

# Incidence, risk factors, and phenomenological characteristics of postoperative delirium in patients receiving intravenous patient-controlled analgesia: a prospective cohort study

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**Background:** Intravenous patient-controlled analgesia (IVPCA) is a common method of relieving pain which is a risk factor of postoperative delirium (POD). However, research concerning POD in IVPCA patients is limited.

**Objective:** We aimed to determine the incidence, risk factors, and phenomenological characteristics of POD in patients receiving IVPCA.

**Methods:** A prospective, cohort study was conducted in post-general anesthesia IVPCA patients aged  $\geq 60$  years. POD was measured by the Nursing Delirium Screening Scale (NuDESC; 0–10). Delirium, pain severity at rest and/or on movement, and side effects of IVPCA during 3 postoperative days were examined twice-daily by the acute pain service team. Pain severity is measured by an 11-point verbal numerical rating scale (11-point VNRS) (0–10). An 11-point VNRS  $> 3$  was considered inadequate pain relief. If POD (detected by NuDESC  $\geq 1$ ) is suspected, consulting a neurologist or a psychiatrist to confirm suspected POD is required.

**Results:** In total, 1,608 patients were included. The incidence rate of POD was 2.2%. Age  $\geq 70$  years and American Society of Anesthesiologists physical status  $> III$  were the risk factors of POD in IVPCA patients. Approximately three-quarters of all POD cases occurred within the first 2 postoperative days. For pain at rest, patients with inadequate pain relief had significantly greater rates of POD than patients with adequate pain relief (day 1, 8.4% vs 1.5%,  $P < 0.001$ ; day 2, 9.6% vs 2.0%,  $P = 0.028$ ; day 3, 4.1% vs 2.1%,  $P = 0.412$ ). However, the incidence of POD was not associated with movement-evoked pain relief. Most (79.9%) POD cases in IVPCA patients showed either one or two symptoms. The symptoms of POD were ranked from high to low as disorientation (65.7%), illusions/hallucinations (37.1%), inappropriate communication (31.4%), inappropriate behavior (25.7%), and psychomotor retardation (14.2%).

**Conclusion:** The incidence rate of POD in IVPCA patients was low. Further research is warranted concerning POD and IVPCA pain management.

**Keywords:** postoperative delirium, postoperative analgesia, patient-controlled analgesia

## Introduction

Delirium is an acute and fluctuating brain dysfunction characterized by conscious disturbance and cognitive impairment. Delirium can be recognized as hyperactive, hypoactive, or a mixed type. Postoperative delirium (POD) occurs after surgery and is associated with prolonged hospitalization, greater health care costs, and higher mortalities.<sup>1</sup> Risk factors of POD include old age, the American Society of Anesthesiologists (ASA) physical status of III or more, severe illness, types of surgery

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and anesthesia, postoperative hypoxemia, and severe acute pain.<sup>2–5</sup> Interestingly, effective pain management reduces the incidence and severity of POD.<sup>6–8</sup> Intravenous patient-controlled analgesia (IVPCA) is a common method of relieving postoperative pain. However, research concerning POD in patients receiving IVPCA is limited.<sup>7–9</sup> In particular, phenomenological characteristics of POD in IVPCA patients have not been reported.

Delirium is a clinical diagnosis. Based on the criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, the confusion assessment method (CAM) that enables nonpsychiatric clinicians to detect delirium was developed and validated in 1990.<sup>10</sup> Although it is considered the gold standard assessment tool for delirium,<sup>10</sup> accurate clinical information and adequate trained researchers are needed for accurate CAM ratings. Delirium in hospitalized older adults is significantly under-recognized by nurses compared to physician/researchers while using the CAM.<sup>11,12</sup> The prevalence of POD grows with an aging population. In a busy hospital environment, a more convenient tool is needed. In 2005, the Nursing Delirium Screening Scale (NuDESC) was developed by Gaudreau et al, which is a five-item observational screening tool<sup>13</sup> that nurses can complete easily within 1 minute, thus making it suitable for use in busy wards. More importantly, the NuDESC has high sensitivity and high specificity for examining patients in the surgical wards and post-anesthetic recovery room.<sup>14,15</sup>

In this study, the NuDESC is used to identify the risk factors, incidence, and phenomenological characteristics of POD in elective noncardiac surgical patients receiving IVPCA. Moreover, the associations between rest/movement-evoked pain and the risk of POD in IVPCA patients were examined.

## Materials and methods

### Patient population

Data for the present study were extracted from the databank of Chi Mei Medical Center by a computerized system. A total of 1,740 surgical patients receiving intravenous morphine via a PCA device for at least 3 continuous postoperative days were assessed from January 2012 to December 2013. Finally, only 1,608 patients aged  $\geq 60$  years who received elective noncardiac surgery and general anesthesia were analyzed. Exclusion criteria included intensive care unit patients, those who were sedated, those who could not communicate immediately after surgery, and non-Chinese speakers. Based on chart review and/or statements of patients' family members, patients suffering from preoperative cognitive impairment and/or dementia

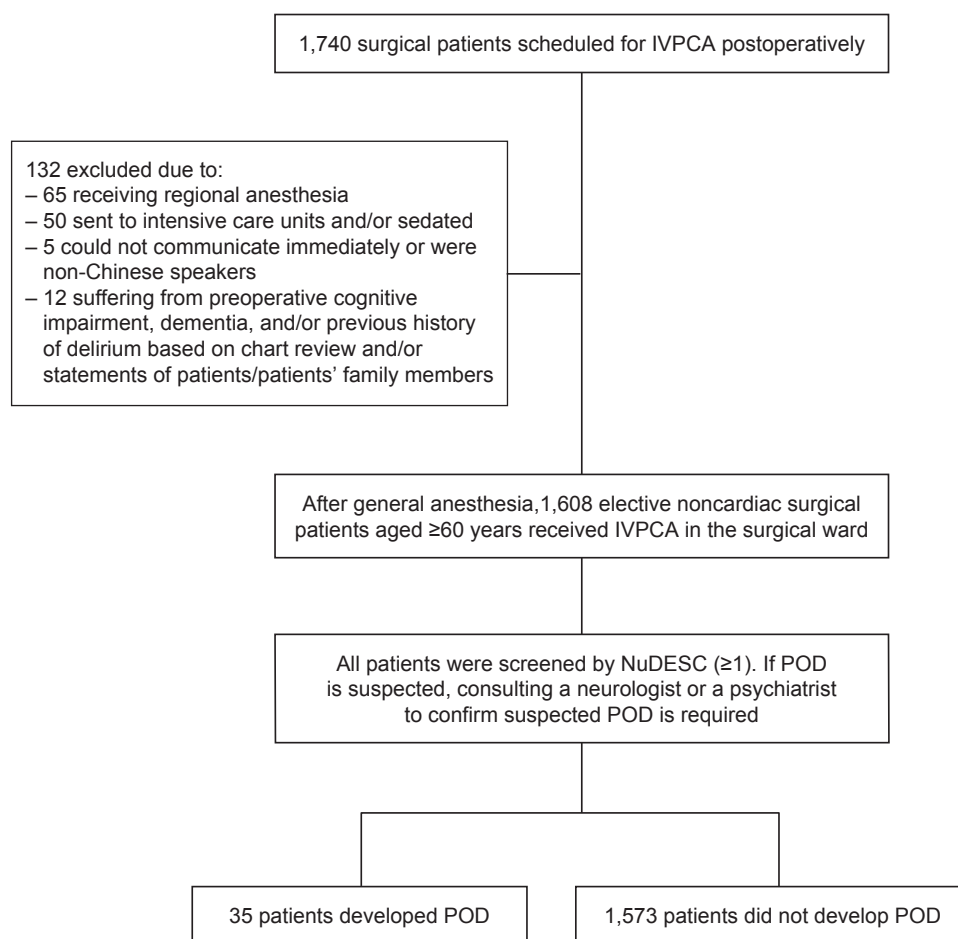
were excluded. Preoperative dementia/cognitive impairment was diagnosed if the patient had a previous mini mental state examination with a score  $< 24$  or clinical diagnosis of dementia by a geriatrician/physician during the preoperative evaluation.<sup>16</sup> Also, based on chart review and/or statements of patients/patients' family members, patients suffering from previous history of delirium or preoperative delirium were excluded because these are relevant confounders.<sup>17</sup> Preoperative delirium was diagnosed if the patient had a previous examination with NuDESC  $\geq 2$ <sup>15</sup> or clinical diagnosis of delirium by a physician during the preoperative evaluation. A data collection flowchart is shown in Figure 1.

### Acute pain service team

The acute pain service team including attending anesthesiologists, residents, pain nurses, and pharmacists provide pain management in Chi Mei Medical Center. PCA machines are routinely set up using the bolus dose without continuous doses. The acute pain service team members regularly visit surgical patients receiving IVPCA at least twice daily. The initial visit is provided by an attending anesthesiologist and a pain nurse, whereas the follow-up visits are usually performed at least twice daily by pain nurses. The first day visit is performed around 4 pm (from 3 to 5 pm) and 9 pm (from 8 to 10 pm). The interval between the first assessment and the surgery is  $\sim 4$ –6 hours. The following day visit is performed around 9 am (from 8 to 10 am) and 4 pm (from 3 to 5 pm). The regular interval in the next 2 days is  $\sim 7$  hours. Effectiveness of analgesia, delirium assessment, and side effects are assessed in every visit for each patient. If delirium, inadequate pain control, or any problem related to IVPCA is suspected, an anesthesiologist responds immediately and performs an extra visit 2–4 hours later.

### Delirium assessment

The NuDESC test assesses disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations, and psychomotor retardation.<sup>13</sup> Each item of the NuDESC is rated as 0, 1, or 2 based on the severity of symptoms (0: absence, 1: minor, and 2: severe). After being trained by a psychiatric expert, the acute pain service team in Chi Mei Medical Center has performed the NuDESC test for screening POD routinely since April 2011. In every visit, the trained anesthesiologists and pain nurses regularly examine each surgical patient receiving IVPCA by using the NuDESC (threshold  $\geq 1$ ), which has high sensitivity, but less specificity.<sup>18</sup> If POD is suspected, consulting a neurologist or a psychiatrist to confirm suspected POD is required.



**Figure 1** Data collection flowchart of POD in surgical patients scheduled for postoperative IVPCA.

**Abbreviations:** IVPCA, intravenous patient-controlled analgesia; NuDESC, Nursing Delirium Screening Scale; POD, postoperative delirium.

## Pain and daily assessment

During the first postoperative days, the intensity of rest/movement-evoked pain, and side effects of IVPCA including nausea, vomiting, and itching are also examined and recorded by acute pain service team members during each visit. Pain severity is measured by an 11-point verbal numerical rating scale (11-point VNRS) (0: no pain; 10: the worst imaginable pain). Patients are categorized as having adequate or inadequate pain relief. An 11-point VNRS score of  $\leq 3$  is considered adequate while a score  $> 3$  is considered inadequate.

Basic recorded patient characteristics include age, gender, body height/weight, ASA physical status scale, type of anesthesia, preoperative cognitive impairments, dementia, delirium, and comorbidities. Data are prospectively collected and stored electronically.

## Ethical approval

This prospective cohort study was approved by the Institutional Review Board (IRB) of Chi Mei Medical Center, Tainan, Taiwan (IRB number: 10009-012) and registered in a publicly accessible database (University Hospital Medical

Information Network (UMIN), Japan; <http://www.umin.ac.jp/ctr/index.htm>; Trial ID: UMIN:lin-yt). The research involved the routine procedures for daily services and presented no risk to the subjects, therefore, the IRB of Chi Mei Medical Center approved the use of an oral consent procedure rather than a written consent form for the use of the medical information of all patients.

## Statistical analysis

Potential predictors in IVPCA patients without POD versus with POD were analyzed by univariate and multivariate logistic analysis. Risk of POD was presented as odds ratio (OR) and 95% confidence intervals (CI). All selected predictors and the association of POD development were examined by univariate logistic regression analysis. An entry criterion for multivariate selection was set as  $P < 0.2$ . Multivariate logistic regression with backward eliminating procedure was applied to determine the final model, and an exit criterion was set as  $P > 0.05$ . All possible remaining two-way interactions were examined in addition to interactions of any given variable with POD. A stratified regression model was conducted when

a significant interaction was found. Adequate pain relief compared to inadequate pain relief in delirious patients and non-delirious patients were measured by chi-square test or Fisher's exact test. Data were analyzed using STATA 12.0 (Stata Corp, College station, TX, USA) statistical software. A *P*-value of <0.05 was considered significant.

## Results

In this study, 1,608 IVPCA patients who were aged  $\geq 60$  years and received general anesthesia were included. Of 1,608 patients, 362 patients were graded as ASA physical status I or II (22.5%), 1,088 patients as ASA III (67.7%), and 158 patients as ASA IV (9.8%). A total of 35 patients were diagnosed with POD using NuDESC with a score of  $\geq 1$ . The incidence of POD was 2.2% in IVPCA patients.

## Risk factors of POD in IVPCA patients

The characteristics of patients are shown in Table 1. Univariate logistic analysis of potential predictors for POD in IVPCA patients identified two predictors – patients aged  $\geq 70$  years (crude OR =2.38, 95% CI =1.14–4.99, *P*=0.018) and ASA physical status >III (crude OR =2.81, 95% CI =1.25–6.30, *P*<0.001). Gender, comorbidities (hypertension/diabetes mellitus), types of surgery, duration of surgery/anesthesia, total morphine dose/day, and postoperative nausea/vomiting were not associated with the risk of POD (all *P*>0.05).

As shown in Table 2, multivariate logistic analysis revealed that age  $\geq 70$  years (adjusted OR =2.18, 95% CI =1.13–4.69, *P*=0.023) and the ASA physical status >III (adjusted OR =2.46, 95% CI =1.09–5.56, *P*=0.029) were the risk factors of POD in IVPCA patients aged  $\geq 60$  years.

**Table 1** Univariate logistic analysis of potential predictors for POD in IVPCA patients

Predictors	No delirium, n (%) N=1,573 (97.9)	Delirium, n (%) N=35 (2.1)	Crude odds ratio (95% CI)	P-value
Age groups				
60–69 years	767 (98.7)	10 (1.3)	1.0	
$\geq 70$ years	806 (97.0)	25 (3.0)	2.38 (1.14–4.99)	0.018
Gender				
Female	866 (98.1)	17 (1.9)	1.0	
Male	707 (97.6)	18 (2.4)	1.30 (0.66–2.54)	0.554
ASA physical status				
I, II, III	1,423 (99.2)	27 (1.8)	1.0	
IV	150 (95.0)	8 (5.0)	2.81 (1.25–6.30)	<0.001
Hypertension				
No	693 (99.0)	15 (2.1)	1.0	
Yes	880 (97.8)	20 (2.2)	1.05 (0.53–2.07)	0.887
Diabetes mellitus				
No	792 (98.3)	14 (1.7)	1.0	
Yes	781 (97.4)	21 (2.6)	1.52 (0.77–3.01)	0.225
Types of surgery				
Others (thoracotomy, lower abdomen, breast, head, and neck surgery)	170 (99.4)	1 (0.6)	1.0	
Nephrectomy	70 (97.2)	2 (2.8)	4.86 (0.43–54.43)	0.210
Upper abdomen	568 (97.3)	16 (2.7)	4.79 (0.63–36.37)	0.139
Orthopedic surgery	765 (98.0)	16 (2.0)	3.56 (0.47–27.00)	0.335
Duration of surgery				
<195 min	1,006 (98.3)	18 (1.7)	1.0	
$\geq 195$ min	567 (97.1)	17 (2.9)	1.67 (0.86–3.28)	0.127
Duration of anesthesia				
<229 min	906 (97.7)	21 (2.3)	1.0	
$\geq 229$ min	667 (98.0)	14 (2.0)	0.91 (0.46–1.79)	0.775
Total morphine dose/day				
$\leq 20$ mg/day	1,196 (97.71)	28 (2.29)	1.0	
>20 mg/day	377 (98.18)	7 (1.82)	0.79 (0.34–1.83)	0.731
Postoperative nausea/vomiting				
No	1,322 (97.6)	32 (2.4)	1.0	
Yes	251 (98.8)	3 (1.2)	0.49 (0.15–1.62)	0.236

**Notes:** Duration of surgery/anesthesia is divided by the mean (195 in surgery, 229 in anesthesia). *P*<0.05, statistical significance.

**Abbreviations:** IVPCA, intravenous patient-controlled analgesia; POD, postoperative delirium; CI, confidence interval; ASA, American Society of Anesthesiologists.

**Table 2** Multivariate logistic analysis of potential predictors for POD in IVPCA patients

Predictors	Adjusted odds ratio (95% CI)	P-value
Age groups		0.023
60–69 years	1.0	
≥70 years	2.18 (1.13–4.69)	
ASA physical status		0.029
I, II, III	1.0	
IV	2.46 (1.09–5.56)	

**Abbreviations:** IVPCA, intravenous patient-controlled analgesia; POD, postoperative delirium; CI, confidence interval; ASA, American Society of Anesthesiologists.

No significant two-way interaction was found among the final prognostic variables (data not shown). Other variables that were examined did not affect the development of POD. Taken together, multivariate regression analyses after adjusting for potential confounders revealed that being aged ≥70 years as well as the ASA physical status >III are independent predictors for POD.

## Phenomenological characteristics of POD assessed by NuDESC

A total of 28 patients (80%) experienced POD within the first 2 postoperative days (Table 3). Table 4 shows that 71.4% of these POD patients had a NuDESC score ≤2. Only 11.4% of POD cases had a score ≥5. Based on the rates, the symptoms of POD were ranked from high to low as disorientation (23 patients, 65.7%), illusions/hallucinations (13 patients, 37.1%), inappropriate communication (11 patients, 31.4%), inappropriate behavior (9 patients, 25.7%), and psychomotor retardation (5 patients, 14.2%). In total, 19 patients (54.2%) showed one symptom and nine patients (25.7%) had two symptoms. Only one patient (2.8%) displayed all five symptoms.

## Associations between rest/movement-evoked pain and POD

As shown in Table 5, patients with inadequate rest pain relief (VNRS >3) within the first 3 postoperative days had greater incidence rates of POD than patients with adequate rest pain relief. However, statistical differences were found only on day 1 and 2 (day 1, 8.4% vs 1.5%,  $P<0.001$ ; day 2,

**Table 3** Occurrence of postoperative delirium in IVPCA patients

Postoperative days	Incidence of postoperative delirium	Prevalence of postoperative delirium
Day 1	17 (1.1%)	17 (1.1%)
Day 2	10 (0.6%)	11 (0.6%)
Day 3	8 (0.5%)	9 (0.5%)

**Abbreviation:** IVPCA, intravenous patient-controlled analgesia.

**Table 4** Phenomenological characteristics of delirium detected by NuDESC in IVPCA patients

Symptoms	Patients, n (%)
NuDESC scores (1–10)	
1	16 (45.7)
2	9 (25.7)
3–4	6 (17.2)
≥5	4 (11.4)
Features	
Disorientation	23 (65.7)
Inappropriate behavior	9 (25.7)
Inappropriate communication	11 (31.4)
Illusions/hallucinations	13 (37.1)
Psychomotor retardation	5 (14.2)
Number of symptoms	
1	19 (54.2)
2	9 (25.7)
3	5 (14.2)
4	1 (2.8)
5	1 (2.8)
Mean (SD)	1.7 (1.0)

**Abbreviations:** NuDESC, Nursing Delirium Screening Scale; IVPCA, intravenous patient-controlled analgesia; SD, standard deviation.

9.6% vs 2.0%,  $P=0.028$ ; day 3, 4.1% vs 2.1%,  $P=0.412$ ). Interestingly, there were no significant differences in the incidence of POD between patients with inadequate and adequate movement-evoked pain relief (day 1,  $P=0.147$ ; day 2,  $P=0.726$ ; day 3,  $P=0.490$ ).

## Discussion

This study is the first prospective study using NuDESC to identify the risk factors and incidence of POD in elective noncardiac surgical patients receiving IVPCA. Risk factors are generally divided into predisposing and precipitating factors. Predisposing factors for POD include advanced age, preexisting dementia, ASA physical status, and functional disabilities. They can be assessed before surgery and identified easily.<sup>8,19</sup> In this study, two identified risk factors including age and the ASA physical status are consistent with the previous findings.<sup>2,14</sup> Both are predisposing factors that are not modifiable in general.<sup>4</sup> Precipitating factors for POD, such as types and duration of surgery, hypoxemia, and postoperative pain, occur intraoperatively and postoperatively.<sup>4</sup> Among them, pain is modifiable. In this study, POD incidence in elderly Chinese IVPCA patients was 2.2% which was lower than 5.1%–13% – the overall incidence of POD in elderly Chinese patients.<sup>5,20</sup> These results support the previous findings that better pain control lowers the incidence of POD.<sup>7,8</sup> However, previous reviews reported that the incidence of POD in general surgical patients ranges from 10% to 46%.<sup>21,22</sup> A retrospective study regarding POD showed that the



**Table 5** Adequate pain relief compared to inadequate pain relief in delirious patients versus nondelirious patients

Postoperative days	VNRS score	Pain at rest		P-value	Movement-evoked pain		P-value
		Delirium, n (%)	No delirium, n (%)		Delirium, n (%)	No delirium, n (%)	
Day 1	≤3	23 (65.7)	1,443 (91.7)	<0.001	13 (37.1)	779 (49.5)	0.147
	>3	12 (34.3)	130 (8.3)		22 (63.9)	794 (50.5)	
Day 2	≤3	32 (91.4)	1,545 (98.2)	0.028	25 (71.4)	1,080 (68.7)	0.726
	>3	3 (8.6)	28 (1.8)		10 (28.6)	493 (31.3)	
Day 3	≤3	34 (97.1)	1,550 (98.5)	0.412	31 (88.6)	1,326 (84.3)	0.490
	>3	1 (2.9)	23 (1.5)		4 (11.4)	247 (15.7)	

**Notes:** VNRS is an 11-point verbal numeric rating pain scale with a score range of 1–10. An 11-point VNRS score of ≤3 is considered adequate pain relief. Categorical variables were measured by chi-square test or Fisher's exact test.  $P < 0.05$ , statistical significance.

**Abbreviation:** VNRS, verbal numerical rating scale.

incidence of POD in IVPCA patients undergoing orthopedic surgery in Korea was 8%, which was a result based on chart reviews.<sup>9</sup> Possible explanations for the result of the retrospective study are provided. First, delirium is a clinical syndrome. The method of assessing delirium is a major factor which results in the variation of the reported incidence of delirium.<sup>4</sup> Second, different types of surgery which introduce considerable heterogeneity may have different inherent risks of delirium.<sup>4</sup> Third, race has been found to be statistically related to the development of delirium.<sup>23</sup> Accordingly, different methods and more research on populations may yield different results.

The NuDESC test has been validated for screening delirium in the surgical wards.<sup>13–15</sup> In this study, POD patients had relatively low scores measured by the NuDESC. Approximately 80% of POD cases showed either one or two symptoms. Only one patient showed all the five symptoms. This may be due to the effective pain treatment that decreases the risk and severity of POD.<sup>6–8</sup> The most common symptom was disorientation, followed by illusions/hallucinations. The least common symptom was psychomotor retardation. In the delirious cancer patients assessed by the memorial delirium assessment scale, the most frequent symptoms are impaired digit span and psychomotor abnormality, followed by disorientation and inattention. Perceptual disturbance (eg, hallucinations) and delusion have relatively lower percentages.<sup>24</sup> However, disorientation was the least frequent cognitive deficit in delirious adults assessed by the delirium rating scale-revised-98.<sup>25</sup> No consistent phenomenology was found between the results of this study and previous reports. Despite major advancements in delirium research, medical articles concerning the phenomenology of POD are limited. More phenomenological research of POD is needed to find association between symptoms of POD and the etiology, pathophysiology, and treatment.<sup>26,27</sup>

In the present study, the intensity of patients' pain was measured with the 11-point VNRS. The 11-point VNRS has

been shown to be effective and validated for the assessment of acute pain in older patients and those with a mild/moderate cognitive impairment.<sup>28</sup> A concept concerning acute pain at rest and on movement is that adequate relief of rest pain after surgery is important for making the patient comfortable in bed. However, adequate relief of movement-evoked pain after surgery is critical for reducing risks of postoperative cardiopulmonary and thromboembolic complications.<sup>28</sup> During the first 2 postoperative days, IVPCA patients with inadequate rest pain relief had a significant increased risk of POD. However, movement-evoked pain was not significantly associated with POD incidence in IVPCA patients. The results are similar to previous findings showing the risk of POD associated with higher rest pain levels but not with movement-evoked pain.<sup>7</sup> Taken together, better control of postoperative rest pain by IVPCA is effective in reducing the incidence of POD. As for postoperative opioid consumption, this study revealed no significant association between the POD incidence and the total morphine dose per day. The finding is consistent with that of Sieber et al.<sup>29</sup> However, a previous study discovered that patients receiving less parenteral morphine per day were more likely to develop POD than those receiving more analgesics. Inadequately treated pain was considered as a risk factor for POD in older adults.<sup>30</sup> By contrast, exposure to high-dose opiates has been found to be a minor precipitating risk factor of POD.<sup>31,32</sup> More studies are needed to clarify the associations among uncontrolled pain, opiates doses, and POD. In this study, there was no significant association between the POD incidence and surgical duration as reported previously.<sup>33</sup> However, another research study reports that longer surgical duration increases the risk of POD.<sup>34</sup> There is no consensus on the effect of longer surgical duration with delirium risk. Similarly, surgical duration is another controversial factor that needs more studies to elucidate its associations with the risk of POD.

This study had several limitations. First, delirium assessment was measured only twice-daily by the acute pain service

team. POD incidence may be lower than the true incidence because of the fluctuating nature of POD. Second, the patients were monitored for only 3 postoperative days because most POD occurs during this period. However, delirium may occur after day 3 that may not be detected.<sup>2</sup> Third, only Chinese patients were included in this study. Race could possibly play a role in the results as the rate (2.2%) of POD in this study was much lower than that in other studies.<sup>9,21,22</sup> Fourth, this research was conducted in a single hospital. More information from multiple centers is required to validate the findings.

## Conclusion

The incidence of POD in IVPCA patients was low. The risk of POD was significantly associated with inadequate rest pain relief but not with inadequate movement-evoked pain relief. Most POD cases in IVPCA patients showed either one or two symptoms. Disorientation was the most common, whereas psychomotor retardation was the least common. Further research is warranted concerning POD and IVPCA pain management.

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## Disclosure

The authors report no conflicts of interest in this work.

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