Family Medicine and Community Health
ORIGINAL RESEARCH

Risk factors for post-operative delirium in elderly Chinese patients

Xiaoli Yuan, Zhixia Jiang, Lingxia Song, Li Yang, Ying He, Gongyin Luo

Abstract

Objective: The purpose of this study was to systematically analyze the risk factors for post-operative delirium (PD) in elderly patients in an effort to provide a basis for developing relevant clinical interventions in China.

Methods: All published studies focusing on the risk factors for PD among elderly patients in Wanfant Data, China National Knowledge Infrastructure (CNKI), and VIP were collected according to the inclusion and exclusion criteria of this study. A meta-analysis was performed on case-control studies using RevMan5.2 software, and the incidence of PD risk factors was calculated among case series.

Results: Sixteen studies, including 8 case-control studies and 8 case series, were included in the current study. There were 353 cases and 2008 controls in the case-control studies. The pooled odds ratios (95% CI) of PD risk factors were as follows: hypoxemia, 2.58 (1.59~4.18); pulmonary infection, 4.51 (2.23~9.13); hypertension, 2.16 (1.20~3.89); coronary heart disease, 1.50 (0.82~2.73); post-operative pain, 3.18 (1.63~6.20); general anesthesia, 3.64 (0.94~14.11); operative time, 1.70 (0.79~3.66); and senility, 0.52 (–0.25~1.29). The meta-analysis showed that hypoxemia, pulmonary infection, hypertension, coronary heart disease, post-operative pain, general anesthesia, operative time, and senility were significant risk factors for PD. There were 404 cases in the case series, and the incidence of hypoxemia, hypertension, general anesthesia, diabetes mellitus, senility, coronary heart disease, pulmonary infection, and cerebrovascular disease was 62.62%, 55.90%, 33.7%, 24.8%, 16.58%, 15.3%, 13.9%, and 12.1%, respectively, which was much higher than other risk factors.

Conclusion: Senility, hypertension, coronary heart disease, diabetes mellitus, pulmonary infection, hypoxemia, post-operative pain, and general anesthesia are significant risk factors for PD among elderly Chinese patients.

Keywords: Elderly patient, Post-operative delirium, Risk factor, Systematic review, Meta-analysis

Nursing Department, Zunyi Medical College Affiliated Hospital, Guizhou 563003, China

CORRESPONDING AUTHOR: Zhixia Jiang
Nursing Department, Zunyi Medical College Affiliated Hospital, Guizhou 563003, China
E-mail: jzxhl@126.com

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Introduction

Delirium, one of the acute organic brain syndromes, is an important complication that commonly occurs in post-operative senile patients; the incidence of delirium is 8%~78%. Post-operative delirium (PD) cannot only increase the morbidity and mortality of pressure sores, pulmonary infections, falls and phlebothromboses, but can also lead to depression or self-mutilation. Thus, the duration of hospitalization can be prolonged. There is no scientific consensus regarding

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the pathogenesis, epidemiologic status, diagnosis, therapy, and risk factors for PD [1, 2]. In the current study, meta-analysis-based qualitative and quantitative assessments of case-control studies and a statistical summary of case series and reports were made to investigate the risk factors for PD in elderly patients.

Data and methods

Retrieval strategy

All published articles which focused on the risk factors for PD among elderly patients before December 2013 in the Wanfang Data, CNKI, and VIP databases were collected. Based on several pre-checks, specific co-locations of subject headings and free words were determined and searched, and references were traced when necessary. CNKI retrieval serves as an example (Fig. 1).

Inclusion and exclusion criteria

For case-control studies, the inclusion criteria were as follows: (1) published studies focused on the risk factors for PD among Chinese patients >60 years of age; (2) studies with a consistent definition of disease diagnosis and study essentials, and the diagnostic criteria for delirium according to the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR); (3) research time and site specified; and (4) study design and sample size clearly stated. The exclusion criteria were as follows: (1) study replicated a previously published study; (2) poor quality; and (3) first-hand data were incomplete.

For case series, the inclusion criteria were: (1) diagnostic criteria for delirium were in accord with DSM-IV-TR; (2) with highly suspected and clearly described etiological factors. The exclusion criteria were: cases without clearly described etiological factors or sufficient diagnostic evidences.

#1 senility
#2 elderly
#3 patient
#4 sufferer
#5 postoperative delirium
#6 influencing factor
#7 relevant factor
#8 #1 OR #2
#9 #3 OR #4
#10 #6 OR #7
#11 #8 AND #9AND #5 AND #10

Fig. 1. CNKI retrieval strategy.

Statistical analysis and methods

RevMan 5.2 software was used for analysis. The included studies were heterogeneity-tested, and the pooled odds ratio (POR) with 95% CI (in parentheses) was calculated. If homogeneity existed between various study results, a fixed-effect model was used. If homogeneity did not exist, a random-effect model was used. A $P<0.05$ suggested that a risk factor might be related to senile PD. The proportional occurrence of each risk factor was compared between high risk factors among case reports and case series (Charts 1–7, Tables 1 and 2).

Results

Included articles

Fifty-nine study-related articles were retrieved. Among the retrieved articles, 16 (8 case-control studies and 8 case series) were selected as follows: 1) 15 replicated studies or studies with incomplete data sets were deleted; 2) 3 studies were excluded based on a review of the titles and abstracts; 3) studies which met the inclusion criteria after scanning the full content were selected (Chart 8). There were 26 risk factors analyzed among these articles (Tables 3 and 4).

Discussion

Risk factors

A number of studies with a focus on delirium have followed the first relevant research conducted by Engel and Romano in the 1840s, but the results differ due to various study methods, patient selection, and diagnostic criteria [1]. Based on an analysis of delirium-related articles (8 case-control studies and 8 case series), the current study shows that pre-operative complications (hypertension, CHD, DM, and pulmonary infection), post-operative hypoxemia, post-operative pain, and general anesthesia are significant risk factors for delirium in elderly patients (≥70 years of age).

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
Chenghua Zhang 2011	8	28	12	92	22.1%	2.67 [0.96, 7.40]
Liumei Pan 2012	9	17	32	159	16.1%	4.46 [1.60, 12.48]
Mingxiu Kan 2002	17	45	73	320	61.8%	2.05 [1.07, 3.96]
Total (95% CI)		90		571	100.0%	2.58 [1.59, 4.18]
Total events	34		117			

Heterogeneity: Chi² = 1.56, df = 2 (P = 0.46); I² = 0%

Test for overall effect: Z = 3.84 (P = 0.0001)

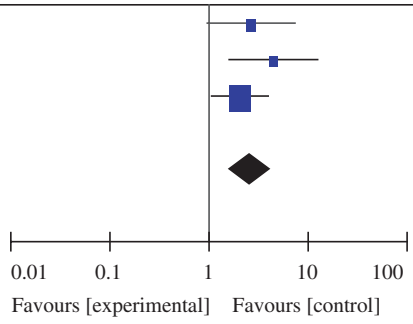

Chart 1. Meta-analysis forest plot of hypoxemia and PD in elderly patients.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Chenghua Zhang 2011	13	28	8	92	49.3%	9.10 [3.22, 25.70]
Wei Wang 2011	10	42	9	82	50.7%	2.53 [0.94, 6.83]
Total (95% CI)		70		174	100.0%	4.76 [1.36, 16.67]
Total events	23		17			

Heterogeneity: Tau² = 0.55; Chi² = 3.05, df = 1 (P = 0.08); I² = 67%

Test for overall effect: Z = 2.44 (P = 0.01)

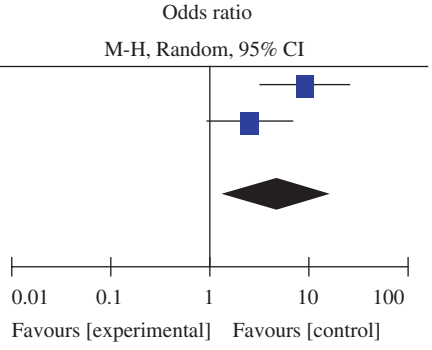

Chart 2. Meta-analysis forest plot of pre-operative pulmonary infection and PD in elderly patients.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
Chenghua Zhang 2011	16	28	37	92	48.1%	1.98 [0.84, 4.67]
Wei Wang 2011	31	42	45	82	51.9%	2.32 [1.03, 5.23]
Total (95% CI)		70		174	100.0%	2.16 [1.20, 3.89]
Total events	47		82			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%

Test for overall effect: Z = 2.56 (P = 0.01)

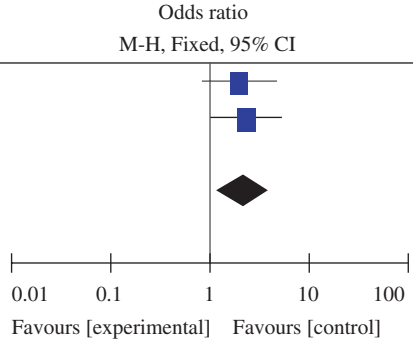

Chart 3. Meta-analysis forest plot of pre-operative hypertension and PD in elderly patients.

Physiologic functions degenerate in older people. Indeed, brain function degeneration and a decline in the synthesis of acetylcholine, one of the central neurotransmitters, may be a key etiologic factor for delirium. Comparative studies have shown that the incidence of PD in patients >65 years of age is 4–10 times higher than young people and 3 times higher in

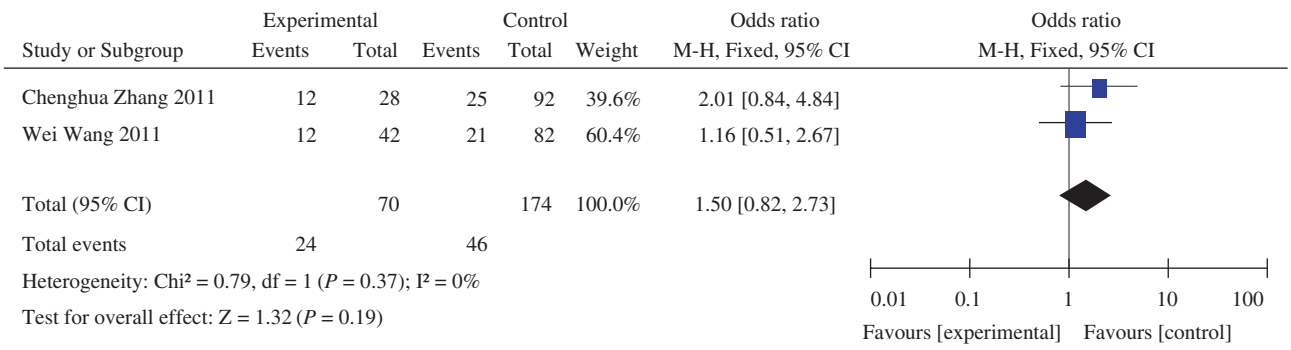

Chart 4. Meta-analysis forest plot of pre-operative coronary heart disease and PD in elderly patients.

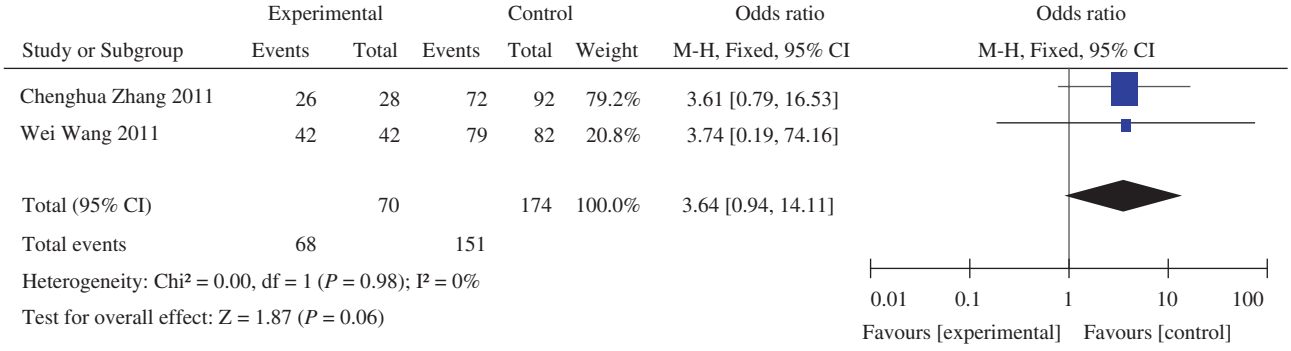

Chart 5. Meta-analysis forest plot of general anesthesia and PD in elderly patients.

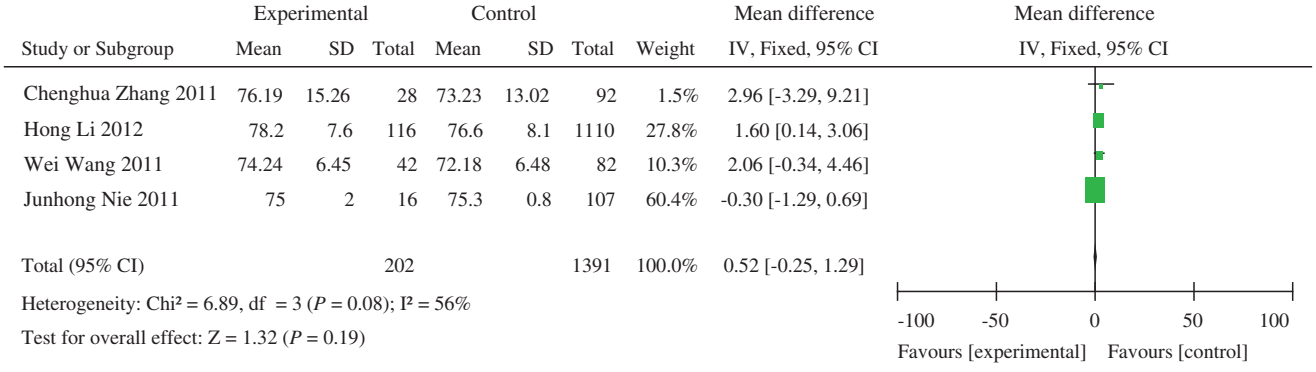

Chart 6. Meta-analysis forest plot of senility (≧70 years of age) and PD in elderly patients.

patients >75 years of age than patients >65 years of age [19]. Case-control studies [5, 6, 9] have shown that senility (≥70 years of age) is a risk factor for PD, with but one exception [7], while the combined analysis of the studies did not demonstrate senility (≥70 years of age) to be a risk factor for PD; however, based on a case series senility (≥70 years of age) was

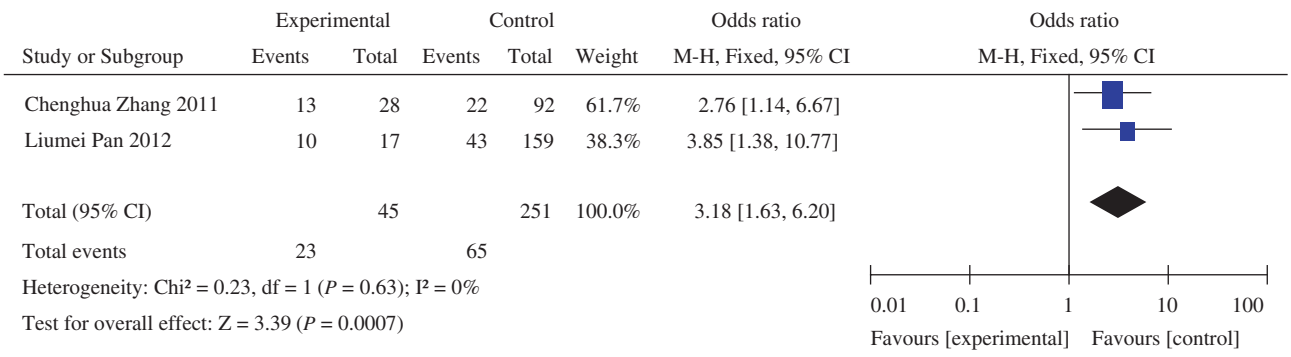

Chart 7. Meta-analysis forest plot of post-operative pain and delirium in elderly patients.

Table 1. Meta-analysis results of PD risk factors in elderly patients

Risk Factor(s)	Homogeneity and Heterogeneity Tests				Meta-analysis Results		
	Number of Articles	*P*-value	I^2 value (%)	Model	OR	95%CI	*P*-value
Hypoxemia	3	0.46	0.00	fixed	2.58	1.59~4.18	<0.01
Pre-operative pulmonary infection	2	0.08	0.67	random	4.76	1.36~16.67	0.01
Pre-operative hypertension	2	0.80	0.00	fixed	2.16	1.20~3.89	0.01
Pre-operative CHD	2	0.37	0.00	fixed	1.50	0.82~2.73	0.19
Post-operative pain	2	0.63	0.00	fixed	3.18	1.63~6.20	<0.01
General anesthesia	2	0.98	0.00	fixed	3.64	0.94~14.11	0.06
OPT	3	<0.01	0.99	random	1.41	–1.03~3.85	0.26
Senility (≧70 years of age)	4	0.08	0.56	random	0.52	–2.5~1.29	0.19

Table 2. Statistical data of case series (*n*=404)

Risk Factor	Number of Occurrences	Incidence (%)	Number of Article(s)
Hypoxemia	253	62.62	4
Pre-operative hypertension	226	55.90	5
General anesthesia	136	33.70	5
Pre-operative DM	100	24.80	4
Senility (≧70 years of age)	67	16.58	3
Pre-operative CHD	62	15.30	4
Pre-operative pulmonary infection	56	13.90	1
Pre-operative cerebrovascular disease	49	12.10	4

shown to have a high incidence among all risk factors (16.58% [67/404]). Thus, it can be concluded that senility (≥70 years of age) should not be dismissed as a causative factor for PD.

Chronic hypertension has a negative influence on patient memory, abstract reasoning ability, attention, and cerebral auto-regulation, which collectively make the cerebrum more

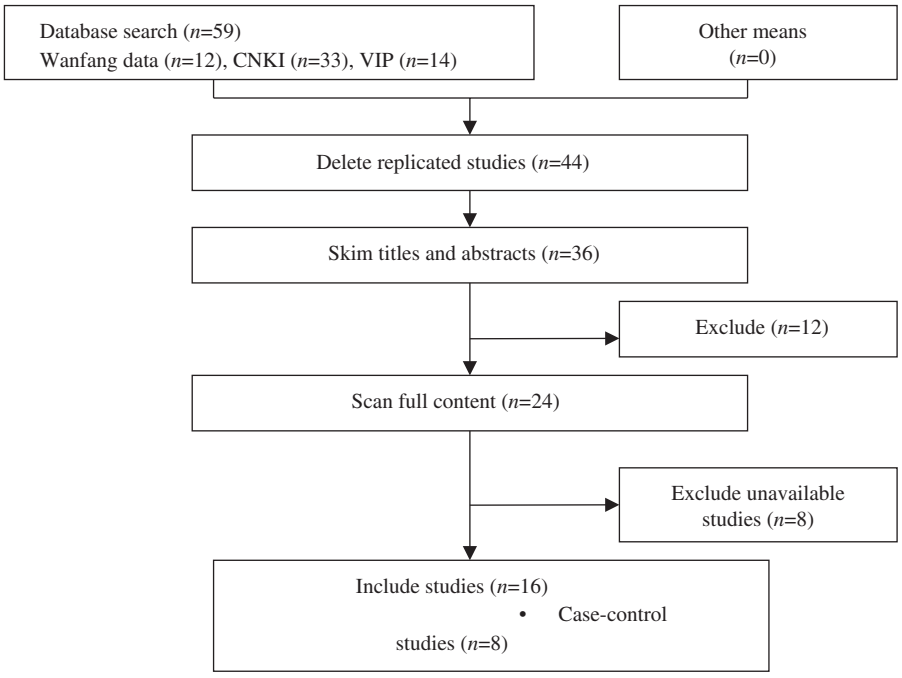

Chart 8. Screening process.

Table 3. Characteristics of case-control studies

No.	Publication year	Author	Number of cases	Number of controls	Risk Factor(s)
1	2002	Mingxiu Kan [3]	45	320	Hypoxemia and high-scoring post-operative pain
2	2004	Weiping Yu [4]	56	82	OPT, cerebrovascular disease, malnutrition, and electrolyte and acid-base balance disturbances
3	2011	Chenghua Zhang [5]	28	92	Senility (≥70 years of age); pre-operative pulmonary heart disease, pre-operative pulmonary infection, general anesthesia, post-operative hypoxemia, and post-operative pain (≥4 scores)
4	2011	Hongjun Nie [6]	16	107	Cognitive dysfunction
5	2011	Wei Wang [7]	42	82	Pre-operative stroke and length of ICU stay
6	2012	Liumei Pan [8]	17	159	Senility (≥70 years of age), hypoxemia, post-operative pain (≥4 scores), and decreased sleep time
7	2012	Hong Li [9]	116	1110	Long operative time, intra-operative blood loss, post-operative hypoxemia, post-operative fever, post-operative high-dose methylprednisolone and morphine, and cerebrospinal fluid leak
8	2013	Huanqing Chen [10]	33	56	Senility (≥70 years of age), body mass index (BMI), pre-operative cognitive dysfunction, OPT, transfusion, and low hemoglobin

Table 4. Characteristics of case series

No.	Publication year	Author	Period	Number of cases	Risk Factor(s)
1	2013	Wanhua Dong [11]	January 2008~October 2010	21	Hypoxemia, general anesthesia, pre-operative hypertension, pre-operative DM, pre-operative CHD, and pre-operative cerebrovascular disease
2	2012	Fangliu [12]	December 2009~December 2011	36	General anesthesia, intra-operative blood loss, pre-operative hypertension, pre-operative cerebrovascular disease, and pre-operative DM
3	2012	Ying Tu [13]	September 2007~September 2010	206	Senility (≥70 years of age), surgical stress response, hypoxemia, pre-operative hypertension, pre-operative DM, pre-operative CHD, pre-operative pulmonary infection, respiratory failure, and tumor
4	2009	Zhuyun Gong [14]	December 2005~December 2007	75	Senility (≥70 years of age), pre-operative encephalitis, surgical site, and general anesthesia
5	2008	Jingping Gu [15]	2004~2007	12	Senility (≥70 years of age), hypoxemia, separate from family, change of environment, post-operative pain (≥4 scores), and decreased sleep time
6	2007	Yanxia Guo [16]	January 2002~December 2005	22	Hypoxemia, general anesthesia, decreased sleep time, and post-operative pain (≥4 scores)
7	2006	Yongle Zhang [17]	August 2004~April 2005	20	Senility (≥70 years of age), hypoxemia, post-operative pain (≥4 scores), and decreased sleep time
8	2006	Linghua Zhang [18]	January 2003~August 2005	12	Pre-operative CHD, pre-operative hypertension, pre-operative cerebrovascular disease, general anesthesia, and decreased sleep time

sensitive to changes in blood pressure; when the blood pressure drops, cerebral ischemia and anoxia will develop and delirium will occur. This process takes place in patients with pulmonary infections because the decrease in effective ventilation will have a negative effect on the cerebral oxygen supply. Oh and other researchers [20] have shown that the level of blood glucose has a positive correlation with the incidence of delirium; controlling blood glucose can reduce the incidence of delirium. Based on case-control studies, pre-operative pulmonary heart disease and pulmonary infections have been shown to be independent risk factors for PD [5]. Pre-operative hypertension and DM are also independent risk factors of PD [7], while any pre-operative disease is a significant risk factor for PD [6]. Based on an analysis of all relevant studies, we conclude that pre-operative hypertension, DM, CHD, and pulmonary infection are key risk factors for PD. The pertinent case series have confirmed that the incidence of pre-operative hypertension, DM, CHD, and pulmonary infection (55.90% [226/404], 24.80% [100/404], 15.30% [62/404], and 13.90% [56/404]) are higher among all the risk factors for PD in elderly patients.

An anesthetic-related study showed that [21] benzodiazepines and propofol have high affinities for GABA receptors in the central nervous system; the mimetic effect of GABA may cause changes in neurotransmitters and lead to delirium. Another study [22] showed that general anesthesia can decrease the cerebral metabolic rate, which in turn may cause delirium. There are several studies, however, that show general anesthesia cannot lead to delirium [23]. General anesthesia has been reported to be an independent risk factor for senile PD [5], but anesthesia methods are not related to PD [7]. A combined analysis of these studies showed that general anesthesia is a risk factor for PD in elderly patients, which was confirmed in a case series (33.70% [136/404]).

Pain is a form of an acute stress disorder. When people are stressed, blood epinephrine and norepinephrine levels will increase, the rate of cerebral blood flow will increase, and oxygen consumption will increase. As a result, the metabolism of brain cells will be affected negatively, thus decreasing the information exchange capabilities of cells. Post-operative pain reflects the body's response to noxious stimulation. Post-operative pain can initiate changes in neuroendocrine function, especially an excess secretion of serum cortisol, can inhibit hippocampal cortex function and cause cognitive dysfunction [24] as well as delirium. In addition, post-operative pain can seriously impact patient sleep quality, and result in an irregular sleep cycle, including sleep deprivation, thus prompting the development of delirium. Post-operative pain has been shown to be a risk factor for delirium by one study [8], but not another study [5]. The current study showed that post-operative pain is an important among risk factor for senile PD.

Diminished respiratory function and cardiocerebral vascular diseases will cause dysfunction of cerebral blood flow post-operatively and lead to hypoxemia. There is a significant correlation between hypoxemia and PD; specifically, hypoxemia is a precipitating factor for early post-operative cerebral dysfunction [25]. Rosenberg and other researchers [26] have shown that post-operative hypoxia is a key factor causing dysphrenia, and inadequate oxygen can prevent PD. Another study [27] showed that among 92 surgery patients, there were 39 (42%) who developed delirium post-operatively. Post-operative delirium commonly manifests on the second post-operative day, reflecting the level of hypoxia on the first day post-operatively [27]. Case-control studies [3, 5, 8] which have focused on the correlation between hypoxemia and PD have shown that hypoxemia is a risk factor for senile PD. In a case series involving 404 participants, there were 253 PD patients (62.62% [253/404]) with hypoxemia, which is consistent with the above findings.

Interventions of PD

PD prevention is important; to do so requires elimination of the risk factors [28]. Due to the characteristics of delirium, acute onset (within hours or days) and undulatory state (the occurrence, exacerbation, remission, and disappearance of symptoms often occurs within 24 h), delirium is easily underestimated and missed in clinical practice [7]. Considering all of the risk factors and characteristics of PD, the following interventions should be developed: (1) Elderly patients should be assessed comprehensively and accurately pre-operatively for multiple organ function, and the complications should be treated to improve general health status, thus reducing the incidence and severity of PD. (2) Blood gases and electrolytes should be monitored pre- and post-operatively to maintain water, electrolyte, and acid-base balance, and preserve circulatory stability. (3) Implement preventive analgesia to reduce neurotransmitter release and prevent the occurrence of PD. Large doses of steroids and morphine should be used with caution. (4) Preventive oxygen therapy should be classified as routine treatment to control pulmonary infection and hypoxemia. (5) Security measures and intensive perambulate should be taken to ensure the safety of patients with delirium-related dysphoria and hallucinations. Sedatives and analgesics should be given accurately according to medical orders. Observe the changes in patient vital signs and consciousness, and closely evaluate the severity of disease properly. (6) Add a daily delirium assessment to the post-operative nursing routine, and improve early identification and prevention capabilities of medical workers to reduce the incidence of delirium.

Limitation and enlightenment of this study

Through a systematic review, the current study showed that senility, pre-operative hypertension, DM, pulmonary infection, post-operative hypoxemia, pain, and general anesthesia are significant risk factors for PD; however, because the sample size in this study was not large enough, the power of testing may be on the low side, thus affecting the veracity of the meta-analysis. Indeed, a quality case-control study with a larger sample size is needed to verify the conclusions reached in the current study.

Conflict of interest

The authors declare no conflict of interest.

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