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REVIEW ARTICLE

Research Progress of Biomarkers of Sepsis-Associated Encephalopathy

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Abstract
Sepsis-associated encephalopathy (SAE) is a common complication of sepsis, raise the mortality rate with an incidence of up to 71%. Pathological neuroinflammation after sepsis leads to acute brain dysfunction, survivors may remain long-term cognitive impairment. At present, the evaluation of SAE severity and prognosis mainly depends on clinical manifestations and imaging features, but lack of effectiveness and timeliness. Biomarkers of nerve injuries nowadays, have shown good application value and perspectives in the diagnosis and evaluation of SAE. This article will review the current biomarkers for accurate diagnosis and evaluation, basing on the possible pathophysiological mechanism of different stages of SAE.

Keywords Sepsis-associated encephalopathy · Biomarkers · Diagnosis and evaluation

1 Introduction

Sepsis-associated encephalopathy (SAE) is a common neurological complication of sepsis, with an incidence of up to 71% [1]. It is not caused by direct infection of the central nervous system (CNS), but a diffuse cerebral dysfunction induced by the systemic inflammatory response [2]. Clinical features include: disorders of consciousness ranging from delirium to coma; cognitive impairment dominated by the decline of concentration, memory, comprehension, speech, orientation, execution and social interaction ability; emotional disorders such as depression, anxiety and irritability, focal neurological dysfunction, motor coordination problems and seizures, and may leave long-term cognitive impairment [3–5].

The pathophysiology of SAE is incompletely clarified. A prospective observational study in the US showed that plasma biomarkers including endothelial biomarkers such as vascular cellular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) had different expression levels within 24 h of admission between SAE, sepsis and delirium patients, suggesting that the pathophysiological mechanism of SAE differs from delirium and from sepsis itself [6]. Due to the complexity of SAE, and a single marker is influenced by numerous factors, a group of biomarkers according to its pathophysiological process may be more beneficial for the diagnosis and the assessment of the extent of SAE.

Jean-Louis Vincent proposed that from the perspective of pattern recognition, screening a group of validated biomarkers targeting different stages of SAE pathophysiological process might be more conducive to detect and monitor SAE. There are three steps involved (Fig. 1). First, systemic inflammation leads to endothelial dysfunction, including cerebrovascular system [7]. Second, the evolution of SAE is the activation of microglia cells, supposed to be imminent in inducing neuroinflammation in the central nervous system [8]. Third, the most striking importance is the development of structural brain injury, apparent as subsequent neurocognitive deficit [9]. Therefore, this article will review the current biomarkers of SAE in terms of different stages of possible pathophysiological mechanism (Table 1).

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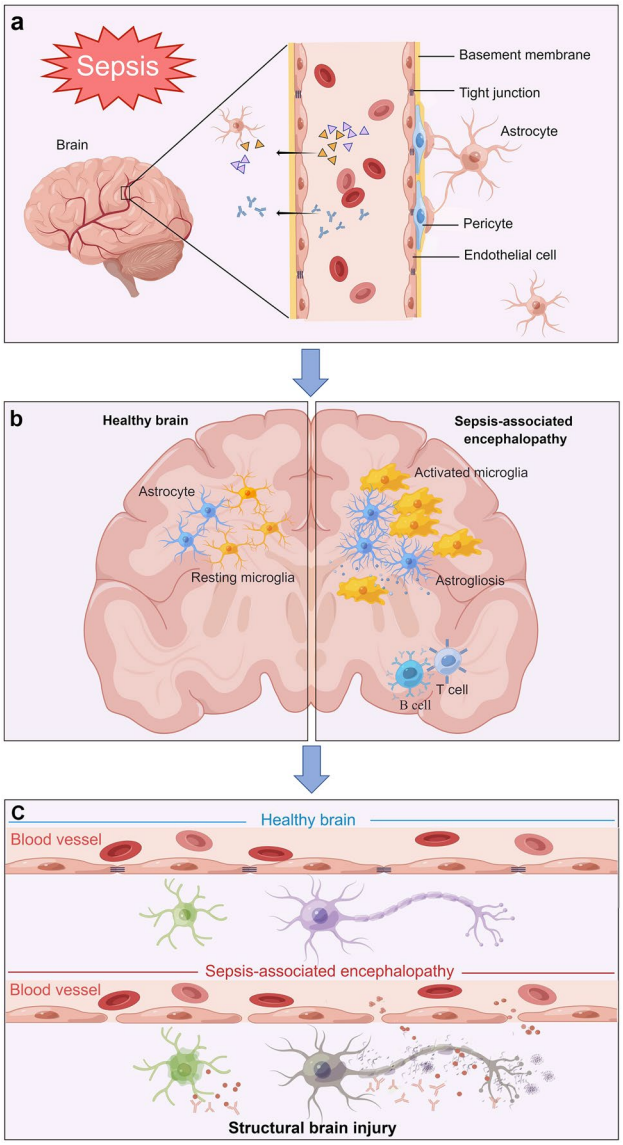

Fig. 1 Pathogenesis of sepsis-associated encephalopathy (SAE) **a** First, systemic inflammation leads to endothelial dysfunction, including cerebrovascular system [7]. **b** Second, SAE develops into microglia activation [8]. **c** Third, developing into structural brain injury [9]

2 Biomarkers of Endothelial Activation and Dysfunction, Disruption of Blood Brain Barrier (BBB)

The primary constituent of the BBB is the brain microvascular endothelial cell, tight junction protein, astrocyte foot process, perivascular pericyte and capillary basement membrane [10]. The BBB is the anatomical channel of the cerebrovascular system, responsible for the immune privilege of the central nervous system, isolating the central nervous system from the peripheral immune system, regulating the physiological communication between them [11], and protecting the CNS from pathogens and toxins. Its morphological and functional alterations are the key factors leading to SAE and final systemic damage, while the sepsis related pathological neuroinflammation causes acute or long-term brain dysfunction.

Endothelial dysfunction is a pathogenic factor of many potentially serious infectious diseases and syndromes, including sepsis and septic shock, hemolytic uremic syndrome, severe malaria, and dengue hemorrhagic fever [12]. Researchers pointed out that the activation of cerebral endothelial cells (CECs) was the earliest event during the advancement of systemic inflammation into the central nervous system [11]. Impaired endothelial function corresponds to longer delirium or coma [13].

2.1 Adhesion Molecules: Intercellular Adhesion Molecule-1, Vascular Cell Adhesion Molecule-1, Platelet-Endothelial Cell Adhesion Molecule-1 (ICAM-1, VCAM-1, PECAM-1)

ICAM-1, VCAM-1 and PECAM-1 are members of cell adhesion molecules belonging to the immunoglobulin superfamily. The expression of adhesion molecules in BBB endothelial cells and choroid plexus epithelial cells increases during sepsis [14]. The endothelial barrier function diminishes due to the junctional disassembly and cytoskeletal reorganization after the ligation of neutrophil adhesion molecules with their counter-receptors on endothelial cells, such as the binding of β-2 integrins with either ICAM-1 or VCAM-1 [15]. Neutrophils then enter the brain parenchyma, inducing astrocyte activation and promoting brain inflammation [16]. A study compared the rat sepsis models induced by lipopolysaccharide and cecal ligation puncture (CLP). Brain immunohistochemistry showed that the expression of ICAM-1 peaked 24 h after the induction of sepsis in all groups, and there was no difference in the expression of PECAM-1 among sham operation group, endotoxemia group and CLP group, suggested that the integrity of the BBB of central nervous system changed in the early stage of sepsis, which was caused by inflammatory mediators rather than bacteria [13]. A prospective observational study noted that the levels of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) in serum had great predictive value for 90-day mortality in patients with severe sepsis and septic shock [17]. In addition, SAE patients with delirium have higher levels of ICAM-1 and VCAM-1 in plasma compared with patients with delirium caused by other diseases [6]. But the application of adhesion molecules in SAE with other clinical manifestations remains to be further studied.

Table 1 Summary of biomarkers in different stages of SAE pathophysiological process

Biomarker	Different stages of SAE	Expression	Source	Main findings
ICAM-1 VCAM-1 PECAM-1	Endothelial activation and dysfunction, disruption of blood brain barrier (BBB)	Endothelial cell	Plasma	SAE patients with delirium have higher levels of ICAM-1 and VCAM-1 in plasma compared with patients with delirium caused by other diseases
NT-proCNP		Endothelial cell	Plasma	The plasma NT-proCNP level may better reflect the neurological impairment The peak concentration of NT-proCNP in plasma in the early stage of sepsis might help to predict the occurrence of SAE
Histones		Apoptotic cell	Blood	Histones can cause reversible and regional increase in BBB permeability of hippocampus
S100β	Astrocytic and microglial activation	Astrocyte	Serum	S100β in patients with sepsis have a high sensitivity (89.7%) but a low specificity (57.3%) for diagnosing SAE
GFAP		Astrocyte	Serum	Serum GFAP levels within 24 h after ICU admission may be more suitable for SAE diagnosis, with an AUROC of 0.803
MMPs		Microglia	Brain tissue	The expression of MMP-9 may play a key role in the maintained BBB deterioration by degrading the basement membrane
Iba1		Microglia	Brain tissue	Septic mice with impaired working and associative memory expressed higher levels of Iba1 in prefrontal cortex and hippocampus
NSE	Structural brain injury	Neuronal cell body	Serum	NSE have a high sensitivity (75.9%) and specificity (72.3%) in diagnosing SAE
UCH-L1		Neuronal cell body	Serum	The elevation of serum UCH-L1 is related to the occurrence, prognosis and long-term quality of life of SAE, with the AUC of 0.812 in predicting SAE, and the specificity and sensitivity are 93.6% and 62.1% respectively
miR-370-3P		Neuronal cell body	Plasma	The expression increased in the plasma of SAE patients, but not sepsis alone or uremia, and elevated as early as 6 h after CLP on the mouse model, suggesting the high specificity and sensitivity for SAE detection
Neurofilament protein		Axon	Plasma	Elevated levels of plasma neurofilament protein indicate a poor prognosis of SAE brain function or cognitive function The relationship between the levels of neurofilament protein and the time from sepsis onset may be of prognostic value
Aβ, βAPP		Axon	Brain tissue	The deposition of amyloid-beta plaques in hippocampus could be seen 7 days after lipopolysaccharide administration, and accompanied by specific behavioral deficits
BDNF		Axon	Blood	Using BDNF level in venous blood within 24 h of admission to predict SAE had an AUC of 0.74

SAE sepsis-associated encephalopathy, *BBB* blood brain barrier, *ICAM-1* intercellular adhesion molecule-1, *VCAM-1* vascular cell adhesion molecule-1, *PECAM-1* platelet-endothelial cell adhesion molecule-1, *NT-proCNP* amino-terminal propeptide of the C-type natriuretic peptide, *GFAP* glial fibrillary acidic protein, *ICU* intensive care unit, *AUROC* area under ROC, *MMPs* matrix metalloproteinases, *Iba1* ionized calcium binding adapter molecule 1, *NSE* neuron specific enolase, *UCH-L1* ubiquitin C-Terminal hydrolase-L1, *AUC* area under curve, *CLP* cecal ligation puncture, *Aβ* β-amyloid peptide, *βAPP* β-amyloid precursor protein, *BDNF* brain-derived neurotrophic factor

2.2 Natriuretic Peptide: NT-proCNP

C-type natriuretic peptide (CNP) and its amino-terminal propeptide NT-proCNP belong to the natriuretic peptide family, with the highest concentration in the central nervous system [18]. NT-proCNP can be triggered to release by inflammatory mediators such as IL-1β and TNF-α from vascular endothelium [19], indicating a relationship between systemic inflammation and the secretion and regulation of NT-proCNP. CNP has been shown to play multiple functional roles in the endothelial glycocalyx, potentially regulating vascular permeability [20]. Johannes Ehler et al. found that the plasma NT-proCNP levels of SAE patients peaked at day 1 and decreased over time, and CSF NT-proCNP levels tended to be higher in septic patients with brain lesions seen on MRI. In contrast to CSF, the plasma NT-proCNP may better reflect the neurological impairment, suggesting that the peak concentration of NT-proCNP in plasma in the early stage of sepsis might help to predict the occurrence of SAE and correspond to a greater probability of organic brain lesions [8]. NT-proCNP has a long half-life in circulation and does not easy to cross react with other natriuretic peptides [19], which makes NT-proCNP an ideal marker for SAE.

2.3 Histones

Histones are small, positively charged nucleoproteins, which form nucleosomes with negatively charged DNA, but only recently have histones been found as potent proinflammatory molecules extracellularly [21]. When tissues are exposed to adverse microenvironments, such as sepsis, trauma or pancreatitis, histones are released into blood from apoptotic cells, and play a role as damage-associated molecular pattern (DAMP) molecules, which mediate inflammatory response, organ injury and death by activating Toll-like receptors (TLR) and NLRP3 inflammasome pathways [22]. Because of the regional susceptibility of histones, compared with the cerebral cortex, tight junction (TJ) proteins and adherens junctions (AJs) in the hippocampus are more vulnerable, causing reversible and regional increase in BBB permeability, leading to cerebrovascular injury or brain dysfunction [21]. It has been proved that in the early stage of Alzheimer's disease dementia, cerebrovascular dysfunction is a strong predictor of cognitive decline [23]. Since the hippocampus is the first place affected by Alzheimer's disease, it is reasonable to hypothesize that histones have potential in serving as diagnostic or prognostic biomarkers for SAE with clinical manifestations of dementia.

3 Biomarkers of Astrocytic and Microglial Activation

In systemic inflammation, the number of activated microglia significantly increased in the brain tissue of sepsis patients [24]. Compared with microglia, astrocytes constitute a substantial part of the BBB, controling its permeability, modulating microglial activation, upregulating the production of proinflammatory cytokines and chemokines, and developing more delayed proinflammatory phenotype [25, 26]. A study declared that CECs are the earliest sensors in the CNS to the peripheral inflammation, the activation of microglia is later than that of CECs [27]. After the initial CEC activation and inflammatory signaling, microglial activation and reactive astrogliosis occur, resulting in neuroinflammation and an increase of cytokine levels, and thus causing delirium and sickness behavior [28, 29].

3.1 Astroglial Biomarkers

3.1.1 S100 Proteins

S100 proteins (10–12 KDa) are a group of acidic calcium-binding proteins, which show both cell- and tissue-specific expression and participate in cell apoptosis, proliferation, differentiation, inflammation, etc. S100β is highly expressed in astrocytes, while S100A8 and S100A9 are mainly produced by macrophages, monocytes [30]. Studies have demonstrated that serum S100β in patients with sepsis have a high sensitivity (89.7%) but a low specificity (57.3%) for diagnosing SAE, but the diagnosis of SAE and the prognosis of sepsis are both better than NSE [31, 32]. Taking 1.93 ng/ml of serum S100A8 within 24 h after admission as the cut-off value have a high accuracy in diagnosing SAE, the area under the ROC curve (AUC) is 0.86 (95% confidence interval [CI]: 0.76–0.95), and the specificity is 92.90%. Taking 2.41 ng/ml as the cut-off value, the AUC and specificity of predicting 28-day mortality are 0.88 and 90.00% respectively [33]. Liao et al. found that S100A9 expression was significantly increased in the hippocampus of septic mice. S100A9 may lead to learning and memory impairments by promoting M1 microglia polarization in septic survivors [34].

3.1.2 Glial Fibrillary Acidic Protein (GFAP)

GFAP is an intermediate filament protein, which exists specifically in astrocytes, non-myelinating Schwann cells and enteric glial cells. Its level is proportional to the degree of astroglial activation [16], and its decomposition products can be biomarkers of glial cell injury. Researchs showed that the serum GFAP levels in septic patients were correlated

with the occurrence, severity and prognosis of SAE, which increased in the early stage, and the patients with higher GFAP levels often had worse performances of daily activities [31, 35]. Compared with NSE and S100β, serum GFAP levels within 24 h after ICU admission may be more suitable for the diagnosis of SAE, taking 0.67 μg/L of GFAP as the cut-off value, the AUROC of diagnosing SAE is 0.803, greater than 0.795 of NSE and 0.750 of S100β [31].

3.2 Microglial Biomarkers

3.2.1 Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are a large family of zinc-dependent endopeptidases. Activated microglia express MMPs including MMP-3 and MMP-9 [36, 37]. MMP-9 aggravates the development of vasogenic edema by degrading the basement membrane between the endothelium and the end of astrocytes [38]. The expression of MMP-9 by perivascular Iba-1-positive microglial cells may play a key role in the maintained BBB deterioration [39]. Inflammatory factors enter the brain parenchyma of sepsis patients through the damaged BBB and directly act on neurons, leading to apoptosis.

3.2.2 Ionized Calcium Binding Adapter Molecule 1(Iba1)

Iba1 is a 17 kDa calcium-binding protein that is specifically expressed on microglia. It is the most commonly used biomarker to evaluate microglia activation (M1 type). Animal experiments showed that septic mice with impaired working and associative memory expressed higher levels of Iba1 in prefrontal cortex and hippocampus [40]. Since most Iba-1 positive cells were found near vessels, it was speculated that the continuous activation of microglia may be related to endothelial function [41]. Unfortunately, there is no humoral biomarker of microglia activation in vivo, which limits its clinical application. In contrast, astrocyte activation or damage markers are the best choice for detecting this stage.

4 Biomarkers of Structural Brain Injury

The most key mechanism of SAE is the development of structural brain injury, apparent as subsequent neurocognitive deficit. During inflammation, inflammatory signals are transmitted and microglia are activated by cytokines produced by astrocytes, promoting the microglial migration to inflamed foci and production of reactive oxygen species (ROS), ultimately resulting in excitotoxic neuronal death [42]. Therefore, neuronal biomarkers of sepsis-induced brain injury will be a valuable tool to supplement current clinical data and to help medical decision-making.

4.1 Biomarkers of Neuronal Cell Body Damage

4.1.1 Neuron Specific Enolase (NSE)

NSE is an isoenzyme of the glycolytic enzyme enolase, which is mainly expressed in the mature neurons and the late differentiation of oligodendrocytes. It's a marker of mature neurons and neuroendocrine cells [43]. Similar to S100β, it can be used as a biomarker reflecting acute brain injury for brain trauma, stroke, hypoxic-ischemic encephalopathy, sepsis-associated encephalopathy, etc. [32]. Yan et al. found that for patients with sepsis, the sensitivity (75.9%) and specificity (72.3%) of diagnosing SAE were high when taking 15.57 μg/L of serum NSE within 24 h after ICU admission as the cut-off value, but the NSE level was not statistically significant between the 28-day survival group and the death group (P = 0.087), and had no significant prognostic value [31].

4.1.2 Ubiquitin C-Terminal Hydrolase-L1 (UCH-L1)

UCH-L1 is a ligase and hydrolase with various biological activities, and is mainly expressed in the cytoplasm of neurons, scavenging oxidized or misfolded proteins [44]. Wu et al. single-center prospective cohort study demonstrated that the elevation of serum UCH-L1 in patients with sepsis in the early stage (within 24 h after ICU admission) was related to the occurrence, prognosis and long-term quality of life of SAE. Taking 7.72 ng/ml as the cut-off value, the AUC of predicting SAE is 0.812 (95% CI: 0.76–0.95), and the specificity and sensitivity are 93.6 and 62.1% respectively. Moreover, patients with high UCH-L1 level are more likely to accompany chronic somatic pain (P = 0.026) [35].

4.1.3 miR-370-3P

MicroRNA (miR) is an endogenous noncoding RNA. Its molecular weight is lower than protein and it is easier to pass through the BBB. Severe hypoxia and significant cytokine storm (especially TNF-α) during sepsis probably enhance the expression of miR-370-3p of neurons, and promote miR transfer from brain to blood circulation through BBB impairment induced by sepsis. A study showed that the expression of miR-370-3p increased in the plasma of patients with SAE, but not sepsis alone or uremia, and elevated as early as 6 h after CLP, compared to the undetectability of Plasma S100β and BBB defect (EB dye assay) at the meantime, suggesting the high specificity and sensitivity of miR-370-3p for SAE detection [45]. Sepsis, as a systemic inflammatory response, involves multiple organ dysfunction. Some studies have indicated that miR-370-3p could be a biomarker for early diagnosis of sepsis-associated acute kidney injury (SA-AKI). Compared with non-AKI invalids, miR-370-3p were

obviously lower in the urine of AKI invalids [46]. Since miR-370-3p is stable enough in blood and has a correlation with GCs and SOFA score, it may be a sensitive biomarker for sepsis induced neuronal damage or BBB impairment [45].

4.2 Biomarkers of Axonal Injury

4.2.1 Neurofilament Protein

Neurofilament protein is an intermediate filament found in the neuronal cytoplasm. It forms the neuronal cytoskeleton together with microtubules and microfilaments. Experimental sepsis, autopsy and vivo MRI all confirmed that there were two distinct patterns of neuroaxonal injury in sepsis: scattered ischemic lesions and diffuse neuroaxonal injury [47]. Therefore, neurofilament protein, reflecting axonal injury, can be used as a biomarker of structural brain injury caused by sepsis. Elevated levels of plasma neurofilament protein indicate a poor prognosis of SAE brain function or cognitive function [9], in addition to the correlation between the time from sepsis onset and the tissue neurofilament levels ($R = 0.53$, $p = 0.045$), we draw a conclusion that the relationship between the levels of neurofilament protein and the time from sepsis onset may be of prognostic value [48].

4.2.2 β-amyloid Peptide (Aβ) and β-Amyloid Precursor Protein (βAPP)

β-amyloid peptide (Aβ) is produced by the hydrolysis of β-amyloid precursor protein (βAPP), which exists in blood and CSF, the accumulation of Aβ forms neurotoxic amyloid plaques in the septic brain, causing long-term cognitive deficits, probably. βAPP staining is usually restricted to the neuronal cell soma and the proximal axonal hillock, while more widespread axonal staining can be seen in the brain tissue of septic rats [48]. At the meantime, survival rats of severe sepsis had increased concentrations of Aβ and decreased levels of synaptophysin in brain tissues, indicating long-term cognitive impairment [49]. The deposition of amyloid-beta plaques and intracellular phosphorylated tau in hippocampus could be seen 7 days after lipopolysaccharide administration, and resulted in specific behavioral deficits attributable to the dorsal dentate gyrus [50], which provided a basis for the high incidence of dementia in the longitudinal study of sepsis survivors.

4.2.3 Brain-Derived Neurotrophic Factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is a secreted protein in the neurotrophic factor family, which promotes neuronal survival and regulates synaptic connection. It plays a key role in the process of learning and memory as a biomarker of synaptic plasticity [51]. A study involving 30 patients with sepsis caused by community-acquired pneumonia pointed out that using BDNF level in venous blood within 24 h of admission to predict SAE had an AUROC of 0.74 [6]. Even if critically ill patient had no brain dysfunction, the BDNF level was still related to prognosis [52]. Animal studies have shown that systemic inflammation could cause cognitive impairment, accompanied by increased expression of proBDNF in hippocampus. 24 h after sepsis onset, the ratio of mature brain-derived neurotrophic factor (mBDNF)/brain-derived neurotrophic factor precursor (proBDNF) in hippocampus decreased significantly [53].

5 Conclusion

The experimental transcriptional profiles simulating the process of SAE systemic inflammation progressing to the central nervous system reveals that the cerebral vascular system is the earliest receptor of peripheral inflammation. The activation of endothelial cell apoptotic signaling and alteration of BBB jointly lead to the apoptotic cascade of CECs, affecting the barrier integrity. After the initial CEC activation and inflammatory signaling, microglial activation and reactive astrogliosis occur [27]. Activated microglia can cause neuronal cell death by producing cytotoxic factors, including nitric oxide, TNF-α, IL-1β and reactive oxygen species (ROS) [54]. The activation of microglia potentially initiates neuroinflammatory and neurodegenerative processes [55].

Sepsis-associated encephalopathy, as a common complication of sepsis patients leading to a higher mortality, may cause long-term cognitive dysfunction and impose a huge burden on society and families. At present, the diagnosis of SAE mainly depends on altered mental status, Glasgow Coma Scale (GCS), Confusion Assessment Method-ICU (CAM-ICU), EEG and neuroimaging, but still have some defects. In view of the limitations of a single marker and the heterogeneity of different factors, a group of biomarkers according to its pathophysiological process combined with other assessment methods may be more helpful for early diagnosis, evaluation of the severity and judging the prognosis. It is of great significance for us to capture the potential pathophysiological mechanism, dynamic monitoring may provide guidance for the treatment and prognosis.

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Declarations

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