Risk and Protective Factors Analysis for Postoperative Delirium in Elderly Critically Ill Patients: A Multicenter Retrospective Study

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Research

Keywords: Delirium, Critically ill patients, Incidence, Risk factors

Posted Date: November 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-99739/v1

Abstract

Objective: To study the incidence and risk factors of postoperative clinical delirium in critically ill elderly patients in order to devise strategies for prevention and treatment.

Methods: We collected clinical data from 451 critically ill patients in the intensive care unit from four hospitals in Shanghai Pudong New Area. Postoperative delirium was measured using the Confusion Assessment Method for the ICU (CAM-ICU), and then the incidence of postoperative delirium was calculated. We used univariate analysis and multivariate logistic regression analysis to determine the risk factors associated with postoperative delirium in critically ill elderly patients.

Results: Among the 451 critically ill patients, 56 had delirium after operation. The incidence of postoperative delirium was 12.4%. Univariate analysis showed that the incidence of postoperative delirium was significantly higher ($P<0.05$) in patients who had a past history of chronic obstructive pulmonary disease (COPD), underwent emergency surgery, were not administered intraoperative Propofol, had postoperative hypertension, were administered postoperative methylprednisolone, and did not have postoperative analgesia. Multivariate logistic regression analysis showed that age (OR=1.111, 95% CI, 1.056-1.168), surgical timing (OR=1.154, 95% CI, 1.058-7.200), and use of methylprednisolone postoperatively (OR=8.030, 95% CI, 1.050-61.408) were risk factors. Use of Propofol intraoperatively (OR=0.315, 95%CI, 0.124-0.800) was protective factors for postoperative delirium in elderly critically ill patients.

Conclusion: Adavanced age, COPD history, emergency surgery, postoperative hypertension, use of methylprednisolone, and no postoperative analgesia are risk factors for postoperative delirium in critically ill elderly patients. Medical staff should be educated in evaluating delirium in postoperative patients and conducting risk assessment in order to prevent and treat the disease earlier, and reduce the incidence of delirium.

Take-home Message

Among all patients, delirium was identified in 56 cases (12.4%), the subtypes respectively were activity-increasing 30(6.7%), activity-decreasing 15(3.3%) and mixed-typed 11(2.4%).

Physicians should put emphasis on the assessment of delirium and related risk factors to reduce the occurrence of delirium, especially postoperative hypertension, administration of methylprednisolone in the ICU, and postoperative analgesia.

Introduction

Delirium is defined as an acute and reversible disturbance of consciousness and attention that presents during a short period (hours or days) and has a fluctuating course. Delirium is usually accompanied by an unpleasant mood and cognitive dysfunction(1). Clinically, delirium is divided into three subtypes:

activity-increasing, activity-decreasing, and mixed-typed. The activity-increasing subtype manifests as excitement, agitation, restlessness, unstable emotion, or aggressive behavior. Activity-decreasing subtype exhibits apathy, drowsiness, impoverishment, and reduced responsiveness. Mixed-type, on the other hand, is characterized by simultaneous or sequential appearance of the activity-increasing and activity-decreasing subtypes (2, 3).

Generally, delirium causes serious social burdens, such as long-term cognitive impairment, higher mortality rate, prolonged intensive care unit (ICU) stay and hospitalization, and increased costs. Early intervention is expected to improve prognosis, however, there is currently no effective pharmacologic intervention for this disease. Primary prevention with nonpharmacologic multicomponent approaches have gained widespread acceptance as the most effective strategy for delirium(4, 5). Therefore, the aim of this multicenter study was to investigate the incidence and risk factors of postoperative delirium in critically ill elderly patients in the ICU.

Material And Methods

Study design

The study was a multicenter prospective cohort study. The data were collected from four hospitals in the Pudong Area, Shanghai (Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Dongfang Hospital of Tongji University, Shanghai Seventh People's Hospital, and Gongli Hospital of Pudong New Area). All patients in our cohort had critical illness between August 2015 to July 2017. Delirium was diagnosed according to the criteria of the confusion assessment method for the ICU (CAM-ICU) approved by the PAD guidelines. Postoperative delirium was measured 3 times a day (8:00, 16:00, and 24:00). We analyzed the total incidence of postoperative delirium across different operations to unveil potential risk factors. Each patient or caregiver signed informed consent. This study was approved by the Ethics Committee of the Renji Hospital, and registered at the China Clinical Trial Registry (Registration Number: ChiCTR-OOC-16008154, registered 25 March 2016).

Study populations

ICU patients aged ≥ 65 years from August 2015 to July 2017 were included in this study. Patients who signed informed consent, intended to stay in ICU postoperatively > 24h and were evaluated as APACHII ≥ 15, ASA < IV were eligible for inclusion. Patients were excluded from analysis for the following reasons: (1) pre-operative cognitive impairment or pre-existing delirium symptoms; (2) patients used psychiatric medications during the past six months; (3) patients underwent brain surgery (craniocerebral trauma); (4) the operation time < 1h; (5) patients were vision or hearing impaired, or unable to communicate; (6) patients’ estimated survival time < 24h; (7) patients or their family members refused to participate in this study.

Data collection

A validated daily record list was used to collect the demographic data (age, sex, BMI, and education), history of any current illnesses, use of medication, and other relevant information from each participant. Preoperative risk factors including ASA classification, site of surgery, nutritional status, preoperative medication, laboratory results regarding electrolyte examination and arterial blood gas examination were collected by the researchers. Intraoperative risk factors, including intraoperative medication, hypothermia, surgery time, blood loss, blood transfusion volume, intraoperative blood pressure, oxygenation index, arterial blood gas index and arrhythmia were collected by the anesthesiologists. Then, each patient was evaluated for postoperative ICU-related risk factors, including postoperative mechanical ventilation time, pain score, analgesia, sedation, body temperature, postoperative medication, indwelling catheter duration, restraint, quality of sleep, ward conditions, postoperative blood pressure, and blood transfusion. Sleep quality was assessed by self-report from each patient. The participants were then assessed using CAM-ICU to identify the development and subtype of delirium.

Patients were followed for 28 days after the operation and assessed the postoperative outcomes such as duration of ICU stay, duration of postoperative hospitalization, and hospital expense.

Delirium assessment

In this study, a 2-step method as the CAM-ICU criteria was used to identify delirium. The first step was to assess the patients' consciousness via the RASS score. Patients were excluded if their RASS score was -4 (responsive only to physical stimulus) or -5 (unresponsive to physical and verbal stimulus) as it was difficult to determine how conscious the patient was due to unresponsiveness. If the patient was in coma, then they were ineligible for the CAM-ICU assessment and recorded as "unable to evaluate". If the RASS score was ≥ -3 (+4: aggressiveness; +3: extreme restlessness; +2: restlessness; +1: irritability; 0: sober and calm; -1: drowsiness; -2: mild sedation; -3: moderate sedation), then they proceed to step 2 of the CAM-ICU assessment. The second step contains assessing conscious content from 4 diagnostic characteristics: (1) A violent change or fluctuation in the state of consciousness during the past 24 hours, (2) inattention, (3) altered level of consciousness, and (4) confusion in thinking. Each feature was carefully assessed in order to determine whether a patient had delirium. Patients were diagnosed with delirium when feature (1) and (2) plus either feature (3) or (4) were present. Any score other than 0 is a positive value for characteristic (3).

After the patient was admitted to the ICU, CAM-ICU assessments were performed 3 times a day (8:00, 16:00, and 24:00) for 7 consecutive days while in the ICU or until the patient left the ICU. All researchers were professionally trained and are strictly evaluated according to CAM-ICU criteria.

Statistical analysis

Continuous variables were expressed as means ± SD or median and interquartile ranges (IQRs). Categorical data are shown as proportions (number and percentage). The t-test or Wilcoxon test were used to compare the continuous variables in patients with and without delirium. T-test was used when both groups of data were normally distributed. In case of abnormalities, the Wilcoxon test was used.

Categorical variables were compared using χ^2 test (Pearson χ^2 test) or the Fisher exact test. Wilcoxon test was used to compare the variables after sequencing. To examine the effects of various factors on the development of delirium, univariate and multivariate stepwise logistic regression analyses were performed. The *P* values for entry and removal were .05 and .10, respectively. $P < 0.05$ was considered statistically significant. All data were statistically analyzed via SPSS 21.0 software.

Results

Incidence of delirium

During the 2-year study interval, 623 patients were admitted to the ICU, among which 451 (72%) met the inclusion criteria and were enrolled in the cohort while 172 (28%) met exclusion criteria (***Fig.1***). Among all patients, delirium was identified in 56 cases (12.4%), the subtypes of which were shown in ***Table 1*** and ***Table 2***.

Table 1: Incidence of total delirium and different subtypes

With delirium			No delirium	Total
activity-increasing	activity-decreasing	mixed-typed		
30(6.7%)	15(3.3%)	11(2.4%)	395(87.6%)	451(100%)

Table 2: Incidence of delirium across different surgical types

Surgical Type	Total cases	With delirium	Incidence
Thoracic surgery	61	3	4.92%
Abdominal surgery	244	36	14.75%
Spine, limbs and joint surgery	101	12	11.88%
Pelvis surgery	18	1	5.56%
Major vascular surgery	16	4	25.00%
Peripheral vascular surgery	3	0	0.00%
Other surgery	8	0	0.00%

Univariate statistical analysis results

The variables that were potentially related to delirium development were divided in the following 3 categories: preoperative, intraoperative, and postoperative. All the variables included in the study were analyzed via univariate statistical analysis and presented in ***Tables 3-7***.

Patients with previous history of COPD showed significantly increased incidence of delirium (P<0.01), while other perioperative factors showed no statistically differences, as shown in ***Table 3***.

Table 3: Perioperative risk factors of postoperative delirium in ICU patients

Variable	Cases		χ^2	P
	With delirium	No delirium		
Tobacco use	10	93	0.935	0.334
Alcohol use	5	50	0.647	0.421
AF	16	5	2.611	0.106
Arrhythmias（without AF）	9	45	1.019	0.313
Hypertension	28	208	0.139	0.709
Hyperlipidemia	1	25	1.872	0.171
Diabetes	8	96	2.774	0.096
COPD	11	30	8.567	0.003
Surgery history	23	14	0.116	0.734

Next, we evaluated nursing-related factors after the patient entered the ICU, ***Table 4*** showed that there was no statistical differences between different nursing-related factors with regards to presence of delirium.

Table 4: Nursing related risk factors of postoperative delirium in ICU patients

Variable	Cases		χ^2	*P*
	With delirium	No delirium		
Limited mobility of body (Constraint)	39	256	0.473	0.492
Invasive operation in the adjacent beds	10	47	1.389	0.239
New invasive operation	1	11	0.191	0.662
Death in the adjacent beds	2	4	2.335	0.127
Family visit	54	373	0.313	0.567
Natural light	25	226	3.215	0.073
Black out in the night	52	365	0.003	0.953
Partition curtain	53	367	0.243	0.622

Table 5 showed that the use of indwelling catheter was not significantly related to postoperative delirium.

Table 5: Indwelling catheter factors of postoperative delirium in ICU patients

Variable	Cases		χ^2	*P*
	With delirium	No delirium		
Catheter	54	375	0.117	0.732
Arterial catheter	40	306	1.392	0.238
Central venous catheter	51	348	0.265	0.607

Patients' perioperative conditions were closely related to the incidence of delirium. In particular, undergoing emergency surgery (P<0.01), postoperative hypertension (P<0.05), and postoperative analgesia (P<0.05), were found to be significantly related to the incidence of postoperative delirium (***Table 6***).

Table 6: Perioperative risk factors of postoperative delirium in ICU patients

Variable	Cases		χ^2	*P*
	With delirium	No delirium		
Surgery timing				
Selective operation	46	377	14.900	0.001
Emergency operation	10	18		
Intraoperative hypotension	21	142	0.040	0.842
Intraoperative hypertension	8	41	0.725	0.395
Arrhythmias	1	13	0.379	0.538
Postoperative hypotension	15	80	1.316	0.518
Postoperative hypertension	23	108	4.329	0.037
Postoperative analgesia	33	171	5.140	0.023
Postoperative sedation	36	218	1.453	0.228

Table 7 showed that intraoperative administration of propofol and ICU medication of methylprednisolone ($P<0.01$) were risk factors for the development of postoperative delirium.

Table 7: Impact of medication on postoperative delirium

Variable	Cases		χ^2	*P*
	With delirium	No delirium		
Intraoperative medication				
Propofol	42	351	15.211	0.000
Midazolam	47	326	0.029	0.866
Dexmedetomidine	35	280	2.265	0.132
Fentanyl	8	71	0.500	0.479
Remifentanil	40	280	0.001	0.974
Sufentanil	39	278	0.032	0.858
Inhalation anesthetic	44	339	3.426	0.064
Rocuronium bromide	28	230	1.635	0.201
Cisaccuramide	44	320	0.340	0.560
Dexamethasone	31	239	0.456	0.499
Methylprednisolone	4	34	0.121	0.728
Atropine	11	82	0.021	0.885
Neostigmine	4	50	1.357	0.244
Lodocaine	3	15	0.004	0.564
ICU medication				
Dexmedetomidine	2	12	0.042	0.837
Methylprednisolone	3	3	7.604	0.006

Multivariate statistical analysis results

We performed multivariate statistical analysis by using factors that were found to be statistically significant in the univariate analysis as independent variables and delirium as the dependent variable. These variables, that were significantly more prevalent in delirious patients compared to non-delirious patients, were incorporated into a stepwise logistic regression analysis. According to our statistical analysis, the best regression model identified age, surgical timing, and use methylprednisolone medication as risk factors for postoperative delirium (***Table 8***).

Table 8. Multivariate analysis for risk factors associated with post-operative delirium.

Independent variable	Regression coefficient	Standard Error	*P*	OR	95%CI
Age	0.105	0.026	0.000	1.111	1.056-1.168
Sex	0.129	0.339	0.571	1.212	0.642-2.355
COPD	0.287	0.467	0.539	1.333	0.533-3.330
ASA					
ASA Class 1	-1.499	0.923	0.105	0.223	0.036-1.364
ASA Class 2	-1.106	0.708	0.119	0.331	0.083-1.327
ASA Class 3	-0.745	0.740	0.314	0.475	0.111-2.027
ASA Class 4			0.287	0.287	
Surgery timing	1.154	0.489	0.038	2.760	1.058-7.200
Propofol	-1.154	0.475	0.015	0.315	0.124-0.800
Surgery duration	0.003	0.002	0.107	1.003	0.999-1.007
Intraoperative hypertension	0.467	0.461	0.311	1.595	0.646-3.939
Postoperative analgesia	0.476	0.337	0.158	1.610	0.831-3.118
Methylprednisolone (ICU)	2.083	1.038	0.045	8.030	1.050-61.408

Discussion

This study showed that the incidence of postoperative delirium in elderly critically ill patients was 12.4%, which was accord with most recent studies(6). Postoperative delirium incidence differs greatly among surgery types. For instance, the incidence for hip surgery was 4-53%(7), for ENT surgery was 12%(8), and for spine surgery was 0.84%(9). Furthermore, postoperative delirium incidence also differs in different periods. For example, the incidence for cardiac surgery was reported to be 32% in 1999(10), 23-26% in 2008 (11) but 13.3% in recent studies(12). Therefore, its necessary to analyze the risk or protective factors for postoperative delirium according to the latest study.

In this study, activity-increasing subtype accounted for 53.6% (30/56), activity-decreasing subtype accounted for 26.8% (15/56), and mixed-subtype comprised 19.6% (11/56) of all patients that suffered from postoperative delirium according to CAM-ICU, which is specifically designed for non-psychiatrists to evaluate ICU patients. Activity-increasing subtype is easier diagnosed by physicians due to its characteristic features of excitement or aggression, while activity-decreasing delirium is often missed or

misdiagnosed as sedation or depression due to the patients' non-responsiveness(13). Among the misdiagnosed patients, 94% of them comprised the activity-decreasing subtype(14). The relatively low incidence of delirium in this study may be partly due to the presence of missed diagnosis of activity-decreasing subtype.

This study showed that old age is a risk factor for delirium, and while age increases, the number of risk factors for delirium increase gradually as well(15). Besides, our research demonstrated that the incidence of postoperative delirium in patients with a history of COPD was significantly higher than patients without COPD. COPD patients suffer from cerebral ischemia, hypoxia, metabolic disorders due to primary cardiopulmonary insufficiency, and secondary injury of brain function likely induces postoperative delirium. Patients that underwent emergency operation showed abnormal stress state and disordered hypothalamus pituitary adrenocortical axis (HPA axis) activation. Under emergency operation, 5-serotonin, norepinephrine, and dopamine increase, while acetylcholine levels decrease, causing metabolic disturbance. These pathological changes like aggravate brain injury and induce delirium(16).

Uncontrollable factors, such as advanced age, COPD history, emergency surgery, are unmodifiable in the clinical work. So what are controllable factors? How does intraoperative and postoperative medication use affect the incidence of delirium in ICU patients. Sedatives and analgesics, such as lorazepam, midazolam, pethidine, and morphine are most likely to cause mental confusion, which may be due to their long duration of actions and increased risk of drug accumulation with altered organ function (e.g., renal and hepatic insufficiency), compared with propofol, dexmedetomidine and fentanyl(17). Propofol is the most widespread narcotic medicine for anesthesia maintenance and induction(18). The advantages of this medicine include quick onset, short recovery time, and less incidence of adverse effects such as postoperative nausea and vomiting. Our studies adjusted some common confounding factors such as the patient's age, demographic characteristics, comorbidities, use of other drugs, type of surgery, baseline cognitive status, etc. Our studies showed that the incidence of delirium in patients receiving low-dose propofol perioperatively was lower compared to patients that did not receive propofol, consistent with other previous studies that a low amount of propofol could successfully treated delirious patients(19).

Although some studies have proposed specific interventions to reduce the rate of delirium, others have considered evidence-based prevention strategies to assess whether they can further reduce the rate of delirium if applied together in a consistent manner. Usually, pain is the protective response to the nociceptive stimulus. However, continuous postoperative pain could cause negative emotional reactions of anxiety, stress and fear, leading to physical dysfunction. The observational prospective longitudinal cohort study by Alexandra R Feast found a link between pain and delirium, suggesting that pain may be a risk factor for delirium. Because pain and delirium are found to continue and develop during hospitalization, pain and delirium need to be regularly evaluated to effectively manage pain and delirium(20).

Conclusion

Collectively, multivariate statistical analysis results shown that age, COPD history, undergoing emergency surgery, postoperative hypertension, administration of methylprednisolone in the ICU, and postoperative analgesia were the risk factors for postoperative delirium in elderly patients. While many of these risk factors are often uncontrollable for clinicians, several preventative strategies have been demonstrated to reduce the incidence of ICU delirium. For example: pain management and choice of intraoperative and/or postoperative medication (use of dexmedetomidine and small doses of propofol, avoid methylprednisolone, etc.) are interventions that we can change. Physicians should put emphasis on the assessment of delirium and related risk factors to reduce the occurrence of delirium, for early prevention and treatment.

Declarations

Ethical Approval and Consent to participate

The present study was approved by the Ethics Committee of the Renji Hospital, and registered at the China Clinical Trial Registry (Registration Number: ChiCTR-OOC-16008154, registered 25 March 2016). All research has been carried forth in agreement with the principles laid out in the original Declaration of Helsinki and its later amendments, and data were handled in agreement with patient informed consent.

Consent for publication

Not applicable.

Availability of supporting data

Data used for this study are availble upon request.

Competing Interests

The authors have no conflicts of interest to disclose in relation to this article.

Authors’ contributions

Shunpeng Xing, Shaolin Ma are the first authors and have contributed to data collection, data interpretation and writing. Yuxi Zhou, Ming Lei, Feng Gao, Tao Jiang, Baohangxing Sun, Jiemin Wang and Zhengyu He have contributed to data collection, data interpretation, and editing of text. Yuan Gao and Daxiang Wen are the corresponding authors and have contributed to the study concept, study design and perparation of the paper. All the authors read and approve the final manuscript.

Acknowledgements and Funding

This research was supported by grants from Shanghai Pudong New Area Municipal Commission of Health and Family Planning Commission of science and technology development special fund (Nos:PW2014E-1), 2018 Shanghai "Rising Stars of Medical Talent" Youth Development Program

(SHWSRS(2019)-72). The funders had no role in study design, data collection and analysis, the decision to publish, or preparation of the manuscript.

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Figures

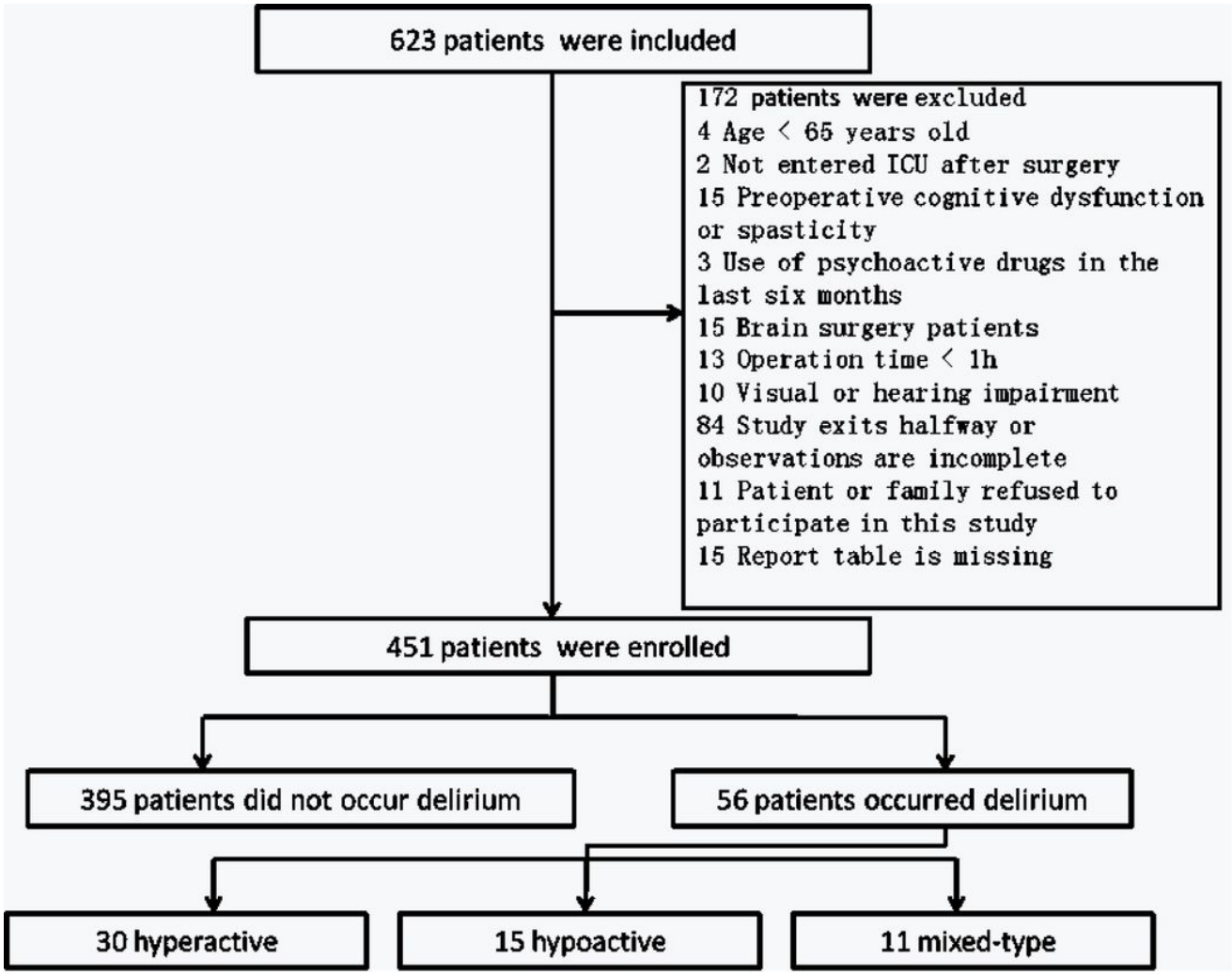

Figure 1

PRISMA Flowchart

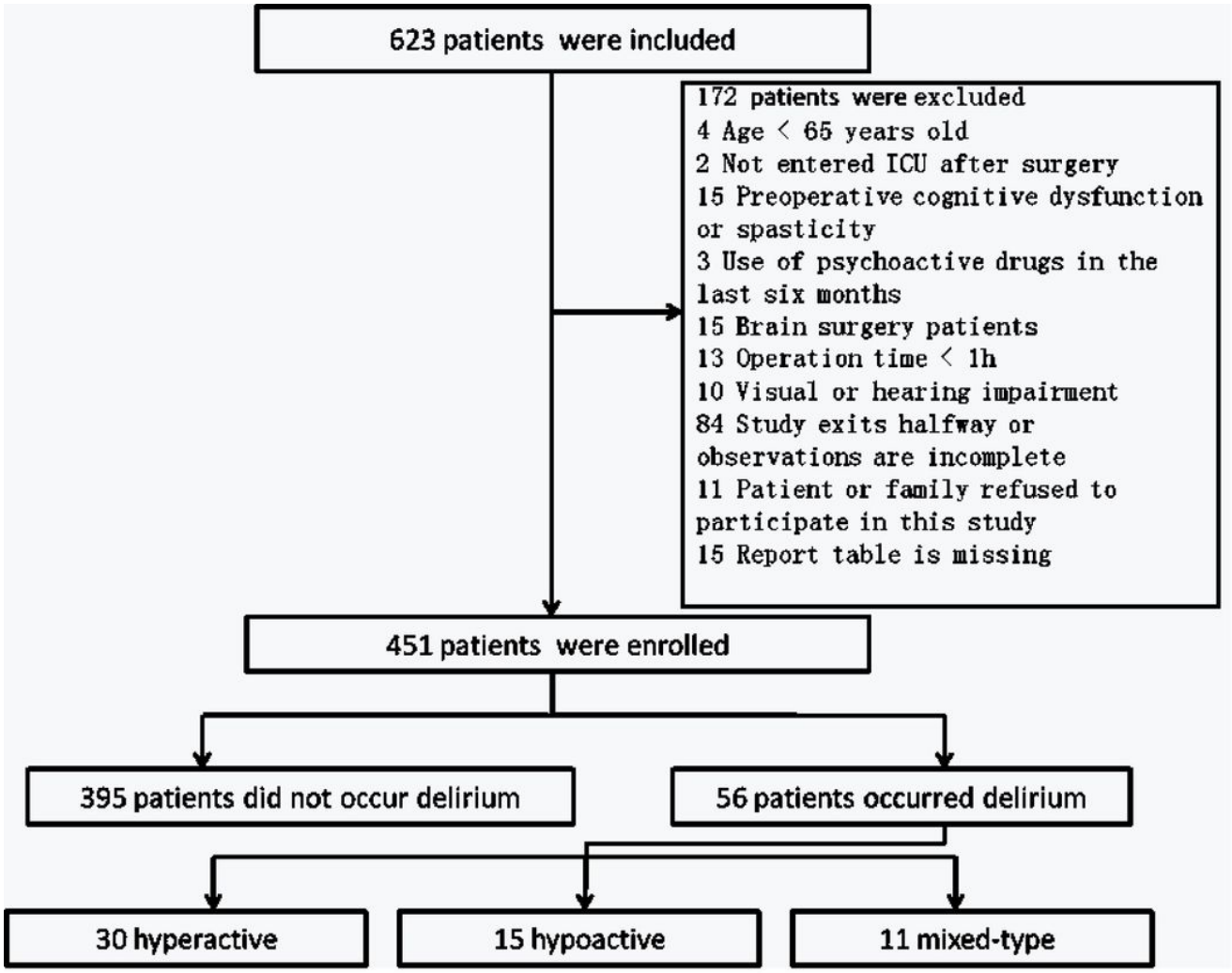

Figure 1

PRISMA Flowchart