ANESTHESIOLOGY

Postoperative Delirium Is Associated with Long-term Decline in Activities of Daily Living

Zhongyong Shi, M.D., Xinchun Mei, M.D., Cheng Li, M.D., Ph.D., Yupeng Chen, M.D., Hailin Zheng, M.D., Yujie Wu, M.D., Hui Zheng, Ph.D., Liang Liu, M.D., Ph.D., Edward R. Marcantonio, M.D., S.M., Zhongcong Xie, M.D., Ph.D., Yuan Shen, M.D., Ph.D.

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ABSTRACT

Background: Postoperative delirium is one of the most common complications in the elderly surgical population. However, its long-term outcomes remain largely to be determined. Therefore a prospective cohort study was conducted to determine the association between postoperative delirium and long-term decline in activities of daily living and postoperative mortality. The hypothesis in the present study was that postoperative delirium was associated with a greater decline in activities of daily living and higher mortality within 24 to 36 months after anesthesia and surgery.

Methods: The participants (at least 65 yr old) having the surgeries of (1) proximal femoral nail, (2) hip replacement, or (3) open reduction and internal fixation under general anesthesia were enrolled. The Confusion Assessment Method algorithm was administered to diagnose delirium before and on the first, second, and fourth days after the surgery. Activities of daily living were evaluated by using the Chinese version of the activities of daily living scale (range, 14 to 56 points), and preoperative cognitive function was assessed by using the Chinese Mini-Mental State Examination (range, 0 to 30 points). The follow-up assessments, including activities of daily living and mortality, were conducted between 24 and 36 months after anesthesia and surgery.

Results: Of 130 participants (80 ± 6 yr, 24% male), 34 (26%) developed postoperative delirium during the hospitalization. There were 32% of the participants who were lost to follow-up, resulting in 88 participants who were finally included in the data analysis. The participants with postoperative delirium had a greater decline in activities of daily living (16 ± 15 *vs.* 9 ± 15, $P = 0.037$) and higher 36-month mortality (8 of 28, 29% *vs.* 7 of 75, 9%; $P = 0.009$) as compared with the participants without postoperative delirium.

Conclusions: Postoperative delirium was associated with long-term detrimental outcomes, including greater decline in activities of daily living and a higher rate of postoperative mortality.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative delirium is common, but its long-term consequences remain unclear

What This Article Tells Us That Is New

- About a quarter of enrolled patients, averaging 80 yr of age, developed delirium after major elective and urgent major orthopedic surgery
- Activities of daily living at 2 to 3 yr and mortality at 3 yr were both worse in patients who experienced delirium

Postoperative delirium, one of the most common postoperative complications among elderly patients,[1,2] is associated with postoperative neurocognitive disorder, increased other postoperative complications, prolonged hospital stays, higher discharge rates to nursing homes and poor survival rates.[3–5] The U.S. healthcare costs attributable to delirium exceed $182 billion per year.[6,7]

Postoperative delirium is not always transient or reversible, and increasing evidence has demonstrated both short-term and long-term poor prognoses in surgical patients who have developed postoperative delirium.[8–10] Large cohort studies suggest that postoperative delirium is associated with a significant impairment in global cognitive function 12 months postsurgery.[8,9] Moreover, such cognitive impairment can persist up to 36 months.[10]

There have been studies to investigate the association between delirium and activities of daily living.[11,12] Specifically, Marcantonio *et al.*[11] reported that postoperative delirium was independently associated with poorer activities of daily living at 1 month after the surgery, but such association disappeared at 6 months postsurgery. A recent study showed that postoperative delirium was associated with persistent activities of daily living impairment after a major elective surgery.[13] However, controversy still exists regarding the causal relationship between delirium and postoperative mortality due to the high risk of confounding

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bias as evidenced by a recent systematic review.[14] Although most studies reported that postoperative delirium was associated with an increased risk of death,[15,16] a few other studies have indicated that the association was not apparent after adjusting for adequate confounders.[17,18] Therefore, the associations among postoperative delirium, the long-term activities of daily living, and mortality remain to be determined.

We therefore set up a prospective longitudinal study using a cohort of patients who had orthopedic surgery under general anesthesia. The objective of this study was to investigate the effects of postoperative delirium on the long-term decline in activities of daily living and postoperative mortality. The primary hypothesis in the present study was that postoperative delirium was associated with greater activities of daily living decline. The secondary hypothesis was that patients with postoperative delirium would have a higher rate of mortality within 24 to 36 months after anesthesia and surgery.

Materials and Methods

Study Population

The study protocol was approved by the Human Research Ethics Committee of Shanghai Tenth People's Hospital affiliated with Tongji University in Shanghai, China (RES-2013015). All participants signed the informed consent before being enrolled in the study.

Eligible participants were screened and enrolled exclusively at Shanghai Tenth People's Hospital, a university-affiliated hospital with about 3 million outpatients and more than 40,000 surgeries every year, from August 2013 to August 2014. The follow-up assessments were carried out within 24 to 36 months after anesthesia and surgery. Participants were included if they met the following eligibility criteria: (1) 65 yr old or older, (2) Chinese Mandarin as the native language, (3) scheduled to undergo orthopedic surgery, and (4) having the ability of verbal communication and writing skills and thus being able to provide informed consent.[13] Eligible surgical procedures included the surgeries of proximal femoral nail, hip replacement, and open reduction and internal fixation. The exclusion criteria were: (1) preoperative delirium according to the Confusion Assessment Method algorithm[19]; (2) prior diagnoses of neurologic diseases, *e.g.*, Parkinson's diseases, multiple sclerosis or stroke according to International Statistical Classification of Diseases and Related Health Problems 10th Revision[20]; (3) a history of mental disorders, *e.g.*, major depressive disorder and schizophrenia diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition[21]; or (4) unwillingness to participate in the study.

Preoperative Interview

After the patients were admitted to the hospital, two trained research assistants (Z.S. and Y.W.) carried out the preoperative screening assessments in person 1 day before the scheduled surgery. The assessments included a review of the patient's medical chart and an interview with the patient. Characteristics of the participants were collected, including age, sex, education, marital status, and living conditions. Moreover, the age-adjusted Charlson comorbidity index[22] was obtained through patient interviews or medical records reviews based on the validated Charlson comorbidity coding algorithms,[23] with higher scores indicating more comorbidities.

Preadmission status of daily function was assessed by using the Chinese version of the activities of daily living scale,[24] which included a physical self-maintenance scale and an instrumental activities of daily living scale. There is a total of 14 items. Specifically, the physical self-maintenance scale is used to assess the fundamental skills typically needed to manage basic physical needs and consists of the following six tasks: transferring/ambulating, eating, dressing, grooming/personal hygiene, bathing, and toileting/continence; the instrumental activities of daily living scale is used to assess more complex activities related to independent living and contains the following eight tasks: taking public transportation, preparing food, housekeeping, taking medications, doing laundry, shopping, making phone calls, and managing finances. For each item, the scoring is determined by a 4-point coding system: 1 = can do it myself, 2 = have some difficulty doing but can still do it by myself, 3 = need help to do it, and 4 = cannot do it at all. The total score of activities of daily living scale ranges from 14 to 56 points, and higher activities of daily living scale scores indicate lower ability to perform activities of daily living. The participants with activities of daily living scale scores more than 22 points (the cutoff score) were defined as having impairment in activities of daily living.[25]

The Chinese Mini-Mental State Examination was performed to assess for global cognitive function. There are 19 items, and the maximum score of the Chinese Mini-Mental State Examination is 30 points. The optimal cutoff points in dementia or abnormal cognitive function screening are stratified by education levels (17/18 for those illiterate, 20/21 for individuals with 1 to 6 yr of education, and 24/25 for individuals with 7 yr or more of education).[26]

Anesthesia and Surgery

All participants were scheduled to undergo orthopedic surgery and had standardized perioperative care, including anesthesia and postoperative pain management, as described in our previous studies.[27] We did not determine the association between the depth of anesthesia and postoperative delirium, because such association has been investigated in the previous studies.[28–30] In addition, by reviewing the patient's anesthesia records, we were able to obtain the information of American Society of Anesthesiologists classification, anesthesia types, estimated blood loss, the length of anesthesia administration and operation, and the length of hospitalization.

Postoperative Delirium Assessment

The assessments of delirium were performed as described in our previous studies.[27] Specifically, postoperative delirium was assessed once daily between 10:00 AM and 4:00 PM on days 1, 2, and 4 postsurgery. The psychiatrists who performed the delirium assessments in the current study had good training and went through quality control procedures. The interrater reliability calculated from the intraclass correlation coefficient was 0.96 (95% CI, 0.92 to 0.98).[31]

The incidence of postoperative delirium was determined according to the Confusion Assessment Method diagnostic algorithm, which was used to determine the presence or absence of delirium.[19] The algorithm consists of four clinical criteria: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. To define a patient as having delirium, both the first and the second criteria have to be present, as well as either the third or the fourth criteria. The Confusion Assessment Method in the Chinese language has been proven to have good reliability and validity among the Chinese elderly population.[32] Patients with a positive diagnosis on postoperative days 1, 2, or 4 would be coded as "having postoperative delirium."

Follow-up Interview

The participants had follow-up interviews within 24 to 36 months after anesthesia and surgery. The following assessments were conducted in the form of face-to-face interviews or phone interviews if the participants were not available for the face-to-face interviews. The interviewers who performed the follow-up assessments were blinded to the diagnosis of postoperative delirium of the participants. During the interviews, the activities of daily living were assessed with the Chinese version of the activities of daily living scale. Moreover, we obtained information on participant's status of death by consulting with their family members and reviewing their electronic medical records. In addition, the diagnosis of postoperative delirium was made only immediately on postoperative days during the hospitalization but not at the time of follow-up.

Statistical Analysis

The study was powered to detect a difference in activities of daily living between the participants with and without postoperative delirium in an orthopedic surgery population, based on the incidence of postoperative delirium (26%) and the between-group differences in preoperative activities of daily living scale score (mean difference ± SD, 4 ± 6), obtained and analyzed from the data in our previous studies.[27] It was estimated that 96 participants would be required to detect a significant difference, at the 5% significance level with 80% power. Moreover, the previous studies demonstrated a recruitment rate of 63%.[27] Thus, we had planned to screen at least 153 patients undergoing orthopedic surgery in 1 yr to be able to recruit 96 participants at the start of the studies.

The Kolmogorov–Smirnov test was used to test for the normality of all variables. The between-group differences were compared using a Student's *t* test for continuous variables (mean ± SD) or a chi-square test for categorical variables (n [%]). A Mann–Whitney U test was used to compare the group difference in the activities of daily living scale score (median ± interquartile range). We estimated the overall mortality rate by using Kaplan–Meier analysis, and the differences were compared using log-rank tests. Cox regression analysis was carried out to determine the association between postoperative delirium and overall survival rate. Factors that showed a significant association with postoperative delirium in the univariate analyses were included as covariates in the Cox survival analysis model. Because the burden of comorbidities has been demonstrated to affect the postoperative short-term and long-term survival rates, it was further included in the model as a covariate. All analyses were performed using the SPSS version 20.0 (SPSS Inc., USA) or Prism 6 software (GraphPad, USA), with $P < 0.05$ as the significance level.

Results

Baseline Characteristics

Figure 1 showed the enrollment, exclusions, and patients available for analysis among 192 participants. At baseline, 62 participants were excluded because of acute cerebral infarction (n = 15), psychosis history (n = 17), uncompleted assessments (n = 27), and the diagnosis of preoperative delirium (n = 3). Thus, a total of 130 participants (80 ± 6 yr, 24% male) provided informed consent and were enrolled in this study. All participants had been scheduled to undergo orthopedic surgery, including proximal femoral nail (n = 67), hip replacement (n = 56), and open reduction and internal fixation surgeries (n = 7) under general anesthesia. The characteristics of these participants are presented in table 1.

Of the 130 participants, 34 (26%) developed postoperative delirium on days 1, 2, or 4 after anesthesia and surgery. The participants who developed postoperative delirium were older (83 ± 5 *vs.* 79 ± 6, $P = 0.001$) and had more severe preoperative cognitive impairment than those without postoperative delirium (Chinese Mini-Mental State Examination score of 18 ± 5 *vs.* 24 ± 5, $P = 0.001$).

There were no significant differences in other characteristics between the participants with and without postoperative delirium. There were also no significant differences in the American Society of Anesthesiologists class, anesthesia types (total intravenous anesthesia with propofol *vs.* inhalational anesthesia with sevoflurane *vs.* mixed with propofol and sevoflurane), surgery types, length of anesthesia and surgery, estimated blood loss, and the length of hospitalization between the participants with postoperative delirium and those without postoperative delirium.

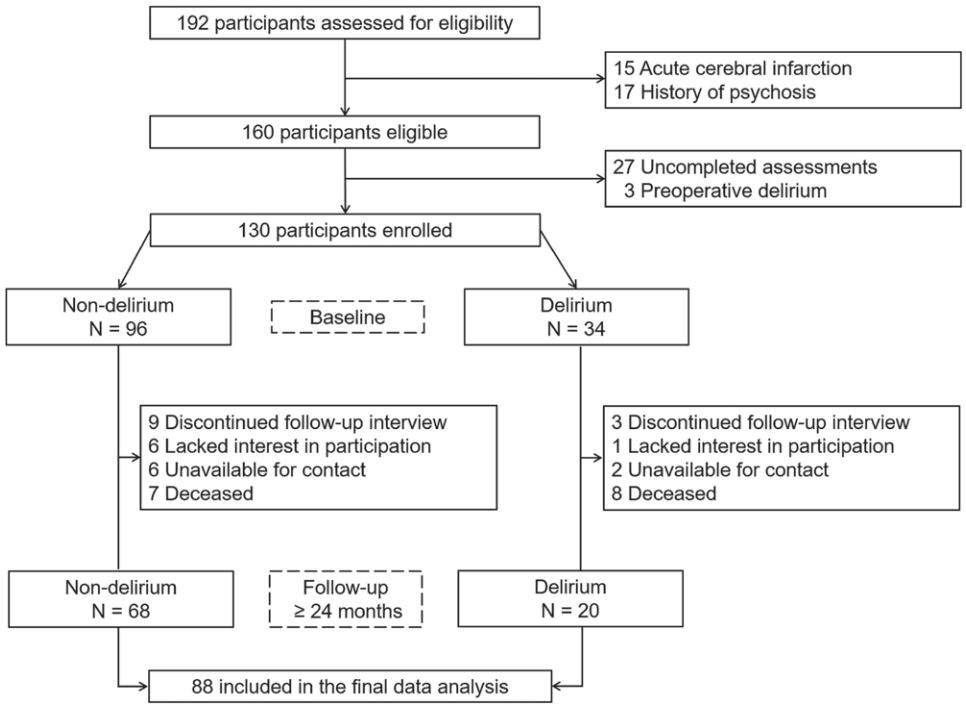

Fig. 1. Consolidated Standards of Reporting Trials diagram shows the enrollment, exclusions, and participants available for analysis.

Association between Postoperative Delirium and the Long-term Outcomes

During the period of follow-up, there were 42 participants (32%) who were lost to the follow-up due to the discontinuation of interviews (n = 12), no more interest in participating in the study (n = 8), and unavailability of contacts (n = 8). In addition, another 15 participants died during the follow-up period, which we confirmed through their family members and by reviewing their electronic medical records. Consequently, 88 participants completed the follow-up assessments and were finally included in the data analysis (fig. 1). The assessments in the follow-up studies included both face-to-face interviews (n = 47) and phone interviews (n = 41). There were no significant differences in regards to the incidence of postoperative delirium and the characteristics between the participants who remained in the study and those who dropped out from the study (table 2).

Activities of Daily Living. In this cohort, 18 of 34 (53%) participants with postoperative delirium had preoperative activities of daily living impairment (more than the cutoff score of 22 points), whereas only 22 of 96 (23%) participants without postoperative delirium had activities of daily living impairment before the surgery ($P = 0.001$; chi-square test). Moreover, 24 to 36 months after anesthesia and surgery, the participants who developed postoperative delirium had a greater decline in activities of daily living, as evidenced by the larger increase in activities of daily livings scores as compared with the participants who did not develop postoperative delirium (median ± interquartile range, 16 ± 15 *vs.* 9 ± 15, $P = 0.037$; Mann–Whitney U test). Specifically, the participants who had developed postoperative delirium after proximal femoral nail surgery (median ± interquartile range, 18 ± 15 *vs.* 10 ± 12, $P = 0.041$; Mann–Whitney U test), but not after hip replacement surgery (median ± interquartile range, 12 ± 13 *vs.* 7 ± 14, $P = 0.283$; Mann–Whitney U test), exhibited significant decline in activities of daily living at the time of the follow-up evaluation. Because only one in four participants had developed postoperative delirium after open reduction and internal fixation surgery, we decided not to determine the association between postoperative delirium and activities of daily living decline in these participants during the follow-up interviews (table 3).

Mortality. The mortality rate of patients with and without postoperative delirium within 24 to 36 months after anesthesia and surgery was calculated using Kaplan–Meyer analysis. In the current cohort, participants who developed postoperative delirium had a higher mortality rate (8 of 28, 29%) as compared with the participants who did not develop postoperative delirium (7 of 75, 9%; $P = 0.009$; log-rank test; fig. 2).

Univariable and multivariable analyses of overall survival were calculated by using Cox regression models. Postoperative delirium was associated with a lower survival rate (unadjusted hazard ratio = 0.28; 95% CI, 0.10 to 0.78; $P = 0.015$). After the adjustment of preoperative

Table 1. Baseline Characteristics of Study Population

Variables (N = 130)	Delirium (N = 34)	Nondelirium (N = 96)	*P* Value
Age, yr, mean ± SD	83 ± 5	79 ± 6	**0.001**
Sex, male, n (%)	9 (27%)	22 (23%)	0.676
Marital status, n (%)			0.058
Married	21 (62%)	74 (77%)	
Single	11(32%)	16 (17%)	
Divorced/widowed	2 (6%)	6 (6%)	
Living condition, n (%)			0.056
Living together	20 (59%)	73 (76%)	
Living alone	14 (41%)	23 (24%)	
Children, n (%)			0.289
Having children	29 (85%)	89 (93%)	
No children	5 (15%)	7 (7%)	
BMI, kg/m^2, mean ± SD	20 ± 6	22 ± 4	0.673
Education, yr, mean ± SD	4 ± 5	5 ± 5	0.229
ACCI, points, mean ± SD	5 ± 1	5 ± 2	0.353
CMMSE, points, mean ± SD	18 ± 5	24 ± 5	**0.001**
CRP, mg/l, mean ± SD	29 ± 26	25 ± 21	0.245
HGB, g/dl, mean ± SD	10 ± 2	10 ± 2	0.123
WBC, K/μl, mean ± SD	8 ± 3	8 ± 3	0.598
ASA class, n (%)			0.580
I	1 (3%)	1 (1%)	
II	20 (59%)	64 (67%)	
III	13 (38%)	31 (32%)	
Anesthesia type, n (%)			
Propofol	1 (3%)	5 (5%)	
Sevoflurane	10 (29%)	21 (22%)	0.620
Propofol and sevoflurane	23 (68%)	70 (73%)	
Surgery type, n (%)			0.160
Proximal femoral nail	22 (65%)	45 (47%)	
Hip replacement	10 (29%)	46 (48%)	
Open reduction and internal fixation	2 (6%)	5 (5%)	
Length of anesthesia, min, mean ± SD	128 ± 49	132 ± 50	0.729
Length of operation, min, mean ± SD	88 ± 46	100 ± 44	0.174
Estimated blood loss, ml, mean ± SD	329 ± 286	316 ± 264	0.814
Length of hospitalization, days, mean ± SD	20 ± 6	18 ± 5	0.127

Statistically significant results are boldface.

ACCI, age-adjusted Charlson comorbidity index; ASA, American Society of Anesthesiologists; BMI, body mass index; CMMSE, Chinese Mini-Mental State Examination; CRP, C-reactive protein; HGB, hemoglobin; WBC, leukocyte.

cognitive function (determined by Chinese Mini-Mental State Examination score) and the age-adjusted comorbidities (determined by the age-adjusted Charlson comorbidity index score), we found that postoperative delirium was still independently associated with poor long-term survival rate (adjusted hazard ratio = 0.22; 95% CI, 0.07 to 0.67; $P = 0.007$). These results suggested that participants with postoperative delirium had an increased risk of mortality in the long-term after anesthesia and surgery.

Discussion

This prospective study demonstrated that postoperative delirium was associated with greater decline in activities of daily living and higher postoperative mortality within 24 to 36 months after anesthesia and surgery. It has been reported that the prevalence of preoperative delirium in elderly patients with hip fractures was 4 to 6%.[33,34] The prevalence of preoperative delirium in the present study was 2% (3 of 133), which could be partially due to the strict exclusion of participants. Specifically, the participants with acute cerebral infarction (n = 15) or history of psychosis (n = 17) were excluded from the studies and did not receive the assessment of preoperative delirium. In addition, another 27 participants were excluded because they had refused to complete the assessment of preoperative delirium. The prevalence of preoperative delirium could have been different if these participants had not been excluded.

The observed incidence of postoperative delirium in current study was 26%, which was comparable with that obtained in other studies for noncardiac surgeries[13,35–37] with a range from 9 to 28%,[38] thus demonstrating the validity of our assessment of postoperative delirium. However, Bitsch *et al.*[39] reported an average incidence of postoperative delirium of 35% in their studies. Moreover, the incidence was higher in intensive care unit patients with critical illness (19 to 82%) and in patients who received emergent hip

Table 2. Demographic and Clinical Characteristics between the Participants Who Stayed in the Studies and the Participants Who Dropped from the Studies

Variables (N = 130)	Followed (N = 88)	Dropped Out (N = 42)	*P* Value
Age, yr, mean ± SD	80 ± 7	81 ± 5	0.586
Sex, male, n (%)	19 (22%)	12 (29%)	0.382
Marital status, n (%)			
Married	64 (73%)	31 (74%)	0.450
Single	20 (23%)	7 (17%)	
Divorced/widowed	4 (4%)	4 (9%)	
Living condition, n (%)			
Living together	65 (74%)	28 (67%)	0.395
Living alone	23 (26%)	14 (33%)	
Children, n (%)			0.900
Having children	79 (90%)	38 (90%)	
No children	9 (10%)	4 (10%)	
BMI, kg/m^2, mean ± SD	23 ± 5	23 ± 3	0.902
Education, yr, mean ± SD	5 ± 5	4 ± 5	0.272
ACCI, points, mean ± SD	5 ± 2	4 ± 5	0.939
CMMSE, points, mean ± SD	22 ± 5	22 ± 6	0.823
CRP, mg/l, mean ± SD	29 ± 24	20 ± 19	0.082
HGB, g/dl, mean ± SD	11 ± 2	11 ± 2	0.879
WBC, K/μl, mean ± SD	8 ± 3	8 ± 3	0.521
ASA class, n (%)			0.613
I	1 (1%)	1 (2%)	
II	55 (63%)	29 (69%)	
III	32 (36%)	12 (29%)	
Anesthesia type, n (%)			0.620
Propofol	3 (3%)	3 (7%)	
Sevoflurane	22 (25%)	9 (21%)	
Propofol and sevoflurane	63 (72%)	30 (72%)	
Surgery type, n (%)			0.743
Proximal femoral nail	47 (53%)	20 (48%)	
Hip replacement	37 (42%)	19 (45%)	
Open reduction and internal fixation	4 (5%)	3 (7%)	
Length of anesthesia, min, mean ± SD	129 ± 46	134 ± 58	0.585
Length of operation, min, mean ± SD	93 ± 41	103 ± 51	0.231
Estimated blood loss, ml, mean ± SD	304 ± 241	351 ± 322	0.372
Length of hospitalization, day, mean ± SD	19 ± 6	19 ± 5	0.973
Postoperative delirium, n (%)	20 (23%)	14 (33%)	0.198

ACCI, age-adjusted Charlson comorbidity index; ASA, American Society of Anesthesiologists; BMI, body mass index; CMMSE, Chinese Mini-Mental State Examination; CRP, C-reactive protein; HGB, hemoglobin; WBC, leukocyte.

fracture repair surgery (41%).[2,11] The exact reasons for such differences are not clear at the present time. It might be related to the different healthcare environment and settings, predisposing conditions, and types of surgery.

Previous studies have reported that postoperative delirium was associated with cognitive impairment upon discharge and decline in activities of daily living during 1 to 3 months after hip surgery.[11,40] However, the associations between postoperative delirium and long-term (*e.g.*, more than 24 months) activities of daily living and mortality have not been investigated. The current study showed that the participants who had postoperative delirium experienced a greater decline in activities of daily living and exhibited higher mortality within 24 to 36 months after anesthesia and surgery.

Activities of daily living, an important component of assessment for major surgery,[41] have been widely used as an index for the measurement of postoperative recovery as demonstrated in previous studies.[24,25] It has been found that patients who developed postoperative delirium had poorer recovery within 6 months after the surgery as compared with those did not develop it.[11,12,15,40] The current study found that all of the participants showed declined activities of daily living (increase of activities of daily living scale scores) after anesthesia and surgery. Specifically, the participants who developed postoperative delirium had a greater decline in activities of daily living 24 to 36 months after anesthesia and surgery as compared with those who did not develop it. Furthermore, participants undergoing the surgery of proximal femoral nail demonstrated greater decline in activities of daily living than the participants having hip replacement during the time of follow-up interviews, which was likely due to the different age distributions (82 ± 6 *vs.* 78 ± 7, $P = 0.040$) and surgical indications (*e.g.*, femoral intertrochanteric fracture). Collectively, these findings suggested that the occurrence of postoperative delirium among the elderly surgical population could worsen the long-term activities of daily living.

The current study reported that patients who had postoperative delirium would have a higher mortality rate even after controlling for age-adjusted Charlson comorbidities and preoperative cognitive status. Consistently, most studies supported that patients who developed delirium were at an increased risk of death[14] and that delirium was associated with 6-month,[15] 12-month,[16] and 5-yr[42] postoperative mortality. These results suggest that efforts should be implemented in the elderly population at high risk of developing postoperative delirium after orthopedic surgery. Note that there were potential confounders during the follow-up 24 to 36 months postsurgery, which could influence the outcomes of the current studies. Future studies to determine such influences are warranted.

Limitations

The current study has several limitations. First, the sample size was relatively small. However, the 88 participants in the follow-up studies were sufficient to illustrate the association between postoperative delirium and long-term decline in activities of daily living. The current study has mainly established a system and generated a hypothesis for the future larger-scale studies. Note, the retention rates (20 of 34, 59% *vs.* 68 of 96, 71%; $P = 0.601$) and the total follow-up time (28 ± 3 months *vs.* 27 ± 3 months; $P = 0.724$) were comparable between the participants with and without postoperative delirium. Second, the need for informed consent in the studies could limit the participation into a group that has less risk of developing postoperative delirium, declined activities of daily living, or death. Third, we did not assess whether the participants had postoperative delirium daily

Table 3. Comparison of Activities of Daily Living between Participants with and without Postoperative Delirium

	Delirium	Nondelirium	*P* Value*
Overall (N = 88)	N = 20	N = 68	
Baseline ADLs, points, median ± IQR	22 ± 11	15 ± 5	**0.005**
Follow-up ADLs, points, median ± IQR	40 ± 23	27 ± 17	**0.002**
ADL decline, points, median ± IQR†	16 ± 15	9 ± 15	**0.037**
Proximal femoral nail (n = 47)	n = 13	n = 34	
Baseline ADLs points, median ± IQR	23 ± 10	15 ± 4	**0.002**
Follow-up ADLs points, median ± IQR	43 ± 21	28 ± 16	**0.001**
ADL decline, points, median ± IQR†	18 ± 15	10 ± 12	**0.041**
Hip replacement (n = 37)	n = 6	n = 31	
Baseline ADLs points, median ± IQR	20 ± 14	16 ± 7	0.432
Follow-up ADLs points, median ± IQR	33 ± 24	27 ± 19	0.147
ADL decline, points, median ± IQR†	12 ± 13	7 ± 14	0.283
Open reduction and internal fixation (n = 4)	n = 1	n = 3	N/A‡

*Statistically significant results are highlighted in bold. †ADL decline was calculated by using follow-up ADLs score minus baseline ADLs score, which indicated the decline of activities of daily living. A larger ADL change score indicates a greater ADL decline. ‡Only one in four participants developed postoperative delirium after open reduction and internal fixation surgery at the time of follow-up evaluation. Thus, we did not determine the association between postoperative delirium and the decline of ADL in these participants.

ADL, activities of daily living; ADLs, activities of daily living scale; IQR, interquartile range; N/A, not applicable.

until the discharge, which may lead to missing the detection of postoperative delirium. However, ample evidence has suggested that most postoperative delirium occurred within the first 3 days after anesthesia and surgery.[9,43] Moreover, we purposely did not evaluate the postoperative delirium diagnosed after 7 days to avoid the influence of postoperative neurocognitive disorder, another common postoperative complication among elderly patients, on the activities of daily living and postoperative mortality.[44] Finally, we did not evaluate the association between postoperative delirium and pre- or postoperative cognitive function. However, such a relationship has been well established in previous studies.[8–10]

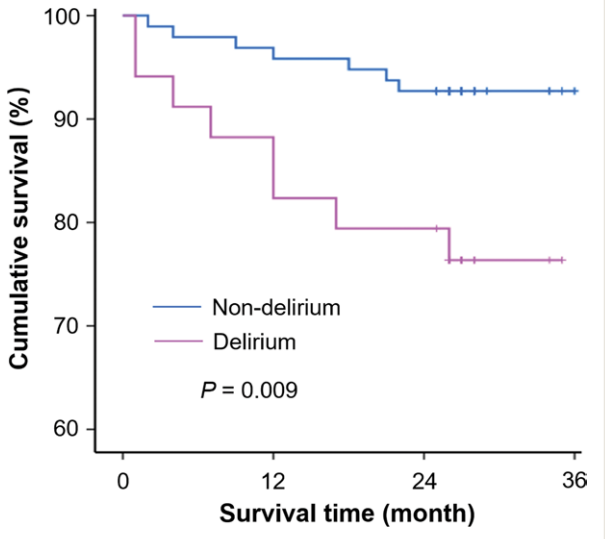

Fig. 2. Cumulative survival rates according to the presence of postoperative delirium. The postoperative morality rates within 24 to 36 months of the followed participants after orthopedic surgery were calculated by using the Kaplan–Meyer analysis. Specifically, the 36-month mortality rate of participants with postoperative delirium (8 of 28, 29%) was significantly higher than that of participants without postoperative delirium (7 of 75, 9%) at the follow-up ($P = 0.009$, log-rank test). Symbols (+) indicate the censored data.

In conclusion, the current study showed that postoperative delirium was associated with the combination of a greater decline in activities of daily living and a higher mortality rate within 24 to 36 months after anesthesia and surgery. These findings highlight the need to prevent postoperative delirium whenever possible, particularly among geriatric patients who are vulnerable to developing preoperative and postoperative neurocognitive disorder.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Shen: Shanghai Tenth People's Hospital, Anesthesia and Brain Research Institute,

Tongji University School of Medicine, 301 Yanchang Road, Building 9, Room 4405, Shanghai 200072, China. kmshy@tongji.edu.cn.

References

1. Inouye SK: Delirium in older persons. N Engl J Med 2006; 354:1157–65
2. Inouye SK, Westendorp RG, Saczynski JS: Delirium in elderly people. Lancet 2014; 383:911–22
3. Moskowitz EE, Overbey DM, Jones TS, Jones EL, Arcomano TR, Moore JT, Robinson TN: Postoperative delirium is associated with increased 5-year mortality. Am J Surg 2017; 214:1036–8
4. Sprung J, Roberts RO, Weingarten TN, Nunes Cavalcante A, Knopman DS, Petersen RC, Hanson AC, Schroeder DR, Warner DO: Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. Br J Anaesth 2017; 119:316–23
5. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA: Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis. JAMA 2010; 304:443–51
6. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK: One-year health care costs associated with delirium in the elderly population. Arch Intern Med 2008; 168:27–32
7. Leslie DL, Inouye SK: The importance of delirium: Economic and societal costs. J Am Geriatr Soc 2011; 59:S241–3
8. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Moons KG, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW; BRAIN–ICU Study Investigators: Long-term cognitive impairment after critical illness. N Engl J Med 2013; 369:1306–16
9. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, Jones RN: Cognitive trajectories after postoperative delirium. N Engl J Med 2012; 367:30–9
10. Inouye SK, Marcantonio ER, Kosar CM, Tommet D, Schmitt EM, Travison TG, Saczynski JS, Ngo LH, Alsop DC, Jones RN: The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. Alzheimers Dement 2016; 12:766–75
11. Marcantonio ER, Flacker JM, Michaels M, Resnick NM: Delirium is independently associated with poor functional recovery after hip fracture. J Am Geriatr Soc 2000; 48:618–24
12. Marcantonio E, Ta T, Duthie E, Resnick NM: Delirium severity and psychomotor types: Their relationship with outcomes after hip fracture repair. J Am Geriatr Soc 2002; 50:850–7
13. Hshieh TT, Saczynski J, Gou RY, Marcantonio E, Jones RN, Schmitt E, Cooper Z, Ayres D, Wright J, Travison TG, Inouye SK; SAGES Study Group: Trajectory of functional recovery after postoperative delirium in elective surgery. Ann Surg 2017; 265:647–53
14. Hamilton GM, Wheeler K, Di Michele J, Lalu MM, McIsaac DI: A systematic review and meta-analysis examining the impact of incident postoperative delirium on mortality. ANESTHESIOLOGY 2017; 127:78–88
15. Mosk CA, Mus M, Vroemen JP, van der Ploeg T, Vos DI, Elmans LH, van der Laan L: Dementia and delirium, the outcomes in elderly hip fracture patients. Clin Interv Aging 2017; 12:421–30
16. Dubljanin-Raspopović E, Markovic Denić L, Marinković J, Grajić M, Tomanovic Vujadinović S, Bumbaširević M: Use of early indicators in rehabilitation process to predict one-year mortality in elderly hip fracture patients. Hip Int 2012; 22:661–7
17. Gottschalk A, Hubbs J, Vikani AR, Gottschalk LB, Sieber FE: The impact of incident postoperative delirium on survival of elderly patients after surgery for hip fracture repair. Anesth Analg 2015; 121:1336–43
18. Furlaneto ME, Garcez-Leme LE: Impact of delirium on mortality and cognitive and functional performance among elderly people with femoral fractures. Clinics (Sao Paulo) 2007; 62:545–52
19. 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; 113:941–8
20. WHO: ICD-10-version: 2016. Available at: http://apps.who.int/classifications/icd10/browse/2016/en. Accessed December 1, 2015
21. American-Psychiatric-Association: Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, DC: American Psychiatric Association, 1997
22. Charlson M, Szatrowski TP, Peterson J, Gold J: Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47:1245–51
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987; 40:373–83
24. Chen P, Yu ES, Zhang M, Liu WT, Hill R, Katzman R: ADL dependence and medical conditions in Chinese older persons: A population-based survey in Shanghai, China. J Am Geriatr Soc 1995; 43:378–83

25. Lawton MP, Brody EM: Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179–86
26. Katzman R, Zhang MY, Ouang-Ya-Qu, Wang ZY, Liu WT, Yu E, Wong SC, Salmon DP, Grant I: A Chinese version of the Mini-Mental State Examination: Impact of illiteracy in a Shanghai dementia survey. J Clin Epidemiol 1988; 41:971–8
27. Shi Z, Wu Y, Li C, Fu S, Li G, Zhu Y, Swain CA, Marcantonio ER, Xie Z, Shen Y: Using the Chinese version of Memorial Delirium Assessment Scale to describe postoperative delirium after hip surgery. Front Aging Neurosci 2014; 6:297
28. Sieber FE, Zakriya KJ, Gottschalk A, Blute MR, Lee HB, Rosenberg PB, Mears SC: Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clin Proc 2010; 85:18–26
29. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group: BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013; 25:33–42
30. Luk TT, Jia B, Pang EY, Lau VN, Lam CK, Chu MH, Han R, Chan MT: Depth of anesthesia and postoperative delirium. Curr Anesthesiol Rep 2015; 5: 1–9
31. Wu Y, Shi Z, Wang M, Cao J, Zhu Y, Shen Y: Chinese version of the Memorial Delirium Assessment Scale (MDAS): Clinical validity and reliability in old postoperative patients. Chinese Mental Health Journal 2014; 28: 937–41
32. Leung Jl, Leung Vc, Leung CM, Pan PC: Clinical utility and validation of two instruments (the Confusion Assessment Method Algorithm and the Chinese version of Nursing Delirium Screening Scale) to detect delirium in geriatric inpatients. Gen Hosp Psychiatry 2008; 30:171–6
33. Brauer C, Morrison RS, Silberzweig SB, Siu AL: The cause of delirium in patients with hip fracture. Arch Intern Med 2000; 160:1856–60
34. Kagansky N, Rimon E, Naor S, Dvornikov E, Cojocaru L, Levy S: Low incidence of delirium in very old patients after surgery for hip fractures. Am J Geriatr Psychiatry 2004; 12:306–14
35. Xie Z, Swain CA, Ward SA, Zheng H, Dong Y, Sunder N, Burke DW, Escobar D, Zhang Y, Marcantonio ER: Preoperative cerebrospinal fluid β-amyloid/Tau ratio and postoperative delirium. Ann Clin Transl Neurol 2014; 1:319–28
36. Guo Y, Jia P, Zhang J, Wang X, Jiang H, Jiang W: Prevalence and risk factors of postoperative delirium in elderly hip fracture patients. J Int Med Res 2016; 44:317–27
37. Zhou M, Wang H, Zhu J, Chen W, Wang L, Liu S, Li Y, Wang L, Liu Y, Yin P, Liu J, Yu S, Tan F, Barber RM, Coates MM, Dicker D, Fraser M, González-Medina D, Hamavid H, Hao Y, Hu G, Jiang G, Kan H, Lopez AD, Phillips MR, She J, Vos T, Wan X, Xu G, Yan LL, Yu C, Zhao Y, Zheng Y, Zou X, Naghavi M, Wang Y, Murray CJ, Yang G, Liang X: Cause-specific mortality for 240 causes in China during 1990-2013: A systematic subnational analysis for the Global Burden of Disease Study 2013. Lancet 2016; 387:251–72
38. Bruce AJ, Ritchie CW, Blizard R, Lai R, Raven P: The incidence of delirium associated with orthopedic surgery: A meta-analytic review. Int Psychogeriatr 2007; 19:197–214
39. Bitsch M, Foss N, Kristensen B, Kehlet H: Pathogenesis of and management strategies for postoperative delirium after hip fracture: A review. Acta Orthop Scand 2004; 75:378–89
40. Rudolph JL, Inouye SK, Jones RN, Yang FM, Fong TG, Levkoff SE, Marcantonio ER: Delirium: An independent predictor of functional decline after cardiac surgery. J Am Geriatr Soc 2010; 58:643–9
41. Wijeysundera DN, Pearse RM, Shulman MA, Abbott TEF, Torres E, Ambosta A, Croal BL, Granton JT, Thorpe KE, Grocott MPW, Farrington C, Myles PS, Cuthbertson BH; METS study investigators: Assessment of functional capacity before major non-cardiac surgery: An international, prospective cohort study. Lancet 2018; 391:2631–40
42. Lundström M, Edlund A, Bucht G, Karlsson S, Gustafson Y: Dementia after delirium in patients with femoral neck fractures. J Am Geriatr Soc 2003; 51:1002–6
43. Lee H, Oh SY, Yu JH, Kim J, Yoon S, Ryu HG: Risk factors of postoperative delirium in the intensive care unit after liver transplantation. World J Surg 2018; 42:2992–9
44. Dokkedal U, Hansen TG, Rasmussen LS, Mengel-From J, Christensen K: Cognitive functioning after surgery in middle-aged and elderly Danish twins. Anesthesiology 2016; 124:312–21