuppression by reducing opioid drugs consumption [165]. Dexmedetomidine is beneficial for the patients with compromised immune function. It does not

impair lymphocytes' function or proliferation at clinically relevant plasma concentrations [155].

3.6.5 Midazolam

It is the benzodiazepine derivative and used in clinical practice for anti-anxiety, sedation and general anesthesia. It impacts the immune regulatory properties of immune cells besides having effect on central nervous system. Previously, it was known to reduce the elevation of catecholamines induced by surgical stress for diminishing side effects of elevated cortisol on immune defense in perioperative period [166]. Recent study indicated that midazolam also affected the quantity and function of immune cells. Intraperitoneal injection of midazolam in a mouse model of liver cancer reduced the proportions of $CD4^+$ T cells, $CD8^+$ T cells, NK cells, monocytes, Treg cells, and M2 macrophages, while increased the DCs proportion [167]. Another similar study showed that midazolam impaired the monocyte and neutrophil function. It did not affect cytotoxic T-lymphocyte (CTL) activity [168]. Midazolam also induced phenotypic changes in DCs, reduced the expressions of CD80, CD68 and major histocompatibility complex II (MHC II) in mouse DCs, and inhibited the DC antigen presentation capacity (DCs are the antigen-presenting cells that present antigens to naive T cells for differentiating into T helper 1 and other effector molecules). It thus suppressed the immune response induced by mouse DCs [169].

Midazolam also inhibits the macrophages immune activation [170]. It inhibits immune response of macrophages stimulated by LPS through the translocator protein (TSPO) signaling pathway [171]. It suppresses NF-κB activation in macrophages and reduces release of pro-inflammatory factors like Inducible Nitric Oxide Synthase (iNOS) and COX2 [172]. COX2 induces immune evasion and suppresses immune responses. Kang *et al.* [167] suggested that midazolam also reduced Programmed Death-Ligand 1 (PD-L1) expression in hepatocellular carcinoma to weaken the PD-L1 inhibitory effect on T cell immune activity and reduce CD8 T cells exhaustion in liver cancer. These factors have made the midazolam a potential anti-tumor drug for cancer immunotherapy.

3.6.6 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are the first-line conventional drugs in treating pain of all levels. They are recommended for acute perioperative pain management when there are no contraindications. Adding NSAIDs to multimodal analgesia has improved perioperative pain management, reduced adverse effects associated with opioid drugs, and decreased the perioperative complications.

Unlike opioid drugs acting on central nervous system, NSAIDs alleviate pain by reducing inflammation caused by tissue damage and preventing peripheral and central sensitization. NSAIDs possess antipyretic, analgesic, and anti-inflammatory effects. Studies have shown that excessive prostaglandin (PG) release leads to postoperative immunosuppression. PGE2 is a major metabolite produced from arachidonic acid as catalyzed by cyclooxygenase (COX). It is among the most biologically active and widely studied prostaglandins. It inhibits cell-mediated immune response, upregulates immune suppressive cytokines such as IL-10 and TGF, and suppresses normal T cell proliferation response [173]. PGE2 also reduces NK cells cytotoxicity and cytokines production [174]. It impairs proliferation and activation of effector T cell and increases Tregs infiltration [175, 176]. On the contrary, NSAIDs inhibit PG synthesis by blocking COX, reducing PGE2 levels, and improving immunosuppression. NSAIDs enhance NK cell-mediated cytotoxicity and promote proliferation and function of $CD4^+$ and $CD8^+$ T cells to enhance anti-tumor immunity and reduce tumor metastasis risk [177, 178]. However, a previous study reported that these drugs inhibit humoral immunity [179].

A clinical study, on liver cancer patients undergoing hepatectomy, made comparisons of using fentanyl alone or in combination for the pain relief. Patients in perioperative fentanyl combined with parecoxib sodium group had faster recovery of NK cell percentages compared to preoperative levels along with the higher levels of $CD3^+$ T cells. This indicated that parecoxib sodium alleviated immunosuppression caused by surgery and opioid drugs [180]. It was also found in a study of laparoscopic surgery for cervical cancer patients that parecoxib sodium could balance cytokines levels produced by Th1/Th2, Th17 and Treg, reduce postoperative elevation of IL-2, IFN-γ and IL-17 levels, and inhibit excessive production of IL-4, IL-10 and TGF-β to alleviate the surgery-induced immunosuppression [181]. Parecoxib sodium also inhibits the increase in neutrophil-to-lymphocyte ratio (NLR) after the modified radical mastectomy, suppresses inflammatory response in breast cancer patients, and enhances patient immune function [182].

3.6.7 Lidocaine

Lidocaine modulates the immune cells activity. Clinical studies indicate that lidocaine alleviates postoperative immune suppression and inhibits inflammatory cytokines expressions [183, 184]. Clinical doses of lidocaine enhance NK cells cytotoxicity [185]. Lidocaine reduces lung injury and neutrophil infiltration in acute pulmonary edema mice [186]. Moreover, it decreases circulating NET [187]. *In vitro* study has shown that lidocaine reduces inflammatory cytokines release from dendritic cells and macrophages to exert anti-inflammatory and anti-tumor effects [188, 189]. Lidocaine enhances cellular and humoral immunity in the patients. Animal experiments demonstrate that lidocaine injection increases immunoglobulins levels in dogs [96]. Perioperative administration of lidocaine in breast cancer patients undergoing surgery, increases the percentages of NK cells, $CD3^+$ cells, $CD4^+$ cells and $CD4^+/CD8^+$ ratio to enhance the cellular immunity [190]. Immunomodulatory effects of lidocaine can be attributed to its anti-inflammatory characteristics, direct action on immune cells, or modulation via the sympathetic nervous system/hypothalamic-pituitary-adrenal (HPA) axis. Lidocaine injection in non-small cell lung cancer patients decreases serum cortisol levels [191].

The effects of mentioned drugs on innate and adaptive immune functions are summarized in Table 1.

TABLE 1. Effects of volatile anesthetic agents, intravenous anesthetic agents, and perioperative adjuvant agents on innate and adaptive immunity.

	Innate immunity			Adaptive immunity	
	Macrophage	Neutrophil	Natural killer cell	T cell	B cell
Morphine	TLR4↓ [104] Phagocytosis↓ [115]	Infiltration↑ [112]	Cytotoxicity↓ [104]	$CD8^+$ T↓ [113] Th1/Th2↓ [110, 114]	Humoral immunity↓ [115]
Fentanyl	Function↓ Phagocytosis↓	/	Activity↓ [115, 116]	Treg cell↑ [116] Proliferation↓ [115]	Humoral immunity↓ [115]
Remifentanil	Activity↓ [119]	Activity↓ [119]	Activity↓ [104]	Proliferation↓ [118]	Proliferation↓ [118]
Oxycodone	Phagocytosis— [121]	Phagocytosis— [121]	Activity— [121]	IL-6 production↓ [121] Effector phase↓ [122, 123]	/
Tramadol	/	/	Activity↑ [124, 125]	Function↑ [126]	/
Naltrexone	M1-type↑ [128]	/	Count↑ [127] Cytotoxicity↑ [129]	CD4/CD8 T↑ [129] Proliferation↑ [129] Th1/Th2↑ [130]	Proliferation↑ [129]
Sevoflurane	M1-type↑ [137] Phagocytosis [139]	Recruitment and phagocytosis↓ [138]	Cytotoxicity↓ [104]	Apoptosis↑ [134] Function↓ Th1/Th2↓ [133, 134]	Apoptosis↑ [134] Function↓ [136]
Isoflurane	M1-type↑ [137] Infiltration↓ [132] Phagocytosis [139]		Cytotoxicity↓ [104]	Apoptosis↑ [133] Count↓ [132] Th1/Th2↓ [133, 134]	Apoptosis↑ [133] Function↓ [136]
Desflurane	/	/	/	Apoptosis— [134] Th1/Th2, IL2/IL4— [135]	Apoptosis— [134] Function↓ [136]
Propofol	Activation and function↓ [146]	NET↓ [145]	Cytotoxicity— [147–149]	Proliferation↓ [151] $CD4^+$ T↓ (apoptosis↑) [152] Th1/Th2— [151, 153]	/
Dexmedetomidine	$F4/80^+Ly6G^+$↑ [152] TGF-β1 production↑ [152]	/	Cytotoxicity↓ [164] Count— [159]	IL-6↓, TNF-α↓ [159, 160] $CD4^+$ T↓ (apoptosis↑) [152] Th1/Th2— [159] Proliferation— [155, 164]	/
Midazolam	Activation↓ [170] Function↓ [168, 171, 172] The proportion of M2↓ [167]	Function↓ [168]	Proportion↓ [167]	CTL activity— [168] The proportions of $CD4^+$ T cells, $CD8^+$ T cells and Tregs↓ [167]	/
NSAIDs	/	/	Cytotoxicity↑ [177, 178]	Proliferation and function of $CD4^+$ and $CD8^+$ T cells↑ [177, 178] Cellular immunity↑ Th1/Th2↑ [177, 181]	Humoral immunity↓ [179]
Lidocaine	Inflammatory cytokines↓ [189]	Infiltration↓ [186] NET↓ [187]	Cytotoxicity↑ [185] Percentage↑ [190]	$CD3^+$ cells, $CD4^+$ cells, $CD4^+/CD8^+$ ratio↑ [190]	Immunoglobulins↑ [96]

Abbreviations: /: indeterminate or limited data; —: no change; ↑: increase; ↓: decrease; TLR4: Toll-Like Receptor 4; CD: Cluster of Differentiation; NET: Neutrophil Extracellular Trap; TGF-β1: Transforming Growth Factor Beta 1; IL: Interleukin; TNF-α: Tumor Necrosis Factor Alpha; CTL: Cytotoxic T Lymphocyte; NSAID: Non-Steroidal Anti-Inflammatory Drug.

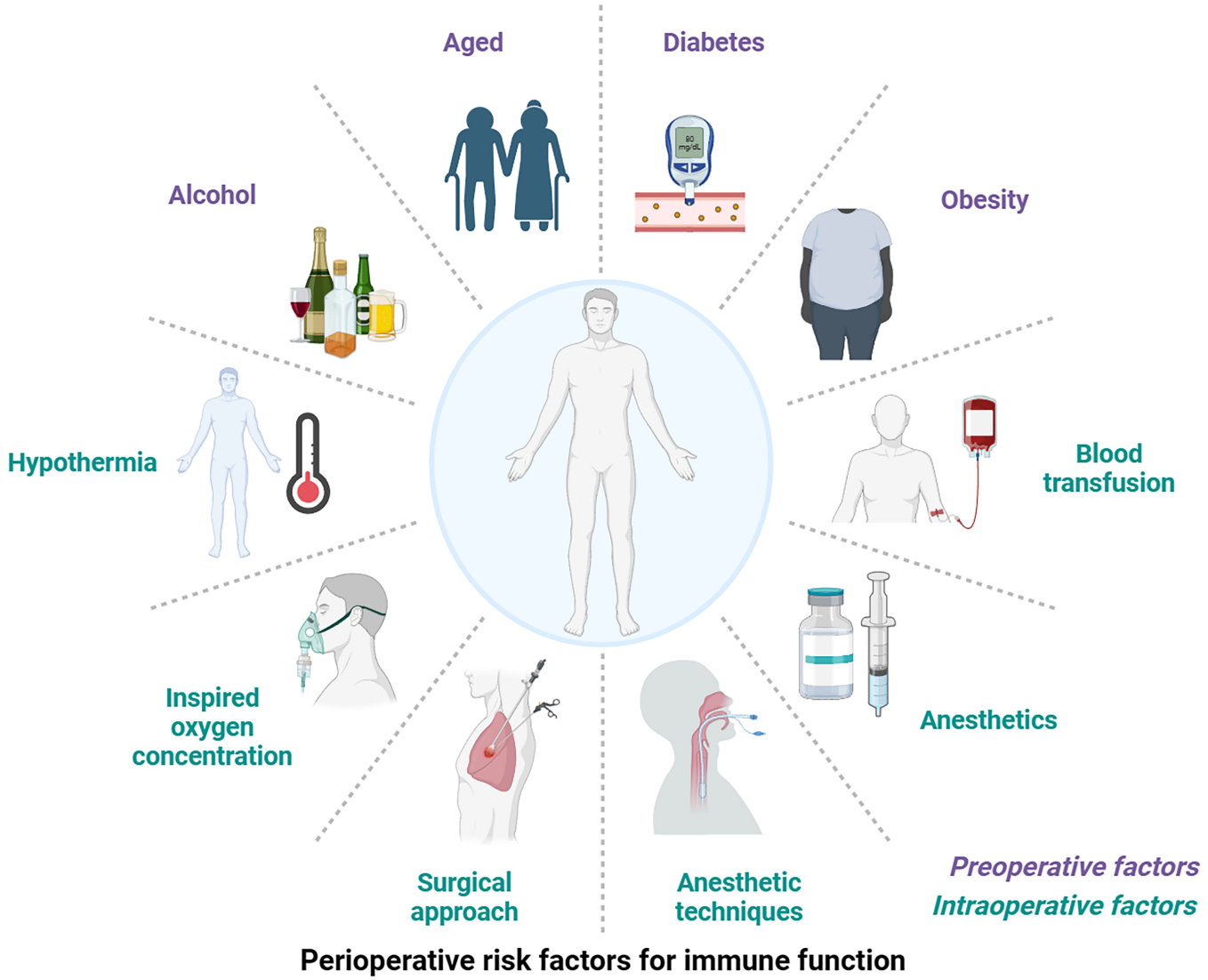

FIGURE 2. The effects of perioperative factors on immune function.

4. Conclusion

The perioperative factors have influence on patients' immune function and thus cause changes in immune function among the patients (Fig. 2). The compromised immune function affects patients' prognosis and facilitates tumor recurrence in cancer patients. Perioperative anesthesia management is thus important. It is imperative to minimize the overall systemic stress response in patients, alleviate systemic inflammatory reactions, and safeguard patient's immune function. Preoperative assessment of patient's immune function based on individual conditions should guide the selection of surgical procedures. A careful consideration of pros and cons is warranted in cases where blood transfusion is necessary, along with the preference for judicious blood transfusion, advocating for component transfusion, and autologous blood transfusion. Perioperative body temperatures are properly monitored and thermal conservation measures are accordingly implemented. The utilization of higher inhaled oxygen concentrations mitigates immunosuppression by reducing pro-inflammatory cytokines release. Compared to the inhalation anesthetics and opioid-class drugs, the combination of general anesthesia with regional anesthesia reduces overall dosage of general anesthetics. This concurrently mitigating immunosuppression enhances patient's prognosis. All the mentioned factors should be designated as the standard care for all patients instead of only for immunocompromised.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

XXP—designed the research study. YNC and JWK—performed the research and wrote the manuscript. YLW—collected and analyzed the data. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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