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REVIEW ARTICLE

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Delirium in the ICU: how much do we know? A narrative review

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ABSTRACT

Delirium in critical ill patients is a complex and common neurological syndrome in the intensive care unit (ICU) that is caused by a range of structural or functional abnormalities. ICU Delirium is associated with reduced compliance, prolonged hospital stays, greater use or delayed withdrawal of sedatives, higher rates and durations of mechanical ventilation, and higher rates of mortality. The aetiology and pathogenesis of ICU delirium are unclear, and the lack of better prediction, prevention, and treatment measures leads to a non-standardized control of delirium. By searching the relevant literature, we aim in this narrative review to describe progress in the pathogenesis, predictive biomarkers, diagnosis, and treatment of ICU delirium.

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1. Foreword

Delirium is a common acute disturbance of mental status, with an incidence rate of 20–50% in the intensive care unit (ICU) [1] and up to 80% in patients on mechanical ventilation [2]. Once delirium occurs, patient compliance is severely compromised. Severity of illness, prolonged sedation and mechanical ventilation are independent risk factors associated with in-hospital mortality in patients with delirium [2,3]. Although local recommendations and international guidelines have been published [4,5], they are often not followed [6,7]. A worldwide online survey disclosed that although respondents acknowledged the need for delirium monitoring, more than 58% of them did not use specific tools to monitor delirium [7]. For a long time, insufficient attention has been given to the normative diagnosis and management of delirium in the ICU, in both adult and paediatric patients [6–8]. Second, the tools used for diagnosis and treatment evaluation differ between countries, regions, hospitals, and even departments [9–11]. In recent years, with the continued development of diagnostic criteria for delirium and the gradual exploration of treatment interventions, clinicians have gradually paid more attention to delirium in the ICU [5,12]. This narrative review summarizes the pathogenesis, predictive biomarkers, diagnostic criteria, prevention and treatment measures, and potential therapeutic targets of ICU delirium by systematically reviewing recent works to provide a theoretical basis for further research and clinical practice.

2. Pathogenesis and biomarkers

The pathophysiology of delirium is complex, involving multiple interactions between aetiologies and precipitating factors that are still poorly explored. Understanding the mechanisms will help to predict the risk of delirium as early as possible and will encourage clinicians to implement interventions to reduce the incidence of delirium.

2.1. Neurological disease and imaging biomarkers

Aging and neurological diseases are important susceptibility factors for delirium. Patients with delirium observed more brain atrophy, white matter lesions,

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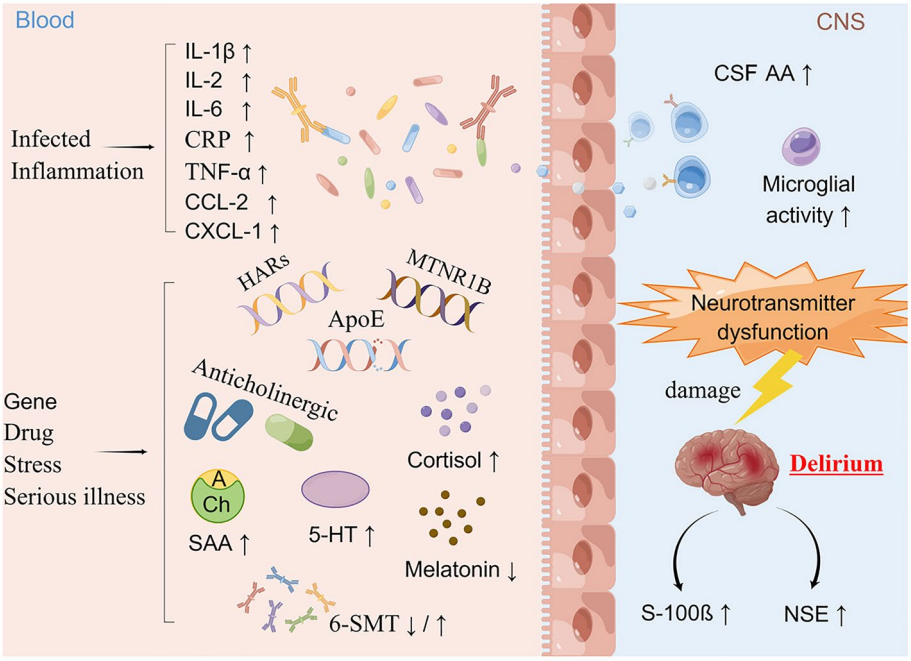

Figure 1. Potential pathophysiology of delirium. IL-1β, interleukin 1β; IL-2, interleukin 2; IL-6, interleukin 6; CRP, C-reactive protein; TNF-α, tumour necrosis factor α; CCL-2, C-C chemokine ligand 2; CXCL-1, chemokine C-X-C motif ligand 1; HARs, human accelerated regions; MTNR1B, melatonin receptor 1B gene; Apo-E, apolipoprotein E; SAA, serum anticholinergic activity; CSF AA, cerebrospinal fluid anticholinergic activity; 5-HT, serotonin; 6-SMT, 6-hydroxymelatonin sulfate; S-100β, S100 calbindin B; NSE, neuron-specific enolase. Drawn with Figdraw.

and ischemic and hypoxic vascular lesions, as indicated by different MRI sequences [13–15]. About 54.9% of patients with delirium have brain lesions, and 16.1% have brain atrophy on MRI; these abnormal MRI findings are associated with reduced C5a and IC3b levels and increased tau levels [15]. Decreased arousal network activity and an imbalance in cortico-subcortical hemispheric connectivity have also been associated with the onset of delirium in patients with MRI abnormalities [16]. Compared with other biomarkers, preexisting brain atrophy and brain lesions before delirium onset may help to rapidly identify individuals at high risk of delirium. However, the relationship between these imaging changes and the development of delirium remains unclear. The value of imaging findings in predicting ICU delirium needs further study.

2.2. Metabolic disorders and humoral biomarkers

Metabolic disorders contribute to delirium onset or act as mediators between drugs [17,18], systemic inflammation [19,20], sleep deprivation [21], physical restraints [21,22], and other changes in the surrounding environment and acute abnormalities of the nervous system (Figure 1).

Neurotransmitter imbalances, especially of acetylcholine, are among the most reported risk biomarkers for delirium [23]. In patients with respiratory failure or shock, a higher daily plasma acetylcholinesterase was associated with an increased risk of delirium compared with a normal mental status on the same day [24]. In patients with sepsis, approximately 90% exhibit statistically significant decreases in acetylcholinesterase activity over a period of at least 5 consecutive days from baseline [25], while longitudinal changes were observed only in patients with suspected septic-associated encephalopathy and could be used to diagnose septic-associated encephalopathy in patients with delirious symptoms [25]. In addition, postoperative plasma gamma-aminobutyric acid was independently associated with delirium in critical illness patients [26]. Although neurotransmitter testing has not been included in the scope of laboratory testing, making bedside testing difficult to achieve at present. However, it has been gradually incorporated into disease screening in hospitals, and may become a bedside monitoring biomarker in the future.

Systemic inflammation is another common risk factor for delirium in critical illness patients. Inflammatory mediators may cross the blood–brain barrier, leading to functional or structural impairment in the central nervous system [27–29]. Significantly higher serum neutrophil–lymphocyte ratios were found in elderly patients with critical illness with delirium than in those

Table 1. Common diagnostic methods for ICU delirium in the clinic and related studies.

Type of tools	Methods	Abbreviations
Diagnosis	Diagnostic and statistical manual of mental disorders-5	DSM-5
Screening	Confusion assessment method for the intensive care unit	CAM-ICU
	Intensive care delirium screening checklist	ICDSC
	The confusion assessment method	CAM
Delirium severity	Confusion assessment method-severity	CAM-S
	Confusion assessment method for the intensive care unit-7	CAM-ICU-7
	Delirium rating scale-revised-98	DRS-R-98
	Memorial delirium assessment score	MDAS
Sedative level	Richmond agitation and sedation scale	RASS
	Sedation-agitation scale	SAS
	Ramsay sedation scale	Ramsay
	Observer's assessment of alertness/sedation scale (OAA/S)	(OAA/S)

ICU, intensive care unit.

with a normal mental status [30]. A prospective study enrolled 78 patients admitted over 24 h in the ICU and collected blood samples within 12 h of enrolment. The results showed that soluble tumour necrosis factor (TNF) receptor-1 and -2, adiponectin, and interleukin (IL)-1β levels were higher in patients with delirium occurrence during the first 72 h of ICU admission [31]. IL-6, IL-8, IL-10, IL-18, TNF-α, and chemokines (CCL2, CCL3, CXCL1, and CXCL10) have also been reported to be elevated in ICU delirium patients and are associated with delirium severity [19,31,32]. Therefore, inflammatory markers and cytokines are potential biomarkers for the prediction of ICU delirium.

Other metabolic biomarkers have also been related to ICU delirium. One of the most important stress hormones is cortisol. Under stress conditions, increased adrenal axis reactivity, excessive secretion of cortisol, and the use of glucocorticoids can cause cognitive and mental disorders such as mood and memory disturbances [17,33]. Patients with septic delirium had significantly higher plasma cortisol levels than patients without delirium [34].

No delirium-specific serum markers have been identified. Analyses of relevant humoral metabolic biomarkers after ICU admission and before the onset of delirium are useful for identifying the prevalence of delirium, so these may become therapeutic targets for reducing the risk of delirium, especially the levels of neurotransmitters and inflammatory mediators.

3. Tools for screening, diagnosis, and therapeutic effect assessment

Delirium can be divided into hyperactive, hypoactive, and mixed delirium according to the characteristics of the symptoms [35]. In the clinic, hyperactive delirium and mixed delirium are more easily identified, while hypoactive delirium is often overlooked due to the lower state of consciousness. Many methods for screening and diagnosing delirium are often used in the clinic and in research [9,11,36–44] (Table 1). The Statistical Diagnostic Manual of Mental Disorders (DSM) published by the American Psychiatric Association and the International Classification of Diseases are the gold standard for diagnosing mental disorders worldwide [45] and are the strictest criteria based on symptoms and aetiology; this standard mostly needs to be applied by neurologists and psychiatrists. The DRS-R-98 assessment method is more rigorous and detailed, and can be used to distinguish between hyperactive and hypoactive delirium, with a sensitivity of 92% and specificity of 95% [41], though it still has shortcomings and suffers from too little evidence in ICU patients [46]. As delirium assessment in the ICU is carried out mostly by bedside nurses, a simple and fast score based on symptoms is more applicable for screening. Compared with CAM [36,47], the Confusion Assessment Method for the Diagnosis of Delirium in the ICU (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) are more often used for the diagnosis of critical illness and are recommended by ICU guidelines [5,8]. CAM-ICU is superior in ruling out patients without ICU delirium and in detecting delirium in patients with ventilation and has higher summary specificity than ICDSC [48,49]. In randomized controlled trials, CAM-ICU is the most used tool to evaluate the effects of pharmacological and nonpharmacological therapies on the primary outcome of delirium incidence in randomized controlled trials (RCTs) [50–52].

For adult ICU patients with hyperactive delirium, sedatives such as continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions are preferred by clinicians according to guideline recommendation [53]. These patients may need to be evaluated for both sedation level and delirium control. Two tools are most often used to assess the effect of sedation: the Richmond Agitation and Sedation Scale (RASS) [54] and the Sedation-Agitation Scale (SAS), which are also recommended by ICU guidelines [4,5].

Table 2. Drugs often used in the ICU that increase the risk of delirium.

Type of drugs	Measures to avoid delirium onset or recurrent if must be used	Typical drugs
Corticosteroids	Low-dose	Glucocorticoids
Benzodiazepine, benzodiazepine receptor antagonist	Low-dose, avoid sudden withdrawal, and weaned over several days	Alprazolam, Lorazepam, Midazolam, flumazenil
Opioids, opioid antagonist, naloxone, or mixed agonist/antagonists	Low-dose, avoid sudden withdrawal, and weaned over several days	Sufentanil, Nalbuphine
Anaesthetic	Low-dose, avoid sudden withdrawal, and weaned over several days	Propofol, Ketamine
Anticholinergic drugs	Low-dose	Atropine

RASS is supported by the most evidence from RCTs [55–57]. CAM-ICU combines the degree of sedation and can be assessed at the same time as RASS [10]. Sedatives can be titrated to maintain either light or deep sedation. Multiple studies support lighter sedation levels in adult ICU patients to improve outcomes, including a shortened duration of mechanical ventilation, a shorter hospital stay, and less long-term cognitive dysfunction [53], and it was beneficial for delirium screening and monitoring.

Based on the above evidence, CAM-ICU is the most appropriate tool for screening and monitoring ICU delirium, especially for patients under sedation.

4. Prevention and treatment

There is a comprehensive management system of nonpharmacological and pharmacological interventions for the prevention and treatment of delirium in the ICU. Intervention of primary disease and the reduction of medical triggers, such as inflammatory responses [27–29], abnormal energy metabolism caused by hypoxia and ion disturbance [58,59], an uncomfortable environment [21], and drugs, such as the intraoperative application of dopamine and analgesic ketamine [60], sedative midazolam [61], and benzodiazepines [62,63] (Table 2), are important measures for preventing delirium.

Nonpharmacological interventions, which mainly include control of the environment (avoiding noise, confusing stimuli, continuous light stimulation, sleep deprivation, maintaining circadian rhythm, etc.), cognitive functional rehabilitation training, family nursing knowledge training, and music training, are the cornerstone of delirium prevention/management and are recommended first line by all guidelines published to date, both adult and paediatric [4,5,64–70]. If the effectiveness of nonpharmacological interventions I limited, pharmacologic treatment with antipsychotics (or other agents) should be limited to those with severe symptoms and/or those with nonpharmacologic interventions that have failed. The treatment of elderly critically ill patients is often complicated by the presence of multiple diseases, an attention should be given to controlling the types or standard use of drugs (Table 2) in high-risk patients. Reducing or avoiding the use of analgesic, delirium-active sedatives such as benzodiazepines, psychotropic and hormonal drugs during procedures and after ICU admission can reduce the onset or recurrence of delirium [18,71,72], which need a cooperated attention of anaesthesiologists, surgeons, and practicing intensivists, as an exposure to these drugs such as benzodiazepine has been reported to be correlated with an increased risk of delirium [73,74]. If drug application cannot be avoided, low-dose, serological drug concentration testing or the avoidance of sudden withdrawal may be important preventive measures [18].

Drugs used for delirium prevention and treatment are mainly divided into antipsychotic drugs and nonpsychotic drugs (Figure 2). Antipsychotics have been reported to improve clinical symptoms, shorten duration, and reduce the severity of delirium [75]. However, antipsychotics such as haloperidol and ziprasidone have not been shown to reduce the rate of delirium occurrence [72,76,77] or shorten the duration of ICU delirium, and their high incidence of adverse reactions has also been criticized, as confirmed in recent years, by numerous large-scale placebo-controlled RCTs and meta-analyses [78–81]. For nonpsychotic drugs, the use dexmedetomidine was related with reduced risk of ICU delirium [72,73,82], duration of mechanical ventilation and ICU length of stay comparing to other sedatives, due to its low risk of respiratory depression [73]. Among atypical antipsychotic drugs, ICU patients with delirium who received quetiapine had a reduced duration of delirium [83]. A recent meta-analysis showed that olanzapine did not have a clear beneficial effect compared with other delirium drugs [84]. At present, few scholars have studied the safety of delirium drugs in nonmechanically ventilated ICU populations [3]. This field requires further exploration.

Several studies have developed and tested other delirium drugs with potential therapeutic targets. The application of exogenous melatonin and melatonin

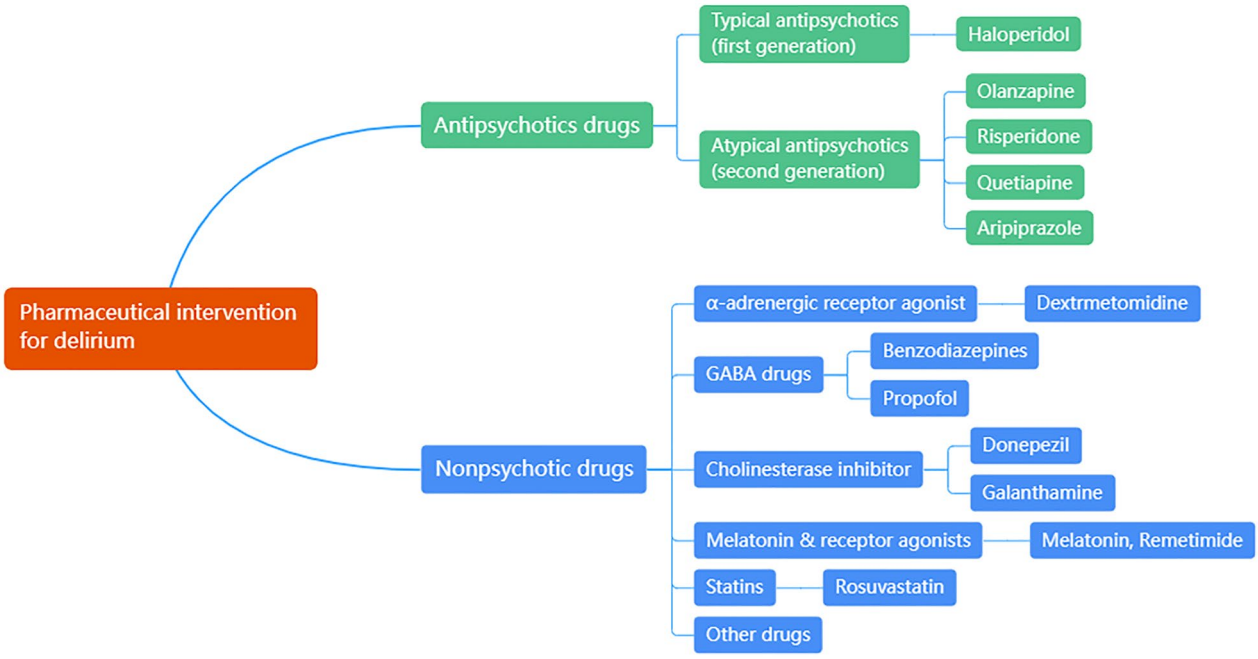

Figure 2. Classification of pharmaceutical interventions for delirium.

receptor agonists such as ramelteon was associated with improved sleep, reduced the incidence of delirium, and shortened period of ventilators [85–87]. The inflammatory response is another important target of current research, and critically ill patients often have complications such as organ infection or systemic inflammatory responses. Patients with delirium have been reported to benefit from statins, probably through their anti-inflammatory effects [88–90]. Further high-quality studies focused on delirium prevention and treatment are still needed.

5. Summary and outlook

Delirium is a state of abnormal brain function due mostly to pathological or functional changes in the brain parenchyma. Different patients may face different contributing factors, such as sleep deprivation and abnormal sleep rhythm caused by continuous ECG monitoring; light stimulation and noise; the application of hormones, anaesthetics and cholinergic drugs; ischemia; hypoxia; and cerebrovascular disease. Early assessment of risk factors in high-risk patients to predict the occurrence of delirium and avoid the contributions of known factors is an ideal management strategy for such patients. There is currently no good method for predicting and preventing delirium. Whether delirium can be predicted and how to develop a good prediction and prevention method will continue to challenge intensivists and neurologists. Further research into delirium treatment drugs and neurocritical care practice strategies is warranted to determine both their efficacy and safety.

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Authors contributions

S.B.L.: conceptualization, software, formal analysis, investigation, writing-original draft. H.Y.W.: software, formal analysis, investigation. M.L.D.: formal analysis, investigation. R.L.Y.: visualization, supervision. C.H.J.: visualization, supervision. J.J.L. and H.Z.: writing-reviewing and editing, project administration, funding acquisition.

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Data availability statement

Data availability is not applicable to this article, as no new data were created or analyzed in this study.

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