CHAPTER 2

LITERATURE REVIEW

2.1 Postoperative Cognitive Dysfunction

Postoperative cognitive dysfunction is a condition of cognitive decline following an operation or surgery. The occurrence of cognitive decline is indicated by testing the patients before and after the surgery using specific neuropsychological tests. The differences in the pre and post-results of the neuropsychological test discriminate the state of cognitive function of the patients before the surgery and also an objective measure in determining the occurrence of POCD. According to the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) (Berger et al., 2018), POCD is not listed as one of the diseases related to mental condition. Even though the characteristic of POCD is similar to the diagnosis of other neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease, there are no definitive guidelines for diagnosing POCD. The closest definition would be a mild cognitive disorder (Czyż-Szypenbejl et al., 2019). Androsova (2015) describes POCD as a progressive decline in cognitive and sensory. The condition is related to DSM-5 guidelines number 294.10/11 'Major Neurocognitive Disorder Due to Another Medical Condition Without/With Behavioral Disturbance' or 331.83 'Mild Neurocognitive Disorder Due to Another Medical Condition' (Rudolph et al., 2009).

In another perspective, Evered et al. (2018) suggested that POCD was the extension of postoperative delirium. They lay out a time frame of postoperative cognitive disorder starting from emergence from anaesthesia in the recovery room, followed by delirium up to discharge from the hospital and POCD for months until years after surgery (Figure 2.1). Hence, the term 'perioperative neurocognitive disorders' is primarily used for cognitive impairment identified pre- or postoperative period. The nomenclature was discussed due to other definitions in the DSM-5 being used outside of surgery and anaesthesia. However, it is still recommended to be used for clinical purposes.

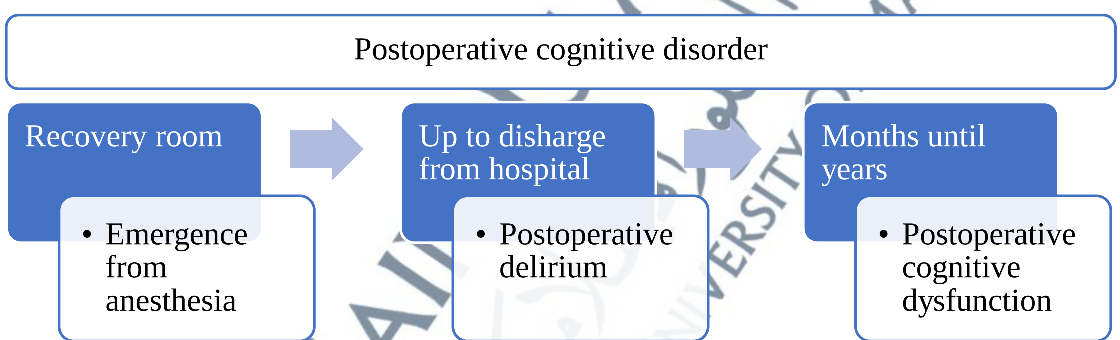

Figure 2.1: Timeframe of postoperative cognitive disorder, starting from the recovery room up to years after surgery.

The scarcity of defining and understanding the development of POCD has led researchers to come out with different definitions and criteria regarding POCD. To the extent of current knowledge, there is no definition of POCD that is universally established and accepted. In 1998, the International Study of Postoperative Cognitive Dysfunction (ISPOCD) group published papers about long-term POCD in the elderly conducted in 13 hospitals in 2 countries (Moller et al., 1998). The findings of the study have sparked the interest of researchers to explore more. Pappa et al. (2017) define POCD as the differences in neurocognitive patients' condition and behaviour that starts from weeks to months after the surgery. Rundshagen (2014), on the other hand, describes POCD as a newly arising cognitive impairment following a surgical procedure. In the same review, he elaborates on the differential diagnosis commonly used in differentiating POCD, postoperative delirium and postoperative neurological disturbance with impaired cognitive performances. Manifestation of POCD is the cognitive deficits that newly appear postoperatively that can be diagnosed by psychometric testing during pre- and postoperative. The condition starts immediately after surgery that lasts up to 6 months but is reversible. By having this differential diagnosis, the occurrence of POCD can be distinctly diagnosed and help clinicians and researchers to manage patients efficiently. The manifestation of POCD also agreed by Schenning et al. (2019), characterizes POCD as having an objective decline in cognition that is tested using a neuropsychological test battery pre- and postoperatively. Even though different definitions used by researchers, some authors agree that POCD are poorly defined, but the alarming situation still needs to be addressed well (Kotekar et al., 2018).

The variation of operational definitions makes diagnosing POCD harder, as the neuropsychological test used in each study differs. However, regardless of the variation of the test, what the test measures is important to ensure that most of the cognitive domains are covered.

2.2 Cognition

The term 'cognition' refers to internal mental representation that can be portrayed by ideas and thoughts (Allan, 2013). It is a mental process that involves multiple operations such as memory, reasoning, perception, judgment, intuition and problem-solving. These internal processes cannot be observed directly, hence researchers agreed to study them using scientific methods. As a result, various cognitive tests were developed to allow researchers to study cognition in detail. Cognitive function is described as the several different functions of this mental process. These functions are thought to be the components of the mind (Benjafield et al., 2010).

2.2.1 Cognitive Impairment

Cognitive impairment is a condition of reduced cognitive function in normal aging. It is also known as cognitive frailty, where cognitive decline and physical frailty occur simultaneously in older people without dementia (Jongsiriyanyong & Limpawattana, 2018). According to CDC (2011), cognitive impairment is defined as memory loss or confusion in the past year. The spectrum of cognitive impairment ranges from mild to severe, where mild cognitive impairment may result in loss of cognitive ability but ability to do daily activities. Whereas severe impairment may cause the person to lose the ability to live independently due to the inability to understand daily tasks.

Cognitive impairment and POCD can be differed by several means. POCD, in the first place, involves the insult of surgery that triggers cognitive decline, whereas cognitive impairment is a condition that occurs between normal ageing and dementia in older people (Jongsiriyanyong & Limpawattana, 2018). Secondly, the stages of cognitive impairment include mild, moderate and severe (CDC, 2011), while POCD is classified into early and late POCD. Early POCD were detected during the hospital stay, while late POCD were tested months and years after surgery (Evered et al., 2018).

2.2.2 Cognitive Domains

In clinical neuropsychology, characterization and classification of cognitive performance are typically based on the cognitive domains. Many subdomains lie under each domain. This subdomain is used in neuropsychological tests to measure discrete abilities (Lezak et al., 2012). The conceptualization of cognitive ability varies from grouping by general process, regional brain function, and hierarchical and operation complexity (Harvey, 2019). Typically, hierarchical and operation complexity often be used. The concept is that basic sensory and perceptional are the least complex operation, while executive functions like problem-solving and reasoning are the most complex (Al-Aidroos et al., 2012). Hence, it is easier for researchers to study cognition based on the domains related and be focus on each ability. Some cognitive function domains are sensation, perception, motor skills and construction, attention and concentration, memory, executive functioning, processing speed and language.

Sensation and perception are the simplest operations in cognition. The ability of a person to detect stimulus from one out of five sensory modalities is the definition of sensory. When the sensory information is processed and integrated, it becomes the perception that can be seen in the ability to recognize sounds and objects (Harvey, 2019). To test any deficits in these domains, structured recognition tests are available for each sensory such as the visual recognition test, auditory and olfactory recognition assessment.

Motor skills are another domain that involves fine motor abilities, manual dexterity, and speed, as in reaction time. The assessment in this domain is useful in identifying basic motor skills problems as it requires minimal cognitive demands, i.e. less instruction to be understood. Some of the most common tests for motor skills include finger tapping tests as well as simple and grooved pegboard tasks (Ashendorf et al., 2009). Construction, on the other hand, does include motor skills, as it is the ability to produce or copy drawings of common objects. Some authors classified it under perceptual and executive functioning (Lezak et al., 2012). Construction assessments are included in Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), as well as the clock drawing test.

Next, attention and concentration are another domain that is further subdivided into selective attention and sustained attention. Selective attention is when only relevant information is gathered while ignoring the nonrelevant information. This situation does applicable in daily life that is full of information yet able to select the right information needed. Hence, in a selective attention task, there will be distracting information given to the examinee, and they are required to attend to the relevant information only. In sustained attention, a person's attentiveness is usually tested by detecting a stimulus that appears infrequently over a period of time. This is called a continuous performance task (CPT). The correct detection of missed target stimuli and response to nontarget stimuli are the indicator of performance in CPT. An example of neuropsychiatric condition related to attention deficits is Attention Deficit Hyperactivity Disorder (ADHD) (Vadalà et al., 2011).

Memory is another domain that is complex and consists of multiple subdomains. Many assessments were developed to cover each of the subdomains. Firstly, working memory involves maintaining and manipulating information (Jablonska et al., 2020). This means the capability to store information and use it in different ways, either in verbal or nonverbal ways. One famous example of a working memory task is the digit span task (de Paula et al., 2016). Digit span has two sections, digit span forward and digit span backwards. In the digit span forward task, subjects are required to recall a series of ascendingly digits in the correct order. This is where the maintenance of information takes place. At the same time, manipulation information can be seen in digit span backwards where the subject has to recall the digits in reversed order.

Apart from working memory, other components required for memory performance are episodic memory. This includes encoding, storage and retrieval of memory. For example, the Ray Auditory Verbal Learning Test (RAVLT) has 15 unorganized items for participants to encode with five learning trials (Strauss et al., 2006). They must recall the items after a period to test their retrieval ability. Other subdomains of memory are procedural, semantic and prospective memory, which particularly involve long-term memory and future planning. Assessment development in these subdomains is still scarce (Harvey, 2019).

Another domain is executive functioning which includes a set of complex tasks such as reasoning, problem-solving, planning, manipulating and management of many cognitive abilities (Cristofori et al., 2019). This system is able to control and manages other cognitive abilities hence give the ability for individuals to learn and adapt to the new situation in life daily (Collette et al., 2006). Executive function also has an impact on daily life. For example, higher executive function is associated with better quality of life (Davis et al., 2010), and good predictors of reading and mathematical abilities (Blair & Razza, 2007).

On the other hand, poor executive functions are related to mental disorders (Lui & Tannock, 2007; Tavares et al., 2007), lower work productivity and difficult job findings (Bailey, 2007), as well as reduced physical health (Will Crescioni et al., 2011; Miller et al., 2013).

2.3 Diagnosing POCD

Definitions of POCD differ across studies. A meta-analysis by Greaves et. al (2019) summarizes the methods used in 215 POCD studies worldwide to classify patients with POCD or not. Many studies used cognitive assessments as an indicator for POCD. The assessments usually conducted by researcher to the patients using pen and paper based, verbal or physical assessment, depending on the types of test used. The tests typically consist of several assessments that covers different cognitive domains as mention earlier, to ensure a comprehensive neurocognitive assessment.

Current study has chosen five tests as the cognitive assessment to classify POCD. The tests are Mini-mental State Examination (MMSE), Trail Making Test (TMT), Digit Span, Digit Symbol Substitution Test (DSST) and Clock Drawing test (CDT). The chosen test was selected by experts after considering the holistic approach of each test, and time taken to complete the whole assessments. It is common to conduct the test at two timepoint, preoperative as baseline, and few days postoperative.

From the results of pre and postoperative assessments, researchers calculated the scores difference using several calculation methods. The methods include 1 standard deviation (SD), 20:20 decline method, reliable change index (RCI), and cut-off method.

One SD (1-SD) method is defined as a decline of one or more standard deviations in patients' postoperative scores to preoperative scores (Newman et al., 1987). The SD can be calculated in two ways, either from published works or from sample norms derived from the preoperative scores of the study. In a study with no control group, the sample norm can be defined by individual decrement of ≥1 standard deviation of the whole population at baseline (Evered et al., 2018). By using this method, it portrays the relative individual changes from the sample norms or population data.

A 20:20 decline method is utilized when: - 1) 20% or more decline of the postoperative scores to the preoperative scores, 2) the decline must be on at least 20% of all the tests performed (Stump, 1995). For example, in a set of cognitive tests consist of 5 different tests, postoperative scores of at least one out of the five tests need to have declined more than 20% from preoperative scores. Another method is the reliable change index (RCI). RCI calculation method varies from study to study, yet widely define as RCI decline ≥1.64, in at least 20% of the tests (Rasmussen et al., 2001). For cut-off method, a specific value is use as a cut-off in assessments to define cognitive impairment. The cut-off value is referred from population norms, or decrease by points that is known as threshold of decline (Chakravarthy et al., 2008). This method indicates individual’s performance on that particular tests.

With various methods that can be utilised to classify POCD, it is important to choose the correct method that fits the definition that represents each study. The prevalence of POCD is highly dependent on the definition that varies in each study, nonetheless, there is a need to have a gold standard definition of POCD to enhance the efficacy in managing this specific post-surgical complication.

2.4 Risk Factor of POCD

Individuals with risk factors have a higher chance of developing POCD. Generally, the risk factors can be classified into patient and surgical factors. Yazit et. al (2020) has illustrated the risk factors in a comprehensive diagram (Figure 2.2).

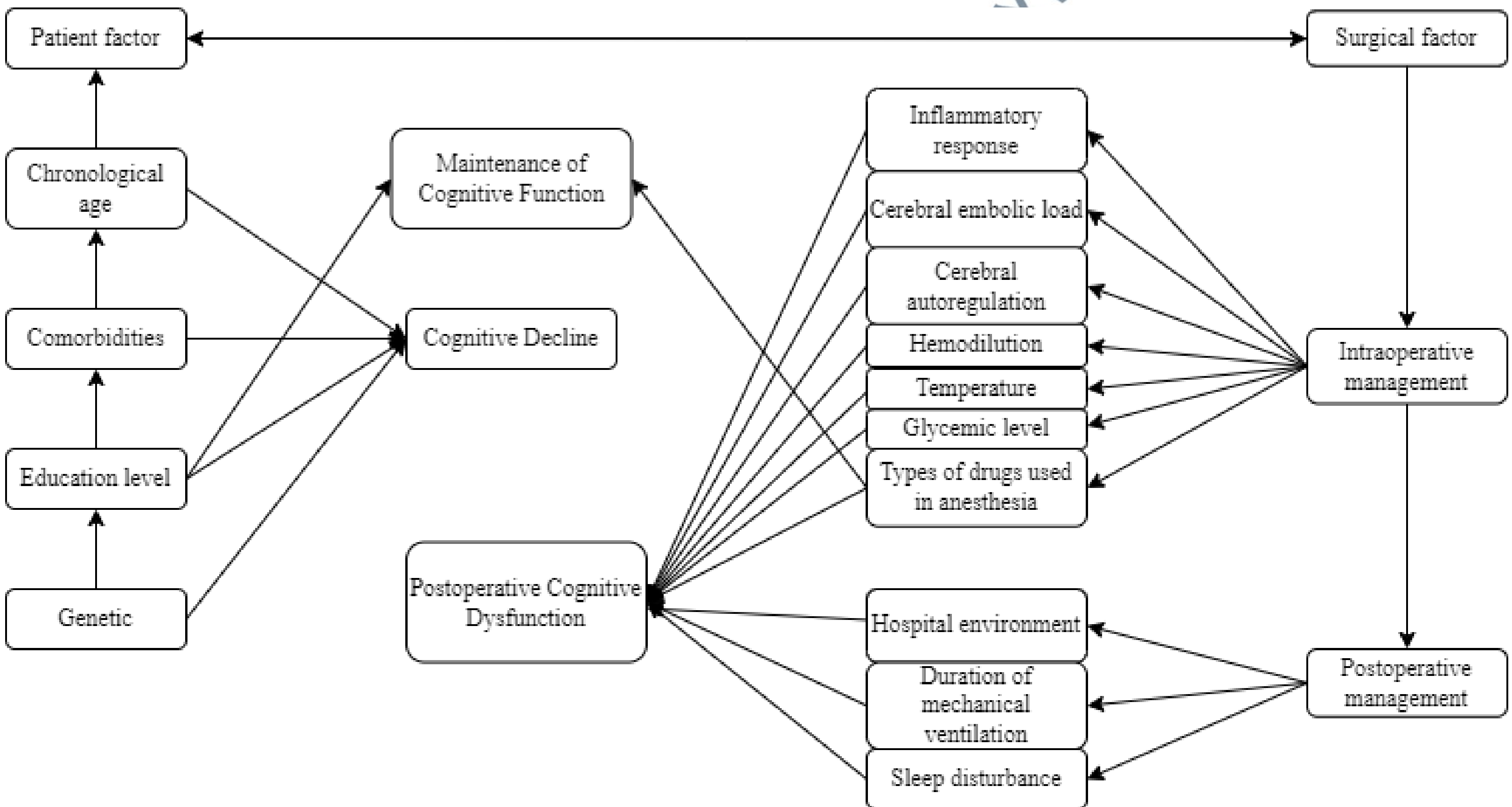

Figure 2.2: Factors contributing to occurrence of POCD. Individuals with predisposed risk factors may experiences cognitive decline. When exposed to surgery, surgical-related factors will increase the risk of developing POCD. Figure adapted from Yazit et al. 2020.

Factors that were predisposed in an individual before surgery are classified as patient-related factors. Some of the factors are non-modifiable, while some are partially modifiable. Risk factors such as patients' age and genetic predisposition are examples of non-modifiable risks. Increasing age was known as the cause of degenerative changes (Moller et al., 1998; Yang et al., 2022a), hence increasing the risk for cognitive related conditions such as mild cognitive impairment (MCI), dementia and POCD. Other individuals with predisposed genes related to degenerative diseases such as APOE-ε4 increases the chances of cognitive decline (Kotekar et al., 2018; Tardiff et al., 1997). Next, partially modifiable factors would be comorbidities and education level. Comorbidities such as diabetes and hypertension were shown to be associated with POCD (Feinkohl et al., 2017a, 2017b). For education level, the study revealed that the risk of POCD is inversely proportional to the level of education (Newman et al., 2001; Yang et al., 2022a). Hence, if patients could control their comorbidities and education, they might improve their cognitive function and eventually reduce the risk of cognitive decline. These mentioned patient-related factors may lead to cognitive decline without any surgical intervention. When exposed to surgery, the risk of POCD increased due to multiple factors during the intervention.

Factors related to surgery include intraoperative and postoperative management. Factors affecting POCD during the procedure commencing involve inflammatory responses due to systemic inflammation (Terrando et al., 2011), formation of microemboli (Berger et al., 2018), autoregulation of blood flow in the brain (Newman et al., 1995), and hemodilution (Mathew et al., 2007). Those factors are easily disrupted during surgery, hence may affect blood flow to the brain. Other factors are temperature, glycemic level, and types of anaesthesia used. Some study involving animals revealed that hypothermia may decrease neurological injury (Choi et al., 2012). In practical application, clinicians were recommended to slow the pace of rewarming process intraoperatively to reduce brain injury (Engelman et al., 2015). High levels of glucose in the blood were triggered by surgery via oxidative stress, cellular acidosis or brain oedema (Hogue et al., 2008). Controlling hyperglycemia during surgery helps in preserving cognitive function (Schricker et al., 2014).

Another important factor is the type of anaesthesia used during surgery. There are general and local anaesthesia, where general anaesthesia was used during cardiac surgery. General anaesthesia will affect the whole body in four main components, which are loss of consciousness, amnesia, analgesia and muscle relaxation (Alwardt et al., 2005). These may affect patients' brains differently, either due to it duration and depth of anaesthesia. Even though anaesthesia possesses its own risk of brain injury, some may help to preserve brain injury. Studies regarding dexmedetomidine use in cardiac surgery help to reduce the incidence of POCD when compared to control anaesthesia (Liu et al., 2017). Hence, the type of drugs used during the surgery may become a risk factor for POCD but also can be a way to maintain cognitive function.

The hospital environment also plays a role to improve patients' cognitive function postoperatively. An environment not conducive to patients' recovery will disturb their sleep, mood and well-being. These factors were found to be part of the contributors to POCD (Glumac et al., 2019), however, the settings cannot be modified to cater for the personalised need of each patient. This is a partially modified factors that may or may not influenced individuals, that is highly varies across patients.

2.5 Cardiothoracic Surgery in Malaysia

Cardiothoracic surgery focuses on surgical procedures involving the heart, lungs, esophagus, and other organs within the chest cavity. The purposes are to diagnose, treat and manage the disease conditions. It encompasses a wide range of surgical interventions, from coronary artery bypass grafting (CABG) and heart valve repairs/replacements to lung transplants and surgeries for congenital heart defects. Cardiovascular diseases have been reported as number 1 cause of death in Malaysia (Department of Statistics Malaysia, 2021). This led to an increase in demand for cardiothoracic surgery, which gives rises to multiple issues nationwide.

Firstly, the high demand for these specialized procedures leads to longer waiting time, particularly in major hospitals and medical centre. Some patients were reported to wait up to 16 weeks for outpatient cardiac appointment (British Heart Foundation, 2022). In Malaysia, the average waiting time were reported to be around 12 weeks (Yusoff 2023). This might lead to delays in treatment for patients who require urgent intervention, and increasing the risk of disease deterioration. Surgery waiting time is closely associated with easy access to specialized procedures. These specialized procedures only to be conducted by trained surgeon. Shortage of skilled personnel in the country become a concern and some patients opt for performing surgery overseas. Currently, there are 68 cardiothoracic surgeons in Malaysia, with 1905 patients listing for surgery as of first quarter of 2022 (Babulal, 2022). Although Malaysia has a relatively good healthcare system, there are few factors that deter patients from getting proper cardiac treatment. The problems include difficult access to hospitals or medical centre for rural patients, high cost for cardiac surgery, patient refusal for surgery especially in older age groups, etc. The later a patient seek out for treatment, the higher the risk for disease worsening. This may lead to various complications after surgery which eventually prolonged ICU and hospital stay. This is a domino effect that cause unavailability of hospital beds, increase in treatment cost, prolonged rehabilitation and postoperative management. In short, the issues may influence the morbidity and mortality of patients, which in turn cause burden to our healthcare systems.

Nevertheless, cardiothoracic care in Malaysia has evolved significantly for the past 3 decades (Firus Khan et al., 2022). To compensate for the high demand for cardiothoracic services, medical centre specialized in cardiac care was built. Some private hospitals also perform cardiothoracic services to cater patient load in government hospitals. Parallel to the rise of facilities, many training and education session was executed to train skilled workforce (Babulal, 2022). The personnel include surgeons, anaesthesiologists, nurses, perfusionists and healthcare workers. The rise in trained and skilled personnel is important to ensure the competency of the staff in performing specialized procedures properly. Besides, the adoption of advanced medical technologies and surgical techniques has changed and improved the quality of surgery. Clinicians can now use various methods including robot-assisted surgery, minimally invasive procedures and imaging techniques that allow more precise and safe procedures. This in turn will benefit patients in terms of fast procedures and quicker recovery time. Further, research and innovation in the healthcare sector has taken place rapidly in Malaysia. Local researchers actively engage in clinical trials, device development, and new surgical techniques that will improve patient outcomes. This will ensure our healthcare system particularly cardiac care is up-to-date and reliable which aligns with evidence-based medicine.

Despite the advancement in our healthcare sector, the prevalence of cardiovascular diseases is still high. The most common cardiac surgery performed is coronary artery bypass graft (CABG). It is estimated that 4000 cases of CABG are done each year in Institut Jantung Negara (IJN). IJN is a private hospital that specialized in cardiology and cardiothoracic care. They received referral patients from hospitals around Malaysia as well as private paying patients. The flow for cardiothoracic patients undergoing surgery in National Heart Institute is illustrated in Figure 2.3 below.

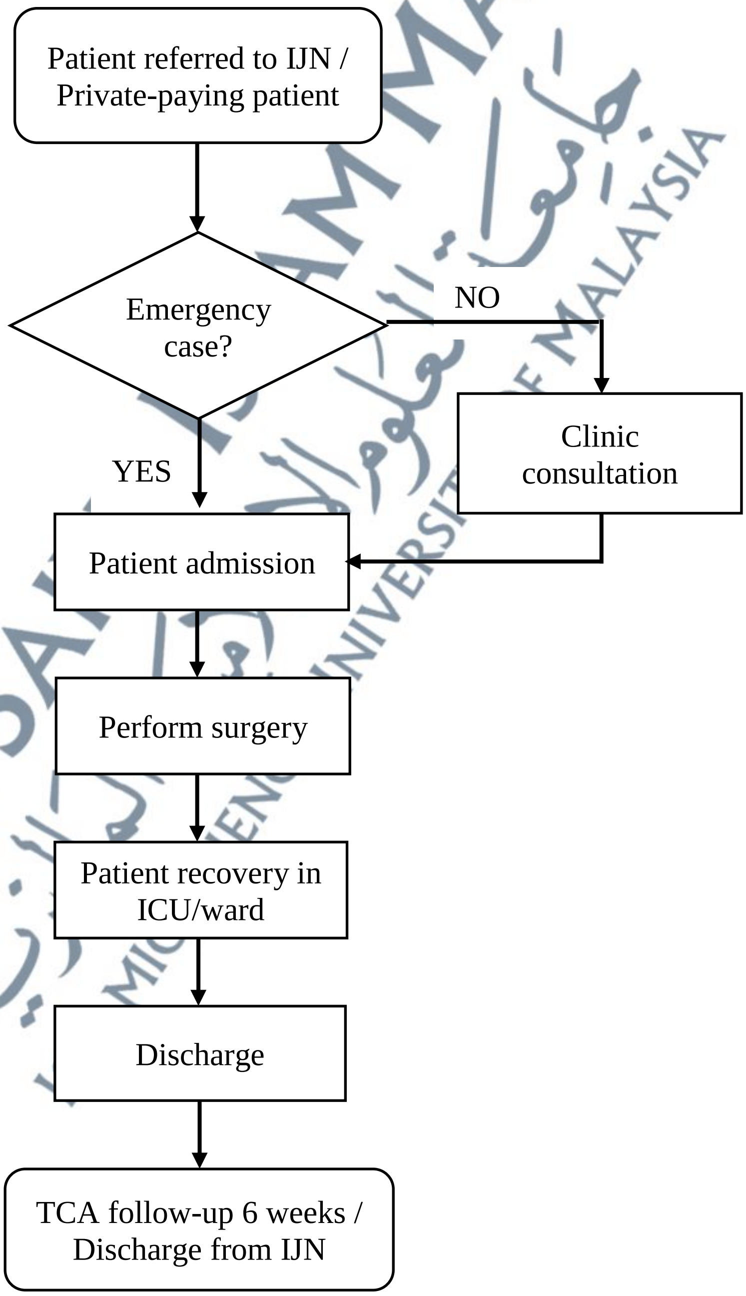

Figure 2.3: The flowchart for patients undergoing cardiothoracic surgery in IJN. TCA: to come again.

Equipped with state-of-the-art facilities and renown surgeons, IJN become our national referral center for cardiology and cardiothoracic cases. Despite hundreds of cardiothoracic surgeries being done monthly with their excellent healthcare services, postoperative complications are unavoidable. Common postoperative complications include arrhythmia, atrial fibrillation, renal failure requiring dialysis, stroke and mortality (Juliana et al., 2021). Another complication that has been long existed but not getting the limelight is cognitive dysfunction. Postoperative cognitive dysfunction may happen as during hospital stay up till years after surgery. POCD disturbs patients' cognitive ability in memory, recognising familiar things, concentration and reduce motor function. Eventually, patients may experience longer hospital stay, increase rehabilitation session, early retirement, and reduced quality of life (Duan et al., 2018). This in turn will burden our healthcare system in term of costing and workforce in managing patients with POCD.

2.6 Role of Blood Biomarkers in POCD

An alternative to neuropsychological assessment in diagnosing POCD is using blood biomarkers. Blood biomarkers can be used to predict the occurrences of POCD. Common biomarkers include neuron-specific enolase (NSE) and S100 beta (S100B). Both NSE and S100B are known as potential biomarkers of neuronal injury (Bo¨hmer et al., 2011; Wang et al., 2018). The close relationship between cognitive function and brain damage has led many authors to use the biomarkers of brain injury in predicting the outcome of cognitive dysfunction after cardiac surgery (Silva et al., 2016).

S100 beta (S100B) is a calcium-binding protein in astrocytes and Schwann cells. Under metabolic stress, glial cells are activated, and S100B is released into the bloodstream (Silva et al., 2016). The concentration of S100B circulating in the bloodstream is proportional to blood-brain barrier dysfunction (Blyth et al., 2009). Hence, S100B has become a reliable indicator of brain damage. NSE is a glycolytic protein mostly located in a neuron's cytoplasm. It plays a role in neuronal activity such as neuroinflammation, neuroprotection in spinal cord injury and other neurodegenerative diseases (Haque et al., 2018). When neuronal damage occurs, NSE level increased in serum and last longer than 20 hours. The delayed cell death that occurs has resulted in the prolonged release of NSE into the bloodstream (Majewski et al., 2020).

S100B and NSE were observed to be elevated together after cardiac surgery and their relation to neurocognitive decline. A study by Westaby et al. (2000) reported a good correlation between S100B concentration and postoperative cognitive decline after a few hours of cardiopulmonary bypass. However, for 5 days and 3 months after surgery, S100B failed to show a significant correlation with POCD. Another study reported a correlation between NSE level 24-hour post-surgery with neurocognitive test scores at 52 weeks (Jones et al., 2012). The authors concluded NSE as a potential biomarker to identify POCD as compared to S100B as they found no correlation between s100B and POCD. On the other hand, a study in 2016 by Silva et al found a correlation regarding S100B and POCD but not NSE. Silva et al (2016) specifically examined the time point of S100B serum level at surgery ends to predict POCD at 21 days, as well as correlate S100B at 6 and 24 hours to predict POCD at 180 days.

A meta-analysis has reported the peripheral inflammatory biomarkers that correlate with POCD, which includes S100B and IL-6 (Peng et al., 2013). However, the meta-analysis only includes limited studies about S100B and NSE. Furthermore, the analysis mostly involved non-cardiac surgery. The cardiac-related surgery study was still scarce due to the inconsistent findings from the authors. Even with evidence of S100B as a marker of outcome after surgery and traumatic brain injury (Connoly et al., 2001; Nylén, 2008), the utilization of S100B and NSE in predicting, particularly, long-term cognitive decline is still limited. The problem may lie due to the inconsistent timepoint of biomarker level tested, the type of surgery, and different neurocognitive assessments.

2.7 Gene Involvement in POCD

To elucidate the mechanism of POCD occurrence, authors have associated genetic disposition in the equation. Other neurodegenerative diseases, such as Alzheimer's and Parkinson's, have their specific gene involved in the pathway. The predispose gene in individuals enables researchers to predict the outcome of the disease. Similarly, many authors have investigated the genetic aspect in elucidating the POCD pathway.

Previous studies explored on the role of RNA in POCD pathophysiology, particularly the non-coding RNA (ncRNA). The ncRNAs possess critical roles in mediating post-transcriptional regulation of gene expression. Hence, any dysregulation of ncRNAs may become the root of molecular mechanism of POCD (Yang et al., 2022b). The family of ncRNAs include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), etc. Many studies have elaborated the role of ncRNAs in POCD (Zhang et al., 2018; Li et al., 2019; Wu et al., 2016). However, current study focused on coding RNA genes that encodes protein that potentially applied as biomarker or such. With abundance of evidences on ncRNAs and POCD, the specific coding RNA is still scarce and needs further exploration.

Even with limited studies, some genes have been associated with POCD ever since. The application of the genes beyond POCD pathophysiology is still debatable, allowing researchers to dig deep in this field.

2.7.1 APOE-ε4

The earliest study that suggests apolipoprotein epsilon 4 (APOE-ε4) plays a role in POCD dated back to 1997 (Tardiff et al., 1997). Apolipoprotein epsilon 4 (APOE-ε4) is a polymorphic glycoprotein. The central nervous system produces it primarily by astroglia and microglia. It is involved brain injury response, neuroinflammation and activation of glial (Bartels et al., 2015). APOE-ε4 is known as the genetic risk factor for Alzheimer diseases (Sadigh-Eteghad et al., 2012).

In 1997, Tardiff and the group provided evidence of APOE-ε4 and cognitive impairment. They found a significant association between APOE-ε4 presence with cognitive impairment at 6 weeks. Lelis et al (2006) also agree that the APOE-ε4 genotype increases the risk of POCD. Similar results were found by Bartels et al. (2015) at the longer duration of five years after cardiac surgery. Apart from cardiac surgery, authors also found a correlation between this genotype and cognitive decline in non-cardiac surgery (Heyer et al., 2005; Cai et al., 2012).

Even though evidence of the correlation seems promising, several contradicting findings exist. Askar et al (2005) did not find any significant correlation between those whose cognitive decline and not decline after 3 months with APOE-ε4. The authors also failed to correlate the pre-existing APOE-ε4 genotype with pre-existing cognitive impairment and POCD (Silbert et al., 2008). They concluded that although the genotype exists in 37.2% of their total sample, they still do not find the association of APOE-ε4 with POCD. The finding is concurrent with a later study by Bryson et al (2011), who support that APOE-ε4 presence did not statistically significantly correlate with POCD. A meta-analysis by Cao et al. (2014) was conducted to see whether the findings were consistent with each other. The total number of studies included was nine studies that comprised of 1063 carriers and 2983 non-carriers of APOE-ε4. The findings show a significant correlation between APOE-ε4 and POCD at 1-week after surgery but not in the long-term. However, the significance only depends on one large study. Other studies failed to prove the significant correlation between APOE-ε4 and POCD.

In conclusion, it is difficult to utilize the APOE-E4 allele to predict the outcome of POCD. The allele has many traits, and the genetic disposition varies according to ethnicity. Hence, we could not homogenize the presence of APOE-ε4 to the occurrence of POCD yet did not reject the claim that genetic predisposition influences POCD together with other pre-existing risk factors.

2.7.2 BDNF

Brain-derived neurotrophic factor (BDNF) is a protein encodes from BDNF genes. It belongs to neurotrophic family that is highly expressed in the central nervous system. It is the most abundance and intensively studied member of the neurotrophic family. The main function of BDNF includes maintaining neuronal survival and differentiation, assisting synaptic transmission, enhancing synaptic plasticity and strengthening synaptic growth (Lu et al., 2013).

BDNF was shown to associate with cognition. The study shows a depletion of serum BDNF expression and signaling after surgery. Thereby, the reduced BDNF concentration was correlated with POCD (Travica et al., 2022). However, it is important to note that the depletion of BDNF may due to the insult of surgery, or the effect of anesthetic agents, which both are still uncertain. The changes of BDNF concentration and POCD association mainly studied using animal model, hence the application to humans are still limited. A similar study also examines the role of BDNF and its precursor, proBDNF in POCD in mice. They reported a reduction in BDNF/proBDNF ratio after surgery, which negatively regulates the synaptic function in hippocampus. This eventually leads to POCD in aged mice (Ziyi et al., 2022). The study also believed that altering the ratio of BDNF/proBDNF plays a role and could become a promising therapeutic target for POCD.

BNDF shows a promising genetic indicator POCD. However, the studies primarily evolved in animal model, with no specificity to cardiac surgery. The application of BDNF further in predicting POCD for human still a long journey, hence the discovery of other related genes is sensible.

2.8 Cerebral Oximetry and Cardiac Surgery

Cerebral oximetry (CeOx) is the measurement of oxygen concentration in the brain. Cerebral oximeters allow continuous monitoring of cerebral oxygenation in a non-invasive way. The principles used in cerebral oximeters were similar to pulse oximeters. Light transmission and absorption methods were used to measure the ratio of oxygenated and deoxygenated blood (Végh, 2016). Pulse oximeters utilize plethysmography for pulse rate and photo absorption for the measurement of peripheral oxygen. On the contrary, cerebral oximeters use near-infrared spectroscopy (NIRS) without plethysmography. NIRS will detect the balance between regional oxygenated and deoxygenated blood.

The application of CeOx intraoperatively focuses on the regional cerebral oxygen saturation ($rScO_2$). Usage of $rScO_2$ allows monitoring of oxygen saturation in the brain's prefrontal cortex during surgery. The CeOx was placed on the forehead of the patients, and the saturation was monitored on screen. Before the induction of anaesthesia, the baseline $rScO_2$ value was taken. During surgery commenced, a decrease of $rScO_2$ value below 20% from the baseline will be taken immediate action to maintain the $rScO_2$ value. The standardized intervention includes – 1) elimination of mechanical obstruction, either by repositioning the head or bypass cannula, 2) increasing the oxygen-delivering strategy, or 3) reducing the cerebral oxygen consumption strategy (Juliana et al., 2021). Hence, clinicians were able to do a proper intervention to maintain $rScO_2$ value intraoperatively if CeOx monitoring is utilized.

In cardiac surgery, particularly, cerebral oxygenation is important to ensure the brain is well-perfused to reduce damage to brain cells. The prevalence of brain injury after cardiac surgery remains high, despite advancements in technology. Postoperative complications such as stroke are serious and affect almost 10% of susceptible patients (Tarakji et al., 2011). Postoperative stroke still becomes the independent risk factor for mortality (Mazzeffi et al., 2014). Hence, studies were conducted to see the efficacy of using cerebral oxygenation monitoring during cardiac surgery in reducing postoperative complications. Juliana et al. (2021) reported that the prevalence of stroke, renal failure requiring dialysis and mortality rate were reduced in patients that utilised cerebral oximetry monitoring compared to controlled patients. In this case-control study, they examined high-risk cardiothoracic surgery patients, where 240 patients were in the case, and 407 patients were in control group. The incidence of stroke was 7 times more likely in control patients. In another study, the rate of stroke incidence was lower in the monitored patient group compared to controls (Goldman et al., 2004).

Other postoperative complications that associated with CeOx monitoring intervention were studied, including length of ICU stay, acute kidney injury (AKI), atrial fibrillation and mortality rate. In a meta-analysis consisting of 10 trials, authors found out the length of ICU stay in the intervention group is lesser than control (Tian et al., 2022). Even though the weighted mean difference was -0.22 days, the outcome was significant as it involved 1459 patients. This reduction in ICU stays benefits healthcare providers and patients concurrently. Authors believed that in-hospital morbidity and mortality tend to occur in the first week after surgery. They are highly influenced by underlying patient and surgical factors (Mazzeffi et al., 2014). Hence, a reduction of ICU stays and overall hospital stays was believed to alleviate in-hospital morbidity and mortality. Besides, $rScO_2$ monitoring was also found to be a predictor for renal failure requiring dialysis and mortality (Juliana et al., 2021). There was increasing attention from researchers and clinicians to explore further on utilization of $rScO_2$ monitoring in clinical settings. More evidence is needed to convince clinicians to utilize CeOx monitoring as the standard of care so that the benefits outweigh the drawbacks.

2.8.1 Cerebral oximetry and POCD

Complications related to cerebral injury has mainly focused on more serious and detrimental effect like stroke. However, the frequency of stroke incidence is lesser when compared to other cognitive complications like cognitive dysfunction (Colak et al., 2015). Even though cognitive dysfunction may not be life-threatening, it possesses a significant impact on a patient's quality of life postoperatively (Likosky et al., 2004). With multifactorial risk intraoperatively, cerebral oxygen demand and supply may worsen the patient's cognitive state. Studies about cerebral oximetry monitoring and postoperative cognitive dysfunction are getting rising attention nowadays. A clinical trial conducted on 200 patients revealed that the incidence of POCD was significantly lesser in CeOx monitored group (28%) compared to the control (52%) (Colak et al., 2015). Further analysis using multivariate logistic regression has shown that the monitoring becomes a predictor of reducing POCD incidence. In another study, Holmgaard et al. (2019) found a contradicting result, where there is no association between $rScO_2$ values intraoperatively with POCD. They also questioned the rationale of using CeOx monitoring for the purpose of reducing POCD.

The current meta-analysis has concluded the above debate. Tian et al. (2022) confirmed that $rScO_2$ monitoring during cardiac surgery correlates with a lower risk of POCD. The results were analyzed from 5 clinical trials, with an odd ratio of 0.38. Together with other outcomes of interest, $rScO_2$ monitoring lowers the incidence of postoperative delirium (POD). An earlier meta-analysis also shows similar results, where usage of $rScO_2$ could reduce the risk of POCD (Ding et al., 2020). The incidence of POCD was significantly lowered higher in the intervention group with $rScO_2$ monitoring. However, the analysis was also included non-cardiac surgery. Some randomized control trials analyzed in the latter study were identical to the former study. Nevertheless, both meta-analyses suggested that $rScO_2$ monitoring benefits patients in cardiac surgery, particularly in neurocognitive outcomes.