Int Surg 2019;**104:**542–549
DOI: 10.9738/INTSURG-D-16-00112.1

Emergency Surgery and Male Gender Are Risk Factors of Postoperative Delirium After General or Gastrointestinal Surgery in Elderly Patients: A Multicenter Cohort Study

Kazuyoshi Yamamoto[1], Noriko Shimakawa[2], Takao Mizumoto[3], Kazuhisa Shiroyama[4], Tsutomu Shichino[5], Kenji Yuzawa[6], Masato Kataoka[7], Tetsuya Horiuchi[8], Shin Teshima[9], Shinichi Shibasaki[10], Motohiro Hirao[1], on behalf of the Surgery and Anesthesia Network Group of the National Hospital Organization

[1]*Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan*

[2]*Department of Anesthesia, National Hospital Organization Osaka National Hospital, Osaka, Japan*

[3]*Department of Surgery, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan*

[4]*Department of Anesthesia, National Hospital Organization Kure Medical Center, Kure, Japan*

[5]*Department of Anesthesia, National Hospital Organization Kyoto Medical Center, Kyoto, Japan*

[6]*Department of Surgery, National Hospital Organization Mito Medical Center, Mito, Japan*

[7]*Department of Surgery, National Hospital Organization Nagoya Medical Center, Nagoya, Japan*

[8]*Department of Surgery, National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan*

[9]*Department of Surgery, National Hospital Organization Sendai Medical Center, Sendai, Japan*

[10]*Department of Surgery, National Hospital Organization Ureshino Medical Center, Ureshino, Japan*

Corresponding author: Kazuyoshi Yamamoto, MD, Department of Surgery, National Hospital Organization Osaka National Hospital, 2-1-14 Hoenzaka, Chuo-ku, Osaka, 540-0006, Osaka, Japan.
Tel.: +81 6 6942 1331; Fax; +81 6 6943 6467; E-mail: kazuyoshi0208yamamoto@yahoo.co.jp

Objective: The aim of this study was to investigate the incidence and risk factors of postoperative delirium (PD) in elderly patients after general or gastrointestinal surgery.

Summary of background data: Societies worldwide are rapidly aging, and the number of surgeries in elderly patients has been increasing. PD, which adversely influences postoperative course, has thus become more common.

Methods: The Surgery and Anesthesia Network Group of the National Hospital Organization in Japan conducted this retrospective cohort study of patients older than 70 years of age who underwent general or gastrointestinal surgery.

Results: A total of 219 patients from 9 participating institutes underwent surgery between July 2013 and August 2014. We excluded 2 patients who died within 2 weeks after surgery. Of the remaining 217 cases, 31 (14.3%) developed PD. These patients were older (80 versus 76 years, $P = 0.013$), more likely to be male (74.2 versus 54.8%, $P = 0.039$), and had higher American Society of Anesthesia Physical Status scores than those without PD. Emergency surgery was more common than elective surgery in the PD group (41.9 versus 10.2%, $P < 0.0001$). Multivariate analysis showed that male gender (odds ratio, 3.31; 95% confidence interval, 1.32 to 9.39; $P = 0.0098$) and emergency surgery (odds ratio, 7.47; 95% confidence interval, 2.79 to 20.83; $P < 0.0001$) were independent risk factors of PD.

Conclusions: The incidence of PD was high in male patients and those undergoing emergency surgery. Effective interventions in these groups will be necessary to improve treatment outcomes in elderly patients.

Key words: Postoperative delirium – General or gastrointestinal surgery – Elderly

Postoperative delirium (PD) is an acute, fluctuating disorder of attention and cognition.[1] It is one of the most common serious postoperative complications in elderly patients, with a reported incidence of 9.0% to 13.2% in gastrointestinal and general surgery,[2–5] 33% in colorectal emergency surgery,[6] 9.1% to 28.6% in orthopedic surgery,[7–9] and 23.0% and 32.0% in cardiovascular surgery.[10,11] In addition to being subjectively uncomfortable, PD is associated with accidental removal of drains or catheters, worsened treatment compliance, exhaustion of medical staff, and medical accidents such as falls.

PD is also associated with impaired treatment outcomes, including impaired activities of daily living,[7] prolonged hospitalization[2,3,5] and intensive care unit stays,[2] elevated morbidity[2,3,6] and mortality,[9,12,13] and increased hospital costs.[2]

Several studies have identified risk factors of PD, including advanced age, cognitive impairment, preoperative nutritional status, alcohol abuse, increased comorbidity, impaired American Society Anesthesiologists Physical Status (ASA-PS) score, exposure to sedating medications, high-risk surgical procedures, emergency surgery, general anesthesia, elevated intraoperative blood pressure, poorly controlled postoperative pain, and major postoperative complications.[2,4,8,11,14–18]

However, PD remains frequently unrecognized and poorly understood by surgeons, anesthesiologists, and surgical ward staff members in general hospitals.[19] Because many countries face aging populations and the demand for surgical services for elderly patients is growing significantly,[20] it is critical to be able to detect risk factors of PD in this age group and to develop optimized interventions for PD. To this end, this multicenter retrospective cohort study was conducted by the National Hospital Organization Surgery and Anesthesia Network Group (PD cohort study) in Japan. The study sought to determine the prevalence and risk factors of PD among elderly patients undergoing general or gastrointestinal surgery based on cohort data on patient backgrounds and surgery and anesthesia parameters.

Methods

Study design and participants in the PD cohort study

The PD cohort study protocol was designed by the Surgery and Anesthesia Network Group of the National Hospital Organization in Japan. The study

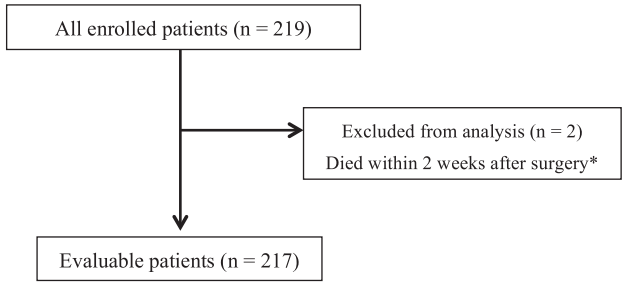

Fig. 1 Study flowchart. * Patients died on postoperative days 2 and 12 after emergency surgery for perforation peritonitis.

protocol was approved by the institutional review board of each participating hospital and was registered in the University Hospital Medical Information Network (UMIN R000022185). This retrospective observational study analyzed data from the clinical records of all elderly patients older than 70 years of age who underwent general or gastrointestinal surgery during the latest 1 month after study protocol approval, from July 2013 to August 2014. Data were collected on patient background, surgery and anesthesia factors, and details regarding PD. Patient background data included age; gender; history of cerebrovascular disease, dementia, and depression; daily alcohol consumption; current smoking; and ASA-PS. Anesthesia data included type of anesthesia, which anesthetics were used, and whether or not bispectral index (BIS) monitoring was performed. Surgical factors included disease; type and approach of surgery; operative time and blood loss; insertion of urinary catheters, venous catheters, and drains; and total number of drains and catheters. Patients were divided into 2 groups: those who developed PD (PD group) and those who did not (nondelirium group).

Table 1 Summary data on postoperative delirium (n = 31)

	n (%)
Symptoms of delirium	
Abnormal behavior	26 (83.9%)
Hallucinatory episode	4 (12.9%)
Oversedation	1 (3.2%)
Postoperative day of delirium onset (median)	1 (0–7)
Days needed to recover from delirium (median)	
1	9 (29.0%)
2–3	11 (35.5%)
4–6	6 (19.4%)
≥7	5 (16.1%)
Treatment for postoperative delirium	
Typical antipsychotic drug	11 (35.5%)
Atypical antipsychotic drug	4 (12.9%)
None	16 (51.6%)

The 2 groups were compared in terms of patient background, surgery and anesthesia factors, and postoperative clinical course. Using data from the PD cohort study database, we analyzed the risk factors of PD and explored the optimal targets for prevention of PD in elderly patients undergoing general or gastrointestinal surgery.

Definition of PD

PD is an acute decline in attention and cognition after surgery.[17] In reference to the criteria of the Diagnostic and Statistical Manual Mental Disorder 4th edition,[21] it was diagnosed in the current study if patients presented with at least 1 of the following 3 fluctuating symptoms within 7 days after surgery: (1) abnormal behavior, (2) one or more hallucinatory episodes, and (3) oversedation. PD was diagnosed by attending physicians or study investigators at each institute based on patient medical records.

Statistical analysis

We expressed continuous variables as medians (range). Fisher's exact test was used to compare binary variables, and the Mann-Whitney U test was used to compare continuous variables. Univariate and multivariate analyses were carried out using logistic regression. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using JMP software (SAS Institute, Cary, North Carolina).

Results

A total of 219 elderly patients older than 70 years of age underwent general or gastrointestinal surgery from July 2013 to August 2014 at the 9 institutions enrolled in this PD cohort study. We excluded 2 patients who died within 2 weeks after surgery (1 patient died on the 2nd postoperative day, and the

Table 2 Patient backgrounds and surgery and anesthesia data of patients with PD and without PD (nondelirium)

	PD (n = 31)	Nondelirium (n = 186)	*P* value
Age, years	80 (71–94)	76 (70–96)	0.013
Gender, n (%)			0.039
Male	23 (74.2)	102 (54.8)	
Female	8 (25.8)	84 (45.2)	
BMI, kg/m^2	21.9 (12.5–24.3)	21.9 (15.1–43.6)	0.33
History of			
Cerebrovascular disease, n (%)	6 (19.4)	32 (17.2)	0.77
Dementia, n (%)	3 (9.7)	5 (2.7)	0.096
Depression, n (%)	2 (6.5)	4 (2.2)	0.23
Daily alcohol consumption, n (%)	7 (22.6)	26 (14.0)	0.24
Current smoking, n (%)	4 (12.9)	17 (9.1)	0.53
ASA-PS, n (%)			0.046
1–2	20 (64.5)	151 (81.2)	
3–5	11 (35.5)	35 (18.8)	
Anesthesia, n (%)			
General anesthesia	29 (93.5)	164 (88.2)	0.35
Intravenous anesthesia	20	91	0.17
Inhalation anesthesia	9	73	
Spinal anesthesia	2 (6.5)	10 (5.4)	
Local anesthesia	0	12 (6.5)	
Use of BIS monitor			0.43
Yes (%)	17 (54.8)	116 (62.4)	
No (%)	14 (45.2)	70 (37.6)	
Type of disease requiring surgery			0.12
Malignant	14 (45.2)	112 (60.2)	
Benign	17 (54.8)	74 (39.8)	
Type of surgery, n (%)			<0.0001
Elective	18 (58.1)	167 (89.8)	
Emergency	13 (41.9)	19 (10.2)	
Surgical approach, n (%)			0.14
Open laparotomy	21 (67.7)	100 (53.8)	
Laparoscopic	10 (32.3)	86 (46.2)	
Operative time, min	154 (51–478)	170 (7–637)	0.61
Operative blood loss, ml	45 (0–712)	20 (0–1970)	0.61
Insertion of urinary catheter			0.23
Yes (%)	31 (100.0)	172 (92.5)	
No (%)	0	14 (7.5)	
Insertion of central venous catheter			0.88
Yes (%)	5 (16.1)	28 (15.1)	
No (%)	26 (83.9)	158 (84.9)	
Number of drains inserted	1 (0–6)	1 (0–4)	0.99
Total number of drains and catheters	3 (1–8)	3 (2–6)	0.80

BMI, body mass index.

other died on the 12th postoperative day after emergency surgery for perforation peritonitis). The remaining 217 patients were analyzed (Fig. 1). Their median age was 77 (70 to 96) years old, and there were 125 males and 92 females. The numbers (percentage) of patients with a history of cerebrovascular disease, dementia, or depression were 38 (17.5%), 8 (3.7%), and 6 (2.8%), respectively. In terms of surgical factors, 126 patients underwent surgery for malignant disease (esophageal, 2; gastric, 26; colorectal, 67; hepato-biliary-pancreatic, 18; breast, 10; and others, 3), and 91 patients had benign disease (inguinal hernia, 33; gallbladder stone, 27; appendicitis, 8; peritonitis, 4; ileus, 4; and others, 15). There were 185 elective and 32 emergency surgeries. Open surgery was performed in 121 patients, and a laparoscopic approach was used in 96. Regarding anesthesia factors, the ASA-PS was 1 to 2 in 171 patients and 3 to 5 in 46 patients; 193 patients received general anesthesia (intravenous anesthesia, 111; inhalation anesthesia, 82), and 133 patients were monitored by BIS during anesthesia.

Of the 217 evaluable patients, 31 (14.3%) developed PD; details are summarized in Table 1.

Table 3 Postoperative complications and durations of hospitalization in PD and nondelirium patients

	PD (n = 31)	Nondelirium (n = 186)	*P* value
All complications, n (%)	10 (32.3)	39 (21.0)	0.18
SSI	3 (9.7)	19 (10.2)	0.93
Leakage	1 (3.2)	3 (1.6)	0.57
Superficial SSI	2 (6.5)	10 (5.4)	0.81
Others	0	6 (3.2)	0.17
Non-SSI	7 (22.6)	22 (11.8)	0.13
Ileus	2 (6.5)	6 (3.2)	0.41
Pneumonia	1 (3.2)	3 (1.6)	0.57
Cardiovascular	2 (6.5)	1 (0.5)	0.054
Others	2 (6.5)	13 (7.0)	0.91
ICU stay			0.011
Yes, n (%)	11 (35.5)	28 (15.0)	
No, n (%)	20 (64.5)	158 (85.0)	
Duration of postoperative hospitalization, days	18 (4–74)	10 (1–101)	0.0006

ICU, intensive care unit; SSI, surgical site infection.

Observed symptoms were abnormal behavior in 26 patients, 1 or more hallucinatory episodes in 4 patients, and oversedation in 1 patient. The median onset of PD was postoperative day 1 (0 to 7). The median recovery duration was 1 day in 9 patients, 2 to 3 days in 11 patients, 4 to 6 days in 6 patients, and more than 7 days in 5 patients. Eleven patients who developed PD received typical antipsychotic drugs, 4 patients received atypical antipsychotic drugs, and 16 patients did not receive any pharmacologic treatment for PD.

Table 2 presents perioperative patient data with a focus on the development of PD. PD patients were older (80 versus 76 years, $P = 0.013$) and were more likely to be male (74.2 versus 54.8%, $P = 0.039$) compared with those without PD (nondelirium). More PD patients underwent emergency surgery (41.9 versus 10.2%, $P < 0.0001$) and had ASA-PS scores worse than 3 (35.5% versus 18.8%, $P = 0.046$). There were no significant differences between the 2 groups in anesthesia type (general anesthesia versus other), intravenous or inhalation anesthesia during general anesthesia, disease type, surgical approach, operative time, operative blood loss, or number of drains and catheters. Of the 14 patients who did not undergo perioperative urinary catheter insertion, none developed PD.

In terms of postoperative complications and clinical course, there was no significant difference in overall or specific complication rates between the PD and nondelirium patients (Table 3); however, PD patients were more likely to require intensive care unit treatment (35.5% versus 15.0%, $P = 0.011$) and had a longer postoperative hospital stay (18 versus 10 days, $P = 0.0006$).

Table 4 Risk factors for PD in evaluable patients (n = 217)

		Univariate analysis			Multivariate analysis		
Variable	n	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, years							
≥80	73	2.41	1.11–5.26	0.026	1.70	0.72–3.99	0.23
<80	144						
Gender							
Male	125	2.37	1.04–5.90	0.039	3.31	1.32–9.39	0.0098
Female	92						
Type of surgery							
Emergency	32	6.35	2.68–15.03	<0.0001	7.47	2.79–20.83	<0.0001
Elective	185						
ASA-PS							
≥3	46	2.37	1.02–5.34	0.046	1.18	0.44–2.99	0.73
1–2	171						

Table 4 shows the risk factors of PD in the 217 evaluable patients. Age, gender, type of surgery, and ASA-PS were extracted from the analysis of patient background and surgery and anesthesia factors in PD and nondelirium patients, as shown in Table 2. In the univariate analysis, age greater than 80 years, male gender, emergency surgery, and ASA-PS score worse than 3 were significantly correlated with the incidence of PD. In the multivariate analysis, male gender (odds ratio [OR], 3.31; 95% confidential interval [CI], 1.32 to 9.39; $P = 0.0098$) and emergency surgery (OR, 7.47; 95% CI, 2.79 to 20.83; $P < 0.0001$) were the only independent risk factors associated with the incidence of PD. The incidences of male (n = 14) and female (n = 18) patients who underwent emergency surgery and male (n = 111) and female (n = 74) patients who underwent elective surgery were 50.0%, 33.3%, 14.4%, and 2.7%, respectively.

Discussion

PD is a common and deleterious postoperative complication[1] that is becoming more prevalent in rapidly aging societies. Identifying patients at higher risk of PD is important to improve outcomes in elderly patients undergoing surgery.

In this cohort study, we focused on the incidence of PD and its risk factors after general or gastrointestinal surgery in elderly patients older than 70 years of age. Of 217 evaluable patients, 31 (14.3%) developed PD. The independent risk factors identified by multivariate analysis were emergency surgery and male gender, findings that are consistent with previous reports.[11,22]

In our series, male patients were significantly more likely to be current smokers and to consume alcohol daily and were less likely to undergo general anesthesia and BIS monitoring during anesthesia (data not shown). Other biological and sociocultural differences between genders, such as brain function, pain tolerance, and adaptability, might have influenced the results.[23–25]

Intervention to prevent PD in elderly patients undergoing general or gastrointestinal surgery should be targeted at males and at patients requiring emergency surgery. Several studies, including a randomized controlled trial and a meta-analysis, evaluated various approaches to the complex task of predicting and treating PD in elderly patients undergoing surgery.[26,27] Pharmacologic prevention of PD remains controversial; whereas most medications evaluated were ineffective, including haloperidol,[28,29] donepezil hydrochloride,[30] tryptophan,[31] and rivastigmine.[32] several trials of prophylactic antipsychotic administration showed efficacy in reducing the incidence of PD in several surgical settings.[1,26,27,33] Multicomponent intervention, BIS-guided anesthesia, and dexmedetomidine sedation were reported to be useful in preventing PD.[27,34,35] However, preventive interventions for PD are difficult to conduct in patients undergoing emergency surgery.

The primary limitation of our study was its retrospective cohort design. The accurate diagnosis of PD is difficult for surgeons, anesthesiologists, and the medical staff of surgical wards, and PD is often unrecognized and easily overlooked.[1,19] PD should be diagnosed by psychiatrists using established diagnostic criteria or instruments such as the Diagnostic and Statistical Manual Mental Disorder 4th edition,[21] the International Classification of Diseases-10,[36] and the Confusion Assessment Method.[37] Although this is not always possible in clinical practice, it should be emphasized, along with assessment of preoperative cognitive function, in prospective interventional studies for PD.

In conclusion, this study demonstrated that elderly patients undergoing general or gastrointestinal surgery were at higher risk of PD if they were male or undergoing emergency surgery. These subpopulations are the optimal targets of interventions such as multicomponent programs to prevent PD and improve treatment outcomes.

Acknowledgments

This study was performed by the Surgery and Anesthesia Network Group of the National Hospital Organization that includes the following institutions: Kumamoto Medical Center, Kure Medical Center, Kyoto Medical Center, Mito Medical Center, Nagoya Medical Center, Osaka Minami Medical Center, Osaka National Hospital, Sendai Medical Center, and Ureshino Medical Center.

References

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;**383**(9920):911–922
2. Markar SR, Smith IA, Karthikesalingam A, Low DE. The clinical and economic costs of delirium after surgical resection for esophageal malignancy. *Ann Surg* 2013;**258**(1):77–81
3. 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): 134–139
4. Tei M, Ikeda M, Haraguchi N, Takemasa, I, Mizushima T, Ishii H *et al*. Risk factors for postoperative delirium in elderly patients with colorectal cancer. *Surg Endosc* 2010;**24**(9):2135–2139
5. Ansaloni L, Catena F, Chattat R, Fortuna D, Franceschi C, Mascitti P *et al*. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. *Br J Surg* 2010;**97**(2):273–280
6. Engelberger S, Zürcher M, Schuld J, Viehl CT, Kettelhack C. Postoperative course after emergency colorectal surgery for secondary peritonitis in the elderly is often complicated by delirium. *Int Surg* 2012;**97**(2):129–134
7. Liang CK, Chu CL, Chou MY, Lin YT, Lu T, Hsu CJ *et al*. Interrelationship of postoperative delirium and cognitive impairment and their impact on the functional status in older patients undergoing orthopaedic surgery: a prospective cohort study. *PLoS One* 2014;**9**(11):e110339
8. Wang NY, Hirao A, Sieber F. Association between intraoperative blood pressure and postoperative delirium in elderly hip fracture patients. *PLoS One* 2015;**10**(4):e0123892
9. Bellelli G, Mazzola P, Morandi A, Bruni A, Carnevali L, Corsi M *et al*. Duration of postoperative delirium is an independent predictor of 6-month mortality in older adults after hip fracture. *J Am Geriatr Soc* 2014;**62**(7):1335–1340
10. Soehle M, Dittmann A, Ellerkmann RK,Baumgarten G, Putensen C, Guenther U. Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. *BMC Anesthesiol* 2015;15:61
11. Koebrugge B, van Wensen RJ, Bosscha K, Dautzenberg PL, Koning OH. Delirium after emergency/elective open and endovascular aortoiliac surgery at a surgical ward with a high-standard delirium care protocol. *Vascular* 2010;**18**(5):279–287
12. Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY *et al*. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med* 2004;**32**(11):2254–2259
13. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr *et al*. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; **91**(14):1753–1762
14. Marcantonio ER, Juarez G, Goldman L, Mangione CM, Ludwig LE, Lind L *et al*. The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994;**272**(19): 1518–1522
15. Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg*. 1998; **86**(4):781–785
16. Marcantonio ER. Postoperative delirium: a 76-year-old woman with delirium following surgery. *JAMA* 2012;**308**(1):73–81
17. Inouye SK. Delirium in older persons. *N Engl J Med* 2006; **354**(11):1157–1165
18. Hempenius L, Slaets JP, van Asselt DZ, Schukking J, de Bock GH, Wiggers T *et al*. Interventions to prevent postoperative delirium in elderly cancer patients should be targeted at those undergoing nonsuperficial surgery with special attention to the cognitive impaired patients. *Eur J Surg Oncol* 2015;**41**(1): 28–33
19. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. *J Am Coll Surg* 2015;**220**(2):136–148
20. Etzioni DA, Liu JH, Maggard MA, Ko CY. The aging population and its impact on the surgery workforce. *Ann Surg* 2003;**238**(2):170–177
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. 4*. Washington, DC: American Psychiatric Association; 1994.
22. Takeuchi M, Takeuchi H, Fujisawa D, Miyajima K, Yoshimura K, Hashiguchi S *et al*. Incidence and risk factors of postoperative delirium in patients with esophageal cancer. *Ann Surg Oncol* 2012;**19**(12):3963–3970
23. Vigil JM, Rowell LN, Chouteau S, Chavez A, Jaramillo E, Neal M *et al*. Sex differences in how social networks and relationship quality influence experimental pain sensitivity. *PLoS One* 2013;**8**(11):e78663
24. Mogil JS. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. *Nat Rev Neurosci* 2012;**13**(12):859–866
25. Harrison PJ, Tunbridge EM. Catechol-O-methyltransferase (COMT): a gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. *Neuropsychopharmacology* 2008;**33**(13): 3037–3045
26. Fok MC, Sepehry AA, Frisch L, Sztramko R, Borger van der Burg BL, Vochteloo AJ *et al*. Do antipsychotics prevent postoperative delirium? A systematic review and meta-analysis. *Int J Geriatr Psychiatry* 2015;**30**(4):333–344
27. Zhang H, Lu Y, Liu M, Zou Z, Wang L, Xu FY, et al. Strategies for prevention of postoperative delirium: a systematic review and meta-analysis of randomized trials. *Crit Care* 2013;**17**(2): R47
28. Fukata S, Kawabata Y, Fujisiro K, Katagawa Y, Kuroiwa K, Akiyama H *et al*. Haloperidol prophylaxis does not prevent postoperative delirium in elderly patients: a randomized, open-label prospective trial. *Surg Today* 2014;44(12):2305–2313
29. Schrijver EJ, de Vries OJ, Verburg A, de Graaf K, Bet PM, van de Ven P *et al*. Efficacy and safety of haloperidol prophylaxis for delirium prevention in older medical and surgical at-risk patients acutely admitted to hospital through the emergency department: study protocol of a multicenter, randomised, double-blind, placebo-controlled clinical trial. *BMC Geriatr* 2014;14:96

30. Sampson EL, Raven PR, Ndhlovu PN, Vallance A, Garlick N, Watts J *et al*. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int J Geriatr Psychiatry* 2007;**22**(4):343–349
31. Robinson TN, Dunn CL, Adams JC, Hawkins CL, Tran ZV, Raeburn CD *et al*. Tryptophan supplementation and postoperative delirium—a randomized controlled trial. *J Am Geriatr Soc* 2014;**62**(9):1764–1771
32. Gamberini M, Bolliger D, Lurati Buse GA, Burkhart CS, Grapow M, Gagneux A *et al*. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery—a randomized controlled trial. *Crit Care Med* 2009;**37**(5):1762–1768
33. Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ *et al*. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. *Crit Care Med* 2012;**40**(3):731–739
34. Mouchoux C, Rippert P, Duclos A, Fassier T, Bonnefoy M, Comte B *et al*. Impact of a multifaceted program to prevent postoperative delirium in the elderly: the CONFUCIUS stepped wedge protocol. *BMC Geriatr* 2011;**11**:25
35. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013;**25**(1):33–42
36. Word Health Organization. *The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research*. Geneva, Switzerland: World Health Organization; 1993
37. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;**113**(12):941–948