

# Postoperative Delirium in Open Cardiac Surgery Patients

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**Abstract:** *Delirium, a syndrome characterised by disturbances in consciousness and attention, is a serious postoperative complication. The incidence of postoperative delirium in open cardiac surgery patients is high. Delirium is associated with prolongation of the hospital stay, deterioration of the prognosis of the patients, increased morbidity and mortality. This article reviews the pathophysiology, specific risk factors and the types of delirium in cardiac surgery patients. Knowing the typical risk factors for cardiac patients, we can change the intraoperative behaviour and the postoperative care for the patients who are in the risk group for development of postoperative delirium.*

**Keywords:** Delirium, cardiac surgery, risk factors, postoperative care

## 1. Introduction

Postoperative delirium (POD) is an adverse complication found in all age groups. The prevention, diagnostics and treatment of POD are challenges for each doctor. References to delirium were made in the earliest medical works of Ambroise Paré and Dupuytren. Postoperative psychosis remains not fully understood and studied even today. Early writers frequently used terms like 'psychosis', 'madness', 'state of arousal', as well as 'delirium of the nervous tissue'. One thing is certain: 'functional psychosis' occurs often after surgery [1]. The interest in this syndrome has considerably increased over the last years due to its remarkable relation to the deterioration of the prognosis for the patients and the significant increase of the postoperative stay and mortality [2].

## 2. Definition

The definition of delirium of the World Health Organization (WHO) is: 'An etiologically nonspecific organic cerebral syndrome characterized by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion, and the sleep-wake schedule. The duration is variable and the degree of severity ranges from mild to very severe' [3]. A publication of the fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5) provides an opportunity to examine the conditions underlying delirium as a clinical unit. According to DSM-5 delirium includes the following criteria: A) Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment); B) The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day; C) An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception); D) The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma; E) There is evidence from the history, physical examination or laboratory findings that the

disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies [4]. Postoperative delirium usually develops on postoperative day 2 through 5.

## 3. Epidemiology

The ICU patients suffering from an acute brain dysfunction may demonstrate a delirium syndrome. The general prevalence of delirium in critically ill patients varies in the various studied populations from 16% to 89% [5]. In the general surgery population, the frequency of postoperative delirium is 2.5-3%. In patients aged 60-70 the frequency of postoperative delirium is significantly higher, reaching 10-20%. Complex surgeries requiring continuous ICU care, such as cardiothoracic and liver surgeries are associated with an increased risk of development of postoperative delirium of up to 20-50%. Postoperative delirium increased the average hospital stay with 2-3 days and the average stay in the ICU unit with 2 days. Postoperative delirium is associated with an increase of the 30-day mortality of 7-10%, as compared to 1% in patients without delirium. The development of delirium is associated with significantly higher healthcare costs [6].

### Pathophysiology:

The pathophysiology of delirium is multicomponent and is the subject of interest and new discoveries and evidence even today and will be so in the future. There are several theories/hypotheses related to the pathophysiology of postoperative delirium, such as:

1. **'Neuronal aging':** According to the neuronal aging hypothesis, the changes accompanying the aging process are associated with diminishing physiologic reserve, making us increasingly vulnerable to physical stress and illness. Aging is associated with a number of age-related cerebral change: changes in the proportion of stress-regulating neurotransmitters, brain blood flow decline, decreased vascular density, neuron loss, and intracellular signal transduction systems [7]. This can explain why patients over 65 more often have symptoms of postoperative delirium.

Volume 9 Issue 12, December 2020

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**2. Neuroinflammation:** According to the neuroinflammatory hypothesis (NIH) delirium is a manifestation of a systemic affection, which has crossed the blood-brain barrier (BBB). Inflammation has long been recognized as a trigger for episodes of delirium, particularly in older adults, with a correlation between the severity of the patient's underlying medical problem and the development of delirium [7]. Systemic inflammatory mediators are increased significantly after surgery and remain high during the postoperative period.

It has been reported that postoperative elevation of peripheral C-reactive protein (CRP) and interleukin 6 concentrations is associated with higher risks of postoperative delirium. Peripheral inflammation can lead to the loss of structural and functional blood brain barrier integrity and subsequently translocation of inflammatory cells and mediators into the CNS. The accumulation of inflammatory mediators then results in the loss of synaptic plasticity, neuro-apoptosis, and impaired neurogenesis [6]. Changes in the white blood cells differential count, as well as the CRP concentration may show that post-cardiac surgery delirium is associated with inadequate immune system response. Growing evidence suggests that neutrophils and lymphocytes are major effectors of acute inflammation, including neuroinflammation in delirium among elderly patients [8]. Cardiac surgery, which together with cardiopulmonary bypass (CPB) causes systemic inflammatory reaction, is a risk factor for systemic embolism. Moreover, the inflammatory response and the positive water-electrolyte balance can cause cerebral swelling, which together with the possible microembolism, increases the risk of postoperative confusion, cognitive deficit and delirium [9].

**3. Neurotransmitters:** It is considered hypothesized that acetylcholine participates in neuroplasticity and is present in several nerve pathways responsible for attention and memory. According to Adam EH, Haas V, Lindau S, et al. development of postoperative delirium after cardiac surgery correlates to postoperative reduction of the Butyrylcholinesterase (BchE) activity. In addition to that, patients with postoperative delirium showed lower preoperative Acetylcholinesterase (AChE) activity compared with patients without delirium [10].

Additional neurotransmitter imbalances, related to the development of delirium, include dopamine, serotonin, and norepinephrine. The increased dopamine level is associated with the development of delirium, in particular the hyperactive motor type [11]. Excess serotonin excess leads to disorders in activities, such as learning, memorization, cognition, which disorders are related to the development of delirium, and the administration of Selective serotonin reuptake inhibitors (SSRIs) has been also associated with delirium. The increased norepinephrine levels lead to arousal, anxiety, disturbed attention and psychosis, associated with the development of hyperactive delirium [12].

Gamma aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system. The GABA levels dysregulation, as well as both the excess and the

deficit, are also associated with a higher frequency of delirium [11].

**4. Oxidative stress (hypothesis):** It is hypothesized that oxidative stress and/or deficit of antioxidants can increase the brain tissue injury, which leads to cognitive deficit and probably irreversible brain degeneration, which in turn leads to development of delirium [13]. Intraoperative oxidative damage is associated with increased postoperative delirium and neuronal injury, and the association between oxidative damage and neuronal injury is stronger among patients with increased blood-brain barrier disruption. [14]. Alterations in systemic and regional perfusion and oxygenation, cardiopulmonary bypass (CPB), and changes in plasma pH and cellular metabolism during cardiac surgery induce an oxidative stress that could contribute to postoperative delirium. [14, 15, 16].

**5. Acute stress reaction:** High levels of cortisol associated with acute stress have been hypothesized to precipitate and/or sustain delirium [17]. Steroids can cause impairment in cognitive function (steroid psychosis), although not all patients treated with high-dose steroids will develop this condition. In elderly patients, feedback regulation of cortisol might be impaired, resulting in higher levels of baseline cortisol and thereby predisposing this population to delirium. A number of studies have identified elevated levels of cortisol in patients who developed POD [18, 19].

#### 4. Risk factors with cardiac surgery patients:

Postoperative delirium is not preventable in all patients, but its severity and duration may be limited, especially if promptly recognized and managed [20]. The presence of postoperative delirium is a result of the complex interaction of various risk factors. According to Inouye and Charpentier, the risk factors are grouped as predisposing and precipitating. The predisposing factors are the baseline conditions, which increase the risk of delirium, while the precipitating factors are the triggers, causing delirium [21]. Patients with a high risk of delirium due to many or serious predisposing factors need minimum precipitating risk factors to provoke and register an episode of delirium. Patients with few predisposing risk factors would need many or serious precipitating risk factors in order to provoke delirium [22, 23]. Predisposing risk factors for the occurrence and development of delirium symptoms are well known and studied. It is of extreme importance to perform preoperative screening of patients exposed to higher risk, while trying to prevent and administer early treatment of the symptoms. Precipitating risk factors must be considered by clinicians when treating any patient at high risk for postoperative delirium. Each type of risk factor can be modifiable or non-modifiable, and if possible, those that are modifiable should be optimized in the perioperative period [24].

**Table 1: Risk Factors for delirium development**

Predisposing risk factors	Cardiac surgery	Non cardiac surgery
Age>65y	+ [25, 26, 27, 31, 34, 35, 39]	+ [25,27,28,29,30,32,34,36,40,41, 42]
Low education	+ [26,33]	
Smoking	+ [26,27,38]	+ [29]
Alcohol consumption		+ [29,32,40]
Depression	+ [25, 27,34,35]	+ [29]
Stroke history/ TIA	+ [25,27,31,35, 39 ]	+ [30]
Dementia or Cognitive impairment	+ [ 25,31,34, 35, 39]	+ [27, 28, 29, 30, 32, 36,40,41,42]
Preoperative AF	+ [25,26,27,31, 35]	
Hypertension	+ [26]	+ [36]
Increased cardiothoracic index	+ [26]	
Preoperative anemia	+ [25,27]	+ [27,29,40]
Low albumin	+ [27,31,35]	+ [27,29,30]
Increased comorbidities		+ [27,28,29,30,32]
Weight loss	+ [27]	+ [27]
Poor vision		+ [27,29,30,43]
Impaired hearing		+ [29,30,34]
Diabetes mellitus	+ [31,35]	+ [41]
Acute Kidney injury III	+ [44]	+ [29,37]
Frailty		+ [27,29,30 ,41, A]
Precipitating risk factors		
Electrolyte imbalance	+ [26]	+ [29,30,32,40]
Hypo/hyperglycemia		+ [32,40]
Hypoxia/hypoxemia	+ [45]	+ [29]
Hyperoxia	+ [o2]	
Dehydration		+ [28,30,32]
Duration of surgery/duration of CPB	+ [ 25,31,35, 45]	+ [32]
Type of surgery (emergency)	+ [ 25,29,35, 39]	+ [28,29,33]
Prolonged intubation	+ [ 25,30]	
Red blood cell transfusion	+ [25,27,31,35 ]	
Elevation of inflammatory markers	+ [ 25,35]	
Plasma cortisol level	+ [ 25,]	+ [28]
Postoperative complications: infection, cardiogenic shock, pneumonia, and low output syndrome, respiratory failure, sepsis, AKI	+ [25, 26,31,35 , 39]	+ [32]
Increased aortic clamping time	+ [ 25,29]	
Intraaortic balloon pump after cardiac surgery	+ [ 25,31,35,39]	
Non-transfemoral approach (TAVR	+ [22]	
Pain	+ [9,27]	+ [27,28,29,32]
Hypothermia	+ [6, 39]	+ [30]
Urinary catheterization		+ [28,29,30,38]
Immobilization		+ [28,32]
Sleep deprivation	+ [46]	+ [28,32, ,43]

The presence of several risk factors considerably increases the risk of development of postoperative delirium. Considering the review of the risk factors we made (Table 1), the risk factors for development of postoperative delirium in open cardiac surgery patients can be clearly differentiated.

**Atrial fibrillation:** Increased risk of delirium in patients with atrial fibrillation can be explained with impairment of the cerebral circulation as a result of a lower cardiac output and increased risk of embolic complications. **Arterial hypertension:** A connection has been established between hypertension and the increased risk of postoperative delirium after CABG. Systemic arterial pressure outside the limits of autoregulation may lead to changes in the tissue perfusion followed by injury of the tissues. Also, atherosclerotic changes and embolism may be the result of systemic hypertension. It is independently related to a MR finding of presence of changes in the white matter. In turn, they are related to impairment of the cognitive function.

**Increased cardiothoracic ratio:** The increased cardiothoracic ratio is an indirect symptom of heart failure. Heart failure may cause brain injury, primary from cerebral ischaemia (low output syndrome) or secondary due to pulmonary or liver congestion. Cognitive deficits are independently related to stagnant heart insufficiency [31].

The type of surgery, whether elective or emergency, is also important. The risks are much higher in case of emergency surgical interventions. Patients undergoing valve surgery with or without Coronary artery bypass grafting (CABG) operation have a greater incidence of postoperative delirium and cognitive dysfunction one week after the surgery compared with patients undergoing CABG surgery alone. The presence of open heart cavities in valve surgery and the increasing of the risk of micro and macroembolism are the reason for the increased incidence of delirium and deterioration of the cognitive functions in plastic surgery and

valve replacement patients [38]. In patients with single-stage replacement of both the mitral and aortic valves the risk of POD increases significantly up to 90% [39]. With regard to the surgical intervention, whether with or without cardiopulmonary bypass, there is no difference in the frequency of POD development.

After longer surgical procedures with considerably increased aortic cross-clamp time patients need more time to warm up after hypothermia. This increases the demand for i.v. application of propofol, protracting of the period of artificial pulmonary ventilation of the patient, which may increase the incidence of postoperative delirium [9]. Intraoperative heat loss is common and is associated with coagulation dysfunction, and a myriad of cardiovascular and immunological changes. According to a cardiac surgery patient study, in patients with hypothermia (<35°C), the frequency of postoperative delirium is higher [6].

Out of the haemodynamic parameters a low cardiac output and use of an intra-aortic balloon pump (IABP) and/or inotropic medication seem to be risk factors associated with a postoperative delirium. It seems that there is a correlation between delirium and severity of heart failure during the postoperative period [31].

Sudden change in the mean arterial pressure during CPB within the scope of cerebral autoregulation is associated with severe injury of the kidneys and increased morbidity and mortality. Arterial pressure below the optimum levels of autoregulation of the cerebral circulation after a cardiac surgery is associated with evidence of brain injury measured by the sensitive biomarker for brain injury glial fibrillary acidic protein. It has been established that the duration of the period when the blood pressure is higher than the upper limit of autoregulation of the cerebral circulation during CPB is associated with postoperative delirium. Some conditions present with cerebral hyperperfusion, including after carotid endarterectomy, where the cerebral hyperperfusion is associated with cerebral edema, delirium and intracerebral haemorrhage. Increased blood pressure under impaired autoregulation increases the cerebral circulation, which results in fluid transudation in the pericapillary astrocytes and the brain interstitium. This leads to vasogenic edema of the white matter, especially in the vertebrobasilar circulation and the territory of the posterior parietal and occipital regions. Cerebral hyperperfusion due to impaired autoregulation is the mechanism of delirium occurring in non-surgery patients with acute hypertonic emergency conditions [47].

Blood loss is also of critical importance for the forecast of patients after cardiac surgery. The presence of hyperperfusion due to loss of intravascular volume may lead to delirium. The RBC concentrates are associated with reduced RBC deformability and increased affinity to oxygen as well as increased release of nitrogen oxide. This in turn causes lowering of oxygenation of the tissue and vasodilation, leading to increased infections. Loss of blood and volume may indirectly lead to delirium by redistribution of the volume and hemodilution (Hct24%) [26]. The intraoperative values of hematocrit during CPB (especially values under 22-23%) are associated with increased brain

injury [48]. Low postoperative hematocrit <30% is also found in patients with delirium [31].

It has been established that in patients with lower preoperative brain saturation or intraoperative brain saturation <50% the risk of development of delirium is increased. Another study demonstrates that intraoperative variations of mean arterial pressure above the upper cerebral autoregulation limit during CPB are associated with a risk of delirium [49].

In elderly cardiac surgery patients POD is associated with absolute decrease of regional cerebral oxygen saturation (SctO<sub>2</sub>), despite the known risk factors. It has been established that patients with POD have had lower SctO<sub>2</sub> values after admission to ICU. Patients with POD more often present with longer cerebral desaturations below the absolute values as compared with the preoperative baseline [50].

Postoperative hypoxemia (PaO<sub>2</sub><60mmHg) is frequent after cardiac surgery and is an independent risk factor for POD development [45]. One of the major roles of the anaesthesiologist during a cardiac surgery is to prevent cellular hypoxia and high oxygen concentrations are often used. On the other side, hyperoxia (PaO<sub>2</sub> ≥ 26.6 kPa) during CPB is a risk factor for POD development. The risk of POD development increases further when after a hypoxia episode long hyperoxia occurs.

Fluid overload may lead to venous hypertension, especially in case of right ventricular dysfunction. Venous hypertension leads to decline in arteriovenous difference in the pressure and may cause interstitial edema [52]. Venous congestion may be responsible for organic dysfunction – for example kidney, liver, lung. It is possible for the venous congestion to affect brain function in some cases, especially in case of heart dysfunction. In critically ill patients the positive fluid balance is an independent risk factor for delirium [53]. This is described in the paper by Akira Ouchi et al., which reviews the link between fluid overload and acute brain dysfunction in patients on mechanical ventilation [54]. Venous congestion is associated with development of encephalopathy and development of delirium [55].

Sternotomy causes strong pain after cardiac surgery. Strong postoperative pain in combination with high levels of opioids is associated with an increased risk of postoperative delirium. Strong pain at rest is a risk factor for POD development [56].

With regard to intraoperative variables, the long duration of CPB, low MAP, low Hg level, hypothermia, high need of noradrenalin and RBC concentrate and platelet transfusion constitute significant intraoperative factors for postoperative delirium [57].

Insufficient sleep is frequent in ICU, which leads to neuropsychological and cognitive impairment. ICU patients demonstrate increase of sleep stages 1 and 2, co-occurring with frequent arousal and awakening. Besides, it is less probable for them to reach stage 3/ slow-wave sleep or REM sleep stage [58, 59]. It is considered that disturbed sleep is a risk factor for delirium in ICU. According to 2018 2018



Clinical Practice Guidelines for Pain, Agitation, and Delirium (PAD), from the Society of Critical Care Medicine it is recommended to use a multicomponent protocol for fostering sleep in severely ill adults based on the summarized analysis of three studies, showing complete decline in the delirium distribution with the application of sleep-enhancement interventions [60, 61]. The circadian rhythm is in many cases disturbed in ICU patients, especially after cardiac surgery. It is hypothesized that the disturbed rhythm is a risk factor for the development of postoperative delirium. A distinctive feature of delirium is the reduced activity of the ascending reticular activating system (ARAS): a neuronal network in the brain stem, which controls the states of awakening, sleep and dreaming by means of connections with suprachiasmatic nucleus and releasing of acetylcholine during the active phase of the individual. In delirium, due to transient hypoxic states, the depletion of acetylcholinergic projections and the dopaminergic overproduction from the ARAS result in alertness and attention disturbances [43].

Pisani et al. demonstrate that acute changes in renal function, diagnosed as an admissible level of creatinine above than 2 mg / dL, are associated with the development of delirium in ICU [62]. Most of the cardiac surgeries are made with CPB, which leads to impairment of the renal function. A possible correlation between the occurrence of a severe injury of the kidneys during the perioperative period or the necessity of continuous renal replacement therapy (haemofiltration) and the occurrence of postoperative delirium in cardiac surgery patients may be attributed to the CPB effect. Ischaemic acute renal failure may lead to brain injury. The underlying pathophysiology of such comorbid neurological disorders in kidney disease is governed by shared anatomic and vasoregulatory systems and humoral and non-humoral bidirectional pathways that affect both the kidney and the brain. During acute kidney injury, the brain and kidney might interact through numerous mechanisms: amplification of cytokine-induced damage, extravasation of leukocytes, oxidative stress, and dysregulation of sodium, potassium, and water channels. A large observational study of Katarzyna Kotfis et al. provides data that acute kidney injury based on AKI staging should be regarded as an important and independent risk factor for postoperative delirium after cardiac surgery [44]. It has been established that there are several cardiovascular medicinal agents associated with delirium, including procainamide, metoprolol, lidocaine, amiodarone and digoxin (reports about clinical cases requiring more confirmation). Lidocaine is associated with a range of psychiatric reactions and is often administered by cardioanaesthesiologists and cardiologists as a continuous infusion [63]. It has been established that the low values of brain saturation and middle cerebral artery-CBFV are found in patients with delirium [64].

## 5. Types of delirium and clinical picture

Delirium (also called acute confusional state) is a complex neuropsychiatric syndrome with an acute change or a variable course of the psychic condition. It is characterized by disturbed attention, disorganized or inconsistent thought and variable level of consciousness (arousal or drowsiness). It usually occurs in adult patients admitted to ICU (65).

All medical specialists must be familiar with the clinical picture of POD to easily identify and manage it. POD usually develops on postoperative day 1 through 3 [66]. Lipowski was the first to categorize delirium on the ground of the psychomotor presentation, suggesting the terms “hyperalert-hyperactive” and “hypoallergic-hypoactive”, adding a mixed phenotype later [67]. Hyperactive delirium – it is characteristic by apparent excitement, excessive arousal, excessive alertness, irritability, anxiety, combativity, fast or loud speaking, singing, cursing, laughter, quick movements, hallucinations, impatience, anger, uncooperativeness, absent-mindedness, easily startling, nightmares or tenacious thoughts, frequently associated with life danger, autonomous instability [29]. Patients with hyperactive delirium frequently obtain the biggest clinical focus in the intensive care unit, due to their destructive behaviour and in some cases the danger they pose for themselves by removing cannulas, catheters and monitors. Patients with hypoactive delirium are less likely to attract attention to in them and the diagnosis of delirium may be fully omitted, unless an active screening is made, because such patients do not have destructive behaviour [68]. Hypoactive delirium – patients withdraw into themselves, they are quiet, subconscious, apparently lethargic or apathetic, weaker alertness, gaze, psychomotor delay, slow movements, absent or slow speech [29]. Patients with hypoactive delirium may suffer from fear or strong emotions. Patients with this type of delirium much often do not remember these periods from the hospital stay [30]. Mixed type, in which the patients frequently fall between the hyperactive and hypoactive extremities, sometimes swaying from one to the other extremity within minutes [29].

In the intensive care unit the level of agitation of the patient is frequently determined according to a scale for sedation evaluation – Richmond Agitation - Sedation Scale (RASS) [69]. RASS was initially designed as a tool to monitor the medications sedation in the intensive care unit. RASS may however be used for patients, who are not pharmacologically sedated as evaluation of their level of agitation. RASS may include the following criteria numbered between -5 and +4: unarousable; deep sedation; moderate sedation; light sedation; drowsy, alert and calm; restless; agitated; very agitated; combative [70].

## 6. Clinical phenotypes

Currently five clinical phenotypes of delirium are identified: Hypoxic, septic, sedative-associated, metabolic and unclassified, with the corresponding frequency 71%, 56%, 51%, 64%, 25% and 22% [71]. Hypoxic delirium is defined as delirium co-occurring with hypoxemia or shock. Hypoxemia is defined as two or more intervals of 15 minutes, during which the lowest level of oxygen saturation in blood is <90% and shock is defined as lactate > 4.4 mmol/l or two or more intervals of 15 minutes, during which the lowest median arterial pressure is < 65 mmHg [71]. Septic delirium is defined as delirium in the presence of a known or suspected infection and  $\geq 2$  criteria of a syndrome of systemic inflammatory response (SIRS) [71]. Sepsis-associated delirium is a cerebral manifestation, often found in patients with other organ dysfunctions related to infections and is caused by a combination of neuroinflammation and disorders of the cerebral perfusion [72]. Sedative-associated

delirium is defined as delirium in the course of administration of at least of one of the following frequently used medicines: Benzodiazepines, propofol, opioids and/or dexmedetomidine [71]. Sedative-associated delirium is divided into two types: rapidly reversible and persistent delirium. The rapidly reversible is defined as delirium which declines soon after sedative interruption, while the persistent continues after stopping of the inducing medications [73]. Metabolic delirium is defined as delirium co-occurring with any of the following metabolic disorders, which constitute renal or liver failure: Blood urea > 17,85 mmol / L, glucose <2,5 mmol / L, INR > 2,5, aspartate transaminase or alanine transaminase > 200 U / L, sodium <120 mmol / L and potassium > 160 mmol / L [71]. Unclassified delirium - a type of delirium which develops in the absence of hypoxia, sepsis, sedation or metabolic disorder.

## 7. Delirium assessment

Several instruments have been developed for fast diagnosis of delirium in the intensive care unit; most used and best validated are Confusion Assessment Method for the intensive care unit (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) [74, 75].

The most used instrument for screening in the studies is the Confusion Assessment Method (CAM). CAM demonstrated high sensitivity and specificity (between 90 and 100%). There are several CAM forms, including the long form, which contains 10 sections, and the short one, which contains 4. The long form is used in the studies and the short is frequently used and the clinical practice. The short form deals with four domains - acuteness/fluctuation, attention, thinking and level of consciousness. As compared with other screening instruments, CAM is the best factor to predict increase increased stay and mortality. CAM benefits from the best evidence of its usefulness and usually may be completed in 5 minutes [27]. The fast screening with the confusion assessment method in the intensive care units established high proliferation of delirium (even in young patients) and is associated with high levels of mortality rate [65]. ICDSC is a checklist with 8 elements. Eight diagnostic criteria are included: altered level of consciousness, inattention, disorientation, hallucination or delusion, psychomotor agitation or retardation, inappropriate mood or speech, sleep/wake cycle disturbance, and symptom fluctuation [75].

## 8. Discussion

Hart writes: "Of the precise processes by which delirium is mediated we know nothing. In discussing at the present time the possible pathogenesis of delirium, we have therefore to leave the sphere of knowledge and enter that of hypothesis and speculation" [76]. Patients who have developed POD after cardiac surgery present with a prolonged ICU stay, extended time on mechanical ventilation, extended hospital stay, high in-hospital mortality rate and cognitive disorders [77]. POD in cardiac surgery patients is even today a challenge to identify and manage. Knowing the risk factors arising from the specificities of cardiac surgery, we can considerably lower its presence in intensive care units. There are several specific risk factors and actions in cardiac

anaesthesia that may call attention of the ICU specialists for the purpose of POD reduction.

## 9. Conclusion

Postoperative delirium after open cardiac surgery is frequent and definitely deserves attention. Postoperative delirium depends on many factors. Identifying the clinical risk factors and the potential major reasons for delirium will facilitate the choice of therapy and forecast of the results, as well as to prevent the complications associated with the development of this multicomplex phenomenon.

The authors declare that they have not received funding for this work.

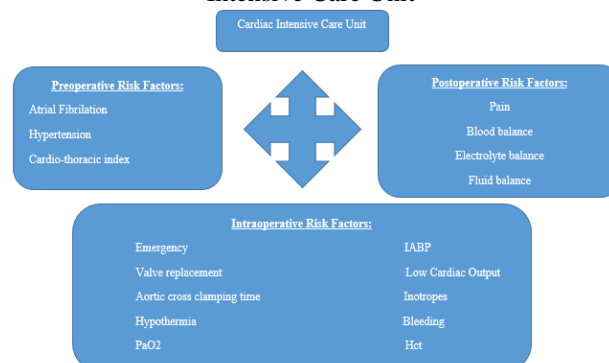
The authors declare that there is no conflict of interest.

## Author Profile



**Boryana Mihalkova MD** graduated with honors medicine at Medical University –Sofia in January 2018. She has been part of anesthesiologists in National Heart Hospital since August 2018. She has been a resident in anesthesiology and intensive care unit since March 2019. She is interested in studying etiology and preventing postoperative delirium development after major cardiac surgery.

**Table 2:** Risk factors for delirium development in Cardiac Intensive Care Unit



## References

- [1] ROBERT M. MORSE, M.D., AND EDWARD M. LITIN, M.D, Postoperative Delirium: A Study of Etiologic Factors
- [2] Karin J. Neufeld and Christine Thomas, Delirium: Definition, Epidemiology, and Diagnosis
- [3] Organization WH. International Statistical Classification of Diseases and Related Health Problems (ICD). Available online: <http://apps.who.int/classifications/icd10/browse/2010/en>
- [4] The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer, European Delirium Association\* and American Delirium Society
- [5] Christopher G. Hughes • Pratik P. PandharipandeE. Wesley Ely, DeliriumAcute Brain Dysfunction in the Critically Ill

- [6] Zhaosheng Jin<sup>1</sup>, Jie Hu<sup>2</sup> and Daqing Ma<sup>1\*</sup>, Postoperative delirium: perioperative assessment, risk reduction, and management; *British Journal of Anaesthesia*, 125 (4): 492e504 (2020)
- [7] José R. Maldonado, Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure
- [8] Katarzyna Kotfis<sup>1</sup>, Justyna Szłowska<sup>1</sup>, Krzysztof Safranow<sup>2</sup>, Aleksandra Szylińska<sup>3,\*</sup>, and Mariusz Listewnik<sup>4</sup>, The Practical Use of White Cell Inflammatory Biomarkers in Prediction of Postoperative Delirium after Cardiac Surgery
- [9] Kati Järvelä, Helena Porkkala, Sari Karlsson, Tero Martikainen, Tuomas Selander and Stepani Bendel, Postoperative Delirium in Cardiac Surgery Patients, *Journal of Cardiothoracic and Vascular Anesthesia*, doi:10.1053/j.jvca.2017.12.030
- [10] Adam EH, Haas V, Lindau S, et al. Cholinesterase alterations in delirium after cardiac surgery: a German monocentric prospective study. *BMJ Open* 2020; 10:e031212. doi:10.1136/bmjopen-2019-031212
- [11] Maldonado JR.: Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry* 2013; 21:1190–222
- [12] Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis of delirium: a synthesis of current evidence. *J Gerontol Biol Sci Med Sci* 2008; 63:764–72.
- [13] Berr C, Balansard B, Arnaud J, Roussel AM, Alperovitch A. Cognitive decline is associated with systemic oxidative stress: the EVA study. *Etude du Vieillessement Arteriel. J Am Geriatr Soc.* 2000; 48(10):1285-1291.
- [14] Marcos G. Lopez, M.D., M.S., Christopher G. Hughes, M.D., M.S., Anthony DeMatteo, B.S., Jason B. O'Neal, M.D., J. Brennan McNeil, B.S., Matthew S. Shotwell, Ph.D., Jennifer Morse, M.S., Michael R. Petracek, M.D., Ashish S. Shah, M.D., Nancy J. Brown, M.D., Frederic T. Billings IV, M.D., M.Sc., Intraoperative Oxidative Damage and Delirium after Cardiac Surgery *Anesthesiology* 2019; XXX:00–00
- [15] Oliver CN, Starke-Reed PE, Stadtman ER, Liu GJ, Carney JM, Floyd RA: Oxidative damage to brain proteins, loss of glutamine synthetase activity, and production of free radicals during ischemia/reperfusion-induced injury to gerbil brain. *Proc Natl Acad Sci U S A* 1990; 87:5144–7
- [16] Lopez MG, Pandharipande P, Morse J, Shotwell MS, Milne GL, Pretorius M, Shaw AD, Roberts LJ 2nd, Billings FT 4th: Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. *Free Radic Biol Med* 2017; 103:192–8
- [17] Trzepacz, PT.; van der Mast, R. *The Neuropathophysiology of Delirium.* Oxford: Oxford University Press; 2002.
- [18] Kudoh A, Takase H, Katagai H, Takazawa T. Postoperative interleukin-6 and cortisol concentrations in elderly patients with postoperative confusion. *Neuroimmunomodulation.* 2005; 12:60–66. [PubMed: 15756054]
- [19] McIntosh TK, et al. Beta-endorphin, cortisol and postoperative delirium: a preliminary report. *Psychoneuroendocrinology.* 1985; 10:303–313. [PubMed: 2932761]
- [20] Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med.* 1999; 340(9):669–676. [PubMed: 10053175]
- [21] Inouye SK, Charpentier PA: Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996; 275:852–857.
- [22] Inouye SK. Delirium in older persons [published correction appears in *N Engl J Med.* 2006; 354(15):1655]. *N Engl J Med.* 2006; 354(11):1157–1165
- [23] Inouye SK. Delirium in hospitalized older patients: recognition and risk factors. *J Geriatr Psychiatry Neurol.* 1998; 11(3):118–125.
- [24] Jason B. O'Neal\* and Andrew D. Shaw, Predicting, preventing, and identifying delirium after cardiac surgery, O'Neal and Shaw *Perioperative Medicine* (2016) 5:7 DOI 10.1186/s13741-016-0032-5
- [25] Yiyun Lin, M.D., Jian Chen, M.D., and Zhinong Wang, M.D., Meta-Analysis of Factors Which Influence Delirium Following Cardiac Surgery
- [26] Franklin Santana Santos, I, Irineu Tadeu Velasco and Ren'erio Fr'aguas Jr 2, **Risk factors for delirium in the elderly after coronary artery bypass graft surgery**, *International Psychogeriatrics* (2004), 16:2, 175–193 C \_ 2004 International Psychogeriatric Association DOI: 10.1017/S1041610204000365
- [27] Jessica Cunningham, Luke Dogyun Kim, Post-operative delirium: a review of diagnosis and treatment strategies, doi:10.21037/jxym.2018.01.03
- [28] Tamara G. Fong, Samir R. Tulebaev, and Sharon K. Inouye, Delirium in elderly adults: diagnosis, prevention and treatment, *Nat Rev Neurol.* 2009 April ; 5(4): 210–220. doi:10.1038/nrneurol.2009.24.
- [29] Siddareddygari Velayudha Reddy, Jawaharlal Narayana Iral, Ananthapuram Srinivasamurthy, Postoperative delirium in elderly citizens and current practice
- [30] Christian Hosker, David Ward, Hypoactive delirium, *BMJ* 2017; 357:j2047 doi: 10.1136/bmj.j2047
- [31] Sandra Koster a,\*, Ab G. Hensens a, Marieke J. Schuurmans b,c, and Job van der Palen d,e, Risk factors of delirium after cardiac surgery: A systematic review, *European Journal of Cardiovascular Nursing* 10 (2011) 197–204
- [32] Bedrettin Yıldızeli, MD, M. Oguzhan Özyurtkan, MD, Hasan F. Batirel, MD, Kemal Kuscu, MD, Nural Bekiroglu, PhD, and Mustafa Yüksel, MD, Factors Associated With Postoperative Delirium After Thoracic Surgery, *Ann Thorac Surg YILDIZELI* 2005; 79:1004–9
- [33] Saljuqi AT, Hanna K, Asmar S, Tang A, Zeeshan M, Gries L, Ditillo M, Kulvatunyou N, Castanon L, Joseph B, Prospective Evaluation of Delirium in Geriatric Patients Undergoing Emergency General Surgery, *Journal of the American College of Surgeons* (2020), doi: <https://doi.org/10.1016/j.jamcollsurg.2020.01.029>
- [34] Tammy T. Hshieh, MD, MPH a,\*, Sharon K. Inouye, MD, MPH b, Esther S. Oh, MD, PhD c, Delirium in the Elderly
- [35] Matthew D. Russell, BS\*, Carolyn Pinkerton, MD\*, Katherine A. Sherman, MS, Thomas J. Ebert, MD,



- PhD\*, Paul S. Pagel, MD, PhD\*,1, Predisposing and Precipitating Factors Associated With Postoperative Delirium in Patients Undergoing Cardiac Surgery at a Veterans Affairs Medical Center: A Pilot Retrospective Analysis
- [36] Wilson JE, Ely EW, Delirium in the ICU, Qatar Medical Journal, Qatar Critical Care conference, 2019:31, <http://dx.doi.org/10.5339/qmj.2019.qcc.31>
- [37] RYY Wan, Ms. MRes a,\*, CA McKenzie, PhD b, e, D Taylor, PhD b, c, L Camporota, PhD d, M Ostermann, PhD d, Acute kidney injury as a risk factor of hyperactive delirium: A case control study
- [38] Judith A. Hudetz, PhD, Zafar Iqbal, MD, Sweeta D. Gandhi, MD, Kathleen M. Patterson, PhD, Alison J. Byrne, PhD, and Paul S. Pagel, MD, PhD, Postoperative Delirium and Short-term Cognitive Dysfunction Occur More Frequently in Patients Undergoing Valve Surgery With or Without Coronary Artery Bypass Graft Surgery Compared With Coronary Artery Bypass Graft Surgery Alone: Results of a Pilot Study
- [39] Evans AS, Weiner MM, Arora RC, Chung I, Deshpande R, Varghese R, et al. Current approach to diagnosis and treatment of delirium after cardiac surgery. *Ann Card Anaesth* 2016;19:328-37.
- [40] Thomas N. Robinson, Ben Eiseman, Postoperative delirium in the elderly: diagnosis and management, *Clinical Interventions in Aging* 2008;3 (2) 351-355
- [41] Rengel KF, et al. Postoperative delirium. *Presse Med.* (2018), <https://doi.org/10.1016/j.lpm.2018.03.012>
- [42] Arissara Iamaroon<sup>1</sup>, Titima Wongviriyawong<sup>2</sup>, Patumporn Sura-arunsumrit<sup>2</sup>, Nattikan Wiwatnodom<sup>1</sup>, Nichakarn Rewuri<sup>1</sup> and Onuma Chaiwat<sup>1,3</sup>, Incidence of and risk factors for postoperative delirium in older adult patients undergoing noncardiac surgery: a prospective study, Iamaroon et al. *BMC Geriatrics* (2020) 20:40 <https://doi.org/10.1186/s12877-020-1449-8>
- [43] Daou M, Telias I, Younes M, Brochard L and Wilcox ME (2020) Abnormal Sleep, Circadian Rhythm Disruption, and Delirium in the ICU: Are They Related? *Front. Neurol.* 11:549908. doi: 10.3389/fneur.2020.549908
- [44] Katarzyna Kotfis<sup>1,\*</sup>, Justyna Szlozowska<sup>1</sup>, Mariusz Listewnik<sup>2</sup>, Aleksandra Szylińska<sup>3</sup> and Iwona Rotter<sup>3</sup>, Article The Impact of Acute Kidney Injury in the Perioperative Period on the Incidence of Postoperative Delirium in Patients Undergoing Coronary Artery Bypass Grafting—Observational Cohort Study, *Int. J. Environ. Res. Public Health* 2020, 17, 1440
- [45] Yanjuan Lin<sup>1\*†</sup>, Qiong Chen<sup>2†</sup>, Haoruo Zhang<sup>3</sup>, Liang-Wan Chen<sup>4\*</sup>, Yanchun Peng<sup>4</sup>, Xizhen Huang<sup>4</sup>, Yiping Chen<sup>2</sup>, Sailan Li<sup>4</sup> and Lingyu Lin<sup>2</sup>, Risk factors for postoperative delirium in patients with triple-branched stent graft implantation, Lin et al. *Journal of Cardiothoracic Surgery* (2020) 15:171 <https://doi.org/10.1186/s13019-020-01217-9>
- [46] Pagad S, Somagutta M R, May V, et al. (August 28, 2020) Delirium in Cardiac Intensive Care Unit. *Cureus* 12(8): e10096. DOI 10.7759/cureus.10096
- [47] Daijiro Hori, Laura Max, Andrew Laflam, Charles Brown, Karin Neufeld, Hideo Adachi, Christopher Sciortino, John Conte, Duke Cameron, Charles Hogue and Kaushik Mandal, Blood Pressure Deviations from Optimal Mean Arterial Pressure during Cardiac Surgery Measured with a Novel Monitor of Cerebral Blood Flow and Risk for Perioperative Delirium: A Pilot Study, *Journal of Cardiothoracic and Vascular Anesthesia*, <http://dx.doi.org/10.1053/j.jvca.2016.01.012>
- [48] Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijeyesundera D, et al. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. *Ann Thorac Surg* 2005;80:1381-7
- [49] Hori D, Brown C, Ono M, Rappold T, Sieber F, Gottschalk A, et al. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. *Br J Anaesth* 2014;113:1009-17.
- [50] Ward Eertmans<sup>1,2,\*</sup>, Cathy De Deyne<sup>1,2</sup>, Cornelia Genbrugge<sup>1,2</sup>, Berend Marcus<sup>2</sup>, Sofian Bouneib<sup>2</sup>, Maud Beran<sup>2</sup>, Tom Fret<sup>2</sup>, Herbert Gutermann<sup>3</sup>, Willem Boer<sup>2</sup>, Margot Vander Laenen<sup>2</sup>,
- [51] Ren\_e Heylen<sup>2</sup>, Dieter Mesotten<sup>1,2</sup>, Pascal Vanelderden<sup>1,2</sup> and Frank Jans<sup>1,2</sup>, Association between postoperative delirium and postoperative cerebral oxygen desaturation in older patients after cardiac surgery, *British Journal of Anaesthesia*, 124 (2): 146e153 (2020), doi: 10.1016/j.bja.2019.09.042
- [52] Anna Kupiec<sup>1</sup>, Barbara Adamik<sup>1</sup>, Katarzyna Forkasiewicz-Gardynik<sup>1</sup>, Waldemar Goździk<sup>1</sup>, Intraoperative hyperoxia and the risk of delirium in elderly patients after cardiac surgery, *AGING* 2020, Vol. 12, No. 8
- [53] Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. *Nat Rev Nephrol* 2010;6:107-15.
- [54] Nguyen DN, Huyghens L, Parra J, et al. Hypotension and a positive fluid balance are associated with delirium in patients with shock. *PloS One* 2018;13:e0200495
- [55] Akira Ouchi<sup>1</sup>, Hideaki Sakuramoto<sup>2</sup>, Haruhiko Hoshino<sup>1</sup>, Yujiro Matsuishi<sup>1</sup>, Tatsuya Sakaguchi<sup>3</sup>, Yuki Enomoto<sup>1</sup>, Tetsuya Hoshino<sup>1</sup>, Nobutake Shimojo<sup>1</sup> and Yoshiaki Inoue, Association between fluid overload and delirium/coma in mechanically ventilated patients, *Acute Medicine & Surgery* 2020;7:e508, doi: 10.1002/ams2.508
- [56] Aymen Benkreira, MD, a William Beaubien-Souligny, MD, a Tanya Mailhot, RN, PhD, b, c Nadia Bouabdallaoui, MD, d Pierre Robillard, MD, e Georges Desjardins, MD, a
- [57] Yoan Lamarche, MD, MSc, f Sylvie Cossette, PhD, b, c and Andr\_e Denault, MD, PhD, a, Portal Hypertension Is Associated With Congestive
- [58] Encephalopathy and Delirium After Cardiac Surgery, *Canadian Journal of Cardiology* 35 (2019) 1134e1141
- [59] Eileen P. Lynch, MD\*, Marissa A Lazor, MD\*, Janice E. Gellis, MDS, John Orav, PhD,
- [60] Lee Goldman, MD, MPH, and Edward R. Marcantonio, MD, SM, The Impact of Postoperative Pain on the Development of Postoperative Delirium. *Anesth Analg* (1998;86:781-5)
- [61] Alain Rudiger<sup>1\*</sup>, Hülya Begdeda<sup>1</sup>, Daniela Babic<sup>1</sup>, Bernard Krüger<sup>1</sup>, Burkhardt Seifert<sup>2</sup>, Maria Schubert<sup>3,4</sup>, Donat R. Spahn<sup>5</sup> and Dominique Bettex<sup>1</sup>,



- Intra-operative events during cardiac surgery are risk factors for the development of delirium in the ICU
- [63] Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med.* (2001) 163:451–1 doi: 10.1164/ajrccm.163.2.9912128
- [64] Gabor JY, Cooper AB, Crombach SA, Lee B, Kadikar N, Bettger HE, et al. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med.* (2003) 167:708–15. doi: 10.1164/rccm.2201090
- [65] Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* (2018) 46:e825–73. doi: 10.1097/CCM.0000000000003299
- [66] Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Executive summary: clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* (2018) 46:1532–48. doi: 10.1097/CCM.0000000000003259
- [67] Pisani, M.A.; Murphy, T.E.; Van Ness, P.H.; Araujo, K.L.; Inouye, S.K. Characteristics associated with delirium in older patients in a medical intensive care unit. *Arch. Intern. Med.* **2007**, 167, 1629–1634.
- [68] Khalil Ibrahim, MD;\* Cian P. McCarthy, MB, BCh, BAO;\* Killian J. McCarthy, MB, BCh, BAO; Charles H. Brown, MD; Dale M. Needham, MD, PhD; James L. Januzzi, Jr, MD; John W. McEvoy, MB, BCh, MHS, Delirium in the Cardiac Intensive Care Unit, American Journal of the American Heart Association, DOI: 10.1161/JAHA.118.008568
- [69] Bernardi MH, Wahrman M, Dworschak M, Kietabl C, Ristl R, Edlinger-Stanger M, Lassnigg A, Hiesmayr MJ, Weber U. Carotid artery blood flow velocities during open-heart surgery and its association with delirium: A prospective, observational pilot study. *Medicine* 2019; 98:50(e18234).
- [70] S Pal, N Sharma, S M Singh, S Kumar, A K Pannu, A prospective cohort study on predictors of mortality of delirium in an emergency observational unit, *QJM: An International Journal of Medicine*, , hcaa183, <https://doi.org/10.1093/qjmed/hcaa183>
- [71] Clinical Practice Guideline for Postoperative Delirium in Older Adults. The American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults., *JAGS* 63:142–150, 2015 Available from: [http://www.geriatricscareonline.org/toc/postoperative\\_delirium/CL018](http://www.geriatricscareonline.org/toc/postoperative_delirium/CL018).
- [72] L. Ansaloni<sup>1</sup>, F. Catenal<sup>1</sup>, R. Chattat<sup>3</sup>, D. Fortuna<sup>5</sup>, C. Franceschi<sup>4</sup>, P. Mascitti<sup>2</sup> and R. M. Melotti<sup>2,3</sup>, Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery, *British Journal of Surgery* 2010; 97: 273–280
- [73] Christina J. Hayhurst, Bret D. Alvis, and Timothy D. Girard Monitoring for Delirium in Critically Ill Adults © Springer Nature Switzerland AG 2020 C. G. Hughes et al. (eds.), *Delirium*, [https://doi.org/10.1007/978-3-030-257514\\_1](https://doi.org/10.1007/978-3-030-257514_1)
- [74] Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002;166(10):1338–44
- [75] Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA.* 2003;289(22):2983–91.
- [76] Girard TD, Thompson JL, Pandharipande PP, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *Lancet Respir Med.* 2018;6(3):213–22.
- [77] Ben Atterton 1, Maria Carolina Paulino 2, Pedro Povoá 2,3,4 and Ignacio Martin-Loeches, Sepsis Associated Delirium, *Medicina* 2020, 56, 240; doi:10.3390/medicina56050240
- [78] Patel SB, Poston JT, Pohlman A, Hall JB, Kress JP. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. *Am J Respir Crit Care Med.* 2014;189(6):658–65.
- [79] Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA.* 2001;286(21):2703–10.
- [80] Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive care Delirium screening checklist: evaluation of a new screening tool. *Intensive Care Med.* 2001;27(5):859–64.
- [81] Hart B: Delirious states. *Br Med J*(70, p. 747) -1936g. 2:745-749, 1936
- [82] Marina Pieri MD, Alessia De Simone , Silvia Rose, Pierfrancesco De Domenico MD , Rosalba Lembo MSc , Giuseppe Denaro MD, Giovanni Landoni MD, Professor , Fabrizio Monaco MD , Trials focusing on prevention and treatment of delirium after cardiac surgery: a systematic review of randomized evidence., *Journal of Cardiothoracic and Vascular Anesthesia* (2019), doi: <https://doi.org/10.1053/j.jvca.2019.09.028>