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Review Article

The importance of a sepsis layered early warning system for critical patients

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Abstract: Critical illness, particularly sepsis, is associated with high mortality, so prevention is more important than effective therapy. Advances in medical science have provided more opportunities for early warning and early intervention to avoid the development of critical illness. Existing early warning systems (EWS) have the advantages of high efficiency and convenience. However, with the development of medical technology, they do not completely meet clinical needs. EWS should contain elements that meet many dimensions of clinical requirements, including risk warning, response warning, injury warning, critical warning, and death warning. By summarizing previous studies, we outlined a layered EWS that follows RISK bundles. RISK represents different warning sign categories: R: host response, I: organ injury, S: changes in vital signs, and K: gradual appearance of "killed" organs. We plan to construct a complete layered EWS to guide clinical activities and subsequent clinical studies in the near future.

Keywords: Layered early warning system, RISK bundles, critical illness, response, injury, intensive care unit

Introduction

Critical illness is associated with a high mortality risk and requires appropriate therapy. Sepsis is a life-threatening critical illness caused by dysregulated host/organ response to various infections and is considered a major cause of mortality and financial loss worldwide [1]. According to the Global Burden of Disease study, there were an estimated 48.9 million sepsis patients worldwide in 2017; among them, 11.0 million mortalities were reported, accounting for 19.7% of deaths. Unlike many other chronic diseases, sepsis develops and progresses quickly without treatment [2]. Timely and effective treatment can greatly improve the prognosis [3-5]. In 2017, the World Health Organization adopted the resolution "Improving the Prevention, Diagnosis and Clinical Management of Sepsis". The prevention and early detection of sepsis are important issues in the future. Global efforts are needed to reduce mortality and mitigate the economic burden of this reversible disease.

Early detection of sepsis is associated with lower mortality [4, 6]. Early warning systems (EWS) that allow the early detection of critical illness have been created for bedside assessments, which is a key strategy for the management of sepsis patients [7]. The most frequently used EWSs the Modified Early Warning Score (MEWS), the National Early Warning Score (NEWS), and the Search Out Severity (SOS) score [8, 9]. The MEWS has been used to predict hospital admission rate and in-hospital mortality, [10] and the NEWS has been used to predict death and intensive care unit (ICU) admission [11, 12]. The SOS score, a scoring system derived from the MEWS, is also used as a screening tool for the early diagnosis and management of sepsis [13]. The 2016 guidelines introduced a new tool to assess possible sepsis, which is named the quick Sepsis-related Organ Failure Assessment (qSOFA). This scoring system has strong practicality because it consists of only three elements (mental status, systolic blood pressure, and respiratory rate) but it has substantial advantages in predicting death

and ICU transfer rate in non-ICU patients [11, 14]. However, all these tools share the problem that they focus only on host response and changes in vital signs. Earlier warning markers that have high sensitivity and specificity to support pathophysiological changes and risk factors have not received enough attention. The progress on exploratory work in recent years has identified more biomarkers for early warning and prognosis in sepsis, including uncoupling protein 2, the Fis1/parkin ratio, and interleukin-6 (IL-6) [15, 16]. Current EWS need to be expanded into layered EWS (LEWS). Layered early warning signs can be broadly divided into the following categories: R: host response, I: organ injury, S: changes in vital signs, and K: the gradual appearance of "killed" organs. In this review, we clarify the pathophysiological changes in sepsis into four steps as RISK bundles, and summarize LEWS at different levels, as described in previous studies. This analysis may help to develop better EWS in the future.

Key points	RISK factors for Layered Early Warning System
R	Host Response to Infections
I	Organ Injury due to Reactions
S	Changes of the Vital Signs
K	'Killed' organs gradually appear

Sepsis RISK bundles (Figure 1) for critical patients

As mentioned above, RISK stands for different levels of warning. Among them, R and I represent advance warning of sepsis in patients and range from general to severe. Early identification and prompt intervention can prevent the development of disease. After experiencing reaction and injury, the internal environment changes considerably and there is a substantial change in S, which indicates that S is a consequence of R and I. S also indicates increased mortality risk. As vital signs can be measured easily and rapidly, the S level is the most commonly used [14]. If the disease continues to progress, organ dysfunction and organ failure occur, so-called "killed" organs. Multiple organ failure can sharply increase mortality.

Predictors and pathogenic microorganisms

Before discussing RISK systems, we must mention the host factor. Sepsis was first described in gram-negative bacterial infections [17]. In fact, sepsis can develop from any infection, and considerably varies in its clinical presentation. Approximately 80% of cases arise in the community [18]. Extremes of age (either very old or very young), inadequate exercise, catheterization or other factors that affect skin integrity, alcohol abuse, diabetes, cancer, acquired immune deficiency syndrome, and immunosuppressive medications predispose patients to infection [19].

Studies have shown that the most frequent infectious site for sepsis is the lung (64%), followed by the abdomen (20%), bloodstream (15%), and urinary tract (14%) [18, 20, 21]. Bacterial infection is the most common cause of sepsis; however, whether the prevalence of gram-positive or gram-negative bacteria is more common remains controversial [22]. Serological evidence of infection includes bacteria, parasites or fungus cultured in various body fluids such as blood, urine, stool, pleural effusion, and ascites; virus DNA or RNA; and 1,3-beta glucan tests. Through serological examination, clinicians can identify the pathogen and provide targeted drug therapy.

R: host response

The host response in sepsis is recognized as acute inflammation caused by the activation of the innate immune system in response to infection. It mainly includes changes in vital signs, inflammatory response, procoagulant response, immune system activation, neuroendocrine reaction, and metabolic changes. Cytokines play a key role in balancing proinflammatory and anti-inflammatory responses, activating and resolving the coagulation and immune response. Sustained production of cytokines in sepsis patients may be necessary to control the infection, and enhances the expression of adhesion molecules on neutrophils and endothelial cells (ECs) [23]. However, complement activation products can be fatal and probably contribute to organ injury in sepsis [23]. Early detection of abnormal cytokines may help to predict occurrence of sepsis. **Table 1** shows the simplified host response monitoring table we have set up. The table lists the available inflammatory factors and nonspecific markers of inflammation.

Inflammatory response (The Innate Immune System): After pathogenic invasion, pathogen-associated molecular patterns can bind to pattern-recognition receptors to trigger intracellular signaling pathways that initiate the production of proinflammatory cytokines such as

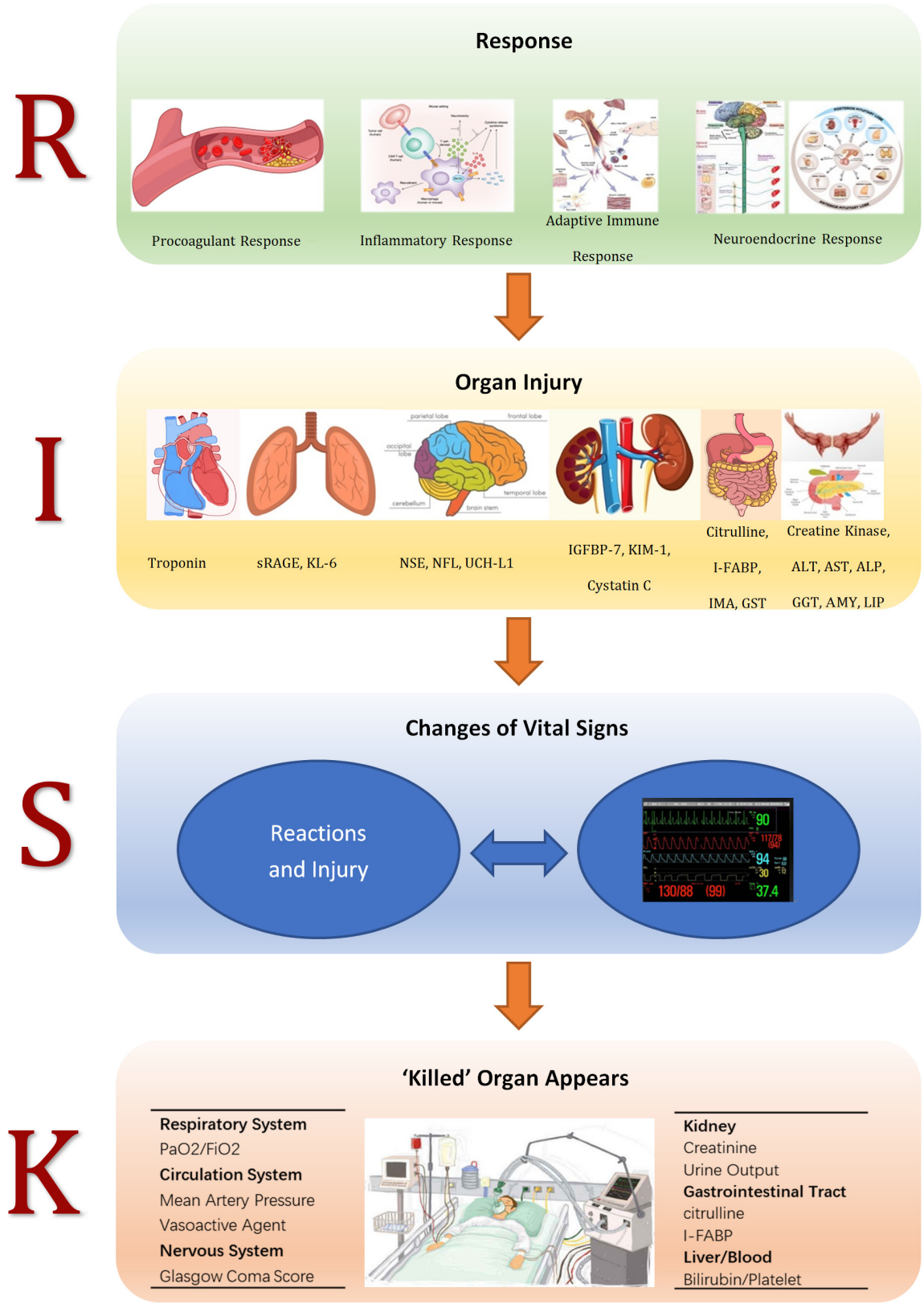

Figure 1. RISK bundles for Layered Early Warning System. RAGE: receptor for advanced glycation end products, KL-6: krebs von den lungen-6, NSE: neuron- specific enolase, NFL: neurofilament light chain protein, UCH-L1: ubiquitin car- boxy-terminal hydrolase l1, IGFBP-7: growth factor-binding protein-7, KIM-1: kidney injury biomarkers include molecule-1, I-FABP: intestinal fatty acid-binding protein, IMA: Ischemia modified albumin, GST: glutathione S-transferase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: Alkaline Phosphatase, GGT: gamma glutamyl transpeptidase, AMY: amylase, Lip: lipase.

Table 1. Simplified host response monitoring table

Name
Time
Proinflammatory Cytokines
IL-6 (Interleukin 6)
IL-8 (Interleukin 8)
TNF-α (Tumor Necrosis Factor-α)
Anti-inflammatory Cytokines
IL-10 (Interleukin 10)
Other inflammatory markers
CRP (C-Reactive Protein)
ESR (Erythrocyte Sedimentation Rate)
Infection Related Markers
White Blood Count
Neutrophilic granulocyte percentage
procalcitonin
Immune-related Biomarkers
C3 (complement 3)
C4 (complement 4)
IgG (immunoglobulin G)
IgM (immunoglobulin M)
Coagulation Related Biomarkers
Fibrinogen
D-dimer
Vital Signs
Heart Rate
Blood Pressure
Temperature
Respiratory Rate

IL-1, IL-6, IL-8, IL-12, IL-17, IL-18, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) [24-26]. Clinically, IFN-γ causes fever, chills, headache, dizziness, and fatigue, and fever can be elicited by IL-1, IL-6, and TNF-α [27]. Highly elevated IL-6 contributes to vascular hyperpermeability, resulting in hypotension, and pulmonary dysfunction through IL-2, IL-5, and IL-17 expression on ECs [28]. TNF-α regulates immunity and induces cellular apoptosis as well as inducing fever and activating antimicrobial responses [28]. IL-18 promotes T helper-1-type inflammatory responses by stimulating secretion of IFN-γ [29]. The elevated levels of C3 and C5 in the complement system and immunoglobulin initiate the recruitment of leukocytes and activate ECs and platelets [30].

After the activation of proinflammatory cytokines, anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13, are secreted to maintain a balance. The elevation of other biomarkers such as C-reactive protein correlate with response severity [31]. The innate immune system also includes natural killer cells, neutrophils, eosinophils, basophils, mast cells, macrophages, and dendritic cells.

5-hydroxytryptamine, prostaglandin, and bradykinin are released. Various blood-count abnormalities can be detected, as well as elevated ferritin, fibrinogen, and D-dimer levels.

Procoagulant response: In sepsis patients, the imbalance in coagulation and fibrinolysis is a serious reaction caused by diffuse activation of the endothelium by proinflammatory cytokines, leukocytes, and other proteins, which is an important part of the host response [32, 33]. The release of C3a and C5a initiates the recruitment of leukocytes and activation of platelets and ECs, which further releases cytokines [30]. When neutrophils are activated, extracellular traps are released to limit infection and minimize injury. DNA, histones, and other neutrophil proteins are the main components of neutrophil extracellular traps, which are prothrombotic [34].

Early in infection, activated ECs express tissue factor, a critical component of the extrinsic coagulation pathway, and release other microparticles that initiate systemic and local coagulation [35]. In addition, activated protein C and tissue factor pathway inhibitor are reduced, promoting clot generation [36]. ECs and non-ECs release plasminogen activator inhibitor-1 (PAI-1) during sepsis [37]. During the systemic inflammation phase in sepsis, levels of PAI-1, fibrin/fibrinogen degradation products, and D-dimer are markedly elevated, which leads to increased mortality [38, 39]. Interestingly, during *Klebsiella pneumoniae* infection, PAI-1 inhibition results in attenuated hypercoagulation and lower mortality rate in animal models [40]. Recombinant tissue plasminogen activator and antithrombin III supplementation may reduce organ failure and mortality [41].

Platelets also play an important role in aggregating adherence to the endothelium, amplifying inflammation, and impairing tissue perfusion, leading to sepsis-related coagulopathy [42]. Platelets are also an important source of microparticles, which amplify systemic procoagulant [43]. Red blood cells in sepsis patients are more spherical and lower in deformability, which promotes aggregation and microvascular thrombosis [44].

Adaptive immune response: Although slower to respond, the adaptive immune system can recognize and memorize unique antigens, which enhances the immune response to the reinvasion of pathogens. The system plays an important role in limiting inflammation after infection and returning the body to homeostasis. Impairments in the system during sepsis increase the likelihood of reinfection and mortality, leading to inadequate defense against infection [45].

Owing to apoptosis, substantial depletion of immune cells has been detected in patients of different ages and etiologies who have died from sepsis [46, 47]. Elevations of caspase 8 and caspase 9 have been detected in T cells in septic patients, indicating the initiation of the programmed cell death process [47]. Pro- and anti-inflammatory cytokine levels and persistently elevated antigen load are prerequisites for T cell exhaustion [48], which is marked by an increase in programmed cell death-1 (PD1) and a decrease in IFN-γ and TNF-α [49]. An elevated level of PD1 in sepsis patients is associated with increased susceptibility to superinfections, which correlates with mortality [50], while inhibition of PD1 reduces mortality in septic animals [51]. CD4+ T cells are most active during sepsis [47, 52]. It has been demonstrated that IL-2, IL-12, and IFN-γ decline in sepsis patients [53]. The regulatory function of T helper-17 cells also deteriorates [54]. Impaired poly-functionality of CD8+ T cells has been found in sepsis patients with cytomegalovirus infection [55]. Higher mortality rates correlate with a depletion in the number of γδ T cells in sepsis patients [56], and impaired γδ T cell function has been detected in patients with sepsis [57, 58]. The number and function of regulatory T cells increases because these are needed to fight infection [59, 60]. The percentage of exhausted CD21+ B cells is substantially higher in sepsis patients, so is the level of serum immunoglobin M [61, 62]. The number of dendritic cells declines in patients with sepsis [63], and dendritic cell production of proinflammatory cytokines (except IL-10) is reduced [64]. One study showed that sepsis-induced T cell apoptosis sharply decreased in mice with overexpression of Bcl-2 in T cells, and the animals showed a higher survival rate [65]. Selective inhibition of caspase-3 also prevents T cell apoptosis and improves the overall survival of septic mice [66]. PD-1 is upregulated in T cells, B cells, and monocytes in sepsis. Anti-PD-L1 antibody greatly improves the survival rate in cecal ligation and puncture mice [67].

Neural and neuroendocrine responses: The central nervous system is considered both a trigger and target organ of sepsis. The neuroendocrine system, the interaction between the nervous system and the endocrine system, is primarily responsible for neural modulation of endocrine function. Sepsis-induced cytokine release promotes blood-brain barrier damage and sepsis-associated encephalopathy. As a result, immune-inflammatory homeostasis is disrupted, and the hemodynamics of the brain change substantially [68, 69].

Neural responses: The autonomic nervous system (ANS) plays a key role in the regulation of bodily responses, which is the main process involved in the pathophysiological mechanism of sepsis [70, 71]. ANS dysregulation may be an early warning sign of sepsis before the occurrence of clinical deterioration [72]. The monitoring of heart rate can indicate the likelihood of deterioration in the next 24 hours in infants with sepsis, and can thus help to reduce mortality by 22% [73]. A hypotension prediction index based on hemodynamic changes has recently been proposed [74].

The parasympathetic and sympathetic nervous systems are the two components that comprise the ANS. The former system reduces inflammation through the cholinergic anti-inflammatory pathway; however, sepsis is characterized by excessive activation of the sympathetic nervous system and the release of endogenous catecholamines [75]. The strong stimulation of the adrenergic receptors in ECs can activate all the mechanisms described above [76]. Reduced vascular tone leads to difficulty in maintaining blood pressure, hypoperfusion, and other consequences. Some analgesic and sedative drugs and beta-blockers can help to regulate ANS overactivation.

Neuroendocrine responses: The main components of the neuroendocrine system are the hypothalamus and the pituitary gland. Hypothalamic dysfunction in sepsis can cause multisystem failure, include problems with respiration, cardiac output, and vasomotor and other reflex activities [77]. In the early phase of infec-

tion, which is characterized by the local production of proinflammatory factors, neuroendocrine hormones are secreted in response to bodily demand, while the activity of processes that are less essential to survival is reduced [78]. Extreme responses of the neuroendocrine system (both overactivation and under-activation) are associated with higher mortality [79].

Hormones secreted by the anterior pituitary: In the early stages of sepsis, serum cortisol and adrenocorticotropic hormone levels increase owing to the activation of the hypothalamic-pituitary-adrenal axis, which is stimulated by IL-1 and IL-6 [80]. Reduced levels of cortisone have been observed in non-survivors of sepsis, whereas corticotropin-releasing hormone is higher in survivors, indicating pituitary or adrenal dysfunction [81, 82].

Thyroidal function is also affected in sepsis [83]. Examination of patients who died from sepsis has shown a reduction in the size and weight of the thyroid gland, as well as reduction in triiodothyronine concentrations [84]. Growth hormone levels are substantially elevated during the early stages of sepsis. However, owing to the development of resistance to growth hormones triggered by TNF-α and IL-6, serum concentration of insulin-like growth factor-1 is reduced [85, 86]. The secretion of luteinizing hormone declines during sepsis. Lower levels of testosterone levels in men and estrogen levels in pre-menopausal women have been detected [87]. In one study, lipopolysaccharide substantially reduced the secretion of luteinizing hormone and gonadotropin releasing hormone [88].

Hormones secreted by the posterior pituitary: Arginine-vasopressin (AVP) and oxytocin are secreted by the posterior pituitary gland. AVP is a major hormone in the regulation of water balance and blood pressure, whereas oxytocin plays an important role in the contraction of smooth muscle. AVP levels increase when blood pressure drops at the very beginning of sepsis but increase despite hypotension in the later phase. Oxytocin shows the same pattern. A possible mechanism for the reduction in AVP secretion is the depletion of neurohypophysis neurosecretory AVP granules during sepsis [78].

Metabolic response: The neuroendocrine alterations in response to sepsis also induce metabolic changes, such as stress hyperglycemia and anorexia. Hyperglycemia is stimulated by hormones and proinflammatory cytokines and is associated with an increased mortality risk in sepsis [89]. Tight blood glucose control, (i.e., normoglycemia in critical patients) reduces morbidity and mortality in critically ill patients [90]. Anorexia often occurs as a result of stress-associated central nervous system and peripheral proinflammatory cytokine production [91]. Although anorexia may have some survival benefits, long-term underfeeding is undoubtedly harmful to patients. Clinical practice guidelines recommend early enteral nutrition supplemented by parenteral nutrition for critical patients [92].

I: Organ injury

Organ injury is the pathophysiological change prior to organ failure. Early and timely detection of organ injury and timely adjustment of comprehensive treatment based on hemodynamic therapy can prevent organ dysfunction and improve prognosis. There are many widely used biomarkers of organ injury and more are gradually being developed. The organ injury monitoring table is shown in **Table 2**.

Heart and skeletal muscle: Indicators of heart and skeletal muscle injury are well established. When myocardial cells are injured, many proteins and enzymes are released into the peripheral blood. The most commonly used myocardial-specific indicators include troponin and creatine kinase MB isoenzyme. Skeletal muscle-specific injury markers include myoglobin and creatine kinase.

Lung: Alveolar type 1 cells contribute to both alveolar fluid clearance and barrier integrity. The receptor for advanced glycation end products (RAGE) in alveolar type 1 cells is a transmembrane pattern-recognition receptor in the immunoglobulin superfamily, and is abundantly expressed in the lung. The soluble form of the RAGE receptor can be considered a marker of lung injury [93]; and plays an important role in formulating mechanical ventilation strategies, diagnosis of acute respiratory distress syndrome, and differentiating direct and indirect acute respiratory distress syndrome [94]. Krebs von den Lungen-6 is secreted by alveolar type 2 cells, and Clara cell protein16 is secreted by bronchiolar Clara cells. Both are associated with lung injury and inflammation. The

Table 2. Organ injury monitoring table

Name
Time
Heart
CK-MB (Creatine Kinase MB)
cTnI (Troponin I)
Lung
sRAGE (Receptor for Advanced Glycation Endproducts)
sICAM-1 (soluble InterCellular Adhesion Molecule-1)
KL-6 (Krebs von den Lungen-6)
Ang-2 (Angiopoietin-2)
Brain
S100B
NSE (Neuron-Specific Enolase)
UCHL1 (Ubiquitin C-terminal Hydrolase-L1)
GFAP (Glial Fibrillary Acidic Protein)
NFL (NeuroFilament Light Chain Protein)
Kidney
IGFBP-7 (Insulin Growth Factor Binding Protein-7)
TIMP-2 (Tissue Inhibitor of Metalloproteinase-2)
Kim-1 (Kidney Injury Molecule-1)
NGAL (Neutrophil Gelatinase-Associated Lipocalin)
L-FABP (Liver-type Fatty Acid-Binding Protein)
Scr (Serum Creatinine)
Cys C (Cystatin C)
pro-enkephalin A
Gastrointestinal Tract
citrulline
I-FABP (Intestinal Fatty Acid-binding Protein)
IMA (Ischemia Modified Albumin)
SM22 (Citrullin and smooth Muscle protein of 22 Ka)
Skeletal muscle
Myoglobin
CK (Creatine Kinase)
Liver and Pancreas
ALT (ALanine aminoTransferase)
AST (ASpartate aminoTransferase)
ALP (Alkaline Phosphatase)
GGT (Gamma Glutamyl Transpeptidase)
Amylase/Lipase

soluble intercellular adhesion molecule-1 is an inducible glycoprotein expressed on the surface of vascular ECs, and indicates lung injury in both plasma and lung edema fluid [95]. Another EC indicator is angiopoietin-2, which has an important role in increasing endothelial junction instability, enhancing vascular leak, naturally antagonizing angiopoietin-1, and inducing vascular regression and EC apoptosis [96].

Brain: The dysregulated host response in sepsis results in vascular injury, increased blood-brain barrier permeability, and activation of glial cells, which leads to a less robust interaction between astrocytes and the blood-brain barrier, causing low neuronal synapse maintenance. As a result, a network of cytokines, chemokines, proteolytic enzymes, oxidants, immune cells, and glial cells is produced and released, which directly affects neurofunction [97]. The most frequently used markers of brain injury include neuron-specific enolase, which is the only guideline-recommended marker [98], and neurofilament light chain protein, a neuroaxonal marker which has previously demonstrated high prognostic accuracy [99]. Studies have also focused on the neuroaxonal marker total tau, the neuronal cell body marker ubiquitin carboxy-terminal hydrolase L1, the astrocytic marker S100B, and glial fibrillary acidic protein. However, most of these markers have relatively high sensitivity and low specificity for the severity of sepsis [100]. One of the directions of future research is to search for indexes with higher brain sensitivity and specificity.

Kidney: Acute kidney injury (AKI) is a complex syndrome with a broad range of clinical manifestations. There are various biomarkers that indicate the syndrome. However, the definition of AKI has relied largely on assessment of serum creatinine (SCr) and urine output, which has various limitations, especially in patients with critical illness. Neither SCr nor urine output has the properties necessary for real-time assessment of kidney function. They also lack sensitivity in tubular injury. Evidence shows that marked tubular damage, histological changes, and kidney function loss both appear before a rise in SCr in AKI [101]. Kidney biomarkers may be released prior to SCr increase and/or urine output decrease [102]. Broadly, there are three types of kidney function biomarkers: stress biomarkers, injury biomarkers, and functional biomarkers. Stress biomarkers include insulin-like growth factor-binding protein-7 and tissue inhibitor of metalloprotease-2. Kidney injury biomarkers include kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, L-type fatty acid-binding protein, and

C-C motif chemokine ligand 14. Functional biomarkers are SCr (used most frequently), cystatin C, and pro-enkephalin A [103]. The development of new biomarkers will provide more information, which will facilitate earlier detection of AKI and help redefinition the term.

Gastrointestinal tract: Gastrointestinal function assessment should receive more attention, particularly in sepsis patients. The gut is a barrier that prevents toxins and pathogenic microorganisms entering tissues from the gut. Gut barrier failure in sepsis is associated with systemic inflammation and development of multiple organ dysfunction syndrome [104]. The gut barrier is composed of a monolayer of enterocytes. A minimum requirement for barrier function is the integrity of the enterocytes and controlled paracellular permeability between adjacent enterocytes. Other important changes in sepsis patients are lower diversity and abundance of key commensal genera and overgrowth by a single bacterial species, which may affect the gut barrier. There are two main biomarkers that can help to identify enterocyte injury and dysfunction. One is plasma citrulline, a marker of functional enterocyte mass, and the other is plasma or urinary intestinal fatty acid-binding protein, a marker of enterocyte damage that can be considered to be the "troponin of the gut". Both provide information about enterocyte injury [104]. Other biomarkers include ischemia-modified albumin, which is a human serum albumin that shows less binding for cobalt in the presence of reduced perfusion [105]. The α-subunit of glutathione S-transferase is present in the liver and small intestine and is regarded as a sensitive marker of small bowel ischemia [106].

Liver and pancreas: The most commonly used markers for liver injury are alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma glutamyl transpeptidase. The pancreas markers amylase and lipase are used to evaluate the level of organ injury.

S: changes in vital signs

Vital sign changes can be artificially divided into two phases in critical illness. In the first phase, changes in vital signs are the sequence of reaction and injury, which is a positive reaction. In contrast, in the second phase, the sequence of organ dysfunction is a negative sign and a warning of sepsis. As we focus here on EWS, we consider only the first phase.

After all the reactions described above, an abnormal vital sign appears. This indicates that the organism is adapting to a new internal environment and helps restore homeostasis. As has been demonstrated, hyperdynamic left ventricular ejection fraction appears owing to low systemic vascular resistance and increased circulating catecholamines [107]. The adaptive role of enhanced respiratory drive has also been demonstrated [108]. Under this condition, heart rate increases gradually along with increased ejection fraction, and respiratory rate also increases. However, changes in vital signs indicate the likelihood of the occurrence of sepsis. Various EWS based on vital signs (temperature, heart rate, respiratory rate, blood pressure, consciousness) have been established, with the aim of the early detection of sepsis. Vital signs themselves have been shown to provide predictive capabilities in advance of sepsis onset and have shown a high level of performance in experiments even with randomly missing data. Different vital sign levels have different predictive efficacy [109]. However, they provide poor specificity and sensitivity [110]. Studies have demonstrated that changes in vital signs in both trauma and nontrauma patients predict mortality [111].

K: "Killed" organs gradually appear

Hemodynamic instability may not be fatal, and may not result in shock [112, 113]. Similarly, acute respiratory failure does not necessarily develop into acute respiratory distress syndrome [114]. However, if the above-mentioned stages are not detected, and not treated with appropriate therapy to control disease onset and progression, then "killed" organs will appear. In this last stage, critical illness will develop. Many biomarkers that are familiar indicators of end-stages of disease can help in the early detection of organ failure, and are strong indicators of ICU mortality. The assessment of organ function is well established and expressed as the Sequential Organ Failure Assessment score. However, this assessment does not include gastrointestinal tract function, which is now receiving considerable attention from researchers and doctors. Currently, the

Table 3. Modified organ failure monitoring table

Name
Time
Respiratory System
PaO_2/FiO_2
Circulation System
Mean Artery Pressure
Vasoactive Agent
Nervous System
Glasgow Coma Score
Kidney
Creatinine
Urine Output
Gastrointestinal Tract
citrulline
I-FABP (Intestinal Fatty Acid-binding Protein)
Liver
Bilirubin
Blood
Platelet

PaO_2, Partial Pressure of Oxygen, FiO_2 Fraction of Inspiration Oxygen.

diagnosis of gastrointestinal failure still depends on clinical manifestations, such as feeding intolerance with elevated residual gastric volume, and ileus, diarrhea, or gastrointestinal bleeding, although ultrasound may help the assessment. Although not available in real time, biomarkers such as plasma citrulline and intestinal fatty acid-binding protein may be potential indicators of gut failure [115, 116]. The Modified Organ Failure Monitoring Table is shown in **Table 3**.

Conclusion

According to the pathophysiological process, critical illness gradually develops from organ injury caused by a series of dysregulated reactions after stress or infection. The RISK bundles describe the main process of the development of disease. The four letters represent different types of warning signs and describe early warning signs associated with the different levels of the occurrence and development of disease. In terms of EWS, in addition to the established MEWS, NEWS, and SOS, a more comprehensive early assessment and warning system should be fully established to predict and evaluate the stages of sepsis more accurately. This review proposes a LEWS framework; however, additional work is needed to fully develop this framework in the future.

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Disclosure of conflict of interest

None.

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