Translational Perioperative and Pain Medicine

ISSN: 2330-4871

Review Article | Open Access Volume 7 | Issue 1

Precision Organ Function Protection for Enhanced Recovery after Surgery

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Abstract

The concept of enhanced recovery after surgery (ERAS) has gained gratifying achievements in clinical practice, but there are still many disputes and incompatibilities in its application. The reasons for this phenomenon are multifaceted, is evident at multilevels and needs further exploration and improvement.

By combining previous studies and our clinical experience, we propose an enhanced concept of ERAS, i.e., precision organ function protection (POFP) for ERAS to promote lasting rehabilitation of patients after surgery. We prefer to use "important organ function outcomes" (IOFOs) as the clinical target of ERAS. Perioperative optimal organ function preservation by using a series of techniques can help patients recover quickly and return to baseline function as soon as possible. This concept has greatly expanded the connotation of the traditional ERAS, whose core idea was reducing stress, providing analgesia and humane care.

Keywords

Enhanced recovery after surgery, Analgesia, Reduce stress, Precision organ function protection

Introduction

Professor Henrik Kehlet from the University of Copenhagen in Denmark first proposed the concept of enhanced recovery after surgery (ERAS) in 1997. At present, the core idea of ERAS is reducing stress, providing analgesia and humane care. Although ERAS has achieved gratifying achievements in clinical practice, there are still many disputes and incompatibilities, which need further exploration and improvement.

ERAS requires multidisciplinary involvement in the prevention, rehabilitation and treatment of perioperative complications

ERAS emphasizes alleviating pain, trauma and stress at all stages of the perioperative period. Firstly, minimally invasive surgery is regarded as a dominant part of ERAS. Secondly, anesthesiologists prefer to reduce stress by providing adequate analgesics and anesthetics. All these are based on ensuring patient safety instead of blindly pursuing the application of high-tech and new medicines [1].

Currently, ERAS systematically integrates the knowledge of various disciplines. The multidisciplinary team (MDT) aims to prevent or reduce perioperative complications and adverse effects. MDT treatment not only helps to reduce postoperative complications but also helps improve patient comfort in the perioperative period [2].

ERAS requires more humanistic care in clinical practice

ERAS promotes the biomedical model to a Bio-Psycho-Social medical model. Humanistic care should integrate all aspects of ERAS. Firstly, doctors should continuously improve their own technical skills. Secondly, the implementation of the ERAS program requires multidisciplinary cooperation according to a patient-centered philosophy [2-4]. Thirdly, the clinical application of ERAS requires active patient cooperation, and adequate communication between doctors and patients. Finally, the use of problem-oriented philosophy may help patients benefit from existing technologies [1,5].

Current ERAS guidelines consider that patient cooperation is a key factor in success. Preoperative education of ERAS is more focused on humanistic care, which includes (1) The transition from "dogmatic communication" to "educational communication" between the medical staff and patients; (2) The transition from "passive acceptance" to "active participation" in patients; (3)

The transition from “post-treatment” to “pre-existing prevention” in clinical practice; (4) The transition from “single surgery” to “multidisciplinary cooperation”. These changes emphasize the problem-oriented philosophy in medical practice, which reflects a patient-centered philosophy. When we communicate with the patient about ERAS, this subtly changes the mindset and work habits of the medical team [6].

Optimization of multidisciplinary cooperation makes ERAS more “individual” and “humanized”

ERAS outcomes stem from minimally invasive techniques, optimizing surgical procedures, and results in the shortening of the average hospital stay. The optimized measures include the reasonable application of tubes (drainage tube and urine, etc.), use of different analgesic methods, rapid recovery of gastrointestinal function, and whether tracheal intubation is required [1,7].

The initial focus of ERAS was to achieve complete recovery of patients. ERAS needs to be developed as a treatment plan from a recovery perspective rather than the treating diseases.

Each discipline prefers selecting the best solution for the professional problem, then choosing the individual treatments. The individual pain treatments may involve MDT collaboration, which include the following points. (1) The nurse informs the patient about his condition and pain treatments and actively guides the preoperative preparation. (2) The anesthesiologist prepares advanced analgesia treatments. (3) The surgeon takes preventive treatment (such as local infiltration of anesthesia around the incision), according to postoperative pain characteristics. (4) Most importantly, the anesthesiologist evaluates the analgesic effect after surgery and adjusts the analgesic program according to the individual’s needs [2].

Individual treatment of ERAS varies from person to person, which also reflects "humanized" care. From evidence-based practice, continuously improving diagnosis, treatment or surgical procedures is essential to improving the quality of recovery after surgery. Special risk factors need to be considered in ERAS during the perioperative period, to optimize the process according to identified high-risk factors and to strengthen perioperative rehabilitation management. The individualization focuses on treatment, while humanization involves prevention, treatment and rehabilitation [7-10].

The role and problem of anesthesia in ERAS

Anesthesiologists play important roles in ERAS. They improve clinical outcomes by taking many measures, including early health education and active preoperative preparation. These measures include optimization of anesthesia, making the fluid therapy plan and monitoring body temperature, and implementing reasonable analgesia after surgery. The field of anesthesiology extends from assessment before surgery to comfort and rapid recovery after surgery.

However, there are still difficulties and controversies in clinical practice, which include the following points. (1) Can surgeons receive early intervention from the anesthesiologist? (2) Can the anesthesiologist agree with the surgical notice? (3) Can appropriate measurements for preoperative fasting and carbohydrate supplementation be selected? (4) How do we choose the sedatives before surgery and make an anesthesia plan? (5) Can local and regional anesthesia widely be accepted in clinical practice? (6) Is laparoscopic surgery compatible with spinal anesthesia? These problems need to be addressed in the future through more randomized controlled trials [11,12].

Some thoughts on medical education in ERAS

At present, the design and implementation of the ERAS program is mainly based on the experience of surgeons. There are a number of deficiencies in this. Firstly, the executors of the program are different from the creators, so the performance evaluation is not enough. Secondly, the standardization process is not easy to adapt to the needs of each patient because of differences in patients’ condition and medical staff. In addition, surgeon-led clinical model in ERAS also has many practical difficulties. The anesthesiologist-led clinical model has been proposed in recent years. However, anesthesiologists do not directly manage patients in the ward, and it is more difficult for them to determine the surgical approach or postoperative management.

It can be concluded that a single subject-led ERAS has some difficulty in covering all related problems, and the process of the MDT-led ERAS is too cumbersome to implement. Therefore, it is essential to integrate ideas and raise awareness of ERAS, in order to break the “fortress” effects of the different disciplines and to emphasize the deep integration of clinical multidisciplinary teams for ensuring the safety and effective development of ERAS.

In future medical education, it is better to recommend training surgeons with an anesthesia background or anesthesiologists with a surgical background [13-15].

The new concept of ERAS------ triple rehabilitation

In early animal experiments and subsequent clinical trials, multimodal pre-rehabilitation programs (including physical, nutritional, and psychological triple rehabilitation) appear to be more effective in helping patients recover quickly [16-18].

The triple pre-rehabilitation strategy is the emerging pretreatment concept in ERAS. The strategies aim to ensure patients getting the best treatment plans and achieving the best functional status with multidisciplinary collaboration before surgery. The extensive development of pre-rehabilitation is becoming a new practice of preoperative medical treatment. Anesthesiologists have the responsibility to promote these strategies to help patients rapidly recover after surgery. At present, most of the clinical trials of triple pre-rehabilitation focus on gastrointestinal surgery [17,19,20], and future trials should expand to more fields. We hope that feasible programs can be validated in families so that more patients can benefit in the future.

Precision organ function protection promotes rapid and long-lasting recovery of patients

One core aim of ERAS is to reduce stress, including physical and psychological stress, in the perioperative period. Therefore, ERAS requires medical staff to optimize clinical techniques and measures (preoperative rehabilitation, optimizing bowel preparation, optimizing anesthesia, multimodal analgesia, rational use of various catheters, early enteral nutrition, getting early out of bed, changing clinical care patterns, controlling gastrointestinal discomfort, intraoperative heat preservation, restriction of fluid input, prevention of antibiotics, strict discharge assessment, and complete post-hospital visit system) [1].

Although ERAS has achieved gratifying achievements in clinical practice, there are still many disputes and incompatibilities, which need further exploration and improvement [21]. Recently, some studies found that the evaluation by the medical staff did not accurately reflect the patient's body condition and feelings. Therefore, some researchers suggested that patient-reported outcomes (PROs) should be one of the clinical targets of ERAS [22-25].

The recovery of symptoms depends on the rapid rehabilitation of vital organs. By combining previous studies and our clinical experience, we propose an enhanced concept of ERAS. That is “Precision organ function protection (POFP) for ERAS to promote the lasting rehabilitation of patients after surgery”.

We prefer to use important organ function outcomes (IOFOs) as the clinical target of ERAS. This is because perioperative optimal organ function preservation by using a series of techniques can help patients recover quickly and return to baseline function as soon as possible. This concept has greatly expanded the connotation of the traditional ERAS, whose core idea was in reducing stress, providing analgesia and humane care.

Organ function protection in perioperative period has been the key point in this area in recent decades

Surgery is an important method of treating diseases. The surgery itself is also a trauma for patients. Severe trauma, shock, infection, organ ischemia-reperfusion injury, sepsis, and the local and systemic severe inflammatory response syndrome caused by the surgery itself are important factors leading to important organ dysfunction in perioperative period. Therefore, organ function protection requires close collaboration from different departments, which is important for patient's prognosis [26-28].

Organ function protection by anesthetics and anesthesia: A large number of animal tests and clinical trials have found that anesthetics and anesthesia have clearly protective effects on heart, brain, lungs, kidneys, and other organs. Autophagy and apoptosis pathways, the PKC system, the ERK 1/2 signaling pathway, the inflammatory response, the NO system, mitochondrial dysfunction, body inflammatory response, intracellular calcium overload, oxidative stress and other pathways have been shown to be involved in these protective effects [29-32]. Therefore, to understanding the mechanisms of anesthetics can promote the progress of related research [33-36].

Organ function protections of non-narcotic drugs and methods: It is necessary not only to use anesthetics to protect organ function but also to combine this with other medicines and methods, such as acupuncture [37,38], hypothermia [39-42], remote ischemic preconditioning [43], and traditional Chinese medicine [44-46]. Related research explores the mechanism of organ function protection from different aspects, including holistic, cellular, molecular changes and gene expression. Protective measures include the protective effects of various non-anesthetics on different organs, as well as ischemic preconditioning. The application of the above non-anesthetics and methods opens up more ways for perioperative organ protection.

Some thoughts about immunosuppression by anesthetics and opioids: Since the 1990s, the study of perioperative organ protection by anesthetics has been ascendant. However, there is no clear evidence that the organ function protection of anesthetics can affect long-term recovery or mortality in surgical patients. Recent studies have found that commonly used anesthetics or opioids may lead to immunosuppression [47]. The immunosuppression by these drugs may help alleviate systemic inflammatory responses but may also increase postoperative mortality and recurrence rates [47].

Anesthetics, especially inhaled anesthetics, can af-

fect the expression of tumor proteins through immune or neuroendocrine effects, thereby affecting patients' long-term prognosis [48,49]. Propofol seems to be an ideal anesthetic for patients undergoing malignant tumor surgery, and satisfactory analgesia [48,49]. Regional anesthesia may be an ideal method for lung cancer and breast cancer [50,51]. Patients should use opioids as little as possible [47,52], and non-steroidal anti-inflammatory drugs (COX-2 inhibitors, others) can be chosen as alternative analgesics [52]. The choice of anesthesia method and anesthetic has different effects on postoperative recurrence, metastasis and long-term survival rate in different tumor patients. The patient's stress response to surgical trauma may also increase the growth and invasion of tumor cells, which may reduce the immune system's defense and surveillance capabilities. Surgery, anesthesia and analgesia may lead to tumor recurrence and metastasis. However, it is too early to draw a clear conclusion about it [48,50-52]. Inhaled anesthetics can induce tumor mitosis, angiogenesis and metastasis by affecting vascular endothelial growth factor, metalloproteinase 2/9 and hypoxia-inducible factors [48,53-55].

Therefore, it should be recognized that organ function protection of anesthetics needs comprehensive analysis. Many factors in the perioperative period have profound impact on immune function. For clinicians, improving perioperative management at multiple levels, reducing the suppression of immune function in tumor patients, and further improving the long-term prognosis of patients are the goals of future work.

Precision organ function protection and precision anesthesia in perioperative period

The connotation of precision anesthesia: Anesthesiology is transforming into a perioperative medicine. Anesthesiology should not be limited to the "intermediate department". Instead, anesthesiologists should pay more attention to the patient's safety and comfort in perioperative period and as well as the long-term prognosis. The anesthesiologist should ensure that the anesthesia be stable, maintain circulation and internal environmental stability, emphasize in medication individualization, and reduce mortality through accurate implementation of anesthesia and anesthetics. We should pay more attention to precision, comfort, remoteness, and extension in the future, which are also the trends of modern anesthesiology.

The meaning of precision anesthesia includes intraoperative monitoring, circulation management, airway management, stress management, etc. Among these, intraoperative monitoring is the basis of precision anesthesia. Anesthesiologists should monitor vital signs through instruments such as electrocardiogram and pulse oximetry, monitoring sedation depth by Bispectral index (BIS) and auditory evoked potential, monitoring the degree of muscle relaxation through four-string stimulation (TOF), and indirectly monitoring the patient's response to surgical trauma and noxious stimulation [56-59].

Accurately regulating the function of important organs in perioperative period is the key factor for rapid and sustained recovery of patients: As mentioned above, the core of ERAS is precision organ function protection, reducing stress, providing analgesia and humane care. Therefore, anesthesia management should also focus on minimal physiological interference, perfect organ function protection, and reduction of stress, which mainly includes the following aspects.

Regulation of stress: Stress or stress response refers to the nonspecific systemic response of the body stimulated by various internal and external factors. Stress is characterized by sympathetic excitation and enhancement of hypothalamic-pituitary-adrenergic cortical function. The stress events include tracheal intubation, mechanical ventilation, surgical trauma, and ischemia-reperfusion injury. The importance of stress regulation lies in organ function protection and improvement of long-term outcomes.

The goal of precise stress regulation is to reduce the incidence of perioperative complications, reduce mortality, and improve long-term outcomes. Anesthesiologists should select effective measures to decrease stress according to the condition of the individual, type of surgery, surgical trauma, etc. Furthermore, anesthesiologists should accurately regulate perioperative internal environment disorders on anesthetics, anesthesia methods, surgical inflammation, pain, volume, endocrine status and other factors [60-62].

Regulation of perioperative inflammation and immune reaction: Stress can regulate immune inflammation, and excessive stress may lead to additional damage through the release of excessive inflammatory factors which may induce postoperative cognitive dysfunction (POCD), postoperative delirium, chronic pain, thrombosis and other risks [63,64]. Tan confirmed that dexmedetomidine exerted renal protection through an anti-inflammatory mechanism. Acute kidney injury is also an inflammatory response caused by ischemia-reperfusion after coronary artery bypass grafting (CABG). Neutrophil gelatinase-associated apolipoprotein (NGAL) is an early and sensitive biomarker of kidney injury, and NGAL in serum generally rises within 2 h after the onset of renal injury [65,66]. Anti-inflammatory effects of dexmedetomidine may enable the patients to have a lower extent of postoperative mental state scale score, POCD, renal injury incidence, and inflammatory factor level [67-69].

Perioperative management of circulation: Circulatory management is an important part of precision anesthesia. The circulatory system has four major factors (myocardial contractility, vascular resistance, blood volume and factors of the neurohumoral regulation), which may mediate blood pressure and cardiac output. Blood pressure stability is the core goal of precision anesthesia [70-73]. Monk confirmed that intraoperative low blood pressure was associated with an increase in mortality 30 days postoperatively whereas intraoperative hypertension was not associated with mortality at 30 days postoperatively [71,74]. Walsh showed that the risk of acute kidney or myocardial injury increased when the mean arterial pressure was below 55 mmHg for an extended time [75].

Common treatments for perioperative hypotension include fluid replacement, reducing the depth of anesthesia, and vasoactive drugs. When the above treatments are not performed correctly, perioperative complications may occur. When there is insufficient capacity and low blood pressure, inappropriate fluid replacement treatment may cause excessive capacity load. Excessive volume overload is the main cause of death and disability in perioperative period in some contexts. Therefore, limiting excessive liquid input can improve postoperative pulmonary function and prevent hypoxemia in ERAS, which can also improve the cardiovascular active hormone concentration. Goal-directed fluid therapy (GDFT) with hemodynamic parameters, mixed venous oxygen saturation and blood lactate level can reduce complications, shorten hospital stays, and optimize liquid therapy for precise anesthesia. Too deep anesthesia is one of the important factors of hypotension. Choosing anesthetics with little effect on circulation and accurate dosage is important for the implementation of accurate anesthesia [76,77].

Precise use of anesthetics in perioperative period: Anesthetics mainly include sedative drugs, analgesics, muscle relaxants, and vasoactive drugs. Choosing appropriate drugs may result in additive, synergistic and antagonistic effects, which can reduce the dose requirement of a single drug and decrease related side effects. Some sedative drugs may act on the same site, but their receptor subtypes and clinical effects may not be the same. The precise compatibility of anesthetics should be based according to pharmacokinetics and pharmacodynamics. Multimode analgesia in ERAS requires that doctors choose the order and time of administration according to the different mechanisms of the analgesics. This can reduce adverse effects and physiological interference [78-83].

It is advisable to choose drugs that are short acting and fast acting. The administration of different drugs should be determined according to the pharmacokinetic parameters. Drugs (e.g., etomidate, propofol, and remifentanil) with fast metabolism and short time-related half-life can be chosen for use in target-controlled continuous infusion, while drugs (e.g., fentanyl, vecuronium bromide) with a long time-related half-life and easy accumulation should be administered as a single intravenous injection. When stopping these drugs, it is necessary to stop the drug in accordance with pharmacokinetics and to manage the anesthetics in a reasonable order to promote recovery of the patient.

Differing from precision anesthesia, precision medicine is based on gene sequencing and molecular targeting technology. Precision anesthesia requires experienced anesthesiologists to determine precise fluid therapy, suitable analgesia, and stationary hemodynamics according to changes and difficulties encountered during operation. To determine the sequence of drugs and the order of use, the anesthesiologist should be familiar with pharmacodynamics and pharmacokinetics of the drug, which may help their patients have a speedy recovery [84-86].

Organ function evaluation is the key to guide ERAS

The optimization of organ function evaluation will be an important part of ERAS in the future. Evaluation methods in the peri-operative period are currently not fully developed. The following are some details of the progress in organ function evaluation:

Monitoring based on hemodynamics and organ perfusion:

Some limitations of traditional fluid therapy in predicting responsiveness in critically patients: Early fluid therapy is the first method of choice to improve hemodynamics in critically ill patients. Reasonable fluid therapy can increase cardiac output (CO), attain stable hemodynamics, and improve patient outcomes. Related indicators include blood pressure, heart rate, central venous pressure (CVP), and pulmonary wedge pressure (PAWP). In some reports, the concept of hemodynamics, oxygen metabolism, and tissue perfusion are often confused. In terms of the order of occurrence, hemodynamics is related to the process of tissue perfusion, while oxygenation is related to the result of tissue perfusion. There is no reliable indicator in clinical practice that can accurately reflect tissue perfusion.

Traditional static stress monitoring indicators, such as CVP, PAWP, and ventricular end-diastolic volume indicators, cannot predict the effectiveness of fluid therapy. Therefore, it is necessary to find new hemodynamic indicators to monitor early fluid therapy [84-86].

Effect of GDFT on postoperative outcome and organ function: In 1988, Shoemaker first proposed the concept of ideal circulation during the perioperative period. The use of dobutamine or mediating fluid load in

critically ill patients increased their CO and oxygen supply resulting in significantly reduced length of stay and mortality.

Optimized hemodynamic parameters (such as stroke volume, cardiac output) are regarded as ideal treatment targets by mediating liquid load, which can be adjusted according to an individual's demand during the perioperative period. This may reduce the risk of insufficient or overall capacity. GDFT to improve post-surgical outcomes through fluid therapy is based on dynamic parameters. Intraoperative and postoperative GDFT for fluid management have been validated in many trials. GDFT can significantly reduce the incidence of postoperative nausea, vomiting, intestinal paralysis and other complications. It promotes gastrointestinal function recovery, and shortens the length of stay in the hospital or ICU. The GDFT aims to adjust the individual's fluid therapy to the most suitable circulatory state by maximizing SV and others.

GDFT is different from the previously described liquid therapy, which targeted predetermined therapeutic indicators. Furthermore, the timing of perioperative fluid therapy may be more important than the choice of method. It is believed that early rational fluid therapy may be important in preventing the occurrence and development of adverse effects. Therefore, the GDFT protocol should be emphasized at all stages during surgery to cater to the requirements of the individual's capacity or major surgery [76,77,87]. Most doctors prefer to use a shorter length of stay in the hospital or ICU as a good outcome of liquid therapy. Vomiting and organ function are also important aspects of the evaluation of the postoperative outcome in GDFT, which needs to be further validated in controlled clinical trials.

Pulse oxygen volume variation index (PVI) and perfusion index (PI): In recent years, some noninvasive dynamic parameters (such as stroke volume variation (SVV), systolic blood pressure variation (SPV), and pulse pressure difference variation (PPV)) based on cardiopulmonary interaction have been shown to be more accurate and sensitive than classical invasive parameters (such as CVP and PAWP) in mechanically ventilated patients.

PVI can predict the expansion response to mechanical ventilation. However, PVI is not suitable for patients with spontaneous breathing, arrhythmia or severe heart failure because the predicted accuracy of PVI is affected by peripheral perfusion factors. In addition, the threshold of the predicted expansion response and clinical effects of fluid therapy with PVI in different patients remain unclear, and more trials needed to be performed.

Pulse amplitude variability (APOP) is a reliable indicator for predicting an expansion response. However, the acquisition of APOP values is complicated, which limits its clinical application. PVI was initially invented to quantify APOP automatically and continuously. A new algorithm module converting PVI into perfusion index (PI) enables clinicians to measure APOP instantly, automatically and continuously. The PVI detector is capable of detecting the values of the body's infrared light in DC and AC, which are the main components of the pulse plethysmographic waveform. PI is defined as the AC/DC ratio, which can promptly reflect the amplitude of the pulse plethysmogram at a certain instant. PVI calculates the variability of PI in the respiratory cycle, so it can essentially reflect APOP. Because the PI can predict neonatal status, anesthesia response or complications, it is widely used in the field of ICU in recent years. As an ideal method for theoretically evaluating tissue perfusion and evaluating critical illness, PI is a new tool for guiding fluid resuscitation and rehabilitation of critically ill patients [88-92].

Pulmonary protection strategies and evaluation of pulmonary function: Lung injury during cardiopulmonary bypass (CPB) is the most common complication in cardiac surgery. Most cases only have transient mild symptoms, but some cases are characterized by acute lung injury or respiratory distress syndrome. Pulmonary insufficiency is one of the main causes of death after CPB. The mortality rate is as high as 50% to 70% in critically ill patients with pulmonary insufficiency. The mechanism of CPB is mainly due to systemic inflammatory response syndrome (SIRS) and lung ischemia-reperfusion injury through complement activation, cytokine release and neutrophil aggregation, oxidative stress, apoptosis, and other insults [93].

Pulmonary function tests are essential for early detection of respiratory diseases, assessing the severity and prognosis, pharmacodynamic evaluations, differential diagnosis of dyspnea, lesions, and evaluation of the tolerance of surgery.

Pulmonary ventilation test: There are many indicators for monitoring ventilation. They include the tidal breathing method, interruptions, surface description techniques, chest and abdominal cavity extrusion techniques, diffusion techniques, pulse oscillation techniques, and airway reactivity measurement. Each has its own advantages and limitations, which should be considered comprehensively when evaluating tidal breathing parameters, respiratory compliance, and airway resistance [94].

In infantile pneumonia, ventilation is mainly characterized by obstruction, while the index reflecting the restriction is not significantly reduced. Left-to-right shunt congenital heart disease can affect lung function in children, which indicates restrictive and obstructive ventilatory dysfunction.

Biochemical indicators of lung injury: NF-kappa B, TNF-α, and IL-8 are central regulators of the inflammatory response and are closely related to ALI/ARDS and multiple-organ failure. The upregulation of the above indicators often accompanies the deterioration of lung function. The expression level of $CD_{11}b/CD_{18}$, which is closely related to PMN adhesion, is highly correlated with the severity of pulmonary capillary leakage, ALI and its development, and pulmonary interstitial edema. As a specific reductase of PMN, the activity of myeloperoxidase may quantitatively reflect the degree of PMN aggregation related to the degree of lung injury. The lung is the main target organ of oxygen free radicals. Malondialdehyde is a lipid peroxidation product and an important indicator of lipid peroxidation. Oxide dismutase is an important antioxidant enzyme that scavenges oxygen free radicals in the body and indicates antioxidant capacity to some extent.

MiRNAs as biomarkers in ALI/ARDS: Although there is increasing evidence that miRNAs are involved in the development of ALI/ARDS, there are few reports on the use of miRNAs as reliable markers for the diagnosis of ALI/ARDS.

Guo reported that miR-125b in the serum of ARDS patients was significantly decreased, which negatively correlated with disease severity. Over-expression of miR-125b may inhibit lung inflammation and increase LPS-induced survival rates in ARDS mice. The above studies suggested that miR-125b-based clinical treatment may improve survival rates with ARDS.

Yang collected miRNA chips from arterial blood samples of patients 16 h after CPB. The microarray results revealed that the expression levels of 11 miRNAs were significantly increased in the reperfusion group, especially miR-499 (0.25 times) and miR-320 (3.56 times). Furthermore, the expression levels of tumor necrosis factor-α (TNF-α) and respiratory index (RI) in blood samples were positively correlated with miR-320 level, while oxidation index (OI) was negatively correlated with miR-320 level. The vitro experiments further confirmed that the expression of miR-320 in the injured A549 cells was significantly increased. Therefore, elevated miR-320 in peripheral blood may be a reliable biomarker for respiratory function failure in ALI patients.

The CPB lung protection strategies are mainly divided into non-pharmaceutical and pharmaceutical protection. Non-pharmaceutical protection includes ultrafiltration, ischemic preconditioning and post-treatment, and lung protective ventilation strategies in clinical practice. Pharmaceutical protection includes glucocorticoids, ulinastatin, sevoflurane, sirolimus, and dexmedetomidine. A large number of basic and clinical studies have found that they all have certain lung protective effects, but clinical evaluation of its safety and reliability is lacking [95,96].

Protection strategies and evaluation of renal function: Although many biomarkers (such as the NGAL, cystatin C, KIM-I, urine interleukin-8) have been discovered, there is no reliable marker that can predict or evaluate renal injury. Scr and urine volume are still the major biomarkers for the diagnostic index of AKI in clinical practice [97-100]. Anesthesiologists need to actively prevent and control these factors to improve renal function and patient survival.

Renal protection strategies including prediction, prevention, monitor, and treatment are maintained throughout the perioperative period. AKI assessment is used to identify high-risk factors before surgery. The anesthesia plan needs to be developed and optimized for renal function during the prevention phase. Sensitive and specific methods should be used to monitor renal function during the monitoring phase. Effective measures should be taken to reduce the degree of renal damage during the treatment phase. Non-pharmacological interventions for renal protection include volume treatment, maintenance of renal blood flow and renal perfusion pressure, avoidance of nephrotoxic drugs, stable blood glucose, and ischemic preconditioning or drug pretreatment. Pharmacological interventions for renal protection include vasodilator, diuretics, natriuretic peptide, and antioxidants. Severe pain after surgery may cause obvious renal injury, aggravate tissue metabolism and delay recovery. Therefore, anesthesiologists need to control the pain with individualized treatment [101-103].

Protection strategies and evaluation of the brain: The brain is the most sensitive organ because ischemia and hypoxia can easily lead to nerve injury. The main mechanisms include mitochondrial damage, abnormal energy metabolism, calcium overload, neurotoxicity of excitatory amino acids (EAAs), accumulation of free radicals, and production of inflammation-related mediators. An in-depth study of the mechanism of nerve injury will be helpful to optimize brain protection strategies with drugs and indicator measurements.

Noninvasive monitoring: Diagnosis and assessment of nerve injury currently depend on clinical symptoms, neurological examination, imaging (MRI, CT), and nerve injury score. Transcranial Doppler (TCD) is a common clinical method for monitoring cerebral blood flow morphology. It is very sensitive to abnormal intubation and embolism in cerebral blood flow. TCD can continuously detect acute intracranial blood flow changes and provide preliminary analysis. Compared with electroencephalography, near-infrared spectroscopy (NIRS) has greater sensitivity in detecting the regional cerebral hemoglobin oxygen

saturation ($rSCO_2$). Jugular bulb venous oxygen saturation ($SjvO_2$) can accurately reflect the balance between the oxygen supply and oxygen demand of the brain.

Biochemical indexes: Neuron-specific enolase (NSE), S100 calcium binding protein B (S100B), Glial fibrillary acidic protein (GFAP), and Myelin basic protein (MBP) are currently used to assess traumatic brain injury. The combination of NSE and S100B may improve the sensitivity and specificity of diagnosis. Combining various monitoring methods to detect cerebral hypoperfusion or cerebrovascular embolism early and help to adjust the treatment and medication accordingly can help reduce the occurrence of adverse events after CBP [104-107].

Non-pharmacological interventions for brain injury include shortening the time of arterial ligation, improvement of extracorporeal circuits, appropriate hypothermia therapy, hyperbaric oxygen therapy, and stem cell therapy. The pharmacological interventions for brain injury include anesthetics, statins, N-acetylcysteine (NAC), opioids, dexmedetomidine hydrochloride, creatine phosphate (phosphocreatine, PCr), ATP, oxiracetam, minocycline, gamma globulin, glucocorticoids, protease inhibitors, calcium channel blockers, and oxygen free radical scavengers and antioxidants [108-110].

The correlation between coagulation function and severity of diseases: Coagulopathy is often present in critically ill patients, which may lead to an extension of hospitalization time and increased fatality rate. Coagulopathy with inflammatory transmitter release, activating leukocyte adhesion molecule and other factors may lead to vascular endothelial cell injury and out-of-control inflammatory responses. These out-of-control responses and injury may affect the coagulation system through several mechanisms, including endothelial cell damage, platelet adhesion and aggregation, tissue factor activation in exogenous coagulation pathway, release of cytokines, and inhibition of the physiological anticoagulant system or fibrinolysis system. The coagulation factors can also stimulate the release of inflammatory factors and promote inflammatory reactions. It can be seen above that the activation of the coagulation system interacts with inflammatory response [111,112].

In the intensive care unit, clinicians should assess the risk of coagulopathy in critically ill patients, pay more attention to those patients with abnormal coagulation (thrombocytopenia, prolongation of PT or APTT, abnormal fibrinogen and hyperfibrinolysis), and prevent coagulation abnormalities in perioperative period.

After a clear diagnosis of coagulopathy, the initial pathogenic factors should be further identified and treated. Furthermore, the persistent coagulation disorder induced by persistence of various causes should be blocked. To avoid deep vein thrombosis and disseminated intravascular hemorrhage, the reasonable treatment plan should be to revise carefully according to the type of coagulopathy [113-115].

With the advancement of medicine, increased treatments for refractory coagulopathies have been clinically applied. Therefore, as a promising strategy, monitoring coagulation function is expected to bring new hope for perioperative treatments in critically ill patients.

Gastrointestinal function evaluations:

AGI and GIF score: Currently, clinicians often diagnose bowel insufficiency according to gastrointestinal digestion, absorption and motor dysfunction, but there are few objective indicators and standards for the evaluation of gastrointestinal function, especially in critically ill patients. Some scholars have presented a new gastrointestinal failure score according to enteral nutrition intolerance and intra-abdominal hypertension in 2008. Based on the GIF score, the European Society of Critical Care Medicine (ESICM) recommended that patients with acute gastrointestinal dysfunction (AGI) be divided into four grades according to food intolerance, intestinal motor function, gastrointestinal bleeding and intra-abdominal pressure, which can help define and manage gastrointestinal function in intensive care patients.

Compared with the GIF score, the AGI score includes more indicators of gastrointestinal disorders and is effective in patients with gastrointestinal function. As an early indicator, AGI score can provide early assessment and diagnosis of intestinal barrier dysfunction in sepsis and determine the severity of intestinal barrier dysfunction, though it still requires further clinical trials for validation, especially in elderly patients [116-118].

Evaluation indexes of intestinal mucosal barrier damage: Abnormal biochemical indicators, morphological changes and intestinal permeability:

(1) Diamine oxidase and Intestinal fatty acid binding protein (I-FABP)

Diamine oxidase (DAO) and intestinal-fatty acid binding protein (I-FABP) can specifically reflect intestinal mucosal damage. DAO is present in the cytoplasm of the upper villus cells of all mammalian intestinal mucosa and has the highest activity in air and ileum. When the intestinal mucosal cells are damaged or necrotic, DAO may be released into the blood or enter the intestinal cavity with the necrotic intestinal mucosal cells. This may lead to increasing DAO activity in plasma and the intestinal cavity. Because the concentration of DAO is stable in plasma, DAO level can be used as a sensitive indicator for early diagnosis of intestinal mucosal injury. I-FABP (15 kD) is a

group of low-molecular-weight cytoplasmic proteins. I-FABP plays an important role in the uptake, transport and metabolic regulation of long-chain fatty acids in the intestinal epithelium. When the intestinal mucosal epithelia are damaged, I-FABP is released and enters the blood circulation through the capillaries, becoming detectable in peripheral blood. I-FABP and DAO can accurately reflect intestinal epithelial damage [119-122].

(2) D-Lactic acid

Due to an impaired intestinal mucosal barrier, increased intestinal permeability can be confirmed indirectly by the presence of peripheral blood endotoxin, D-lactic acid and sugar molecular probes (such as urinary lactulose and mannitol) [123]. D-Lactic acid is a metabolite of bacterial fermentation. Though some types of bacteria in the intestinal tract can produce D-lactic acid, it is rarely absorbed because of the lack of a degrading enzyme system. When the intestinal mucosal barrier is damaged, the bacteria in the intestine produce a large amount of D-lactic acid, which then releases D-lactic acid into the blood through the damaged mucosa. This leads to a rapid increase in plasma D-lactic acid levels. Therefore, monitoring the plasma D-lactic acid level can reflect the extent of intestinal damage and permeability changes with time. The diagnostic reliability of D-lactic acid presence in elderly patients remains unclear. The presence of I-FABP, DAO, and D-lactic acid can reflect intestinal epithelial damage and permeability changes to some extent [124,125], but there is still no reliable indicator for evaluating intestinal epithelial cell function [122].

(3) Citrulline

Citrulline ($C_6H_{13}N_3O_3$), a nonprotein alpha-amino acid, is an intermediate product of the ornithine-urea cycle. In intestinal cells, citrulline is produced from glutamine through the "ornithine-glutamic acid" pathway. Citrulline cannot be metabolized in the liver. After passing through the circulation of the liver, most of the citrulline can be taken up by the proximal convoluted tubules in the kidney and be converted to arginine with argininosuccinate synthetase. This is called "hidden arginine in the body" [126]. The intestinal model established by Poll demonstrates that the intestinal mucosa and intestinal epithelial cells have the ability to produce citrulline and release it to the blood. Then, citrulline is eliminated or metabolized in the renal tubule. As a specific marker of intestinal epithelial dysfunction, citrulline is significantly affected by renal function [127,128]. Whether citrulline can be used as a marker of intestinal dysfunction in elderly patients with sepsis needs further study. Intestinal dysfunction, including intestinal motor function and intestinal mucosal injury, permeability changes, and intestinal epithelial changes, are interrelated. Future studies of the interactions between I-FABP, DAO, D-lactic acid and citrulline and AGI score in septic elderly patients will be helpful to explore the possibility of using the AGI score as an early diagnostic standard of intestinal dysfunction [129,130].

Other potential indicators (such as tight junction protein family proteins, trefoil factor family proteins, adrenal hormone-releasing hormone, nitric oxide, liver fatty acid binding protein, α-glutathione-S-transferase, fibronectin, reduced glutathione) are being validated for assessment of gastrointestinal dysfunction in critically patients. These indicators are mainly verified in malignant tumors and chronic inflammatory diseases.

Single-nucleotide polymorphisms (SNPs) in organ Injury: Genetic polymorphism is important in determining the susceptibility and tolerance to stress, clinical manifestations, and therapeutic effects. It may help to classify illnesses and predict the differences in clinical prognosis in the perioperative period. We improve the prognosis predictions by gene technologies and traditional examination. The development of drug research is intimately connected with modern science and technology. A physician familiar with its actions on pharmacogenomic data will be able to make specific fine-tuned decisions and choose the most appropriate dose for organ protection. The latest scientific and technical innovations (in genomics, biology, and computer technology) are used in drug research. Modern drug research has reached new heights with the help of genetic polymorphisms.

SNPs in sepsis and lung injury: Current studies on the association of SNPs with sepsis or lung injury have focused mostly on pro-and anti-inflammatory cytokine genes, such as IL-1alpha/-889, IL-1beta/-511, IL-1R (psti 1970), TGF-beta/code 10, TNF-alpha/-308, TNF-alpha/-238, IL-6/+565 and IL-10/-1082, and HSP-70. Genes with genetic polymorphisms closely related to acute lung injury (ALI) also include angiotensin-converting enzyme (ACE), surfactant protein (SP), and VEGF [131-135].

Only a small proportion of patients with sepsis die from acute respiratory distress syndrome (ARDS) or multiple-organ failure (MOF). Even if other risk factors are the same, the susceptibility and prognosis of ARDS vary among individuals. Therefore, it can be concluded that gene polymorphism plays an important role in human susceptibility and prognosis for ALI.

Polymorphism in genes coding for inflammatory factors is closely related to the intensity of the inflammatory response after CPB. Shaw found that the -9545 T/G polymorphism of the IL-18 gene in Caucasians was associated with increased postoperative inflammatory response and prolonged ICU stay. Chen found that the

-607C/C polymorphism of the IL-18 gene was closely related to the occurrence of acute lung injury after CPB among the Han Chinese. In addition, Wang found that acute lung injury after CPB was associated with the IL-6-572C/G polymorphism, but not with IL-10-1082A/G or TNF-alpha 308G/A, and the imbalance of pro-and anti-inflammatory factors may be caused by IL-6 gene polymorphism [136-138].

SNPs in renal injury: Many inflammatory factors, such as TNF-alpha, and IL-6, are important risk factors for AKI induced by ischemia or sepsis. AKI patients have high frequencies of AG/GC or AG/CC haplotypes of TNF-alpha and IL-6, which are associated with prognosis. Patients with single-copy or no-copy polymorphisms had lower organ dysfunction and mortality rates compared to those with two copies. IL-10 (592C/734G/3367G) haploid carriers were more prone to develop AKI and often required renal replacement therapy. In addition, ApoE e2/e3/e4 has been associated with AKI [139-143].

SNPs in brain injury: There is significant variation in the prognosis of TBI patients with similar severities of trauma. One of the reasons is that of individual genetic polymorphism, including that of ApoE, neuroglobin, BCL2, PARP-1, p53, ACE, interleukin-1 beta (IL1B) (SNP +3953 C/T), IL6 (SNP-174 G/C), and BDNF genes.

Genetic polymorphism may affect the prognosis of TBI in the following ways: (1) As a response of the brain to injury, apoptosis and vascular reactivity are initiated and strengthened after trauma. (2) The mechanisms of repair and remodeling help to repair damaged neurons and enhance tissue recovery and nerve regeneration after injury. (3) Cognitive ability and neurobehavior can be improved by regulating the synthesis and transportation of neurotransmitters. (4) Epigenetic modifications can change gene expression by regulating chromatin methylation and acetylation. Studying the effects of genetic polymorphisms on the prognosis of TBI can help elucidate the differences between individuals with similar severities of TBI and to find potential treatments [144-147].

Cell-free plasma DNA in organ injury: Cell-free plasma DNA (cf-DNA) is a body-derived DNA that is found outside of cells. Cf-DNA is widely observed in body fluids such as blood, cerebrospinal fluid, synovial fluid, bronchoalveolar lavage fluid, and amniotic fluid. Recent studies have found that the concentration of cf-DNA in trauma patients increased faster in the acute phase of injury. And the concentration of cf-DNA positively correlates with the severity of traumatic and infectious diseases. Trauma was the main cause of death, with up to 50% of deaths due to traumatic brain injury. Plasma cf-DNA level was an independent risk factor related to death in patients with severe traumatic brain injury. Short-term mortality of traumatic brain injury can also be predicted by cf-DNA levels. The dynamic monitoring of cf-DNA in patients with craniocerebral injury is vitally important to predict and assess pathological damage to the central nervous system [148-150].

Detection of cf-DNA can predict posttraumatic organ failure, acute lung injury, acute respiratory syndrome, and death. Studies have found that a significant increase in plasma cf-DNA concentration was also prevalent in a variety of age-related diseases, such as myocardial infarction and stroke [151-153]. In addition, it is important to detect the donor's cf-DNA in order to evaluate the occurrence and development of acute and chronic rejection in organ transplants [154].

SNP detection in cf-DNA in peripheral blood is also important. Luo detected SNPS in plasma samples from 403 patients with non-small cell lung cancer. They found that 9 out of 14 SNPs were associated with hypertriglyceridemia that was caused by bexarotene. Furthermore, targeted treatment can significantly improve the survival rate. Kelsey found that the polymorphism of the TGFBI gene promoter region in lung cancer patients is related to the sensitivity of radiotherapy. These studies suggest that SNP detection of cf-DNA in peripheral blood may be a potential tumor marker for predicting treatment response and prognosis [155,156].

As a new type of clinical molecular marker, cf-DNA still has some shortcomings in accuracy and sampling. At the same time, the sensitivity, specificity and timeliness of cf-DNA still need to be improved. Obviously, we should carefully evaluate the relationship between the cf-DNA markers and other clinical evidence. Discovery and validation of appropriate cf-DNAs for different diseases and populations are important tasks in clinical practice.

Transition from single index to joint scoring system with multiple indexes: In addition to routine monitoring (such as myocardial enzymes, liver enzyme systems, and blood glucose), C-reactive protein and the PCT have been using as biomarkers for the evaluation of organ function. However, their specificity and sensitivity are still controversial. Therefore, some new markers have been validated for the evaluation and prognosis of organ function. Many related studies have shown that the NGAL has a higher accuracy for the diagnosis of sepsis-associated AKI [100].

Since a single biomarker is sensitive only in a certain range, some limitations will exist in the diagnosis and prognosis of sepsis. Therefore, the combination of multiple biomarkers has attracted extensive interest in the field of diagnosis and prognosis of sepsis. Combination markers can also help to choose the appropriate antibiotics, to evaluate their efficacy and

to predict the development of organ dysfunction. Therefore, combined diagnosis in sepsis will become a new hot spot in the future [157-159]. Assessment of the severity or prognosis of sepsis may require a combination of lactic acid, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Sequential Organ Failure Assessment (SOFA) instead of depending on a single indicator. The APACHE II score is popular in assessing the severity of disease in intensive care units. The APACHE II score can reflect the severity of the disease and has a positive correlation with the mortality rate [157-160]. The accuracy of the APACHE II score in predicting mortality may reach 86%, so it can be used as the preferred indicator for assessing the condition and prognosis of sepsis [161,162].

Problems and prospects

1) The connotation of traditional ERAS, centering on analgesia, humane care, and rehabilitation, needs to take precision organ function protection to promote rapid and lasting rehabilitation of patients and precision anesthesia into account. We prefer to use important organ function outcomes (IOFOs) as the clinical target of ERAS.

2) Methodological selection and optimization of organ function evaluation are keypoints.

3) The balance between protection strategies and regulation technologies for different organ functions requires higher theoretical knowledge and abundant clinical experience.

4) Training surgeons with an anesthetic background or anesthesiologists with a surgical background are preferred to better help patients in the future via better perioperative medical education.

5) The evidence-based medicine and ethics in ERAS should strengthen and protect medical staff when they face medical disputes.

References

1. Leissner KB, Shanahan JL, Bekker PL, Amirfarzan H. Enhanced Recovery After Surgery in Laparoscopic Surgery. J Laparoendosc Adv Surg Tech A. 2017;27(9):883-91. PMID: 28829221.
2. Francis NK, Walker T, Carter F, Hubner M, Balfour A, et al. Consensus on Training and Implementation of Enhanced Recovery After Surgery: A Delphi Study. World J Surg. 2018;42(7):1919-28. PMID: 29302724.
3. Sjostedt L, Hellstrom R, Stomberg MW. Patients' need for information prior to colonic surgery. Gastroenterol Nurs. 2011;34(5):390-7. PMID: 21979401.
4. Aasa A, Hovback M, Bertero CM. The importance of preoperative information for patient participation in colorectal surgery care. J Clin Nurs. 2013;22(11-12):1604-12. PMID: 23445552.
5. Alawadi ZM, Leal I, Phatak UR, Flores-Gonzalez JR, Holihan JL, et al. Facilitators and barriers of implementing enhanced recovery in colorectal surgery at a safety net hospital: A provider and patient perspective. Surgery. 2016;159(3):700-12. PMID: 26435444.
6. Liddle C. An overview of the principles of preoperative care. Nurs Stand. 2018. PMID: 30141576.
7. Heiss KF, Raval MV. Patient engagement to enhance recovery for children undergoing surgery.SeminPediatr Surg. 2018;27(2):86-91. PMID: 29548357.
8. Nikodemski T, Biskup A, Taszarek A, Albin M, Chudecka-Glaz A, et al. Implementation of an enhanced recovery after surgery (ERAS) protocol in a gynaecology department - the follow-up at 1 year. Contemp Oncol (Pozn). 2017;21(3):240-3. PMID: 29180933.
9. Pecorelli N, Fiore JF, Kaneva P, Somasundram A, Charlebois P, et al. An app for patient education and self-audit within an enhanced recovery program for bowel surgery: a pilot study assessing validity and usability. Surg Endosc. 2018;32(5):2263-73. PMID: 29098431.
10. Seretis F, Kaisari P, Wanigasooriya K, Rawstorne E, Seretis C. Institutional variations in nutritional aspects of enhanced recovery pathways after elective surgery for colon cancer. J BUON. 2017;22(3):692-5. PMID: 28730776.
11. Rumley S, Schraag S. The role of local anaesthetic techniques in ERAS protocols for thoracic surgery.JThorac Dis. 2018;10(3):1998-2004. PMID: 29707356.
12. Feldheiser A, Aziz O, Baldini G, Cox BP, Fearon KC, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. Acta anaesthesiologica Scand. 2016;60(3):289-334. PMID: 26514824.
13. Wilson RD, Caughey AB, Wood SL, Macones GA, Wrench IJ, et al. Guidelines for Antenatal and Pre-operative care in Cesarean Delivery: Enhanced Recovery After Surgery (ERAS(R)) Society Recommendations (Part 1).Am J Obstet Gynecol. 2018. PMID: 30240657.
14. van Rooijen SJ, Huisman D, Stuijvenberg M, Stens J, Roumen RMH, et al. Intraoperative modifiable risk factors of colorectal anastomotic leakage: Why surgeons and anesthesiologists should act together. International journal of surgery (London, England). 2016;36(Pt A):183-200. PMID: 27756644.
15. Bosslet GT, Carlos WG, Tybor DJ, McCallister J, Huebert C, et al. Multicenter Validation of a Customizable Scoring Tool for Selection of Trainees for a Residency or Fellowship Program. The EAST-IST Study. Ann Am Thorac Soc. 2017;14(4):517-23. PMID: 28362524.
16. Ebner F, Schulz SVW, de Gregorio A, Volz S, Steinacker JM, et al. Prehabilitation in gynecological surgery? What do gynecologists know and need to know.ArchGynecol Obstet. 2018;297(1):27-31. PMID: 29075851.
17. Gillis C, Fenton TR, Sajobi TT, Minnella EM, Awasthi R, et al. Trimodal prehabilitation for colorectal surgery attenuates post-surgical losses in lean body mass: A pooled analysis of randomized controlled trials. Clin Nutr. 2018. PMID: 30025745.
18. Pillinger NL, Robson JL, Kam P. Nutritional prehabilitation: physiological basis and clinical evidence. Anaesth intensive care. 2018;46(5):453-62. PMID: 30189818.
19. Bousquet-Dion G, Awasthi R, Loiselle SE, Minnella EM, Agnihotram RV, et al. Evaluation of supervised multimodal prehabilitationprogramme in cancer patients undergoing colorectal resection: a randomized control trial. Acta oncol. 2018;57(6):849-59. PMID: 29327644.
20. Merki-Kunzli C, Kerstan-Huber M, Switalla D, Gisi D, Raptis DA, et al. Assessing the Value of Prehabilitation in Patients Undergoing

Colorectal Surgery According to the Enhanced Recovery After Surgery (ERAS) Pathway for the Improvement of Postoperative Outcomes: Protocol for a Randomized Controlled Trial. JMIR Res Protoc. 2017;6(10):e199. PMID: 29079551.

21. Abola RE, Bennett-Guerrero E, Kent ML, Feldman LS, Fiore JF, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Patient-Reported Outcomes in an Enhanced Recovery Pathway. AnesthAnalg. 2018;126(6):1874-82. PMID: 29293180.

22. Meyer LA, Lasala J, Iniesta MD, Nick AM, Munsell MF, et al. Effect of an Enhanced Recovery After Surgery Program on Opioid Use and Patient-Reported Outcomes. Obstet Gynecol. 2018;132(2):281-90. PMID: 29995737.

23. Deiss T, Chen LL, Sarin A, Naidu RK. Patient-reported outcomes 6 months after enhanced recovery after colorectal surgery. Perioper Med (Lond).2018;7:19. PMID: 30159140.

24. Kukreja JB, Shi Q, Chang CM, Seif MA, Sterling BM, et al. Patient-Reported Outcomes Are Associated With Enhanced Recovery Status in Patients With Bladder Cancer Undergoing Radical Cystectomy. Surg Innov. 2018;25(3):242-50. PMID: 29557251.

25. Hedrick TL, Harrigan AM, Thiele RH, Friel CM, Kozower BD. A pilot study of patient-centered outcome assessment using PROMIS for patients undergoing colorectal surgery. Supportive care in cancer : official journal of the Multinational Support Care Cance. 2017;25(10):3103-12. PMID: 28439726.

26. Brown JK, Singh K, Dumitru R, Chan E, Kim MP. The Benefits of Enhanced Recovery After Surgery Programs and Their Application in Cardiothoracic Surgery. Methodist DeBakey cardiovascular J. 2018;14(2):77-88. PMID: 29977464.

27. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. JAMA Surg. 2017;152(3):292-8. PMID: 28097305.

28. Manso M, Schmelz J, Aloia T. ERAS-Anticipated outcomes and realistic goals. J Surg Oncol. 2017;116(5):570-7. PMID: 28873504.

29. Beck-Schimmer B, Bonvini JM, Braun J, Seeberger M, Neff TA, et al. Which Anesthesia Regimen Is Best to Reduce Morbidity and Mortality in Lung Surgery?: A Multicenter Randomized Controlled Trial. Anesthesiology. 2016;125(2):313-21. PMID: 27203279.

30. Chen CH, Wu CW, Shih CD, Lien WH, Huang SL. Attenuation of Isoflurane Preconditioning-Induced Acute Cardioprotection in Hypertensive Hypertrophied Hearts. J Cardiothoracic VascAnesth. 2016;30(5):1317-23. PMID: 27474329.

31. Su MW, Chang SS, Chen CH, Huang CC, Chang SW, et al. Preconditioning renoprotective effect of isoflurane in a rat model of virtual renal transplant. J Surg Res. 2014;189(1):135-42. PMID: 24674838.

32. Xu F, Qiao S, Li H, Deng Y, Wang C. The Effect of Mitochondrial Complex I-Linked Respiration by Isoflurane Is Independent of Mitochondrial Nitric Oxide Production. Cardiorenal Med. 2018;8(2):113-22. PMID: 29617003.

33. Anderson SL, Duke-Novakovski T, Singh B. The immune response to anesthesia: part 1. Vet AnaesthAnalg. 2014;41(2):113-26. PMID: 24588928.

34. Nowak-Machen M. [Impact of Cardiac Anaesthesia on Patient Outcome]. AnasthesiolIntensivmed Notfallmed Schmerzther. 2017;52(7-08):498-511. PMID: 28743148.

35. de Vries M, Putter G. Perioperative anaesthetic care of the cat undergoing dental and oral procedures: key considerations. J Feline Med Surg. 2015;17(1):23-36. PMID: 25527491.

36. Jin Z, Piazza O, Ma D, Scarpati G, De Robertis E. Xenon-anaesthesia and beyond: pros-contras. Minerva Anestesiol. 2018. PMID: 30019577.

37. Yoo JE, Oh DS. Potential benefits of acupuncture for enhanced recovery in gynaecological surgery. ForschKomplementmed. 2015;22(2):111-6. PMID: 26021961.

38. Macedo CG, Jain AK, Franz-Montan M, et al.Microneedles enhance topical delivery of 15-deoxy-Δ-prostaglandin J and reduce nociception in temporomandibular joint of rats.J Control Release. 2017;265:22-29.

39. Galvin IM, Levy R, Boyd JG, Day AG, Wallace MC. Cooling for cerebral protection during brain surgery. The Cochrane database Syst Rev. 2015;1:CD006638. PMID: 25626888.

40. Beck C, Schwartges I, Picker O. Perioperative liver protection. CurrOpinCrit Care. 2010;16(2):142-7. PMID: 20134321.

41. Mori Y, Kamada T, Ochiai R. Reduction in the incidence of acute kidney injury after aortic arch surgery with low-dose atrial natriuretic peptide: a randomised controlled trial. Eur J Anaesthesiol. 2014;31(7):381-7. PMID: 24384584.

42. Apostolakis EE, Koletsis EN, Baikoussis NG, Siminelakis SN, Papadopoulos GS. Strategies to prevent intraoperative lung injury during cardiopulmonary bypass. J Cardiothorac Surg. 2010;5:1. PMID: 20064238.

43. Thielmann M, Kottenberg E, Kleinbongard P, Wendt D, Gedik N, et al. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centrerandomised, double-blind, controlled trial. Lancet. 2013;382(9892):597-604. PMID: 23953384.

44. Sahbaie P, Sun Y, Liang DY, Shi XY, Clark JD. Curcumin treatment attenuates pain and enhances functional recovery after incision. AnesthAnalg. 2014;118(6):1336-44. PMID: 24755847.

45. Han JY, Li Q, Ma ZZ, Fan JY. Effects and mechanisms of compound Chinese medicine and major ingredients on microcirculatory dysfunction and organ injury induced by ischemia/reperfusion. PharmacolTher. 2017;177:146-73. PMID: 28322971.

46. Li P, Liao ST, Wang JS, Zhang Q, Xu DQ, et al. Protection by Huang-Lian-Jie-Du decoction and its constituent herbs of lipopolysaccharide-induced acute kidney injury. FEBS Open Bio. 2017;7(2):221-36. PMID: 28174688.

47. Liang X, Liu R, Chen C, Ji F, Li T. Opioid System Modulates the Immune Function: A Review. TranslPerioper Pain Med. 2016;1(1):5-13. PMID: 26985446.

48. Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. J Transl Med. 2018;16(1):8. PMID: 29347949.

49. Cho JS, Lee MH, Kim SI, Park S, Park HS, et al. The Effects of Perioperative Anesthesia and Analgesia on Immune Function in Patients Undergoing Breast Cancer Resection: A Prospective Randomized Study. Int J Med Sci. 2017;14(10):970-6. PMID: 28924368.

50. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study.Br J Anaesth. 2014;113 Suppl 1:i56-62. PMID: 25009196.

51. Li MH, Xu ZZ, Huang SM, Li T, Li XY. Effect of combined epidural anaesthesia on tumor-infiltrating lymphocytes in lung adenocarcinoma: a prospective exploratory sub-analysis. Acta Anaesthesiol Scand. 2018;62(5):687-700. PMID: 29363103.

52. Sekandarzad MW, van Zundert AAJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative Anesthesia Care and Tumor Progression.AnesthAnalg. 2017;124(5):1697-708. PMID: 27828796.

53. Deegan CA, Murray D, Doran P, Ecimovic P, Moriarty DC. Effect of anaesthetic technique on oestrogen receptor-negative breast cancer cell function in vitro. Br J Anaesth. 2009;103(5):685-90. PMID: 19776028.

54. Shi QY, Zhang SJ, Liu L, Chen QS, Yu LN, et al. Sevoflurane promotes the expansion of glioma stem cells through activation of hypoxia-inducible factors in vitro. Br J Anaesth. 2015;114(5):825-30. PMID: 25492570.

55. Wigmore TJ, Mohammed K, Jhanji S. Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. Anesthesiology. 2016;124(1):69-79. PMID: 26556730.

56. Bartha E, Arfwedson C, Imnell A, Kalman S. Towards individualized perioperative, goal-directed haemodynamic algorithms for patients of advanced age: observations during a randomized controlled trial (NCT01141894). Br J Anaesth. 2016;116(4):486-92. PMID: 26994228.

57. Bowyer A, Royse CF. The future of postoperative quality of recovery assessment: multidimensional, dichotomous, and directed to individualize care to patients after surgery. Br J Anaesth. 2016;29(6):683-90. PMID: 27764047.

58. Eldawlatly A, Alshehri H, Alqahtani A, Ahmad A, Al-Dammas F. Appearance of Population, Intervention, Comparison, and Outcome as research question in the title of articles of three different anesthesia journals: A pilot study. Saudi J Anaesth. 2018;12(2):283-6. PMID: 29628841.

59. Marty J, Samain E. Quality organization and risk in anaesthesia: the French perspective. Current opinion in anaesthesiology. 2017;30(2):230-5. PMID: 28118164.

60. Mavropoulos G, Minguet G, Brichant JF. [Alpha-2 adrenoreceptor agonists in anaesthesia and intensive care medicine].Rev Med Liege. 2014;69(2):97-101. PMID: 24683831.

61. Mazzeo AT, Micalizzi A, Mascia L, Scicolone A, Siracusano L. Brain-heart crosstalk: the many faces of stress-related cardiomyopathy syndromes in anaesthesia and intensive care. Br J Anaesth. 2014;112(5):803-15. PMID: 24638232.

62. Moliner Velazquez S, Rubio Haro R, De Andres Serrano C, De Andres Ibanez J. Regional analgesia in postsurgical critically ill patients. Rev EspAnestesiolReanim. 2017;64(3):144-56. PMID: 27939017.

63. Skvarc DR, Berk M, Byrne LK, Dean OM, Dodd S, et al. Post-Operative Cognitive Dysfunction: An exploration of the inflammatory hypothesis and novel therapies.NeurosciBiobehav Rev. 2018;84:116-33. PMID: 29180259.

64. Liebert AD, Chow RT, Bicknell BT, Varigos E. Neuroprotective Effects Against POCD by Photobiomodulation: Evidence from Assembly/Disassembly of the Cytoskeleton. J Exp Neurosci. 2016;10:1-19. PMID: 26848276.

65. Balkanay OO, Goksedef D, Omeroglu SN, Ipek G. The Reliability of the Use of Serum Neutrophil Gelatinase-Associated Lipocalin Levels in the Assessment of Renal Functions after Coronary Artery Bypass Grafting. Cardiol Res Pract. 2018;2018:7291254. PMID: 29692931.

66. Miah OF, Dowel FA, Latif A, Hai AN, Mahmud MA, et al. NGAL (Neutrophil Gelatinase-associated Lipocalin) is an Early Predictor of Acute Kidney Injury after Cardiac Surgery and Variation of NGAL Values in Homogenous Study Subject.Mymensingh Med J. 2018;27(1):212-5. PMID: 29459617.

67. Carr ZJ, Cios TJ, Potter KF, Swick JT. Does Dexmedetomidine Ameliorate Postoperative Cognitive Dysfunction? A Brief Review of the Recent Literature. Curr Neurol Neurosci Rep. 2018;18(10):64. PMID: 30083844.

68. Wang WX, Wu Q, Liang SS, Zhang XK, Hu Q, et al. Dexmedetomidine promotes the recovery of neurogenesis in aged mouse with postoperative cognitive dysfunction. Neurosci Lett. 2018;677:110-6. PMID: 29571823.

69. Balkanay OO, Goksedef D, Omeroglu SN, Ipek G. The dose-related effects of dexmedetomidine on renal functions and serum neutrophil gelatinase-associated lipocalin values after coronary artery bypass grafting: a randomized, triple-blind, placebo-controlled study. Interact Cardiovasc Thorac Surg. 2015;20(2):209-14. PMID: 25392341.

70. Kuck K, Baker PD. Perioperative Noninvasive Blood Pressure Monitoring. AnesthAnalg. 2018;127(2):408-11. PMID: 29189276.

71. Lee JK, Williams M, Reyes M, Ahn ES. Cerebrovascular blood pressure autoregulation monitoring and postoperative transient ischemic attack in pediatric moyamoya vasculopathy. PaediatrAnaesth. 2018;28(2):94-102. PMID: 29205668.

72. Sef D, Skopljanac-Macina A, Milosevic M, Skrtic A, Vidjak V. Cerebral Neuromonitoring during Carotid Endarterectomy and Impact of Contralateral Internal Carotid Occlusion. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2018;27(5):1395-402. PMID: 29397311

73. Skytte Larsson J, Bragadottir G, Redfors B, Ricksten SE. Renal effects of norepinephrine-induced variations in mean arterial pressure after liver transplantation: A randomized cross-over trial. Acta Anaesthesiol Scand. 2018;62(9):1229-36. PMID: 29896798

74. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology. 2015;123(2):307-19. PMID: 26083768

75. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology. 2013;119(3):507-15. PMID: 23835589

76. Chong MA, Wang Y, Berbenetz NM, McConachie I. Does goal-directed haemodynamic and fluid therapy improve peri-operative outcomes?: A systematic review and meta-analysis. Eur J Anaesthesiol. 2018;35(7):469-83. PMID: 29369117

77. Yuan J, Sun Y, Pan C, Li T. Goal-directed fluid therapy for reducing risk of surgical site infections following abdominal surgery - A systematic review and meta-analysis of randomized controlled trials. Int J Surg. 2017;39:74-87. PMID: 28126672

78. Allen TK, Mishriky BM, Klinger RY, Habib AS. The impact of neuraxial clonidine on postoperative analgesia and perioperative adverse effects in women having elective Caesarean section-a systematic review and meta-analysis. Br J Anaesth. 2018;120(2):228-40. PMID: 29406172

79. Lopez MB. Postanaesthetic shivering - from pathophysiology to prevention. Rom J Anaesth Intensive Care. 2018;25(1):73-81. PMID: 29756066

80. Pulikkotil SJ, Nagendrababu V, Veettil SK, Jinatongthai P, Setzer FC. Effect of oral premedication on the anaesthetic efficacy of inferior alveolar nerve block in patients with irreversible pulpitis - A systematic review and network meta-analysis of randomized controlled trials. IIntEndod J. 2018;51(9):989-1004. PMID: 29480930

81. Stripp TK, Jorgensen MB, Olsen NV. Anaesthesia for electrocon-

vulsive therapy - new tricks for old drugs: a systematic review. Acta Neuropsychiatr. 2018;30(2):61-9. PMID: 28462732

82. Weinstein EJ, Levene JL, Cohen MS, Andreae DA, Chao JY, et al. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. Cochrane Database Syst Rev. 2018;4:CD007105. PMID: 29694674

83. Weng D, Huang M, Jiang R, Zhan R, Yang C. Clinical study of etomidate emulsion combined with remifentanil in general anesthesia. Drug Des DevelTher. 2013;7:771-6. PMID: 23990706

84. Sahinovic MM, Struys M, Absalom AR. Clinical Pharmacokinetics and Pharmacodynamics of Propofol. Clin Pharmacokinet. 2018. PMID: 30019172

85. White KL, Paine S, Harris J. A clinical evaluation of the pharmacokinetics and pharmacodynamics of intravenous alfaxalone in cyclodextrin in male and female rats following a loading dose and constant rate infusion. Vet AnaesthAnalg. 2017;44(4):865-75. PMID: 28318987

86. Zakerska-Banaszak O, Skrzypczak-Zielinska M, Tamowicz B, Mikstacki A, Walczak M, et al. Longrange PCR-based next-generation sequencing in pharmacokinetics and pharmacodynamics study of propofol among patients under general anaesthesia. Sci Rep. 2017;7(1):15399. PMID: 29133890

87. Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting-a clinical review. J Intensive Care. 2016;4:27. PMID: 27087980

88. Esteve-Perez N, Ferrer-Robles A, Gomez-Romero G, Fabian-Gonzalez D, Verd-Rodriguez M, et al. Goal-directed therapy in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: a prospective observational study. Clin Transl Oncol. 2018. PMID: 30218305

89. Kratz T, Simon C, Fendrich V, Schneider R, Wulf H, et al. Implementation and effects of pulse-contour- automated SVV/CI guided goal directed fluid therapy algorithm for the routine management of pancreatic surgery patients. Technol Health Care. 2016;24(6):899-907. PMID: 27434283

90. Sawa T, Kinoshita M, Kainuma A, Akiyama K, Naito Y, et al. Effective evaluation of arterial pulse waveform analysis by two-dimensional stroke volume variation-stroke volume index plots. J Clin MonitComput. 2017;31(5):927-41. PMID: 27492429

91. Sundaram SC, Salins SR, Kumar AN, Korula G. Intra-Operative Fluid Management in Adult Neurosurgical Patients Undergoing Intracranial Tumour Surgery: Randomised Control Trial Comparing Pulse Pressure Variance (PPV) and Central Venous Pressure (CVP). J Clin Diagn Res. 2016;10(5):UC01-5. PMID: 27437329

92. Warnakulasuriya SR, Davies SJ, Wilson RJ, Yates DR. Comparison of esophageal Doppler and plethysmographic variability index to guide intraoperative fluid therapy for low-risk patients undergoing colorectal surgery. J Clin Anesth. 2016;34:600-8. PMID: 27687456

93. Guo Z, Gu Y, Wang C, Zhang J, Shan S, et al. Enforced expression of miR-125b attenuates LPS-induced acute lung injury. Immunology letters. 2014;162(1 Pt A):18-26. PMID: 25004393

94. Yang X, Li X.A, Zhou B. A Meta-Analysis of miR-499 rs3746444 Polymorphism for Cancer Risk of Different Systems: Evidence From 65 Case-Control Studies.FrontPhysiol 2018;9:737. PMID:29946268

95. Ball L, Costantino F, Orefice G, Chandrapatham K, Pelosi P. Intraoperative mechanical ventilation: state of the art. Minerva Anestesiol. 2017;83(10):1075-88. PMID: 28528537

96. Buggeskov KB. Pulmonary artery perfusion versus no pulmonary per-fusion during cardiopulmonary bypass. Dan Med J. 2018;65(3). PMID: 29510817

97. Yuan SM. Acute kidney injury after pediatric cardiac surgery. PediatrNeonatol. 2018. PMID: 29891225

98. Evans RG, Lankadeva YR, Cochrane AD, Marino B, Iguchi N, et al. Renal haemodynamics and oxygenation during and after cardiac surgery and cardiopulmonary bypass. Acta Physiol (Oxf). 2018;222(3). PMID: 29127739

99. Andrew BY, Cherry AD, Hauck JN, Nicoara A, Maxwell CD, et al. The Association of Aortic Valve Pathology With Renal Resistive Index as a Kidney Injury Biomarker. Ann Thorac Surg. 2018;106(1):107-14. PMID: 29427619

100. Medic B, Rovcanin B, Vujovic KS, Obradovic D, Duric D, et al. Evaluation of Novel Biomarkers of Acute Kidney Injury: The Possibilities and Limitations. Curr Med Chem. 2016;23(19):1981-97. PMID: 26860999

101. Tan SI, Brewster DJ, Horrigan D, Sarode V. Pharmacological and non-surgical renal protective strategies for cardiac surgery patients undergoing cardiopulmonary bypass: a systematic review. ANZ J Surg. 2018. PMID: 30239089

102. Leow EH, Chan YH, Ng YH, Lim JKB, Nakao M, et al. Prevention of Acute Kidney Injury in Children Undergoing Cardiac Surgery: A Narrative Review. World J PediatrCongenit Heart Surg. 2018;9(1):79-90. PMID: 29310552

103. Deferrari G, Bonanni A, Bruschi M, Alicino C, Signori A. Remote ischaemic preconditioning for renal and cardiac protection in adult patients undergoing cardiac surgery with cardiopulmonary bypass: systematic review and meta-analysis of randomized controlled trials. Nephrol Dial Transplant. 2018;33(5):813-24. PMID: 28992285

104. Michetti F, D'Ambrosi N, Toesca A, Puglisi MA, Serrano A, et al. The S100B story: From biomarker to active factor in neural injury. J Neurochem. 2018. PMID: 30144068

105. Zhang X, Medow JE, Iskandar BJ, Wang F, Shokoueinejad M, et al. Invasive and noninvasive means of measuring intracranial pressure: a review. Physiol Meas. 2017;38(8):R143-R82. PMID: 28489610

106. Korbakis G, Vespa PM. Multimodal neurologic monitoring. Handb Clin Neurol. 2017;140:91-105. PMID: 28187816

107. Bonow RH, Silber JR, Enzmann DR, Beauchamp NJ, Ellenbogen RG, et al. Towards use of MRI-guided ultrasound for treating cerebral vasospasm. J Ther Ultrasound. 2016;4:6. PMID: 26929821

108. Haider Z, Jalal A, Alamgir AR, Rasheed I. Neurological complications are avoidable during CABG. Pak J Med Sci. 2018;34(1):5-9. PMID: 29643869

109. Talma N, Kok WF, de VeijMestdagh CF, Shanbhag NC, Bouma HR, et al. Neuroprotective hypothermia - Why keep your head cool during ischemia and reperfusion. BiochimBiophys Acta. 2016;1860(11 Pt A):2521-8. PMID: 27475000

110. Jiang L, Hu M, Lu Y, Cao Y, Chang Y, et al. The protective effects of dexmedetomidine on ischemic brain injury: A meta-analysis. J Clin Anesth. 2017;40:25-32. PMID: 28625441

111. Rodgers GM. Evaluation of Coagulation in the Neurosurgery Patient. Neurosurg Clin N Am. 2018;29(4):485-92. PMID: 30223961

112. Maegele M, Schochl H, Menovsky T, Marechal H, Marklund N, et al. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management. Lancet Neurol. 2017;16(8):630-47. PMID: 28721927

113. Bartels A, Sarpong Y, Coberly J, Hughes N, Litt J, et al. Failure of the Platelet Function Assay (PFA)-100 to detect antiplatelet agents. Surgery. 2015;158(4):1012-8; discussion 8-9. PMID: 26299285

114. Beynon C, Unterberg AW, Sakowitz OW. Point of care coagulation testing in neurosurgery.J Clin Neurosci. 2015;22(2):252-7. PMID: 25439750

115. Watson VL, Louis N, Seminara BV, Muizelaar JP, Alberico A. Proposal for the Rapid Reversal of Coagulopathy in Patients with Nonoperative Head Injuries on Anticoagulants and/or Antiplatelet Agents: A Case Study and Literature Review. Neurosurgery. 2017;81(6):899-909. PMID: 28368482

116. Poddar U. Diagnostic and therapeutic approach to upper gastrointestinal bleeding. Paediatr Int Child Health. 2018:1-5. PMID: 30058470

117. Terashima T, Yamashita T, Sunagozaka H, Arai K, Kawaguchi K, et al. Analysis of the liver functional reserve of patients with advanced hepatocellular carcinoma undergoing sorafenib treatment: Prospects for regorafenib therapy. Hepatol Res. 2018. PMID: 29845710

118. Zou L, Song X, Hong L, Shen X, Sun J, et al. Intestinal fatty acid-binding protein as a predictor of prognosis in postoperative cardiac surgery patients. Medicine. 2018;97(33):e11782. PMID: 30113465

119. Chen C, Huang P, Lai L, Luo C, Ge M, et al. Dexmedetomidine improves gastrointestinal motility after laparoscopic resection of colorectal cancer: A randomized clinical trial. Medicine. 2016;95(29):e4295. PMID: 27442674

120. Gilani S, Howarth GS, Kitessa SM, Tran CD, Forder REA, et al. New biomarkers for increased intestinal permeability induced by dextran sodium sulphate and fasting in chickens.JAnimPhysiolAnimNutr (Berl). 2017;101(5):e237-e45. PMID: 27730676

121. Louzada ER, Ribeiro SML. Synbiotic supplementation, systemic inflammation, and symptoms of brain disorders in elders: A secondary study from a randomized clinical trial. NutrNeurosci. 2018:1-8. PMID: 29788823

122. Ma L, Li C, Wang S, Wang J, Shao R, et al. Ulinastatin ameliorates gastrointestinal injury sustained in a 2-hit porcine model of septic shock. Am J Emerg Med. 2016;34(8):1497-504. PMID: 27233693

123. Abbas Q, Jamil MT, Jafri L, Haque AU, Khetpal V. Hyperlactetemia And Its Trends In Critically Ill Children Admitted In Pediatric Intensive Care Unit Of A Developing Country. J Ayub Med Coll Abbottabad. 2016;28(4):660-3. PMID: 28586613

124. Al-Ashry H, Abuzaid A, Asim M, El-Menyar A. Microcirculation Alteration and Biomarker Dilemma in Early Septic Shock Diagnosis and Treatment. CurrVascPharmacol. 2016;14(4):330-44. PMID: 26916399

125. Pundir CS, Narwal V, Batra B. Determination of lactic acid with special emphasis on biosensing methods: A review. BiosensBioelectron. 2016;86:777-90. PMID: 27476060

126. Vermeulen MA, van de Poll MC, Ligthart-Melis GC, Dejong CH, van den Tol MP, et al. Specific amino acids in the critically ill patient--exogenous glutamine/arginine: a common denominator? Crit Care Med. 2007;35(9 Suppl):S568-76. PMID: 17713411

127. Curis E, Nicolis I, Moinard C, Osowska S, Zerrouk N, et al. Almost all about citrulline in mammals. Amino acids. 2005;29(3):177-205. PMID: 16082501

128. Noordally SO, Sohawon S, Semlali H, Michely D, Devriendt J, et al. Is there a correlation between circulating levels of citrulline and intestinal dysfunction in the critically ill? Nutr Clin Pract. 2012;27(4):527-32. PMID: 22706681

129. Piton G, Capellier G. Plasma citrulline in the critically ill: intriguing biomarker, cautious interpretation. Crit care. 2015;19:204. PMID: 25930068

130. Piton G, Manzon C, Monnet E, Cypriani B, Barbot O, et al. Plasma citrulline kinetics and prognostic value in critically ill patients. Intensive Care Med. 2010;36(4):702-6. PMID: 20084502

131. Gupta DL, Nagar PK, Kamal VK, Bhoi S, Rao DN. Clinical relevance of single nucleotide polymorphisms within the 13 cytokine genes in North Indian trauma hemorrhagic shock patients. Scand J Trauma ResuscEmerg Med. 2015;23:96. PMID: 26561011

132. Kothari N, Bogra J, Abbas H, Kohli M, Malik A, et al. Tumor necrosis factor gene polymorphism results in high TNF level in sepsis and septic shock. Cytokine. 2013;61(2):676-81. PMID: 23317877

133. Ramakrishna K, Pugazhendhi S, Kabeerdoss J, Peter JV. Association between heat shock protein 70 gene polymorphisms and clinical outcomes in intensive care unit patients with sepsis. Indian J Crit Care Med. 2014;18(4):205-11. PMID: 24872649

134. Zhang A, Gu W, Lu H, Zeng L, Zhang L, et al. Genetic contribution of suppressor of cytokine signalling polymorphisms to the susceptibility to infection after traumatic injury.Clin Exp Immunol. 2018;194(1):93-102. PMID: 29920655

135. Zhang H, Lu Y, Sun G, Teng F, Luo N, et al. The common promoter polymorphism rs11666254 downregulates FPR2/ALX expression and increases risk of sepsis in patients with severe trauma. Crit care. 2017;21(1):171. PMID: 28679406

136. Chen S, Xu L, Tang J. Association of interleukin 18 gene polymorphism with susceptibility to the development of acute lung injury after cardiopulmonary bypass surgery. Tissue antigens. 2010;76(3):245-9. PMID: 20522205

137. Shaw DM, Sutherland AM, Russell JA, Lichtenstein SV, Walley KR. Novel polymorphism of interleukin-18 associated with greater inflammation after cardiac surgery. Crit Care. 2009;13(1):R9. PMID: 19178691

138. Wang JF, Bian JJ, Wan XJ, Zhu KM, Sun ZZ, et al. Association between inflammatory genetic polymorphism and acute lung injury after cardiac surgery with cardiopulmonary bypass.Med Sci Monit. 2010;16(5):CR260-5. PMID: 20424554

139. Belopolskaya OB, Smelaya TV, Moroz VV, Golubev AM, Salnikova LE. Clinical associations of host genetic variations in the genes of cytokines in critically ill patients. Clin Exp Immunol. 2015;180(3):531-41. PMID: 25619315

140. Fatani SH, AA AL, Al-Amodi HS, Kamel HF, Al-Khatieb K, et al. Assessment of tumor necrosis factor alpha polymorphism TNF-alpha-238 (rs 361525) as a risk factor for development of acute kidney injury in critically ill patients.Mol Biol Rep. 2018;45(5):839-47. PMID: 29978383

141. Henao-Martinez AF, Agler AH, LaFlamme D, Schwartz DA, Yang IV. Polymorphisms in the SUFU gene are associated with organ injury protection and sepsis severity in patients with Enterobacteriacea bacteremia. Infect Genet Evol. 2013;16:386-91. PMID: 23538333

142. Vilander LM, Kaunisto MA, Vaara ST, Pettila V, group Fs. Genetic variants in SERPINA4 and SERPINA5, but not BCL2 and SIK3 are associated with acute kidney injury in critically ill patients with septic shock. Crit Care. 2017;21(1):47. PMID: 28270177

143. Lu JC, Coca SG, Patel UD, Cantley L, Parikh CR, et al. Searching for genes that matter in acute kidney injury: a systematic review. Clin J Am Soc Nephrol.2009;4(6):1020-31. PMID: 19443624

144. Bennett ER, Reuter-Rice K, Laskowitz DT. Genetic Influences in Traumatic Brain Injury. In: Laskowitz D, Grant G, editors. Translational Research in Traumatic Brain Injury. Boca Raton (FL)2016.

145. Cotter D, Kelso A, Neligan A. Genetic biomarkers of posttraumatic epilepsy: A systematic review. Seizure. 2017;46:53-8. PMID: 28242442

146. Finan JD, Udani SV, Patel V, Bailes JE. The Influence of the Val-66Met Polymorphism of Brain-Derived Neurotrophic Factor on Neurological Function after Traumatic Brain Injury. J Alzheimers Dis : JAD. 2018. PMID: 30149456

147. Foster PP. Role of physical and mental training in brain network configuration. Front Aging Neurosci. 2015;7:117. PMID: 26157387

148. Fujikawa DG. The role of excitotoxic programmed necrosis in acute brain injury. Comput Struct Biotechnol J. 2015;13:212-21. PMID: 25893083

149. Rodrigues Filho EM, Simon D, Ikuta N, Klovan C, Dannebrock FA, et al. Elevated cell-free plasma DNA level as an independent predictor of mortality in patients with severe traumatic brain injury. J Neurotrauma. 2014;31(19):1639-46. PMID: 24827371

150. Wagner J. Free DNA--new potential analyte in clinical laboratory diagnostics? Biochem Med (Zagreb). 2012;22(1):24-38. PMID: 22384517

151. Cao D, Zheng J, Xian LF, Tang GM, Sun XJ, et al. Role of iron in lung injury-induced by hyperoxia. Undersea Hyperb Med. 2014;41(1):27-31. PMID: 24649714

152. Della Latta V, Cecchettini A, Del Ry S, Morales MA. Bleomycin in the setting of lung fibrosis induction: From biological mechanisms to counteractions. Pharmacol Res. 2015;97:122-30. PMID: 25959210

153. Rajan Radha R, Chandrasekharan G. Pulmonary injury associated with radiation therapy - Assessment, complications and therapeutic targets.BiomedPharmacother. 2017;89:1092-104. PMID: 28298070

154. Verhoeven J, Boer K, Van Schaik RHN, Manintveld OC, Huibers MMH, et al. Liquid Biopsies to Monitor Solid Organ Transplant Function: A Review of New Biomarkers. Ther DrugMonit. 2018;40(5):515-25. PMID: 29957668

155. Luo W, Schork NJ, Marschke KB, Ng SC, Hermann TW, et al. Identification of polymorphisms associated with hypertriglyceridemia and prolonged survival induced by bexarotene in treating non-small cell lung cancer. Anticancer Res. 2011;31(6):2303-11. PMID: 21737656

156. Kelsey CR, Jackson L, Langdon S, Owzar K, Hubbs J, et al. A polymorphism within the promoter of the TGFbeta1 gene is associated with radiation sensitivity using an objective radiologic endpoint. Int J Radiat Oncol Biol Phys. 2012;82(2):e247-55. PMID: 21605940

157. Barbara P, Graziano C, Caputo W, Litvak I, Battinelli D, et al. The quick sequential organ failure assessment (qSOFA) identifies septic patients in the out-of-hospital setting. Am J Emerg Med. 2018;36(6):1022-6. PMID: 29426799

158. Ding R, Meng Y, Ma X. The Central Role of the Inflammatory Response in Understanding the Heterogeneity of Sepsis-3. Biomed Res Int. 2018;2018:5086516. PMID: 29977913

159. J AC, Pinheiro I, Menezes Falcao L. Rethinking the concept of sepsis and septic shock. Eur J Intern Med. 2018;54:1-5. PMID: 29921471

160. Lanspa MJ, Burk RE, Wilson EL, Hirshberg EL, Grissom CK, et al. Echocardiogram-guided resuscitation versus early goal-directed therapy in the treatment of septic shock: a randomized, controlled, feasibility trial.J Intensive Care. 2018;6:50. PMID: 30123511

161. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, et al. Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. Crit Care Med. 2018;46(9):1411-20. PMID: 29979221

162. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis. 2018;18(1):108-20. PMID: 29102324

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Additional publication details

Journal short name: Transl Perioper & Pain Med

Received Date: November 24, 2018

Accepted Date: October 20, 2019

Published Date: October 21, 2019

Citation: Lu J, Xiu-Xiu Y, Jin-Feng W, Zhi-Ping W, Yin Q, et al. Precision Organ Function Protection for Enhanced Recovery after Surgery. Transl Perioper & Pain Med 2020; 7(1):158-167