Neurology Asia 2021; 26(1) : 117 – 127

Understanding risk factors for postoperative delirium after elective surgery in a university-based tertiary hospital

[1]Jun Leong Cheong *MBBS*, [1]Ina Ismiarti Shariffuddin *MBChB MAnaes (Malaya)*, [2]Mahmoud Danaee *M.Sc PhD*, [3]Hui Min Khor *MBBS MRCP (UK)*, [1]Soon Chen Teang *MD,* [1]Pui San Loh *MMED (Anaes) FANZCA*

[1]Department of Anaesthesiology and Intensive Care; [2]Department of Social and Preventive Medicine; [3]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

Abstract

Background & Objectives: The incidence and associations of postoperative delirium (POD) varies in the literature. The objectives of this study were to determine the incidence and preoperative risk factors for POD in elective surgical patients and its association with one month mortality and length of hospital stay (LOS) in a tertiary hospital in Malaysia. *Methods:* A prospective observation study on patients above 65 years old was conducted. Demographic and perioperative data was collected for 5 days postoperatively or until discharge with delirium assessment tools 4-Abbreviation Test (4AT) and Confusion Assessment Method (CAM). *Results:* 447 elective cases were recruited over 6 months. 11.2% developed POD, most frequently on the first day postoperatively. The strongest independently associated risks factors were dependence on activities of daily living, ADL (Odd Ratio, OR:3.92, 95% Confidence interval, CI:1.52-10.11, $p<0.01$) followed by poor cognitive function (Montreal Cognitive Assessment, MOCA scores ≤19, OR:3.90, 95% CI:1.82-8.34, $P<0.01$. Univariate logistic regression showed that pre-existing cerebrovascular event, electrolyte imbalance, nature of surgery, frailty, malnutrition, and depression contribute significant risks. POD itself was associated with longer LOS, median 4(2-5) days with POD vs 1(1-3) day without ($p<0.01$) and one month mortality rate ($p=0.02$). Cases performed under combined regional anaesthesia and general anaesthesia had OR of 3.44 (95% CI:1.57-7.53, $p<0.01$) for POD.
Conclusions: Early identification of high risk patients should include recognizing poor cognitive function especially in ADL dependent elderly patients. Significant risks with types of anaesthesia and surgeries also indicate that future studies should focus on identifying underlying mechanisms of neurocognitive function in POD.

Keywords: Postoperative Delirium; elective surgery; incidence; risk factors; elderly

INTRODUCTION

The population around the world is aging. According to a report from the United Nations in 2015, the number of elderly population has risen in every country over the last few decades, especially those above 60 years old. It is postulated that the elderly will increase from 0.9 billion in 2015 to 1.4 billion in 2030 and in developing countries, life expectancy continues to rise.[1] When people live longer, the risks of requiring some form of surgery also increases.[2-4]

After surgery, a common complication among elderly population is postoperative delirium (POD). This is a symptom which most clinicians miss and take lightly of, but reports have shown that POD is associated with adverse events such as increased morbidity, mortality rates, added medical costs to patients and institutions by prolonging hospital stay.[5-8] Moreover, if left untreated, it will lead to long-term cognitive dysfunction (POCD).[9] Therefore, detection of patients with high risk of developing delirium is not only important to improve their medical care and costs but reduces the burden of long term and possibly, irreversible sequelae.

In 2019, a Malaysian study reported that 26.7% of older medical in-patients presented

Address correspondence to: Assoc Prof. Dr. Loh Pui San, Department of Anaesthesia and Intensive Care, Faculty of Medicine, University of Malaya, 59100 Kula Lumpur, Malaysia. Tel.:+601222698285, Email: lohps@ummc.edu.my

Date of Submission: 19 May 2020; Date of Acceptance: 8 January 2021

with delirium.[10] However, there is no literature to describe the incidence rate and preoperative risk factors of POD among elderly elective surgical populations in the same institution. The primary aim of this study was to identify the prevalence and risk factors of POD among elective elderly surgical patients in our institution and determine the association of POD with adverse events such as mortality and length of hospital stay. Lastly, this study also examines the association of different anaesthetic techniques towards POD in the surgical wards.

METHODS

Study design and participants

Using a cross-sectional design and convenience sampling method, this study was conducted with institutional approval (protocol MREC ID NO: 2019614-7519, ClinicalTrial.gov ID: U1111-1237-9788) in the main operating theatre (OT) and surgical wards in University Malaya Medical Centre from August 2019 to January 2020. A total of 515 electively admitted non-cardiac, non-neuro and non-urgent elderly surgical patients who were 65 years old and above with full Glasgow Coma Scale, American Society of Anaesthesiologists (ASA) score of 1-3, under anaesthesia care and able to communicate well were recruited within 6 months. Those who remained intubated postoperatively were excluded. Their eligibility was determined and screened via Electronic Medical Records preoperatively before being approached for consent. Recruited patients had face-to-face interviews conducted in languages they were most comfortable with, by two trained research assistants in surgical wards to gather all basic demographic data, medical history, frailty, nutritional, depression and cognitive assessments.

Postoperatively, all elderly patients were assessed daily in the ward by using delirium screening tools from the day of surgery until day five postoperatively or when discharged, whichever came earlier. Perioperative details such as mortality and length of hospital stay were traced through electronic medical records and telephone calls.

Instruments

Specific tools were selected based on feasibility and ease of administration within an acceptable timeframe of 30 minutes spent with each geriatric patient. This was taken into serious consideration to avoid a decrease in attention span in many patients due to anxiety, stress or exhaustion from the disease or surgery itself.

Preoperative assessment instruments:

1. *Fried Frailty Index (FFI)* has five components with each scoring either 0 or 1- weight loss, self-reported exhaustion, reduced physical activity, weakness in grip strength and slow walking speed.[11] We standardized the measurement of physical activity by using timed-up and go test (TUG) in patients who could mobilize with or without support on their own by asking them to walk at their normal speed from a sitting position to three meters away to turn back and sit down. Patients who could not walk or took more than 19 sec (>75th percentile) was taken as the cut-off for slow walking speed. An electronic hand dynamometer (Camry Model EH101) measured each patient's grip strength three times and then the highest value was used as the cut-off point compared to ≤25th percentile by gender (21.80 for male and 14.55 for female).[12] A total score of 0-2 as non-frail and 3 and above as frail was used.
2. *Geriatric Depression Scale (GDS)* is a validated 15-item screening test requiring answers 'Yes' or 'No adapted from the 30-item GDS. Fifteen is the maximum score, ≤5 less likely to have depression, >5 is suggestive of depression and ≥10 is almost indicative of depression.[13,14]
3. *Mini-nutritional assessment-Short Form (MNA-SF)* to screen for malnutrition with 6 items: decline in food intake in 6 months, loss of weight, or mobility, psychological stress or acute disease in 3 months, neuropsychological problems and Body Mass Index (BMI) or calf circumference. In bed bound patients calf circumference was taken using a measuring tape and a cut-off point of 31cm was used. MNA-SF scores of >7 represented no malnutrition and ≤7 denoted a state of malnutrition.[15,16]
4. *Montreal cognitive assessment (MOCA)* was used to detect poor cognitive function and has a maximum score of 30 in 8 domains (visuospatial, naming, memory, attention, language, abstraction, delayed recall and orientation). An additional point was added for low education level.[17-19] MOCA is only reliable and valid when a suitable cut-off score is derived to detect mild cognitive impairment in each specific study population.[20]

Delirium screening instruments for outcome measures:

1. *4-Abbreviation Test (4AT)* is a brief and simple delirium screening tool with four domains (alertness, Abbreviated Mental Test-4 (AMT-4), attention testing Months Backwards (MOYTB) and acute change or fluctuation of mental status). The 4AT scores from 0-12; 0 means unlikely delirium or severe cognitive impairment; 1-3 possible indicates cognitive impairment and ≥4, possible delirium ± cognitive impairment.[21-23]
2. *Confusion Assessment Method (CAM)* is a delirium screening tool used worldwide with a brief interview and cognitive testing followed by 4 items algorithm in DSM-III-R criteria. The items are (A) acute onset and fluctuation course, (B) inattention, (C) disorganized thinking and (D) altered level of consciousness. To diagnose delirium via CAM, item A and B must be positive, together with either C or B being positive.[24]

Statistical Analyses

The estimated sample size was calculated based on estimated prevalence of POD as the primary objective by using OpenEpi software.[25] Literature review has shown a 40.0% incidence rate of POD among elective non-cardiac surgical patients aged ≥65 years old.[26,27] Calculated with 95% confidence interval, the minimum sample required was 369. The minimum sample size for logistic regression analysis was also calculated using G power with effect size of 0.2 and 5% type one error (a=0.050) with a power (1-B) of 80% at number required of 384.[28] The estimated sample size needed was 442 after compensating for 15% of possible dropout.

All statistical analyses were performed using IBM SPSS Statistic 21.0. Continuous variables were presented as mean ± standard deviation (SD) for parametric distributed data; median and interquartile range for non-parametric distributed data. Categorical data was presented as frequency and percentage. Tests used were student independent t-tests (parametric distributed data), Mann Whitney U (non-parametric distributed date), Chi-square (categorical data) to compare all variables in patients with POD versus patients without POD. Associative preoperative risk factors for POD were analysed using univariate statistics and those which were significant were then entered in the multivariate logistic regression model. Adjusted odd's ratios (ORs), 95% confidence intervals (CI), and p-values were reported and considered as significant at 0.050 or less. Additional statistical analysis specifically for MOCA using Area under Receiver Operating Characteristics (ROC) curve was conducted in order to find the most suitable cut-off score before analysing its association with POD and reported as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, Youden's index and area under curve[18].

RESULTS

Patient characteristics

A total of 2,882 patients were admitted for elective surgery from August 2019 to January 2020. Eight hundred and seven (28%) patients were aged 65 years and above. Of these, 600 patients fulfilled the inclusion criteria and 515 patients (85.8%) were recruited (Figure 1). Fifty nine patients (11.4%) had their surgery cancelled after admission. Data was analyzed with 447 patients who had completed the pre and post-surgical assessments. Demographic characteristics of the participants are highlighted in Table 1.

The frailty index mean score for all participants was 1.33 ± 1.42, with 170 (38.0%), 181 (40.5%), and 96 (21.5%) categorised as non-frail, pre-frail and frail respectively. More than a quarter of patients had a GDS score of ≥ 5 suggestive of possible depression. MOCA assessment was performed in 444 patients with an average score of 20.38 ± 5.89 (Table 1). MOCA score of 19 was chosen as an optimal cut-off point to gain 72.3% sensitivity, 64.2% specificity, 20.2 positive predictive value and 94.8 negative predictive value and for subsequent analysis, the score was dichotomized to ≤19 for poor cognitive function (Figure 2).

Incidence, risk factor and outcome of postoperative delirium

Delirium was present postoperatively in 38 (8.5%) of patients according to the 4AT and 44 (9.8%) with the CAM assessment. Both the delirium assessment tool had strong positive correlation between them ($r=0.761$, $p<0.001$). Hence, a total of fifty patients (11.2%) were identified to have postoperative delirium from either the 4AT or CAM were included in the comparative analysis. The majority of patients developed POD on the day of surgery (68.0%), followed by 22.0% on day 1, 8.0% on day 2 and 2.0% on day 4 and the duration of postoperative delirium lasted for 24

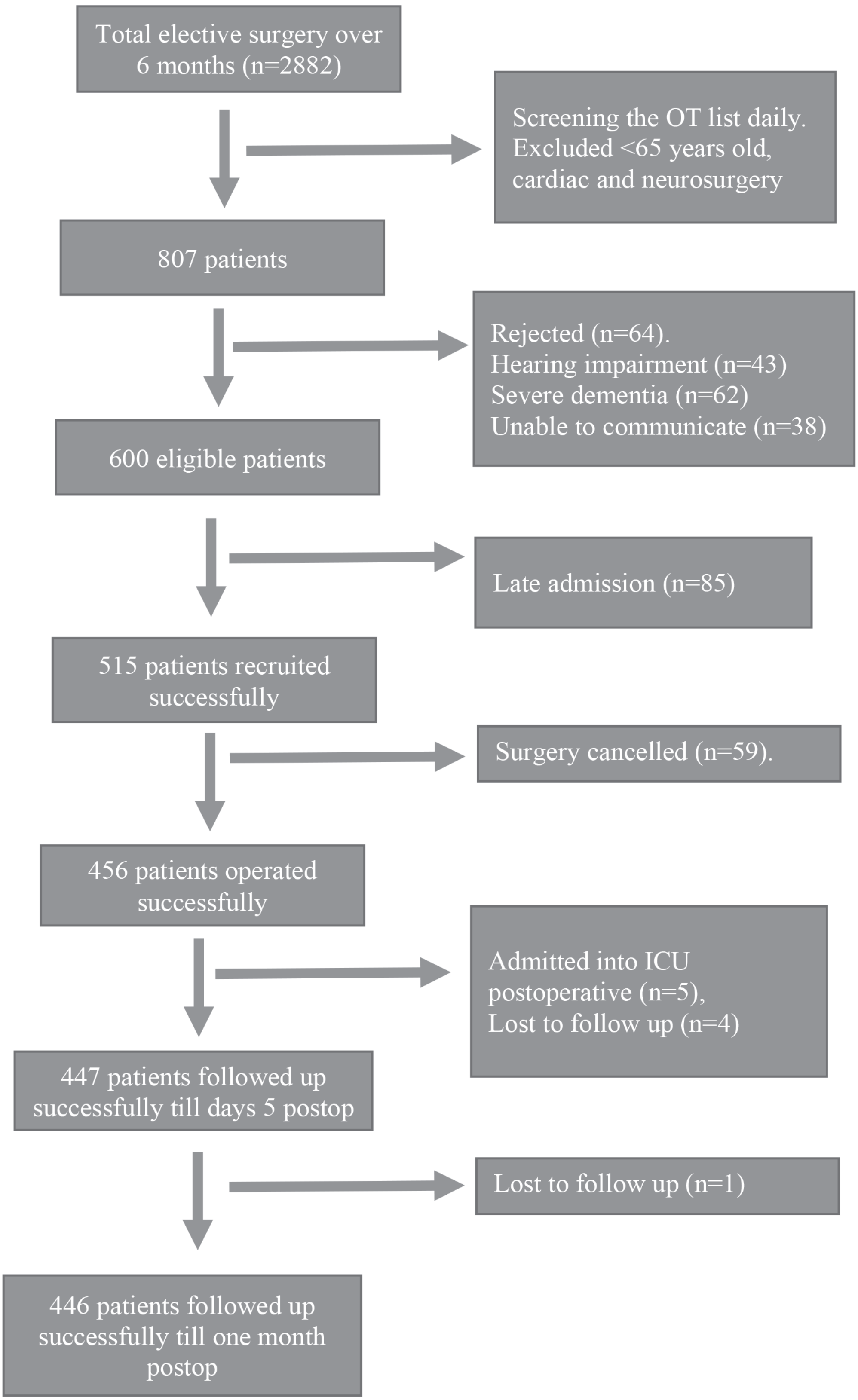

Figure 1. CONSORT diagram. OT, operating theatre; ICU, Intensive Care Unit

Table 1: Association between demographic and clinical data with postoperative delirium

Patient Demographics	Total (n=447)	No delirium (n=397)	Delirium (n=50)	p-value
Female gender, n (%)	240 (53.7)	213 (53.7)	27 (54.0)	0.96
Age (years), mean ± SD	73.23 ± 5.94	72.77 ± 5.56	76.82 ± 7.53	<0.01
Age ≥75 years, n (%)	166 (37.1)	137 (34.5)	29 (58.0)	<0.01
Ethnicity, n (%)				
Malay	107 (23.9)	103 (25.9)	4 (8.0)	0.03
Chinese	243 (54.4)	212 (53.4)	31 (62.0)	
Indian	93 (20.8)	79 (19.9)	14 (28.0)	
Living arrangement, n (%)				
Nursing home	5 (1.1)	4 (1.0)	1 (2.0)	0.81
Alone	34 (7.6)	30 (7.6)	4 (8.0)	
Family	409 (91.3)	363 (91.4)	45 (90.0)	
≤6 years of education, n (%)	193 (43.2)	166 (41.8)	27 (54.0)	0.11
ADL dependency*, n (%)	35 (7.8)	21 (60.0)	14 (28.0)	<0.01
Comorbidities, n (%)				
Diabetes mellitus	177 (39.6)	159 (40.1)	18 (36.0)	0.58
Hypertension	309 (69.1)	279 (70.3)	30 (60.0)	0.14
Asthma or lung disease	37 (8.3)	34 (8.6)	3 (6.0)	0.54
Heart Disease	106 (23.7)	95 (23.9)	11 (22.0)	0.76
Smoker or alcohol	35 (7.8)	33 (8.3)	2 (4.0)	0.29
Malignancy	74 (16.6)	69 (17.4)	5 (10.0)	0.19
Stroke/cerebrovascular accident	32 (7.2)	24 (6.0)	8 (16.0)	0.01
≥4 medications, n (%)	241 (53.9)	212 (53.4)	29 (58.0)	0.54
i **Perioperative details**				
American Society of Anaesthesiologists, n (%)				
1	27 (6.0)	26 (6.5)	1 (2.0)	0.06
2	343 (76.7)	308 (77.6)	36 (72.0)	
3	77 (17.2)	63 (15.9)	14 (28.0)	
Type of surgery, n (%)				
General orthopaedic	114 (25.5)	86 (21.7)	28 (56.0)	<0.01
General surgery	95 (21.3)	90(22. 7)	5 (10.0)	0.04
Other surgery	68 (15.2)	60 (15.1)	8 (16.0)	0.87
Ophthalmology	94 (21.0)	91 (22.9)	3 (6.0)	<0.01
Urology	76 (17.0)	70 (17.6)	6 (12.0)	0.32
Major surgery, n (%)	119 (26.6)	94 (23.7)	25 (50.0)	<0.01
Pre-op medical issue, n (%)				
Anxiety*	114 (25.5)	100 (25.2)	14 (28.0)	0.67
Sensory impairment*	146 (32.7)	127 (32.0)	19 (13.0)	0.39
Arrhythmias	13 (2.9)	10 (2.5)	3 (6.0)	0.17
Electrolyte imbalance*	96 (21.5)	77 (19.4)	19 (38.0)	<0.01
Sleep deprivation*	134 (30.0)	115 (29.0)	19 (38.0)	0.19
Pre-op medications, n (%)				
Benzodiazepines	5 (1.1)	4 (1.0)	1 (2.0)	0.53
Central nervous acting drugs	14 (3.1)	11 (2.8)	3 (6.0)	0.22
FFI, mean ± SD	1.33 ± 1.42	1.19 ± 1.33	2.42 ±1.60	<0.01
Frail (3-5), n (%)	96 (21.5)	72 (18.1)	24 (48.0)	<0.01
MNA, mean ± SD	11.25 ± 2.79	11.47 ±2.63	9.52 ±3.36	<0.01
Malnourished (≤ 7), n (%)	52 (11.6)	35 (8.8)	17 (34.0)	<0.01
GDS, mean ± SD	3.12 ± 2.74	3.30 ± 2.74	5.04 ± 2.86	<0.01
Depressed (≥ 5), n (%)	130 (29.1)	104 (26.2)	26 (52.0)	<0.01
MOCA, mean ± SD	20.38 ± 5.89	21.05 ± 5.25	14.89 ± 7.75	<0.01
Low MOCA (≤ 19), n (%)	178 (40.1)	141 (35.8)	37 (74.0)	<0.01

p<0.05 indicates statistical significance. Abbreviations - FFI: Fried Frailty Index; MNA: Mini nutritional assessment; GDS: Geriatric depression scale; MOCA: Montreal cognitive assessment.

*ADL dependency: Not able to take care of themselves due to immobility, feeding, psychological problems and so on; Anxiety: anxious and daily life affected; Sensory impairment: visual or hearing impairment; Electrolyte imbalance: sodium level <136 or >145 mmol/L, potassium level: 3.6 or >5.2 mmol/L; Sleep deprivation: insomnia or reduced in sleep hours compared to normal sleeping habit.

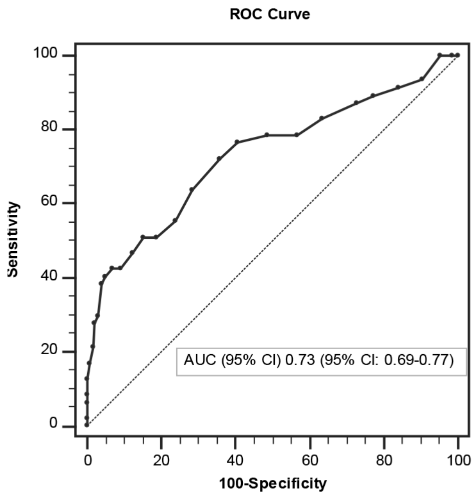

Figure 2. Receiver operating characteristic (ROC) curve of the MOCA classification of delirious patients.

hours in 60.0% of cases, 22% in 48 hours, 14.0% in 72 hours and 4.0% in 96 hours. Orthopedic surgery was the most common (25.5%) type of surgery with the highest rate of post-operative delirium. Of the 28 patients (56.0%) with delirium from orthopedic surgery, 19/28 (67.9%) were patients with hip fractures. Major surgeries compared to minor procedures were also significantly associated with POD (p<0.01) (Table 1).

The multivariate analysis results in Table 2 indicated that ADL dependency (OR: 3.92, 95% CI 1.52-10.11, p<0.01) and poor cognitive function with low MOCA score of <19 (OR: 3.90, 95% CI: 1.82-8.34, p<0.01) were independent predictors of postoperative delirium after adjusting for age ≥ 75 years, pre-existing cerebrovascular event, electrolyte imbalance, general surgery, ophthalmology surgery, nature of surgery, frailty, nutritional status, and depression (Table 2). POD was associated with adverse outcomes such as longer length of hospitalization and higher one month mortality risk, 3.8% deaths within one month postoperatively (p=0.02). The length of hospital stay was higher (median 4 (IQR 2-5) days) in patients who developed POD vs. those who did not (median 1 (IQR 1-3) day), p<0.01 (Table 3).

Table 2: Multivariate logistic regression on risk factors associated with postoperative delirium

Variables	Unadjusted OR, (95% CI)	P-value	Adjusted OR (95% CI)	p-value
Age ≥ 75 years old	2.62 (1.44-4.77)	<0.01	1.67 (0.83-3.35)	0.15
ADL dependency	6.96 (3.26-14.86)	<0.01	3.92 (1.52-10.11)	<0.01
CVA	12.96 (1.25-7.01)	0.01	1.85 (0.65-5.24)	0.25
Electrolyte imbalance	2.55 (1.37-4.75)	<0.01	1.27 (0.60-2.71)	0.54
General orthopaedic	4.60 (2.51-8.45)	<0.01	1.83 (0.81-4.12)	0.14
General surgery	0.38 (0.15-0.98)	0.04	0.63 (0.20-1.97)	0.43
Ophthalmology	0.22 (0.07-0.71)	0.01	0.31 (0.79-1.22)	0.09
Major surgery	3.22 (1.77-5.88)	<0.01	1.38 (0.66-2.88)	0.39
Frail (3-5)	4.17 (2.26-7.67)	<0.01	1.31 (0.60-2.85)	0.50
Malnourished (≤7)	5.33 (2.70-10.52)	<0.01	1.73 (0.71-4.19)	0.23
Depressed (≥5)	3.05 (1.68-5.55)	<0.01	1.89 (0.94-3.79)	0.07
Low MOCA (≤19)	5.11 (2.62-9.93)	<0.01	3.90 (1.82-8.34)	< 0.01

p<0.05 indicates statistical significance. Abbreviations - OR: Odds ratio, 95% CI: 95% confidence interval; MOCA: Montreal Cognitive Assessment; CVA: cerebrovascular event

Table 3: Association between postoperative complication and post-operative delirium

Variables		Total (N=446)	No delirium (n=396)	Delirium n=(50)	p-value
Complications					
LOS, median (IQR)		2 (1-3)	1 (1-3)	4 (2-5.25)	<0.01 e
One month mortality, n (%)	No	429 (96.2)	384 (89.5)	45 (10.5)	0.02 c
	Yes	17 (3.8)	12 (70.6)	5 (29.4)	

p<0.05 indicates statistical significance. Abbreviations - IQR: interquartile range; e: Mann Whitney U test; c: Chi-square; LOS: length of hospital stay

Anaesthetic technique and postoperative delirium

The relationship between types of anaesthesia techniques with POD was examined. In Table 4, results of the univariate logistic regression showed that only patients who were given combination of regional anaesthesia (RA) combined with general anaesthesia (GA) intraoperatively had a significantly higher risk of developing POD compared to patients who were given GA alone (OR: 3.44, 95% CI: 1.57-7.53, p<0.01) (Figure 3). As a description of the types of anaesthesia received for our study population who developed subsequent POD, one-third of them (34.0%) had surgeries done under GA alone, followed by combination of RA + GA (28.0%), RA only (22.0%), RA + sedation (10.0%) and local anaesthesia (LA) ± sedation (6.0%) (Figure 4).

DISCUSSION

The demography of this study population was probably one of the closest available description of the aging surgical population in local data. The elderly comprised 28.0% of all the patients undergoing elective surgery within a six month period in our institution. Considering cases in the emergencies and those outside recruitment hours were excluded, the actual proportion would have been higher and nearer to approximately 53.0% as reported.[29] Otherwise, this cohort represented the clinical geriatric elective patients well in terms of racial mix, gender, age, co-morbidities and types of surgeries.

Results showed that 11.2% postoperative elderly patients developed delirium for the first 5 days after surgery, similar to figures that have been published before; 11.4% after elective major surgery in US[30], 13.2% in Italy[31], 9.9% in Korea[32], and 11.6% in Thailand.[33] A further search in reviews has shown that the true incidence of POD will vary from institution to institution but nevertheless, our reported incidence still occurred within the range from a literature review of 25 cohort studies in 2006 which quoted it to be between 5.1 to 52.2%[34], and a pooled incidence of 18.4% in a meta-analysis.[35] In contrast, the incidence reported by Khor *et al.*, 2019 in the same institution but among a non-surgical population was double of what we found.[10] This provides evidence about the heterogeneity of this complication as a result of difference in characteristics of the study population, medical or surgical background and timing of assessment. With respect to the onset, most patients developed POD even from day of surgery onwards (68.0%) similar to previous studies.[33,36] This suggests that local institution should follow clinical guidelines of American Geriatric Society Expert Panel to assess delirium at least once per day from day one postoperatively.[37]

Table 4: Association of anaesthesia technique and postoperative delirium

Anaesthesia technique	No delirium (n=397)	Delirium (n=50)	OR (95% CI)	p-value
GA, n (%)	171 (43.1)	17 (34.0)	Reference	
RA, n (%)	79 (19.9)	11 (22.0)	1.40 (0.63-3.13)	0.41
RA + GA, n (%)	41 (10.3)	14 (28.0)	3.44 (1.57-7.53)	<0.01
RA + sedation, n (%)	23 (5.8)	5 (10.0)	2.19 (0.74-6.49)	0.16
LA ± sedation, n (%)	83 (20.9)	3 (6.0)	0.36 (0.10-1.28)	0.11

p< 0.05 indicates statistical significance. Abbreviations: OR: Odds ratio, CI: confidence interval; GA: general anaesthesia; RA: regional anaesthesia; LA: local anaesthesia

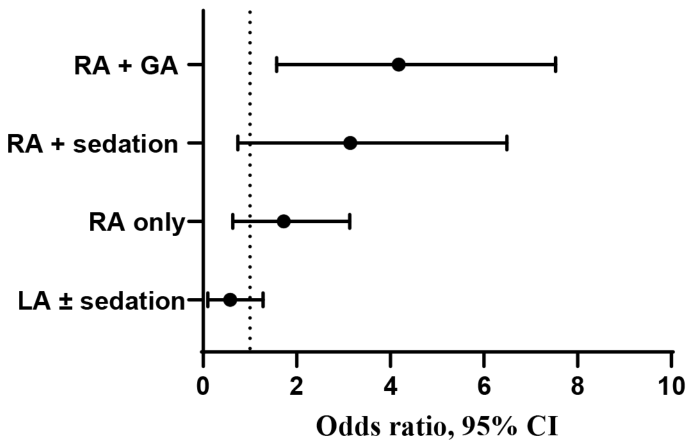

Figure 3. Odds ratio of different anaesthesia technique towards POD with general anaesthesia (GA) only as a reference group. Abbreviations: GA: general anaesthesia, RA: regional anaesthesia, LA: local anaesthesia

The most significant risk factors shown were low MOCA scores ≤19 and ADL dependency with both adjusted odds ratio of 3.90, (95% CI: 1.82-8.34, p<0.01) and 3.92 (95% CI 1.52-10.11, p<0.01) with both reported previously (Table 2).[35,38] Pre-existing cognitive impairment was a common risk factor for delirium among other elderly cohorts in the community-dwellings, nursing homes, medical and surgical wards.[30,33,39,40] Particular attention should be given to the overall low MOCA scores in our population and the derived optimal cut-off score of 19.[41] A validation study for MOCA in 2016 shared similar reports that the optimal cut-off score to detect mild cognitive impairment was 17/18 which is lower than in other countries possibly due to the influence of poorer education levels among the older population.[20] These findings suggest that we must create awareness in all medical staff about early POD screening by detecting not only severe cognitive function in general with Mini Mental State Examination but specifically mild cognitive function with a suitable instrument that can be used by all medical staff with minimal training.

However, many more risk factors which had been significant risk factors were not proven so in the final multivariate analysis. One of them was depression with an odds ratio of 1.89 (95% CI: 0.94-3.79, p=0.07).[42] The finding here should not negate screening of preoperative depression in the

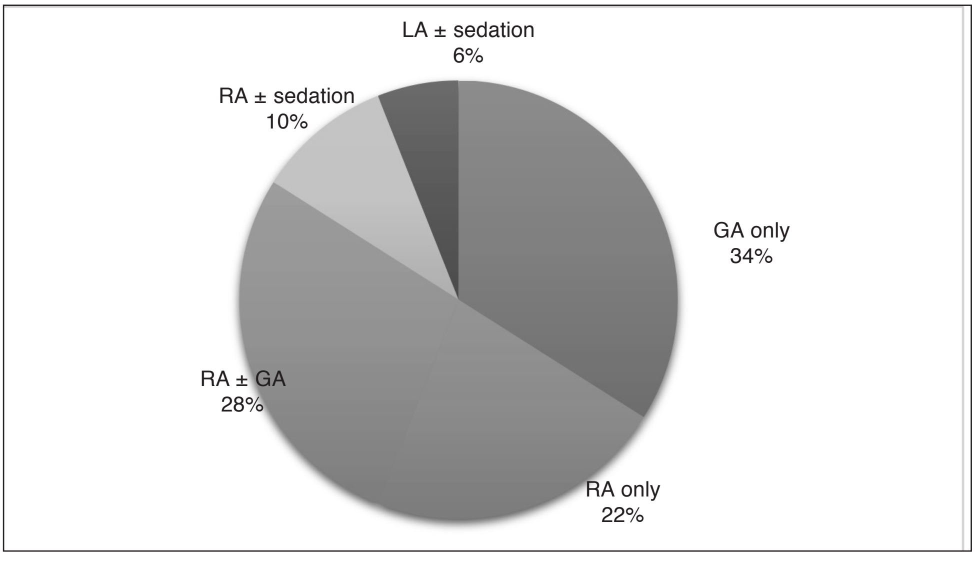

Figure 4. Percentage of anaesthesia technique among patients with POD. Abbreviations: GA: general anaesthesia, RA: regional anaesthesia, LA: local anaesthesia

elderly as it can fluctuate according to the current new situation from environmental stress, anxiety, and fear for the coming surgery.[27] In fact, both preoperative pain and depressive symptoms should be assessed together as they are both associated with increased risk of delirium independently and with substantial interaction suggests a cumulative effect[43]. The other risk factors with significant associations for unadjusted odd ratio were age above 75, major surgeries, pre-existing cerebrovascular event, electrolyte imbalance, frailty, and malnutrition (Table 2).[27,30,42,44,45]

Unlike most studies that focus on specific surgeries, the data collected had been heterogeneous in a way that all surgeries - orthopedic, general surgery, ophthalmology, urology and others were included. Clearly, patients who underwent orthopaedic surgeries had the highest risks of POD apart from ophthalmology, which was inversely so. These findings highlight that the complete mechanism in the development of delirium is still not fully understood. It has been postulated that delirium results from a wide variety of structural or physiological insults to the brain with reversible impairment of cerebral oxidative metabolism and abnormalities of multiple neurotransmitters.[46] Perhaps this proposed theory support the contrasting results and explains how less systemic disturbances in ophthalmology procedures cause less dysregulation of neuronal activity compared to damaging neurobehavioural effects in orthopaedic surgeries.

Unsurprisingly, the lasting effects and sequelae of POD culminates into significantly higher mortality and length of hospital stay with consistent results to strongly suggest that preventive care must be instituted early (Table 3).[8,33] Multifactorial interventions to optimize early mobility, improve sensory perception, cognition, infection control, appropriate pain management, medication review, nutrition support, optimized oxygenation, sleep hygiene and hydration have all been proven to be effective clinical settings.[35,47-49] Although, specialists in geriatric and anesthesiology play important roles, other healthcare personnel especially support from nursing staff should have equal roles in identifying those at high risk. A multidisciplinary approach needs to be taken into account since a lot is known about the association of POD to morbidity, mortality, increased length of hospital stay, institutionalization, ADL dependency and permanent dementia[50]. Reducing these complications will indirectly lessen medical costs to both patient and hospital.

The causative link of POD to the types of anaesthesia has so far been unproven by many systematic reviews.[51-53] But, we found significant association when RA and GA were combined intraoperatively, the risk of developing POD increases (OR: 3.44, 95% CI: 1.57-7.53, $p<0.01$) compared to GA alone and RA with or without sedation (Table 4). Possible explanations would be the undetected depth of anaesthesia during surgery and predominance of orthopaedic cases in this group that required both RA and GA. There is evidence that the depth of anaesthesia is associated with POD and if guided by processed EEG indices could reduce its risk in patients aged 60 years or over undergoing non-cardiac and non-neurological procedures.[54]

There are limitations to the interpretation of these results. It was designed to be cross-sectional, and hence, will be unable to provide inferential causality. Interviewer bias and language barrier can happen during face-to-face interviews by the assessors. The fluctuating change in the presentation of delirium at different times of the day especially at night could have been missed since interviews were conducted only once a day at different times. Lastly, all assessment could potentially be influenced by postoperative events such as uncontrolled pain or drowsiness from analgesia, weakness and exhaustion after surgeries.

In conclusion, this prospective study found an 11.2% incidence of POD among elective elderly surgical patients. ADL dependency, poor cognitive function and hip fracture surgery were found to be the most powerful independent risk factors for development of POD. Early identification of high risk patients is important to implement strategies to reduce the risk of POD. Further studies should focus on identifying underlying mechanisms in different surgeries and effects of neurocognitive function on POD.

ACKNOWLEDGEMENTS

We thank Dr Sumaiyah Binti Mat for her valuable input during the preparation of this manuscript and also acknowledge the contribution of Dr Teng Nien Shoon for helping in data collection.

DISCLOSURE

Financial support: This study was funded by K Inbasegaran Award 2019 under the Malaysian Society of Anaesthesiologists, Malaysia.

Conflict of interest: None

REFERENCES

1. United Nations, Department of Economic and Social Affairs, Population Division (2015) World Population Ageing (Report No. ST/ESA/SER.A/390). Retrieved from https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf.
2. Coale AJ. The effects of changes in mortality and fertility on age composition. The Milbank Memorial Fund quarterly. 1956;34(1):79-114.
3. Lindsay GB, Merrill RM, Hedin RJ. The contribution of public health and improved social conditions to increased life expectancy: An analysis of public awareness. *Community Med Health Edu* 2014;4:311.
4. Yashiro N. The economic factors for the declining birthrate. *Rev Population Social Policy* 1998;7:129-44.
5. Hamilton GM, Wheeler K, Di Michele J, Lalu MM, McIsaac DI. A systematic review and meta-analysis examining the impact of incident postoperative delirium on mortality. *Anesthesiology* 2017;127(1):78-88.
6. Han JH, Zimmerman EE, Cutler N, *et al*. Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. *Acad Emerg Med* 2009;16(3):193-200.
7. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM, Jr. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. *Arch Intern Med* 2001;161(20):2467-73.
8. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing* 2006;35(4):350-64.
9. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304(4):443-51.
10. Khor HM, Ong HC, Tan BK, *et al*. Assessment of delirium using the confusion assessment method in older adult inpatients in Malaysia. *Geriatrics* (Basel, Switzerland) 2019;4(3).
11. Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med* 2001;56(3):M146-56.
12. Sanchez-Garcia S, Sanchez-Arenas R, Garcia-Pena C, *et al*. Frailty among community-dwelling elderly Mexican people: prevalence and association with sociodemographic characteristics, health state and the use of health services. *Geriatr Gerontol Int* 2014;14(2):395-402.
13. Brink TL, Yesavage JA, Lum O, Heersema PH, Adey M, Rose TL. Screening tests for geriatric depression. *Clin Gerontologist* 1982;1(1):37-43.
14. Yesavage JA, Brink TL, Rose TL, *et al*. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;17(1):37-49.
15. Kaiser MJ, Bauer JM, Ramsch C, *et al*. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging* 2009;13(9):782-8.
16. Vellas B, Guigoz Y, Garry PJ, *et al*. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition* 1999;15(2):116-22.
17. Ciesielska N, Sokolowski R, Mazur E, Podhorecka M, Polak-Szabela A, Kedziora-Kornatowska K. Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. *Psychiatria Polska* 2016;50(5):1039-52.
18. Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off value: the case of tests with continuous results. *Biochem Med* 2016;26(3):297-307.
19. Nasreddine ZS, Phillips NA, Bedirian V, *et al*. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53(4):695-9.
20. Din NC, Shahar S, Zulkifli BH, Razali R, Chyn AV, Omar A. Validation and optimal cut-off scores of the Bahasa Malaysia version of the Montreal cognitive assessment (MoCA-BM) for mild cognitive impairment among community dwelling older adults in Malaysia. *Sains Malaysiana* 2016;45(9): 1337-43.
21. Bellelli G, Morandi A, Davis DH, *et al*. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing* 2014;43(4):496-502.
22. Saller T, MacLullich AMJ, Schafer ST, *et al*. Screening for delirium after surgery: validation of the 4 A's test (4AT) in the post-anaesthesia care unit. *Anaesthesia* 2019;74(10):1260-6.
23. Shenkin SD, Fox C, Godfrey M, *et al*. Delirium detection in older acute medical inpatients: a multicentre prospective comparative diagnostic test accuracy study of the 4AT and the confusion assessment method. *BMC Med* 2019;17(1):138.
24. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Int Med* 1990;113(12):941-8.
25. Dean AG, Sullivan KM, Soe MM. (2013) OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. Retrieved from http://www.openepi.com/Menu/OE_Menu.htm.
26. Leung JM, Sands LP, Lim E, Tsai TL, Kinjo S. Does preoperative risk for delirium moderate the effects of postoperative pain and opiate use on postoperative delirium? *Am J Geriatr Psychiatry* 2013;21(10):946-56.
27. Leung JM, Sands LP, Mullen EA, Wang Y, Vaurio L. Are preoperative depressive symptoms associated with postoperative delirium in geriatric surgical patients? *J Gerontol A Biol Sci Med* 2005;60(12):1563-8.
28. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature: standards for use and reporting, with particular attention to one medical domain. *J Clin Epidemiol* 2001;54(10):979-85.
29. Yang R, Wolfson M, Lewis MC. Unique aspects of the elderly surgical population: An anesthesiologist's perspective. *Geriatr Orthop Surg Rehabil* 2011;2(2):56-64.

30. Litaker D, Locala J, Franco K, Bronson DL, Tannous Z. Preoperative risk factors for postoperative delirium. *Gen Hosp Psychiatry* 2001;23(2):84-9.
31. Ansaloni L, Catena F, Chattat R, *et al*. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. *Br J Surg* 2010;97(2):273-80.
32. Kim KI, Park KH, Koo KH, Han HS, Kim CH. Comprehensive geriatric assessment can predict postoperative morbidity and mortality in elderly patients undergoing elective surgery. *Arch Gerontol Geriatr* 2013;56(3):507-12.
33. Iamaroon A, Wongviriyawong T, Sura-arunsumrit P, Wiwatnodom N, Rewuri N, Chaiwat O. Incidence of and risk factors for postoperative delirium in older adult patients undergoing noncardiac surgery: a prospective study. *BMC Geriatr* 2020;20(1):40.
34. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. *J Am Geriatr Soc* 2006;54(10):1578-89.
35. Watt J, Tricco AC, Talbot-Hamon C, *et al*. Identifying older adults at risk of delirium following elective surgery: A systematic review and meta-analysis. *J Gen Int Med* 2018;33(4):500-9.
36. Lee H, Ju JW, Oh SY, Kim J, Jung CW, Ryu HG. Impact of timing and duration of postoperative delirium: a retrospective observational study. *Surgery* 2018;S0039-6060(18)30035-7.
37. Inouye SK, Robinson T, Blaum C, *et al*. Postoperative delirium in older adults: Best practice statement from the American Geriatrics Society. *J Am Coll Surg* 2015;220(2):136-148.e131.
38. Raats JW, Steunenberg SL, de Lange DC, van der Laan L. Risk factors of post-operative delirium after elective vascular surgery in the elderly: A systematic review. *Int J Surg* (London, England) 2016;35:1-6.
39. de Castro SM, Ünlü Ç, Tuynman JB, *et al*. Incidence and risk factors of delirium in the elderly general surgical patient. *Am J Surg* 2014;208(1):26-32.
40. Andrews L. Preoperative cognition screening and postoperative delirium in older surgical patients. 2016.
41. Milani SA, Marsiske M, Cottler LB, Chen X, Striley CW. Optimal cutoffs for the Montreal Cognitive Assessment vary by race and ethnicity. *Alzheimers Dement* (Amst) 2018;10:773-81.
42. Leung JM, Tsai TL, Sands LP. Brief report: preoperative frailty in older surgical patients is associated with early postoperative delirium. *Anesth Analg* 2011;112(5):1199-201.
43. Kosar CM, Tabloski PA, Travison TG, *et al*. Effect of preoperative pain and depressive symptoms on the development of postoperative delirium. *Lancet Psychiatry* 2014;1(6):431-6.
44. Louwers L, Schnickel G, Rubinfeld I. Use of a simplified frailty index to predict Clavien 4 complications and mortality after hepatectomy: analysis of the National Surgical Quality Improvement Project database. *Am J Surg* 2016;211(6):1071-6.
45. Shin JI, Keswani A, Lovy AJ, Moucha CS. Simplified frailty index as a predictor of adverse outcomes in total hip and knee arthroplasty. *J Arthroplasty* 2016;31(11):2389-94.
46. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry* 2013;21(12):1190-222.
47. Inouye SK, Bogardus ST, Jr., Charpentier PA, *et al*. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Eng J Med* 1999;340(9):669-76.
48. Mohanty S, Rosenthal RA, Russell MM, Neuman MD, Ko CY, Esnaola NF. Optimal perioperative management of the geriatric patient: A best practices guideline from the American College of Surgeons NSQIP and the American Geriatrics Society. *J Am Coll Surg* 2016;222(5):930-47.
49. Safavynia SA, Arora S, Pryor KO, Garcia PS. An update on postoperative delirium: Clinical features, neuropathogenesis, and perioperative management. *Curr Anesthesiol Rep* 2018;8(3):252-62.
50. American Phychiatric Association, DSM-5 Task Force (2013), Diagnostic and statistical manual of mental disorders: DSM-5™ , 5th ed. Arlington, VA, US: American Psychiatric Publishing, Inc.
51. Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. *J Alzheimers Dis* 2010;22(Suppl 3):67-79.
52. Patel V, Champaneria R, Dretzke J, Yeung J. Effect of regional versus general anaesthesia on postoperative delirium in elderly patients undergoing surgery for hip fracture: a systematic review. *BMJ Open* 2018;8(12):e020757.
53. World Health Organization (1993), The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. Geneva: World Health Organization
54. Punjasawadwong Y, Chau-In W, Laopaiboon M, Punjasawadwong S, Pin-On P. Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults. *Cochrane Database Syst Rev 2018;5(5):Cd011283*.