THE INCIDENCE OF POST-OPERATIVE DELIRIUM AMONG ELDERLY PATIENTS AND ITS ASSOCIATED FACTORS

DR NG LI EN

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR DEGREE OF MASTERS OF MEDICINE (ANAESTHESIOLOGY AND CRITICAL CARE)

UNIVERSITI SAINS MALAYSIA
2023

ACKNOWLEDGEMENT

Many individuals have participated and contributed to the completion of this study.

First of all, I would like to express my deepest appreciation to my research supervisor, Dr Laila Ab Mukmin, for her continuous guidance and support throughout this research. Without her, I would not be able to complete this study. I am also grateful to have the assistance of my academic supervisors, Associate Prof Saedah Ali and Dr Wan Fadzlina Wan Muhd Shukeri, throughout the conduct of this study.

Many thanks to all the lecturers, staff and students in the Anaesthesiology Department of Universiti Sains Malaysia for helping to recruit and collect the data required for this study. I would also like to acknowledge the statisticians of Units of Biostatistics and Research Methodology. I would not be able to complete this dissertation without their support.

Finally, I would like to extend my sincere thanks to my friends and family members for always being my strong emotional support.

Thank you.

TABLE OF CONTENTS

ABSTRAK

Tajuk: Insiden dan Faktor-faktor yang Menyebabkan Delirium Selepas Pembedahan di Kalangan Pesakit Warga Emas

Pengenalan*:* Peningkatan jangka hayat menyumbang kepada penambahan pesakit warga emas yang menjalani pembedahan. Kesan pembiusan dan pembedahan boleh menyebabkan delirium, iaitu kekacauan minda yang mendorong kepada kekeliruan dan ketidakpekaan sekeliling . Kajian ini adalah yang pertama di Malaysia yang bertujuan untuk menyelidik insiden dan faktor-faktor penyebab berlakunya delirium selepas pembedahan (POD) dalam kalangan pesakit warga emas yang menjalani semua jenis pembedahan.

Kaedah*:* Ini adalah kajian kohort prospektif dalam kalangan pesakit berumur 65 tahun dan ke atas yang menjalani pembedahan elektif atau kecemasan di Hospital Universiti Sains Malaysia (HUSM). Status kognitif dan frailty (kelemahan fizikal) telah dinilai sebelum pembedahan dengan menggunakan Montreal Cognitive Assessment versi Bahasa Melayu (MMoCA) dan Frailty Index for Elderly (FIFE). Selepas pembedahan, pesakit dinilai untuk kejadian POD sebanyak dua kali sehari sehingga 5 hari atau sehingga didiscaj. Analisis faktor terkait insiden POD dilakukan dengan menggunakan analisis regresi logistik univariat dan multivariat.

Keputusan*:* Seramai 153 pesakit telah direkrut. Insiden POD adalah 18.3% (selang keyakinan (CI) 95%: 12.5% – 25.4%). Faktor peramal insiden POD yang signifikan dalam analisis multivariat regresi logistik adalah skor FIFE (nisbah odds diselaraskan (AOR): 1.568; 95% CI: 1.16 – 2.10; p = 0.003), skor "metabolic equivalent task" (METs) < 4 (AOR: 3.228; 95% CI: 1.01 – 10.31; p = 0.048), dan tekanan darah rendah semasa pembedahan (AOR: 7.687; 95% CI: 2.69 – 21.98; p = <0.001). Klasifikasi

New York Heart Association (NYHA), jenis pembiusan, tempoh masa bius dan pembedahan, jangkaan pendarahan, keperluan transfusi dalam pembedahan dan jumlah transfusi adalah faktor yang signifikan hanya dalam analisis univariat. Untuk semua pesakit, POD hilang sepenuhnya, dengan median jangka masa sepanjang 2 hari.

***Kesimpulan**:* Kejadian POD sangat tinggi dalam kalangan pesakit warga emas yang menjalani pembedahan kecemasan dan elektif. Pesakit yang cenderung untuk mengalami POD patut dikenal pasti. Ini membolehkan langkah-langkah pencegahan diambil untuk mengelakkan berlakunya POD dan juga memastikan perawat pesakit utama lebih berwaspada untuk mengenal pasti dan merawat POD dengan lebih awal.

Kata kunci: *delirium selepas pembedahan, kejadian, faktor penyebab, pesakit warga emas, frailty*

ABSTRACT

Title: The Incidence of Post-Operative Delirium Among Elderly Patients and Its Associated Factors

Background*:* Longer life span leads to an increase in elderly patients coming for surgery. The incidence of delirium is reported to be the highest in this population. This study was the first in Malaysia to investigate the incidence and predicting factors for post-operative delirium (POD) among local elderly patients undergoing various types of surgery.

Methods*:* A prospective cohort study was conducted on surgical patients aged 65 years and above who underwent surgery at Hospital Universiti Sains Malaysia (HUSM). Cognitive and frailty statuses were assessed pre-operatively using the Malay version of Montreal Cognitive Assessment (MMoCA) and the Frailty Index for Elderly (FIFE), respectively. Postoperatively, patients were evaluated for the development of POD twice a day for up to 5 days or until discharged.

Results*:* A total of 153 patients were recruited. The incidence of POD was 18.3% (95% CI: 12.5% – 25.4%). Factors found to be significantly associated with POD on multivariate analysis were FIFE score (adjusted odds ratio (AOR): 1.568; 95% CI: 1.16 – 2.10; p = 0.003), METS < 4 (AOR: 3.228; 95% CI: 1.01 – 10.31; p = 0.048), and presence of intra-operative hypotension (AOR: 7.687; 95% CI: 2.69 – 21.98; p = <0.001). New York Heart Association (NYHA) class, type of anaesthesia, duration of anaesthesia and surgery, estimated blood loss, need for intraoperative transfusion, and amount transfused were only significant on univariable analysis. All of our patients had complete resolution of POD, with a median duration of two days.

Conclusion*:* The incidence of POD among elderly patients coming for both emergency and elective surgeries is high. Patients at higher risk for POD should be identified. This allows precautionary steps to be taken to prevent the development of POD and ensure primary teams are more vigilant post-operatively to detect and treat POD earlier.

Keywords*: post-operative delirium, incidence, risk factors, elderly patients, frailty*

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS AND ABBREVIATIONS

AOR	Adjusted odds ratio
ASA	American Society of Anaesthesiologist
CAM	Confusion Assessment Method
CI	Confidence Interval
DBP	Diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
FIFE	Frailty Index for Elders
GA	General Anaesthesia
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive Care Unit
IQR	Interquartile Range
M3D-CAM	Malay 3-Minute Diagnostic Interview for Confusion Assessment Method
MAC	Monitored Anaesthesia Care
MAP	Mean Arterial Pressure
METs	Metabolic Equivalent Task Score
MMoCA	Malay version of Montreal Cognitive Assessment
MoCA	Montreal Cognitive Assessment
Nu-DESC	Nursing Delirium Screening Scale
NYHA	New York Heart Association
OR	Odds Ratio
PACU	Post Anaesthesia Care Unit
POD	Post-Operative Delirium
RA	Regional Anaesthesia

SBP	Systolic Blood Pressure
SpO_2	Oxygen Saturation
%	Percentage
<	Less Than
≥	More Than and Equal To
=	Equal

CHAPTER 1: INTRODUCTION

1.1 Introduction

Improvement in general living standards, health care, nutrition and education leads to a steady increase in the geriatric population. According to the Department of Statistics, Malaysia (1), population aged 65 years and above had been estimated to increase by 0.3 per cent in just over a year. It is postulated that in 2040, they would comprise 14.5 per cent of the population (2). These demographic changes indicate that there will be a significant increase in the geriatric population admitting to the hospital for an operation. However, the geriatric population has a risk of morbidity and mortality (3,4), including post-operative delirium (POD) (5).

American Psychiatric Association (6) defines delirium in DSM-5 as a disturbance of attention or awareness that develops over a short period of time and is accompanied by a change in baseline cognition that a pre-existing or evolving neurocognitive disorder cannot explain. Depending on the type of surgery, post-operative delirium incidence varies from 12% to 51% (7). Silva et al. (8) did a systemic review and found an overall pooled POD frequency of 23.8%. In fact, the incidence of POD increased at an average rate of 3% per year between 1995 and 2020.

Given the high incidence of POD and its associated adverse outcomes, there is a need for early identification and treatment of POD. The best treatment for POD lies in preventing patients from developing it in the first place. Preventive measures have been proven to reduce the incidence and duration of delirium (9–11). However, it is not cost-effective if the preventive strategy is employed for all patients undergoing surgery, thus creating the need to identify patients at higher risk of developing POD.

Recent studies have attempted to relate frailty to post-operative adverse outcomes in elderly patients. Frailty describes patients in a multi-dimensional aspect, where a frail patient has reduced reserves and tolerance for physical, physiological or psychosocial stressors (12,13). Since surgery imposes significant physiologic stress, it is expected that frail patients will not tolerate surgery well and have a higher risk of adverse outcomes. In fact, frailty leads to at least a 2-fold increase in the risk of major morbidity, mortality and readmissions (14,15).

However, it is difficult to define frailty. Until now, there is no universal gold standard definition of frailty. Two main models are commonly referred to: the phenotype model and the accumulating deficits model. The phenotype model states that frailty is exhibited by a decline in walking speed and grip strength, unintentional weight loss, low physical activity and exhaustion (16). Hence, it is usually referred to as physical frailty. On the other hand, the accumulating deficits model is usually referred to as the frailty index (17). This model describes frailty as a biological ageing process instead of a chronologic process. It is measured by counting the sum of a patient's deficits over multiple domains (including medical, social and functional). The frailty index is then quantified by dividing the number of deficits present by the total deficits assessed. Regardless of the model used, higher levels of frailty had been consistently shown to lead to a greater risk of adverse outcomes (14,15).

Delirium leads to significant adverse outcomes, including prolonged hospitalisation, increased cost and increased mortality (18–20). Evidence also showed that patients who developed POD had prolonged cognitive impairment (21–23) and impaired physical function (18). Thus, methods that aim to reduce the incidence of POD will eventually help improve post-operative outcomes, especially in the elderly.

To date, there is no published local data on the incidence of POD for all elective and emergency surgical patients. Frailty is a relatively new concept, and there are limited studies that directly relate frailty with the incidence of POD in elderly populations.

We conducted a single-centred prospective cohort study to investigate the incidence and the associated factors for POD among elderly patients scheduled for surgeries.

1.2 Literature Review

1) Incidence of Post-operative delirium

The incidence of POD currently quoted by different studies is quite variable. Even when done in similar settings, POD incidence in different studies ranged from 13% to 51% (8). One of the explanations for the varying incidence is the differences in the study methodology and the study settings. Another explanation could be the difference in the timing of the studies. Given the change in population age and healthcare system improvement, these factors are expected to affect the incidence of POD.

Jin et al. (24) stated that the incidence of POD in general surgical patients was 2.5-3%, while for patients older than 60 years old, the incidence increased to 10-20%. The types of surgery also influence the incidence of POD. The incidence of POD for elective surgery was 2.5-3% and 10-20% for extremities surgery and truncal surgery, respectively. On the other hand, emergency surgery had an incidence of POD of 20-45%, roughly 3 times higher than elective surgeries. The complexity of the operation also influences the incidence of post-operative delirium. Operations, such as cardiothoracic operations, that needed admission to the intensive care unit post-operatively had a higher incidence of POD (20-50%). Some studies even reported an incidence of up to 80% for

operations requiring post-operative mechanical ventilation and intensive care unit admission (7).

The varying incidence of POD also lies in the variety of tools used to establish the diagnosis. The gold standard to diagnose delirium is following the criteria in The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)(6). However, this requires a trained and experienced physician, such as a geriatrician or psychiatrist, who are not readily available. Hence, various assessment tools, such as the Confusion Assessment Method (CAM) and the Nursing Delirium Screening Scale (Nu-DESC), are developed to facilitate the detection of delirium. Using different assessment tools in different clinical settings leads to vast differences in the reported incidence of POD.

2) Associated Factors for post-operative delirium

Due to the complexity of the pathogenesis of POD, it remains difficult to predict POD occurrence accurately. Nevertheless, numerous studies were conducted to identify risk factors for POD. Noimark (25) states that there were three main variables in predicting POD: the rapidity of onset, the severity of the insult, and the pre-procedural patient condition.

Studies showed that the incidence of POD was higher in emergency operations compared to elective operations (26–28). Thus, one can deduce that the rapid onset of insult leading to the need for emergency operation leads to a higher risk of POD. Other than that, the severity of the illness was also associated with POD occurrence. Baek et al. (29) did a meta-analysis among elderly patients undergoing spine surgery. They found that the occurrence of POD was higher in those undergoing spine fusion (vs simple spine

surgeries, e.g. laminectomy). Operations requiring longer duration were also associated with higher POD incidence (29–31).

Besides that, patients' premorbid condition was a key variable in predicting POD. Age was one factor that was proven to be associated with POD. With increasing age, delirium incidence increases. This association was likely due to increased comorbidities and frailty as one ages. Several studies consistently showed advanced age to be significantly associated with POD (28,30,32,33).

Smoking is also one of the common factors investigated for POD. The increased risk of atherosclerosis and arterial wall stiffening may make the smokers' brain more vulnerable to stressors (25). Studies have shown that POD risk was higher in smokers (30,32). However, Iamaroon et al. (33) did not exhibit this finding in their study, probably because they only compared POD occurrence in smokers more than or less than 30 pack-years. On the other hand, Benoit et al. (34) found that patients who developed POD had a significantly higher number of pack-years smoked. In his study, POD was not related to whether the patient was actively smoking.

Intra-operative hypotension is believed to cause subclinical cerebral vascular events and lead to POD development (25). Patti et al. (35) found that intra-operative hypotension was the strongest predictor of POD. However, other studies could not significantly establish the relationship between intra-operative hypotension and POD (36,37). Instead, Hirsch et al. (37) found that fluctuations in blood pressure played a more important role in POD occurrence.

Although variable factors are identified as predictive of POD, the findings were inconsistent among the studies conducted.

3) Frailty and POD

Attempts had been made to predict POD occurrence based on patients' baseline function. Hence the concept of frailty has become popular, especially among geriatricians. As frailty indicates reduced reserves and tolerance to stressors, it is postulated that frail patients will be more vulnerable to stressful operations, leading to a higher incidence of POD. Several studies proved the relationship between pre-operative frailty and POD (38,39). This finding leads to the practice of performing comprehensive geriatric assessment (CGA) before surgery to identify vulnerable patients (25). CGA involves a multi-discipline effort to evaluate patients systemically in geriatric patients. Evidence showed that these will improves post-operative outcomes and, at the same time, reduce the risk of POD. However, the process is time and effort-consuming.

Several frailty screening tools have been developed to identify individuals with a higher risk of POD and poor surgical outcomes. Regardless of the model used, higher levels of frailty had been consistently shown to lead to a greater risk of adverse outcomes (14,15).

1.3 Study Objectives

1.3.1 General Objective:

To investigate the incidence and associated factors for post-operative delirium (POD) among elderly patients scheduled for surgeries

1.3.2 Specific Objectives:

- To evaluate the incidence of POD among elderly patients scheduled for surgeries across the surgical specialties.
- To investigate the association between the frailty index and the incidence of POD.
- To investigate the factors (age, intraoperative hypotension, number of pack-years smoked) associated with POD.

1.3.3 Null Hypothesis

- There is no association between the frailty index and the incidence of POD.
- There is no association between factors (age, intraoperative hypotension, number of pack-years smoked) and POD.

1.3.4 Alternative Hypothesis

- There is an association between the frailty index and the incidence of POD.
- There is an association between factors (age, intraoperative hypotension, number of pack-years smoked) and POD.

CHAPTER 2: STUDY PROTOCOL

2.1 Research Methods and Methodology

2.1.1 Research Design

Prospective cohort Study

2.1.2 Study Duration

4 months (December 2021 – March 2022)

2.1.3 Study Population

Surgical patients aged 65 and above and planned for general or regional anaesthesia in Hospital Universiti Sains Malaysia (HUSM)

2.1.4 Study Area

Hospital Universiti Sains Malaysia (HUSM)

2.2 Subject Recruitment Criteria

2.2.1 Inclusion Criteria

- Age 65 and above
- Planned for elective or emergency surgery

2.2.2 Exclusion Criteria

- A pre-existing history of psychiatric disease
- Baseline cognitive impairment or dementia (MOCA score <24)
- Illiterate (Unable to read/write)

- Active history of substance abuse
- Significant hearing or speech impediment
- Planned admission to ICU post-operatively
- Planned for second surgery within five days after index surgery

2.3 Sample Size Estimation

Objective 1: Incidence of POD

To determine the incidence of POD among elderly patients scheduled for surgeries, a total of 139 patients is needed to achieve 5% precision in estimating incidence, which was 10% from local data (40).

With a 10% dropout rate, the sample size required is 153 patients.

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where

n = sample size,

Z = Z statistic for a level of confidence,

P = Expected incidence or proportion

d = precision

Objective 2: Frailty and POD

- We use PS software (Dupont & Plummer, 1997) to calculate the sample size by comparing 2 proportions.
- To detect the difference of 26% in the incidence of POD (P0 = 16% versus P1 = 42%) between the 2 study groups with 80% power and alpha 0.05, we need 33 frail and 103.29 non-frail patients (Total = 136.29 patients).
- Po, the incidence of POD among non-frail was estimated as 16% (41)

- The ratio of non-frail: frail cases is 3.13.
- With a 10% dropout rate, the sample size required is 150 patients.

Objective 3: Factors associated with POD

Age

- We use PS software (Dupont & Plummer, 1997) to calculate the sample size by comparing 2 means.
- In a previous study (33), the age of the subjects with and without POD was normally distributed with a standard deviation of 6.9.
- If the true difference in the means is 6.3, we will need to study 11 patients with POD and 84 patients without POD (Total = 95 patients) to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8.
- The Type I error probability associated with this test of this null hypothesis is 0.05.
- With a 10% dropout rate, the sample size required is 105 patients.

Number of pack-years smoked

- We use PS software (Dupont & Plummer, 1997) to calculate the sample size by comparing 2 means.
- In a previous study (34), the number of pack-years smoked for subjects with and without POD was normally distributed with a standard deviation of 27.53.
- If the true difference in the means is 15.63, we will need to study 37 patients with POD and 74 patients without POD (Total = 111 patients) to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8.

- The Type I error probability associated with this test of this null hypothesis is 0.05.
- With a 10% dropout rate, the sample size required is 122 patients.

Intra-operative hypotension

- We use PS software (Dupont & Plummer, 1997) to calculate the sample size by comparing 2 proportions.
- To detect the difference of 32% in the incidence of POD (P0 = 12% versus P1 = 44%) between the 2 study groups with 80% power and alpha 0.05, we need 16 patients with intra-operative hypotension and 73 patients without intra-operative hypotension (Total = 89 patients).
- Po, the incidence of POD among patients without intra-operative hypotension was estimated as 12% (35).
- The ratio of patients without intra-operative hypotension: patients with intra-operative hypotension is 4.56.
- With a 10% dropout rate, the sample size required is 98 patients.

  The final sample size required is 153 patients.

2.4 Sampling Method

Consecutive sampling

2.5 Subject Recruitment

All patients aged 65 and above admitted for operation in HUSM were screened for eligibility to be included in the study. Patients were interviewed using the MMoCA test to assess for baseline cognitive function. Patients were then screened for inclusion and exclusion criteria of the study. Once eligible to participate in the study, research

consent was taken from the patients. If the patient faced a problem in understanding the study process (e.g. due to language or technical terms difficulty), the study process was explained to the primary caretaker. At any time during the study, the participant was allowed to withdraw from the study if they wished to do so. Withdrawal from the study would not affect future treatments that they would receive. The study concluded once the sample size target was achieved.

All recruited patients were interviewed using questionnaires. All patients' demographic profiles (age, race, smoking history, physical functional status using NYHA classification and METs) were collected. These data were routinely asked for prior to all operations. Each patient was screened pre-operatively by interviewing using the MMoCA Test to assess for baseline cognitive function. All investigators underwent training and certification for MoCA Test at www.mocatest.org. Patients were also assessed, pre-operatively by interviewing for the presence of frailty using the FIFE score. If patients were unable to answer, patients' caretakers could answer on behalf of the patients.

In accordance with best practices, patients at risk of developing POD would be counselled before surgery with steps taken to minimise the risk. The conduct of anaesthesia were left to the discretion of the anaesthesiologist in charge. Anaesthetic techniques, intra-operative haemodynamic parameters, and duration of the anaesthesia were recorded.

Post-operatively, patients were assessed for POD development in PACU and in the wards by interviewing them using the M3D-CAM and Nu-DESC screening tools. In PACU, patients were assessed 30-60 mins upon arrival in the PACU. In the wards, patients were assessed twice daily, at 7-8 a.m. and 5-6 p.m., for the immediate five days post-operatively or until discharge (whichever occurred first).

The study flow chart represents the overview of the study.

2.6 Research Tools

2.6.1 Malay version of Montreal Cognitive Assessment (MMoCA)

Montreal Cognitive Assessment (MoCA) has been shown to be a sensitive tool for cognitive assessment. The Malay language is a more familiar language across the multiracial population of Malaysia. The Malay version of Montreal Cognitive Assessment (MMoCA) is validated by Cheah et al. (42). With a cut-off point of less than 22, MMoCA has a sensitivity of 0.824 and a specificity of 0.818 to detect cognitive impairment.

2.6.2 Frailty Index for Elders (FIFE) score

The Frailty Index for Elders (FIFE) was developed by Tocchi et al. (43) to assess frailty risk in older adults using items collected in existing nursing datasets. The aim is to maximise nursing data use and reduce patient testing fatigue.

FIFE is a 10-item assessment instrument with scores ranging from 0-10. A score of 4 or greater indicates frailty. FIFE has strong validity (content validity analysis range 0.50-1.0).

FIFE is a widely available score and has been used in other studies for frailty assessment (44,45).

2.6.3 Malay 3D-CAM (M3D-CAM)

The 3D-CAM tool is validated as a rapid instrument for identifying delirium. The Malay version of the 3D-CAM was validated with a sensitivity of 80% for assessor 1 and 90% for assessor 2, while the specificity was 96.7% for both raters. The inter-observer reliability was 85.3% (40).

2.6.4 Nursing Delirium Screening Scale (Nu-DESC)

The Nu-DESC is a delirium screening instrument. It was validated in 59 oncology/internal medicine inpatients and had a sensitivity and specificity of 85.7% and 86.8%, respectively (46).

The Nu-DESC has also been validated for use in the intensive care unit, with a sensitivity and specificity of 83 and 81%, respectively. When used to evaluate patients in the PACU, Nu-DESC has a sensitivity and specificity of 95 and 87%, respectively. As for post-operative inpatients, Nu-DESC has a sensitivity and specificity of 98 and 92%, respectively.

All the questionnaires were conducted via interview.

2.7 Term of reference

The following table 1 presents the study variables and their operational definitions.

TABLE 1: Operational definitions of the study variables

Variables	**Operational definitions of the study variables**	**Tools used to diagnose**
Age	Age (in years) of the patient during the time of operation	
Number of pack-years smoked	Amount of cigarettes smoked up to the time of operation, with a pack equal to 20 cigarettes	
Intraoperative hypotension	Any documented mean arterial pressure (MAP) less than or equal to 60 mmHg, or MAP dropped more than 20% of baseline, or the prolonged use of a vasoactive substance	
Pre-operative Frailty	Frailty that is detected before operation	A score of equal or greater than 4 in FIFE score
Post-operative Delirium	Development of delirium during five days of hospital stay post-operatively or until discharge from the hospital (whichever occurs first).	Fulfilling criteria 1, 2 and one of the criteria 3 or 4 of the M3D-CAM tool

2.8 Data Collection Method

All the collected data were entered and analysed using IBM SPSS Statistics version 26. Source document verification and accuracy crosschecking were done. All the data were kept under the responsibility of the principal investigator for at least 3 years.

2.9 Proposed Data Analysis

2.9.1 Descriptive data analysis

Numerical data were presented as mean with standard deviation or median with interquartile range based on their normality of distribution. Categorical data were presented as frequency with percentage.

2.9.2 Univariable Data Analysis

Continuous data were analysed using independent t-test if normally distributed; otherwise, a non-parametric test (Mann-Whitney test) was used. Categorical data were analysed using Chi-square test. Significant variables were then analysed using univariable logistic regression analysis. Unadjusted Odds ratio, 95% CI and *p*-values of each variable were obtained.

2.9.3 Multivariable Data Analysis

To adjust for confounding factors, multivariable logistic regression was performed for variables which return a *p*-value ≤ 0.25 from the univariable logistic regression. *P*-values of <0.05 was deemed significant. Results of adjusted odds ratio, 95% CI and *p*-values were reported.

2.10 GANTT Chart

TABLE 2: Gantt chart milestone

Project activities	*2021*												*2022*											
	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
Research proposal planning																								
Proposal presentation at the department level																								
Ethics board presentation and ethical clearance																								
Data collection																								
Data analysis																								
Research write-up																								
Thesis submission																								

2.11 Study Flow Chart

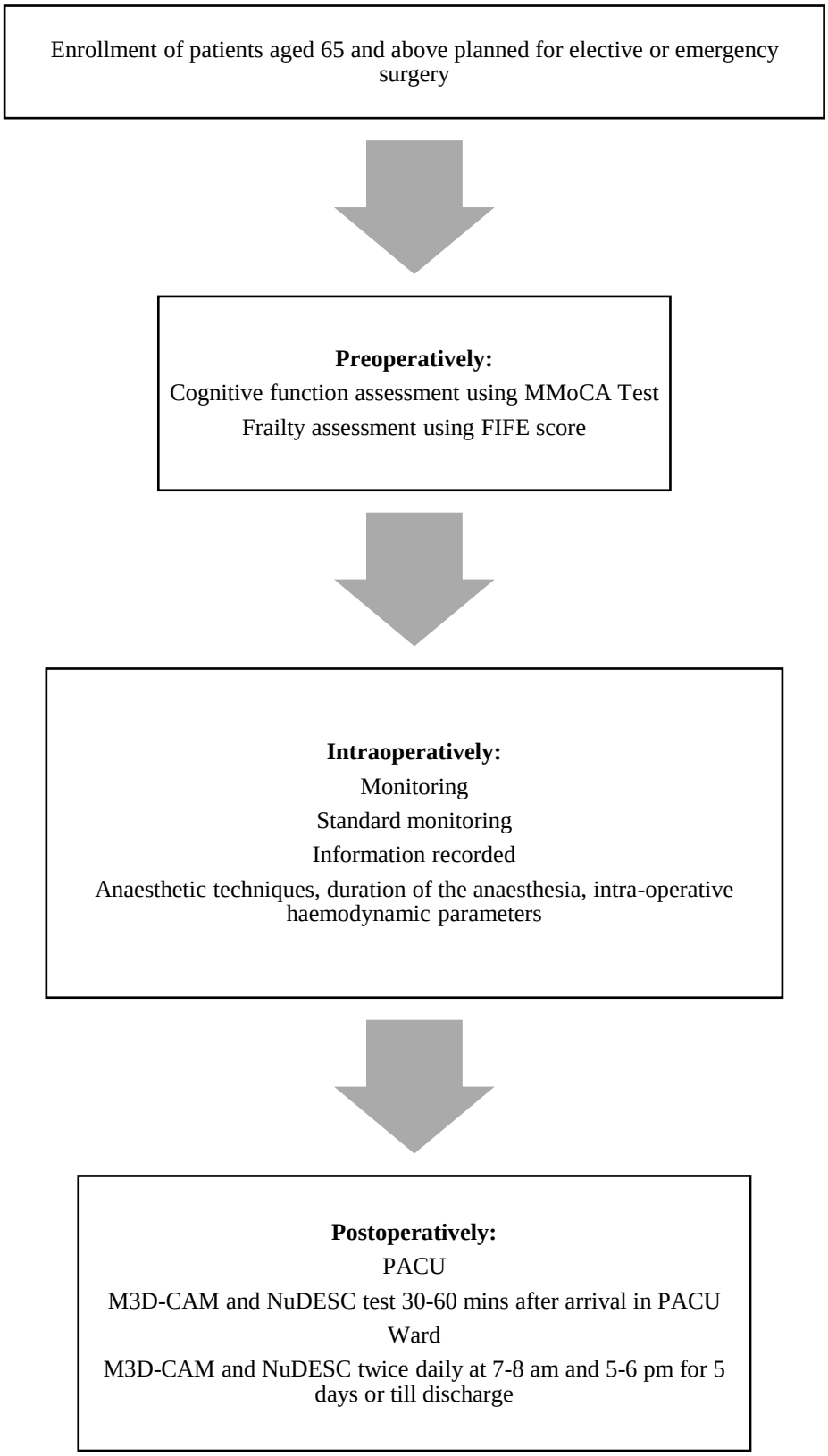


Figure 1: Study Flowchart

2.12 Ethical Consideration

2.12.1 Subject vulnerability

All eligible subjects were counselled for study participation. If they faced problems in understanding the study process, their primary caretaker would be explained. Subjects were given full freedom to participate or not without affecting their anaesthesia care during the operation or post-operatively. Subjects could withdraw from the study at any time without affecting their future treatments.

All subjects who were confirmed to have delirium were investigated for other possible reversible causes of delirium and were managed accordingly, including referrals to other specialties if required, e.g., to geriatrician/psychiatrist.

2.12.2 Declaration of absence of conflict of interest

There is no conflict of interest.

2.12.3 Privacy and confidentiality

All forms were anonymous and were entered into SPSS software. Only research team members were allowed access to the data. Data were presented as grouped data which did not allow the identification of the responders individually.

2.12.4 Community sensitivities and benefits

This study would benefit the community through early identification of subjects developing POD. If indicated, there would be an appropriate referral for cognitive assessment after discharge from the hospital. This study could also be a guide to establishing local guidelines in the intra-operative management of elderly patients.

2.13 Ethical Approval

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)

Human Research Ethics Committee USM (HREC)

Universiti Sains Malaysia
Kampus Kesihatan
16150 Kubang Kerian, Kelantan. Malaysia.
Tel. : +609 - 767 3000/2354/2362
Fax. : + 609 - 767 2351
Email : jepem@usm.my
Laman Web : www.jepem.kk.usm.my
www.usm.my

10th November 2021

Dr. Ng Li En
Department of Anesthesiology
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/21080572
Protocol Title : The Prevalence of Post-Operative Delirium among Elderly Patients and its Associated Factors.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/21080572**, which should be used for all communications to JEPeM-USM in relation to this study. This ethical approval is valid from **10th November 2021** until **9th November 2022.**

Study Site: Hospital Universiti Sains Malaysia.

The following researchers are also involved in this study:
1. Dr. Laila Ab. Mukmin
2. Assoc. Prof. Dr. Saedah Ali

The following documents have been approved for use in the study.
1. Research Proposal

In addition to the above mentioned document, the following technical documents were included in the review on which this approval was based:
1. Patient Information Sheet and Consent Form (English version)
2. Patient Information Sheet and Consent Form (Malay version)
3. Malay version of Montreal Cognitive Assessment (MMoCA)
4. Frailty Index for Elders (FIFE) Score
5. Malay 3D-Cam
6. The Nursing Delirium Screening Scale (Nu-DESC) Score

While the study is in progress, we request you to submit to us the following documents:
1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2019: Continuing Review Application Form.**
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2019: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2019.**

JEPeM
JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2019: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

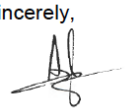
JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"WAWASAN KEMAKMURAN BERSAMA 2030"

"BERKHIDMAT UNTUK NEGARA"

Sincerely,



ASSOC. PROF. DR. AZLAN HUSIN
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

CHAPTER 3: MANUSCRIPT

3.1 Title Page

Title

The Incidence of Post-Operative Delirium Among Elderly Patients and Its Associated Factors

Running Head

To investigate the incidence and associated factors for post-operative delirium (POD) among elderly patients scheduled for surgeries.

Authors

Li En NG[1], Laila Ab MUKMIN[1], Saedah ALI[1], Wan Fadzlina Wan Muhd SHUKERI[1]

Institutional Affiliations:

[1] Department of Anaesthesiology and Intensive Care, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

Correspondence:

Dr Ng Li En

Department of Anaesthesiology and Intensive Care,

School of Medical Sciences, Health Campus,

Universiti Sains Malaysia

16150 Kubang Kerian, Kelantan, Malaysia.

Email: nglien@yahoo.com Mobile: +60146005662

No conflict of interest between the authors and other research parties should be declared.

3.2 Abstract

Background: Longer life span leads to an increase in elderly patients coming for surgery. The incidence of delirium is reported to be the highest in this population. This study was the first in Malaysia to investigate the incidence and predicting factors for post-operative delirium (POD) among local elderly patients undergoing various types of surgery.

Methods: A prospective cohort study was conducted on surgical patients aged 65 years and above who underwent surgery at Hospital Universiti Sains Malaysia (HUSM). Cognitive and frailty statuses were assessed pre-operatively using the Malay version of Montreal Cognitive Assessment (MMoCA) and the Frailty Index for Elderly (FIFE), respectively. Postoperatively, patients were evaluated for the development of POD twice a day for up to 5 days or until discharged.

Results: A total of 153 patients were recruited. The incidence of POD was 18.3% (95% CI: 12.5% – 25.4%). Factors found to be significantly associated with POD on multivariate analysis were FIFE score (adjusted odds ratio (AOR): 1.568; 95% CI: 1.16 – 2.10; p = 0.003), METS < 4 (AOR: 3.228; 95% CI: 1.01 – 10.31; p = 0.048), and presence of intra-operative hypotension (AOR: 7.687; 95% CI: 2.69 – 21.98; p = <0.001). New York Heart Association (NYHA) class, type of anaesthesia, duration of anaesthesia and surgery, estimated blood loss, need for intraoperative transfusion, and amount transfused were only significant on univariable analysis. All of our patients had complete resolution of POD, with a median duration of two days.

Conclusion: The incidence of POD among elderly patients coming for both emergency and elective surgeries is high. Patients at higher risk for POD should be identified. This allows precautionary steps to be taken to prevent the development of POD

and ensure primary teams are more vigilant post-operatively to detect and treat POD earlier.

***Keywords**: post-operative delirium, incidence, risk factors, elderly patients, frailty*

3.3 Introduction

Improvement in general living standards, health care, nutrition and education leads to a steady increase in the geriatric population. According to the Department of Statistics, Malaysia, it is estimated that by 2040, 14.5% of the population would be those aged 65 years and above (1). This indicates that there will be a significant increase in the geriatric population admitting to hospitals for surgeries.

Depending on the type of surgery, the incidence of post-operative delirium (POD) varies from 12% to 51% (2). Silva et al. (3) did a systemic review and found an overall pooled POD frequency of 23.8%. In fact, the incidence of POD increased at an average rate of 3% per year between the year 1995 and 2020. It has been shown that older patients have a significantly higher risk of developing POD (4).

The incidence of POD varies among different countries, probably related to the difference in the healthcare system. European countries reported incidences of 7.5% to 13.2% (5,6), whereas studies done in Thailand reported incidences of 5.4% to 11.6% (7,8). There is limited data regarding incidence of POD in our country. The only local study reported an incidence of 11.2% but that is only for elective surgery (9).

The gold standard to diagnose delirium is by following the criteria in The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)(10). However, this requires a trained and experienced physician, such as a geriatrician or