Perioperative Risk Factors for Recovery Room Delirium After Elective Non-Cardiovascular Surgery Under General Anaesthesia

Jiayi Wu
Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Shaojie Gao
Department of Anesthesiology, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Shuang Zhang
Department of Anesthesiology, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Yao Yu
Department of Anesthesiology, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Shangkun Liu
Department of Anesthesiology, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Zhiguo Zhang
School of Medicine and Health Management, Tongji Medical College, Huazhong University of Science and Technology

Wei Mei (wmei@hust.edu.cn)
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

https://orcid.org/0000-0001-6556-6628

Research

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Abstract

Background: Although postoperative delirium is a frequent complication of surgery, little is known about risk factors for delirium occurring in the post-anaesthesia care unit (PACU). The aim of this study was to determine pre- and intraoperative risk factors for the development of recovery room delirium (RRD) in patients undergoing elective non-cardiovascular surgery.

Methods: RRD was diagnosed according to the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). We collected perioperative data in 228 patients undergoing elective non-cardiovascular surgery under general anaesthesia, and performed univariate and multivariate logistic regression to identify risk factors related to RRD. PACU and postoperative events were recorded to assess the outcome of RRD.

Results: 57 patients (25%) developed RRD. On multivariate analysis, maintenance of anaesthesia with inhalation anaesthetic agents (OR=6.294, 95%CI 1.4-28.8, p=0.018), malignant primary disease (OR=3.464, 95%CI=1.396-8.592, p=0.007), American Society of Anaesthesiologists Physical Status (ASA-PS) III-V (OR=3.389, 95%CI= 1.401-8.201, p=0.007), elevated serum total or direct bilirubin (OR=2.535, 95%CI=1.006-6.388, p=0.049) and invasive surgery (OR=2.431, 95%CI=1.103-5.357, p=0.028) were identified as independent risk factors for RRD. RRD was associated with higher healthcare costs (31,428 yuan [17,872-43,674] versus 16,555 yuan [12,618-27,788], p<0.001), a longer median hospital stay (17 days [12-23.5] versus 11 days [9-17], p<0.001), and a longer postoperative stay (11 days [7-15] versus 7 days [5-10], p<0.001).

Conclusions: Identifying patients at high risk for RRD preoperatively would enable the formation of more timely postoperative delirium management programmes.

Introduction

Delirium is an acute brain organ dysfunction characterized by changes in level of consciousness, inattention, and disorganized thinking. Postoperative delirium, one of the most frequently encountered complications observed postoperatively, is a transient mental dysfunction that can result in increased morbidity, delayed functional recovery and prolonged hospital stay (Lepouse et al., 2006). In clinical practice, it is common to classify delirium as: (1) hypoactive subtype, characterized by reduced alertness, sedation and reduction of motor activity; (2) hyperactive form, associated with hyper-vigilance, psychotic features (e.g. hallucinations and delusions) and agitation (Fields et al., 2018); and (3) a more prevalent, mixed subtype with overlapping features of the previous two forms. Risk factors related to postoperative delirium have been identified in recent years (Inouye and Charpentier, 1996, Marcantonio et al., 1994). Inouye et al. reported that a risk factor intervention strategy significantly reduced the number and duration of delirium episodes (Inouye et al., 1999). Despite the importance of early recognition and timely management of delirium, recovery room delirium (RRD) in the post-anaesthesia care unit (PACU) has not been extensively investigated (Lepouse et al., 2006, Radtke et al., 2008, Sharma et al., 2005). As a result
of different diagnostic criteria and definitions of delirium, the incidence rate of RRD ranges from 3–21.1% (Juliebo et al., 2009, Lepouse et al., 2006, Radtke et al., 2008). Previous studies have mainly considered the hyperactive subtype of postoperative delirium (agitation) and not the hypoactive subtype (Lepouse et al., 2006). Several scales have recently been validated for assessing delirium in the PACU setting (Radtke et al., 2008). User-friendly and reliable tools, such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), allow the clinician to identify both hyperactive and hypoactive delirium in the postoperative setting (Card et al., 2015, Ely et al., 2001). CAM-ICU was validated for delirium assessment for mechanically ventilated critical ill patients (Ely et al., 2001) or non-intubated patients (Van Rompaey et al., 2008) in various setting such as surgical ICU (Guenther et al., 2010), emergency department (Han et al., 2010), mixed intensive care unit (van Eijk et al., 2009), surgical and trauma intensive care unit (Pandharipande et al., 2008), trauma unit (Soja et al., 2008), as well as PACU setting (Card et al., 2015). The CAM-ICU has a higher specificity than sensitivity for delirium when used in the PACU (Neufeld et al., 2013). Identifying patients at high risk for RRD preoperatively would enable the formation of more timely postoperative delirium management programmes (Munk et al., 2016). In this prospective study, we used the CAM-ICU to investigate the incidence of and risk factors associated with RRD in PACU after elective non-cardiovascular surgery under general anaesthesia.

Methods

Patients

This observational study was reviewed and approved by the Hospital Institutional Review Board of Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China, and registered with Clinical Trials (NCT00991913). All patients gave written informed consent before induction of anaesthesia. Patient older than of 18 years, who were admitted to the PACU after elective non-cardiovascular surgery under general anaesthesia during regular working hours, 9:00 am to 5:00 pm, were screened on eight randomly selected working days in June 2010. Patients were not included consecutively, due to a lack of personnel capacity for delirium evaluation in the busy PACU setting, but were representative of the patient population at the Tongji Hospital of the Huazhong University of Science and Technology, Wuhan, with respect to age, comorbidity and surgical procedures. The 12-bed PACU is located next to the operating rooms in Tongji Hospital, a general university teaching hospital. Two well-trained researchers in the PACU were responsible for patient evaluation. The anaesthetist in charge was responsible for patient discharge. Transition from PACU to surgical ward was considered safe when patient had achieved a Modified Aldrete Score of 9 (Aldrete, 1995).

All patients received 1 to 2 mg midazolam soon after arriving at the operating room. General anaesthesia was induced with propofol or etomidate in combination with fentanyl or remifentanil, followed by neuromuscular block with either vecuronium or rocuronium to facilitate endotracheal intubation. Anaesthesia was maintained by total intravenous anaesthesia (TIVA) using propofol or inhalation anaesthetics, either isoflurane or sevoflurane. The anaesthetist in charge was free to use opioid analgesics and muscle relaxants as needed. All patients were extubated in operation theatre at the end of
surgery. Extubation criteria were adequate oxygenation as indicated by oxygen saturation >92% on room
air, adequate ventilation as indicated by tidal volume >5 ml/kg, spontaneous respiratory rate >7 bpm, end
tidal carbon dioxide <50 mmHg and respiratory rate to tidal volume ratio less than 105, hemodynamically
stable, full reversal of muscle relaxation as indicated by sustained 5 second head lift or hand grasp,
neurologically intact as indicated by following verbal commands and intact cough or gag reflex,
normothermic as indicated by body temperature >35.5°C and < 38.5°C, as well as surgical considerations
(bleeding <100 ml within last 30 min). The anaesthesiologist responsible for the patient’s care was not
aware of the inclusion of the patient in the study before or during surgery.

Outcome

Our primary outcome was the presence of delirium in PACU determined by CAM-ICU (Ely et al., 2001). The
CAM-ICU Simplified Chinese version was obtained from http://www.icudelirium.org/. Ten minutes after
the arrival of patients in the PACU, the patients were assessed with Richmond Agitation-Sedation Scale
(RASS). If RASS was <-2, then the patient was assessed again after five minutes. If RASS was ≥-2 or
more, trained research assistants assessed delirium by the CAM-ICU.

Candidate predictors

Predictors in the present study were selected according to their clinical importance and based on the
results of previous studies. Demographic and pre- and intraoperative variables, including age, gender,
weight, American Society of Anaesthesiologists Physical Status (ASA-PS) (III-V versus I- II), preoperative
haemogram (white blood cell count, haemoglobin and haematocrit), preoperative serum biochemistry
(sodium, potassium, chloride, calcium, creatinine, blood urea nitrogen (BUN), cholesterol, uric acid,
glucose, total bilirubin, direct bilirubin, albumin, and total protein), preoperative routine hepatic enzymes
(alanine transaminase and aspartate transaminase), diagnosis of primary disease (malignant versus
benign), type of surgery (invasive versus mini-invasive), location of surgery (head and neck, intrathoracic,
 intra-abdominal, urogenital, musculoskeletal and spinal, or peripheral), maintenance of anaesthesia
(inhalation anaesthetic versus TIVA), preoperative and intraoperative haemodynamic parameters
(maximal and minimal heart rate, maximal and minimal systolic/diastolic blood pressure), preoperative
and intraoperative oxygen saturation, intraoperative fluid application, intraoperative loss of body fluid
(including blood loss, urinary production and any other obvious fluid loss), duration of surgery (≥2h
versus <2h), and perioperative hospital length of stay (LOS) were evaluated by viewing patient data
records. We categorised the laboratory values as normal or abnormal based on the normal values of the
clinical laboratory at Tongji Hospital. We performed univariate and multivariate analyses to identify
independent risk factors for delirium.

We also recorded PACU and postoperative events, including maximal heart rate, maximal and minimal
systolic blood pressure (SBP) in PACU, mean oxygen saturation in PACU, PACU-, postoperative- and total
hospital-LOS, total healthcare costs and healthcare costs per day during hospital stay, to assess the relationship between RRD on these variables.

**Statistical analysis**

Descriptive statistics were computed for all study variables. We used Kolmogorov-Smirnov and Shapiro-Wilk tests and normal-quantile plots to determine whether continuous variables were normally distributed. Because most variables had a non-normal or asymmetric distribution, we have reported results as median [25% - 75% percentiles] rather than mean ± SD and used nonparametric statistical tests. Differences between the two patient groups (delirium versus no delirium) were tested by univariate and multivariate methods. We conducted Chi-square tests (Fisher’s exact test) or Mann-Whitney U tests for each variable to reduce the number of variables included in the multivariate model. Variables with a p-value ≤ 0.05 or those identified in previous studies as potential risk factors were included in the multivariate analysis as described previously (Mei et al., 2010). In brief, we used backward-elimination to examine and determine risk factors for RRD, the entry criteria of 0.05 and removal of 0.10 for the model was set to find the possible risk factors. The statistical significance of partial regression coefficients was analyzed with Wald's chi-square test. Odds ratios (OR) with 95%-confidence intervals and the corresponding p-values were determined for each risk factor. A two-tailed p-value ≤ 0.05 was considered statistically significant. Interactions were not tested. Goodness of fit was determined by the Hosmer-Lemeshow statistic. All tests should be understood as constituting exploratory data analysis, such that no adjustments for multiple testing have been made. We used SPSS (Version 12, Chicago, Illinois 60606, United States) for all statistical analysis.

**Results**

During the study period, 766 patients were admitted to PACU. Exclusion criteria were age < 18 years (n=117), refusal to sign consent form (n=107), operation under regional anaesthesia (n=13), history of substance dependence (including opioid, alcohol or nicotine) (n=83), neurosurgical procedure (n=51), history of primary neurologic disease (n=30), and admission to PACU with stays of less than 10 minutes (n=132). Data from five patients were excluded because of incomplete interviews or missing data (Figure 1). Patients who received general anaesthesia but recovered in locations outside the recovery room (such as ambulance surgery, angiography, endoscopy or electroconvulsive therapy and cardiac surgery) were not included in this study.

Of the 766 patients admitted to the PACU during the study period, 233 were enrolled in this study and data from 228 (30%) patients were analysed (Figure 1). Of these patients, 57 (25%) had delirium and 171 had no delirium by CAM-ICU. On univariate analysis the two groups of patients differed with respect to age, ASA-PS, preoperative serum calcium, creatinine, glucose, total or direct bilirubin, serum albumin or total protein, diagnosis of primary disease (malignant or benign), type of surgery (mini-invasive or
invasive), location of surgery, maintenance of anaesthesia (inhalation anaesthetic or TIVA), total intraoperative fluid application, total intraoperative body fluid loss, and duration of surgery (Table 1).

On multivariate logistic regression analysis, maintenance of anaesthesia with an inhalation anaesthetic agent (OR=6.294, 95%CI 1.4-28.8, p=0.018), malignant primary disease (OR=3.464, 95%CI=1.396-8.592, p=0.007), ASA-PS III-V (OR=3.389, 95%CI=1.401-8.201, p=0.007), elevated serum total or direct bilirubin (OR=2.535, 95%CI=1.006-6.388, p=0.049) and invasive surgery (OR=2.431, 95%CI=1.103-5.357, p=0.028) were identified as independent risk factors for RRD in non-cardiovascular surgery patients (Table 2). The model fitted the data well (p=0.68 by the Hosmer-Lemshow test).

Patients with RRD had significantly higher SBP (141 mmHg [131-151] versus 132 mmHg [122-143], p=0.003), had higher total healthcare costs (31,428 yuan [17,872-43,674] versus 16,555 yuan [12,618-27,788], p<0.001) and healthcare costs per day (1459 yuan [1217-1966] versus 1696 yuan [1285-2106], p<0.05), stayed significantly longer in PACU (34 min [25-43.5] versus 29 min [23-37], p=0.015), had a longer median length of hospital stay (17 days [12-23.5] versus 11 days [9-17], p<0.001), and longer postoperative stay (11 days [7-15] versus 7 days [5-10], p<0.001) (Table 3).

**Discussion**

In order to make a reliable diagnosis of recovery room delirium in the very busy PACU setting, we chosen CAM-ICU based on following consideration: (1), CAM-ICU Flowsheet was proved to be a most reliable instrument for delirium assessment in many settings under various cultures including surgical ICU settings in Germany (Guenther et al., 2010, Luetz et al., 2010), a Swedish ICU setting (Larsson et al., 2007), a mixed medical-surgical ICU setting in Netherlands (Spronk et al., 2009), ICU setting in Chinese populations (Chuang WL et al., 2007) and PACU setting (Card et al., 2015); (2), CAM-ICU Flowsheet allow a quick assessment that need only need 50 seconds (interquartile range, 40–120 seconds) in patients with delirium vs 45 seconds (interquartile range, 40–75 seconds) in those without delirium to complete assessments (Guenther et al., 2010), which would be a great advantage for use of CAM-ICU in the busy settings such as PACU; (3), PACU settings are similar with surgical ICU settings in our hospital, and Chinese version of CAM-ICU was tested in a prior study in Chinese population shown good validity and reliability (Chuang WL et al., 2007).

According to CAM-ICU Flowsheet, one quarter of the patients in our study experienced RRD after general anaesthesia for elective non-cardiovascular surgery. Our results are similar to previous studies. Using the confusion assessment method (CAM) score, Sharma et al. reported 45% of elderly patients have RRD after hip-fracture repair surgery (Sharma et al., 2005). Using the Riker sedation–agitation scale, Lepouse et al. reported a delirium rate of 4.7% in adults in the PACU (Lepouse et al., 2006). Radtke et al reported that delirium in the recovery room was seen in 21 patients (14%) with the Diagnostic and Statistical Manual of Mental Disorders -IV (DSM-IV) criteria, in 11 patients (7%) with the CAM score, in four patients (3%) with the Delirium Detection Score (DDS), and in 37 patients (24%) with the Nursing Delirium Screening Scale (Nu-DESC) in the same patient population (Radtke et al., 2008). The prevalence rate for
delirium is greatly affected by the diagnostic formulation used (Voyer et al., 2009). The definition of the outcome measure, the length of the post-operative observation period and the patient population also cause differences in observed delirium rates. Exclusion criteria may also affect delirium rates, as cardiac surgery and neurosurgery are major contributors to postoperative delirium (Oh et al., 2008, Rudolph et al., 2009). Development of a widely accepted scale for detecting RRD in the postoperative setting would improve the timely diagnosis and management of RRD.

In the present study, a greater proportion of patients who received isoflurane or sevoflurane for maintenance anaesthesia experienced RRD than patients who received TIVA. Multivariate logistic regression analysis confirmed that isoflurane or sevoflurane for maintenance anaesthesia was the strongest risk factor for RRD. Previous studies have shown that inhalation anaesthetics such as isoflurane and sevoflurane are associated with postoperative delirium during recovery, particularly in young children or elderly patients (Aono et al., 1997). Very few studies have compared the incidence of delirium in adults anaesthetised with inhalation anaesthetics and those anaesthetised with propofol (Lepouse et al., 2006, Nishikawa et al., 2004). Lepouse et al. found more agitated patients had been anaesthetised with inhalation anaesthetics (62%) than with propofol (37%), but multivariate analysis did not confirm this result (Lepouse et al., 2006). Several studies have demonstrated a protective effect of propofol on postoperative delirium in children (Aouad et al., 2007), although this is controversial (Konig et al., 2009). Old rats are more profoundly influenced than young adult rats by isoflurane anaesthesia with regard to reductions in acetylcholine release and stress responses (Jansson et al., 2004). In addition, isoflurane-induced beta-amyloid protein oligomerization and apoptosis may contribute to the risk of postoperative cognitive dysfunction (Xie et al., 2006). Inhalation anaesthetic agents may thus increase the risk of postoperative delirium in specific populations. Testing this hypothesis in a well-designed prospective study may give further evidence in this direction.

Our data showed that patients undergoing surgery for malignant disease had higher incidence rate of RRD than patients with benign disease, and our multivariate logistic regression analysis confirmed malignant primary disease as an independent risk factor for RRD. Delirium occurs in 26–44% of cancer patients (Centeno et al., 2004), and 74% of patients with advanced cancer experience an episode of delirium (Bruera et al., 2009). Structural brain lesions and toxic or metabolic encephalopathy are thought to be causes of delirium in cancer patients (Doriath et al., 2007). Our data suggest that cancer patients undergoing surgery are at increased risk of RRD. Whether interventions for the prevention of delirium in cancer patients result in better short- or long-term outcomes after surgery are unknown. Prevention of delirium, however, is desirable for cancer patients and their anaesthetists (Siddiqi et al., 2007).

Univariate analyses showed a higher proportion of patients with RRD were ASA-PS III-V. Multivariate logistic regression analyses confirmed higher ASA-PS to be an independent risk factor for RRD. Clinical studies of such differences have produced conflicting results. Higher ASA-PS was identified as a risk factor after abdominal surgery in univariate but not in multivariate analysis in a previous study with a small patient population (Koebrugge et al., 2009). Illness severity was also associated with risk of delirium in a prospective study in hospitalised elderly (Francis et al., 1990). Moreover, delirium was the
most common neuropsychiatric complication experienced by patients with advanced illness, occurring in up to 85% of patients in the last weeks of life (Breitbart and Alici, 2008). Consistent with our study, Zakriya reported ASA physical status > II to be one of three significant predictors of postoperative delirium in geriatric patients (OR = 11.3, 95% CI 2.6–49.2, p < 0.001) (Zakriya et al., 2002).

Elevated serum total or direct bilirubin was more frequent in the RRD group, and multivariate analysis confirmed elevated total or direct serum bilirubin as an independent risk factor for RRD. Literature examining the relationship between bilirubin and delirium is limited. Dubois et al. demonstrated that abnormal bilirubin levels were associated with delirium in the intensive care unit (Dubois et al., 2001). Direct bilirubin is also assumed to play a role in the pathogenesis of hepatic encephalopathy (Muller et al., 1994). Due to the small number of patients with elevated bilirubin in our population (n = 30), we recommend caution in interpreting this result.

We showed that invasive surgery was an independent risk factor for RRD, in accordance with many previous studies. Low operative stress procedures such as cataract surgery resulted in delirium in 4.4% cases (Milstein et al., 2002), whereas higher stress procedures such as acute hip fracture surgery resulted in delirium in 40% of cases (Marcantonio et al., 2002). Shiiba reported that postoperative delirium was associated with extensive surgery for oral carcinoma (Shiiba et al., 2009). The degree of operative stress may be one of factors affecting RRD. Mini-invasive endoscopic surgery may prevent RRD in high-risk patients, but a proper randomised trial would be required to test this hypothesis.

Several studies demonstrated that older age (Koebrugge et al., 2009), abnormal preoperative sodium, potassium, or glucose levels (Galanakis et al., 2001, Marcantonio et al., 1994), diabetes mellitus (Gao et al., 2008), haemoglobin < 100 g/L (Gao et al., 2008), hypoalbuminemia (Robinson et al., 2009), longer operation time (Yildizeli et al., 2005), massive blood transfusion (Katznelson et al., 2009b), abnormal postoperative sodium, potassium, or glucose levels (Yildizeli et al., 2005), and postoperative haematocrit < 30% (Marcantonio et al., 1998), were important in influencing postoperative delirium. In our study, older age, decreased preoperative serum calcium, elevated preoperative serum glucose, decreased preoperative serum total protein or albumin, location of surgery, total intraoperative body fluid loss and intraoperative fluid application, and duration of surgery were significant in univariate but not multivariate analyses. Difference in study design, study population and the definition of outcome parameters may account for the variance. Some of these parameters seem to play a role, however, and should be included in future prospective studies.

We did not include some variables reported to influence postoperative delirium, such as a history of central nervous system disorder (Gao et al., 2008), pre-existing dementia (Robinson et al., 2009), preoperative depression (Katznelson et al., 2009b), preoperative alcohol use (Williams-Russo et al., 1992), postoperative pain (Oh et al., 2008), and preoperative medication such as beta-blockers (Katznelson et al., 2009a) in our analyses. Many of these variables are not included in our routine clinical data with enough reliability and we excluded patients with central nervous system disease. We are thus unable to report on the relative contribution of these factors in our patients.
Delirium in the surgical/trauma ICU cohort is associated with more days of mechanical ventilation and more days in ICU and hospital (Lat et al., 2009). Elderly subjects with postoperative delirium have a greater hospital LOS, are more likely to be institutionalised after discharge and have a higher six-month mortality than those without delirium (Robinson et al., 2009). As with former studies, our univariate analyses demonstrated that patients with RRD stayed longer in PACU, had longer hospital and postoperative stays, and had higher daily and total healthcare costs.

Our study has several limitations. Due to the observational design, a causal link between the proposed risk factors and RRD cannot be inferred. Choosing exclusion criteria to reduce the possibility of confounding factors may have influenced the results, as excluding patients undergoing cardiac surgery, as well as neurosurgery, may have reduced the incidence of RRD. The patient group we investigated was not a consecutive sample so selection bias is possible. However, the patients in this study were representative of the type of patients treated in our hospital.

**Conclusion**

This is the first study concerning recovery room delirium in Chinese populations. One quarter of elective non-cardiovascular surgery patients experienced RRD after general anaesthesia. On multivariate analysis, maintenance of anaesthesia with inhalation agents (sevoflurane or isoflurane), malignant disease, ASA-PS III-V, elevated serum total or direct bilirubin and invasive surgery were identified as risk factors for RRD in these patients. Our results show delirium is a major complication in the PACU that is associated with higher healthcare costs and increased post-operative LOS. Identifying patients at risk of RRD after non-cardiovascular surgery should enable earlier recognition and intervention in postoperative delirium, which may lead to improved short- and long-term patient outcomes (Siddiqi et al., 2007).

**Abbreviations**

ASA-PS  
American Society of Anaesthesiologists Physical Status;

BUN  
Blood urea nitrogen;

CAM  
Confusion assessment method;

CAM-ICU  
Confusion Assessment Method for the Intensive Care Unit;

DDS  
Delirium Detection Score;

DSM-IV  
Diagnostic and Statistical Manual of Mental Disorders -IV;

LOS  
Length of stay;
Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Hospital Institutional Review Board of Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China. All patients/participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors report no competing interests.

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Authors’ contributions

Study conception and design: WM, YY, SKL

Data acquisition: JYW, SJG, SZ, WM

Data analysis and interpretation: JYW, ZGZ, WM
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References

1. Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth. 1995;7(1):89–91.
2. Aono J, Ueda W, Mamiya K, Takimoto E, Manabe M. Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. Anesthesiology. 1997;87(6):1298–300.
3. Aouad MT, Yazbeck-Karam VG, Nasr VG, El-Khatib MF, Kanazi GE, Bleik JH. A single dose of propofol at the end of surgery for the prevention of emergence agitation in children undergoing strabismus surgery during sevoflurane anesthesia. Anesthesiology. 2007;107(5):733–8.
4. Breitbart W, Alici Y. Agitation and delirium at the end of life: "We couldn't manage him". JAMA 2008, 300(24):2898–910, E2891.
5. Bruera E, Bush SH, Willey J, Paraskevopoulos T, Li Z, Palmer JL, et al. Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. Cancer. 2009;115(9):2004–12.
6. Card E, Pandharipande P, Tomes C, Lee C, Wood J, Nelson D, et al. Emergence from general anaesthesia and evolution of delirium signs in the post-anaesthesia care unit. Br J Anaesth. 2015;115(3):411–7.
7. Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. Palliat Med. 2004;18(3):184–94.
8. Chuang WL, Lin CH, Hsu WC, Ting YJ, Lin KC. SC. M. [Evaluation of the reliability and validity of the Chinese version of the confusion assessment method for the intensive care unit]. Hu Li Za Zhi. 2007;54:45–52.
9. Doriath V, Paesmans M, Catteau G, Hildebrand J. Acute confusion in patients with systemic cancer. J Neurooncol. 2007;83(3):285–9.
10. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. Intensive Care Med. 2001;27(8):1297–304.
11. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29(7):1370–9.
12. Fields A, Huang J, Schroeder D, Sprung J, Weingarten T. Agitation in adults in the post-anaesthesia care unit after general anaesthesia. Br J Anaesth. 2018;121(5):1052–8.

13. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA. 1990;263(8):1097–101.

14. Galanakis P, Bickel H, Gradinger R, Von Gumppenberg S, Forstl H. Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications. Int J Geriatr Psychiatry. 2001;16(4):349–55.

15. Gao R, Yang ZZ, Li M, Shi ZC, Fu Q. Probable risk factors for postoperative delirium in patients undergoing spinal surgery. Eur Spine J. 2008;17(11):1531–7.

16. Guenther U, Popp J, Koecher L, Muders T, Wrigge H, Ely EW, et al. Validity and reliability of the CAM-ICU Flowsheet to diagnose delirium in surgical ICU patients. J Crit Care. 2010;25(1):144–51.

17. Han JH, Shintani A, Eden S, Morandi A, Solberg LM, Schnelle J, et al. Delirium in the emergency department: an independent predictor of death within 6 months. Ann Emerg Med. 2010;56(3):244–52 e241.

18. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA. 1996;275(11):852–7.

19. Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340(9):669–76.

20. Jansson A, Olin K, Yoshitake T, Hagman B, Herrington MK, Kehr J, et al. Effects of isoflurane on prefrontal acetylcholine release and hypothalamic Fos response in young adult and aged rats. Exp Neurol. 2004;190(2):535–43.

21. Juliebo V, Bjoro K, Krogseth M, Skovlund E, Ranhoff AH, Wyller TB. Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. J Am Geriatr Soc. 2009;57(8):1354–61.

22. Katznelson R, Djaiani G, Mitsakakis N, Lindsay TF, Tait G, Friedman Z, et al. Delirium following vascular surgery: increased incidence with preoperative beta-blocker administration. Can J Anaesth. 2009a;56(11):793–801.

23. Katznelson R, Djaiani GN, Borger MA, Friedman Z, Abbey SE, Fedorko L, et al. Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. Anesthesiology. 2009b;110(1):67–73.

24. Koebrugge B, Koek HL, van Wensen RJ, Dautzenberg PL, Bosscha K. Delirium after abdominal surgery at a surgical ward with a high standard of delirium care: incidence, risk factors and outcomes. Dig Surg. 2009;26(1):63–8.

25. Konig MW, Varughese AM, Brennen KA, Barclay S, Shackleford TM, Samuels PJ, et al. Quality of recovery from two types of general anesthesia for ambulatory dental surgery in children: a double-blind, randomized trial. Paediatr Anaesth. 2009;19(8):748–55.

26. Larsson C, Axell AG, Ersson A. Confusion assessment method for the intensive care unit (CAM-ICU): translation, retranslation and validation into Swedish intensive care settings. Acta Anaesthesiol
27. Lat I, McMillian W, Taylor S, Janzen JM, Papadopoulos S, Korth L, et al. The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. Crit Care Med. 2009;37(6):1898–905.

28. Lepouse C, Lautner CA, Liu L, Gomis P, Leon A. Emergence delirium in adults in the post-anaesthesia care unit. Br J Anaesth. 2006;96(6):747–53.

29. Luetz A, Heymann A, Radtke FM, Chenitir C, Neuhaus U, Nachtigall I, et al. Different assessment tools for intensive care unit delirium: which score to use? Crit Care Med. 2010;38(2):409–18.

30. Marcantonio E, Ta T, Duthie E, Resnick NM. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. J Am Geriatr Soc. 2002;50(5):850–7.

31. Marcantonio ER, Goldman L, Mangione CM, Ludwig LE, Muraca B, Haslauer CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA. 1994;271(2):134–9.

32. Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TH. The association of intraoperative factors with the development of postoperative delirium. Am J Med. 1998;105(5):380–4.

33. Mei W, Seeling M, Franck M, Radtke F, Brantner B, Wenecke KD, et al. Independent risk factors for postoperative pain in need of intervention early after awakening from general anaesthesia. Eur J Pain. 2010;14(2):149 e141–7.

34. Milstein A, Pollack A, Kleinman G, Barak Y. Confusion/delirium following cataract surgery: an incidence study of 1-year duration. Int Psychogeriatr. 2002;14(3):301–6.

35. Muller N, Klages U, Gunther W. Hepatic encephalopathy presenting as delirium and mania. The possible role of bilirubin. Gen Hosp Psychiatry. 1994;16(2):138–40.

36. Munk L, Andersen G, Moller AM. Post-anaesthetic emergence delirium in adults: incidence, predictors and consequences. Acta Anaesthesiol Scand. 2016;60(8):1059–66.

37. Neufeld KJ, Leoutsakos JS, Sieber FE, Joshi D, Wanamaker BL, Rios-Robles J, et al. Evaluation of two delirium screening tools for detecting post-operative delirium in the elderly. Br J Anaesth. 2013;111(4):612–8.

38. Nishikawa K, Nakayama M, Omote K, Namiki A. Recovery characteristics and post-operative delirium after long-duration laparoscope-assisted surgery in elderly patients: propofol-based vs. sevoflurane-based anesthesia. Acta Anaesthesiol Scand. 2004;48(2):162–8.

39. Oh YS, Kim DW, Chun HJ, Yi HJ. Incidence and risk factors of acute postoperative delirium in geriatric neurosurgical patients. J Korean Neurosurg Soc. 2008;43(3):143–8.

40. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. J Trauma. 2008;65(1):34–41.

41. Radtke FM, Franck M, Schneider M, Luetz A, Seeling M, Heinz A, et al. Comparison of three scores to screen for delirium in the recovery room. Br J Anaesth. 2008;101(3):338–43.
42. Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: risk factors and outcomes. Ann Surg. 2009;249(1):173–8.

43. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation. 2009;119(2):229–36.

44. Sharma PT, Sieber FE, Zakriya KJ, Pauldine RW, Gerold KB, Hang J, et al. Recovery room delirium predicts postoperative delirium after hip-fracture repair. Anesth Analg. 2005;101(4):1215–20. table of contents.

45. Shiiba M, Takei M, Nakatsuru M, Bukawa H, Yokoe H, Uzawa K, et al. Clinical observations of postoperative delirium after surgery for oral carcinoma. Int J Oral Maxillofac Surg. 2009;38(6):661–5.

46. Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. Cochrane Database Syst Rev 2007(2):CD005563.

47. Soja SL, Pandharipande PP, Fleming SB, Cotton BA, Miller LR, Weaver SG, et al. Implementation, reliability testing, and compliance monitoring of the Confusion Assessment Method for the Intensive Care Unit in trauma patients. Intensive Care Med. 2008;34(7):1263–8.

48. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive Care Med. 2009;35(7):1276–80.

49. van Eijk MM, van Marum RJ, Klijn IA, de Wit N, Kesecioglu J, Slooter AJ. Comparison of delirium assessment tools in a mixed intensive care unit. Crit Care Med. 2009;37(6):1881–5.

50. Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Elseviers M, Bossaert L. A comparison of the CAM-ICU and the NEECHAM Confusion Scale in intensive care delirium assessment: an observational study in non-intubated patients. Crit Care. 2008;12(1):R16.

51. Voyer P, Richard S, Doucet L, Carmichael PH. Detecting delirium and subsyndromal delirium using different diagnostic criteria among demented long-term care residents. J Am Med Dir Assoc. 2009;10(3):181–8.

52. Williams-Russo P, Urquhart BL, Sharrock NE, Charlson ME. Post-operative delirium: predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc. 1992;40(8):759–67.

53. Xie Z, Dong Y, Maeda U, Moir R, Inouye SK, Culley DJ, et al. Isoflurane-induced apoptosis: a potential pathogenic link between delirium and dementia. J Gerontol A Biol Sci Med Sci. 2006;61(12):1300–6.

54. Yildizeli B, Ozyurtkan MO, Batirel HF, Kuscu K, Bekiroglu N, Yuksel M. Factors associated with postoperative delirium after thoracic surgery. Ann Thorac Surg. 2005;79(3):1004–9.

55. Zakriya KJ, Christmas C, Wenz JF, Sr., Franckowiak S, Anderson R, Sieber FE. Preoperative factors associated with postoperative change in confusion assessment method score in hip fracture patients. Anesth Analg. 2002;94(6):1628–32. table of contents.

Tables

Table 1: Patient demographic and clinical characteristics
| Clinical characteristics | No delirium (n=171) | Delirium (n=57) | p-value |
|-------------------------|------------------|----------------|---------|
| Age (years)             | 37 [28-48]       | 46 [37.5-55]   | <0.001  |
| Age (categories)        |                  |                | 0.029   |
| ≥ 60                    | 9 (52.5%)        | 8 (47.1%)      |         |
| ≥ 18                    | 162 (76.8%)      | 49 (23.2%)     |         |
| Gender                  |                  |                | 0.395   |
| Female                  | 101 (77.1%)      | 30 (22.9%)     |         |
| Male                    | 70 (72.2%)       | 27 (27.8%)     |         |
| BMI                     | 21.5 [19.5-24.5] | 21.5 [19.4-25.2] | 0.713  |
| ASA-PS                  |                  |                | <0.001  |
| I-II                    | 158 (79.4%)      | 41 (20.6%)     |         |
| III-IV                  | 13 (44.8%)       | 16 (55.2%)     |         |
| Primary disease         |                  |                | <0.001  |
| Benign                  | 156 (80.0%)      | 39 (20.0%)     |         |
| Malignant               | 15 (45.5%)       | 18 (54.4%)     |         |
| Preoperative LOS        | 4 [3-6]          | 5 [3-7]        | 0.114   |
| Pre-operative blood results |            |                |         |
| White blood cell count  |                  |                | 0.790   |
| 4-10×10⁹/L              | 148 (75.5%)      | 48 (24.5%)     |         |
| <4×10⁹/L                | 15 (75.0%)       | 5 (25.0%)      |         |
| >10×10⁹/L               | 8 (66.7%)        | 4 (33.3%)      |         |
| Haemoglobin             |                  |                | 0.338   |
| 110-150g/L              | 135 (77.1%)      | 40 (22.9%)     |         |
| <110g/L                 | 25 (65.8%)       | 13 (34.2%)     |         |
| >150g/L                 | 11 (73.3%)       | 4 (26.7%)      |         |
| Haematocrit             |                  |                | 0.716   |
| 37-48%                  | 79 (73.1%)       | 29 (26.9%)     |         |
| <37%                    | 91 (76.5%)       | 28 (23.5%)     |         |
|                       | >48% | Serum sodium       | Serum potassium | Serum chloride | Serum calcium | Serum creatinine | BUN | Serum total cholesterol | Serum uric acid |
|-----------------------|------|--------------------|----------------|---------------|--------------|------------------|-----|-------------------------|-----------------|
|                       | 1    | 126 (73.3%)        | 142 (77.2%)    | 146 (74.9%)   | 155 (77.5%)  | 78 (67.8%)        | 143 | 130 (75.6%)             | 10 (83.3%)      |
| Serum sodium          |      | 1 (0.0%)           | 46 (26.7%)     | 49 (25.1%)    | 45 (22.5%)   | 37 (32.2%)        |     | 42 (24.4%)              |                |
| 136-145mmol/L         |      |                    | 2 (40.0%)      | 3 (60.0%)     | 14 (57.1%)   | 83 (82.2%)        |     | 10 (83.3%)              |                |
| <136mmol/L            | 2    |                    | 3 (60.0%)      | 1 (25.0%)     | 12 (42.9%)   | 18 (17.8%)        |     | 12 (22.2%)              |                |
| >145mmol/L            | 43   |                    | 8 (15.7%)      | 7 (24.1%)     | 7 (24.1%)    |                  |     |                        |                |
| Serum potassium       |      |                    |                |              |              |                  |     |                        |                |
| 3.5-5.1mmol/L         | 142  |                    | 42 (22.8%)     | 49 (25.1%)    | 45 (22.5%)   | 37 (32.2%)        |     | 42 (24.4%)              |                |
| <3.5mmol/L            | 28   |                    | 15 (34.9%)     | 1 (25.0%)     | 12 (42.9%)   | 18 (17.8%)        |     | 12 (22.2%)              |                |
| >5.1mmol/L            |      |                    |                |              |              |                  |     |                        |                |
| Serum chloride        |      |                    |                |              |              |                  |     |                        |                |
| 98-107mmol/L          | 146  |                    | 49 (25.1%)     | 49 (25.1%)    | 45 (22.5%)   | 37 (32.2%)        |     | 42 (24.4%)              |                |
| <98mmol/L             | 3    |                    | 1 (25.0%)      | 1 (25.0%)     | 12 (42.9%)   | 18 (17.8%)        |     | 12 (22.2%)              |                |
| >107mmol/L            | 22   |                    | 7 (24.1%)      | 7 (24.1%)     | 7 (24.1%)    |                  |     |                        |                |
| Serum calcium         |      |                    |                |              |              |                  |     |                        |                |
| 2.16-2.60mmol/L       | 155  |                    | 45 (22.5%)     | 45 (22.5%)    | 45 (22.5%)   | 37 (32.2%)        |     | 42 (24.4%)              |                |
| <2.16mmol/L           | 16   |                    | 12 (42.9%)     | 12 (42.9%)    | 12 (42.9%)   | 18 (17.8%)        |     | 12 (22.2%)              |                |
| Serum creatinine      |      |                    |                |              |              |                  |     |                        |                |
| 54-92μmol/L           | 78   |                    | 37 (32.2%)     | 37 (32.2%)    | 37 (32.2%)   | 37 (32.2%)        |     | 37 (32.2%)              |                |
| <54μmol/L             | 83   |                    | 18 (17.8%)     | 18 (17.8%)    | 18 (17.8%)   | 18 (17.8%)        |     | 18 (17.8%)              |                |
| >92μmol/L             | 10   |                    | 2 (16.7%)      | 2 (16.7%)     | 2 (16.7%)    |                  |     | 2 (16.7%)               |                |
| BUN                   |      |                    |                |              |              |                  |     |                        |                |
| 3.2-7.3mmol/L         | 143  |                    | 49 (25.5%)     | 49 (25.5%)    | 49 (25.5%)   | 49 (25.5%)        |     | 49 (25.5%)              |                |
| <3.2mmol/L            | 14   |                    | 4 (22.2%)      | 4 (22.2%)     | 4 (22.2%)    | 4 (22.2%)         |     | 4 (22.2%)               |                |
| >7.3mmol/L            | 14   |                    | 4 (22.2%)      | 4 (22.2%)     | 4 (22.2%)    |                  |     | 4 (22.2%)               |                |
| Serum total cholesterol|     |                    |                |              |              |                  |     |                        |                |
| 2.9-5.2mmol/L         | 130  |                    | 42 (24.4%)     | 42 (24.4%)    | 42 (24.4%)   | 42 (24.4%)        |     | 42 (24.4%)              |                |
| <2.9mmol/L            | 10   |                    | 3 (23.1%)      | 3 (23.1%)     | 3 (23.1%)    | 3 (23.1%)         |     | 3 (23.1%)               |                |
| >5.2mmol/L            | 31   |                    | 12 (27.9%)     | 12 (27.9%)    | 12 (27.9%)   |                  |     | 12 (27.9%)              |                |
| Serum uric acid       |      |                    |                |              |              |                  |     |                        |                |
| Range of Values | Frequency (%) | Total Frequency |
|-----------------|--------------|----------------|
| 214-488μmol/L   | 141 (75.8%)  | 45 (24.2%)     |
| <214μmol/L      | 24 (72.7%)   | 9 (27.3%)      |
| >488μmol/L      | 6 (66.7%)    | 3 (33.3%)      |
| Serum glucose   |              | 0.042          |
| 3.9-6.4mmol/L   | 155 (77.1%)  | 46 (22.9%)     |
| <3.9mmol/L      | 10 (71.4%)   | 4 (28.6%)      |
| >6.4mmol/L      | 6 (46.2%)    | 7 (53.8%)      |
| Elevated serum total or direct bilirubin |          | 0.013          |
| No              | 154 (77.8%)  | 44 (22.2%)     |
| Yes             | 17 (56.7%)   | 13 (43.3%)     |
| Decreased serum albumin or total protein |          | 0.005          |
| No              | 146 (78.9%)  | 39 (21.1%)     |
| Yes             | 25 (58.1%)   | 18 (41.9%)     |
| Elevated hepatic enzymes |          | 0.065          |
| No              | 142 (72.8%)  | 53 (27.2%)     |
| Yes             | 29 (87.9%)   | 4 (12.1%)      |
| Surgical parameters |          |                |
| Type of surgery |              | <0.001         |
| Mini-invasive   | 100 (88.5%)  | 13 (11.5%)     |
| Invasive        | 71 (61.7%)   | 44 (38.3%)     |
| Location of surgery |          | <0.004         |
| Head and neck   | 32 (86.5%)   | 5 (13.5%)      |
| Intrathoracic   | 14 (56.0%)   | 11 (44.0%)     |
| Intra-abdominal | 49 (65.3%)   | 26 (34.7%)     |
| Urogenital      | 62 (80.5%)   | 15 (19.5%)     |
| Musculoskeletal and spinal | 9 (100.0%) | 0 (0.0%)     |
| Peripheral      | 5 (100.0%)   | 0 (0.0%)       |
| Maintenance of anaesthesia |          | <0.001         |
| TIVA            | 40 (95.2%)   | 2 (4.8%)       |

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|                                    | Value                        | Value                        | p     |
|------------------------------------|------------------------------|------------------------------|-------|
| **Inhalation anaesthetic with isoflurane or sevoflurane** | 131 (70.4%)                 | 55 (29.6%)                   |       |
| **Preoperative heart rate**        | 75 [66-88]                  | 76 [70.5-92]                 | 0.318 |
| **Preoperative systolic BP**       | 117 [108-134]               | 124 [111-135]                | 0.103 |
| **Preoperative diastolic BP**      | 72 [63-81]                  | 76 [67-87.5]                 | 0.038 |
| **Preoperative SpO2 (%)**          | 100 [98-100]                | 100 [98-100]                 | 0.885 |
| **Maximal intraoperative heart rate** | 90 [80-102]                | 94[83.5-104.5]               | 0.201 |
| **Minimal intraoperative heart rate** | 59 [55-65]                  | 57 [52-66]                   | 0.343 |
| **Maximal intraoperative systolic BP** | 131 [120-140]              | 134 [127-145.5]              | 0.111 |
| **Minimal intraoperative systolic BP** | 90 [84-96]                  | 89 [82-96]                   | 0.531 |
| **Total intraoperative fluid application** | 1100 [500-1750]            | 1500[1125-2250]              | <0.001|
| **Total intraoperative body fluid loss** | 9 [0-400]                   | 300 [45-800]                 | <0.001|
| **Duration of surgery**            |                              |                              | <0.001|
| <120min                            | 98 (85.2%)                  | 17 (14.8%)                   |       |
| ≥120min                            | 73 (64.6%)                  | 40 (35.4%)                   |       |

Data are median [25% – 75% percentiles] or n (%).

Table 2: Independent risk factors for RRD after general anaesthesia in elective non-cardiovascular surgery patients

|                                    | Regression coefficient (SE) | Odds ratio | 95.0% CI for Odds Ratio | p |
|------------------------------------|-----------------------------|------------|--------------------------|---|
| Maintenance of anaesthesia with inhalation anaesthetic | 1.840 (0.775)              | 6.294      | 1.377 – 28.759           | 0.018 |
| Malignant primary disease          | 1.242 (0.464)              | 3.464      | 1.396 – 8.592            | 0.007 |
| ASA-PS III-V                      | 1.221 (0.451)              | 3.389      | 1.401 – 8.201            | 0.007 |
| Elevated serum total or direct bilirubin | 0.930 (0.472)              | 2.535      | 1.006 – 6.388            | 0.049 |
| Invasive surgery                   | 0.888 (0.403)              | 2.431      | 1.103 – 5.357            | 0.028 |

Other variables included in the model were older age, gender, BMI, location of surgery, decreased serum albumin or total protein, preoperative serum creatinine, preoperative serum calcium, preoperative serum glucose, intraoperative fluid application, total intraoperative body fluid loss and duration of surgery.
Table 3: PACU events, LOS and healthcare costs

|                                | No delirium (n=171) | Delirium (n=57) | p-value |
|--------------------------------|----------------------|-----------------|---------|
| Maximal heart rate in PACU (bpm) | 90 [80-100]          | 86 [77-98]      | 0.26    |
| Maximal SBP in PACU (mmHg)     | 132 [122-143]        | 141 [131-151]   | <0.01   |
| Minimal SBP in PACU (mmHg)     | 115 [106-125]        | 120 [115-131.5] | 0.001   |
| Mean SpO2 (%) in PACU           | 99 [97-100]          | 98 [96-100]     | 0.340   |
| PACU LOS (min)                 | 29 [23-37]           | 34 [25-43.5]    | 0.020   |
| Total hospital LOS (days)      | 11.0 [9.0-17.0]      | 17.0 [12.0-23.5]| <0.001  |
| Postoperative LOS (days)       | 7.0 [5.0-10.0]       | 11.0 [7.0-15.0] | <0.001  |
| Healthcare costs per day (yuan)| 1459 [1217-1966]     | 1696 [1285-2106]| 0.05    |
| Total healthcare costs(yuan)   | 16,555 [12,618-27,788]| 31,428 [17,872-43,674]| <0.001 |
Figure 1

Flow of patients in study cohort