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Risk factors for emergence agitation during the awakening period in elderly patients after total joint arthroplasty: a retrospective observational study

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Abstract

Objectives: This study aimed to explore the incidence and risk factors for emergence agitation (EA) in elderly patients who underwent total joint arthroplasty (TJA) under general anaesthesia and assess their predictive value.

Design: Single-centre retrospective observational study.

Setting: A 1,600-bed general tertiary hospital in China.

Participants: This study enrolled 421 elderly patients scheduled for elective primary TJA under general anaesthesia.

Primary and Secondary Outcome Measures: EA was assessed using the Richmond Agitation Sedation Scale (RASS) during the awakening period after surgery in the post-anaesthesia care unit (PACU). Risk factors for EA were identified using univariate and multivariate logistic analyses. The receiver operating characteristic curve (ROC) was used to assess the predictive value of risk factors for EA.

Results: The incidence of EA in elderly patients who underwent TJA was 37.6%. According to the multivariate logistic analysis, patients' visual analogue scale (VAS) score (95% confidence interval [CI]: 1.951–3.196), male sex (95% CI: 1.781–6.435), catheter-related bladder discomfort (CRBD) (95% CI: 4.001–15.392), fasting time for solids (95% CI: 1.260–2.301), and fasting time for fluids (95% CI: 1.263–2.365) were independent risk factors for EA. As shown by the ROC analysis, patients' VAS score (95% CI: 0.718–0.819), CRBD (95% CI: 0.673–0.775), fasting time for solids (95% CI: 0.699–0.807), and fasting time for fluids (95% CI: 0.719–0.816) showed a good predictive value.

Conclusions: EA was a common complication in elderly patients after TJA. The reduction of risk factors contributes to prevention and treatment of EA.

Keywords: Emergence agitation; Elderly patients; Risk factors; Total joint arthroplasty

Trial Registration: ChiCTR1800020193

Introduction

Emergence agitation (EA) is a common complication of the awakening period after general anaesthesia and refers to a temporary state of mental and motor excitement [1]. There are several clinical features of EA, including disorientation, excitation, agitation, and combative behaviours [2,3]. EA can also lead to an increased risk of wound bleeding or splitting, self-extubation, falling out of bed, and violence against staff [4]. It may also increase the patient's stay in the PACU and demand on medical staff [3], and simultaneously, more medical costs are incurred. The incidence of EA in paediatric patients ranges from 10% to 80% [5]. EA has many risk factors in paediatric patients, including pain, strange recovery surroundings, anaesthesia techniques, anaesthetics, patient features, and operative factors [6,7]. Lehmann et al. [8] reported that propofol was the first choice for preventing and treating EA in paediatric patients. In addition, α2-antagonists (clonidine and dexmedetomidine) have been shown to reduce the occurrence of EA in paediatric patients significantly [1,9,10].

Previous studies indicated that EA is common in children [11,12]; however, more recent studies reported that elderly patients are also prone to EA after surgery [13]. Currently, numerous studies have focused on EA in children, and few have examined elderly patients. EA in elderly adults may cause more serious consequences owing to decreased physiological functions and various complications; therefore, it is necessary to pay more attention to EA in elderly patients.

The incidence of EA varies according to the type of surgery performed. Card et al. [14] reported that the incidence of EA in adults after non-cardiac surgery was 19%. The incidence of EA in adult patients undergoing nasal and thoracic surgery varies from 2.5% to 22% [3,15]. In a retrospective observational study, Yu et al. [16] found that the incidence of EA in adults was 21.3% and that EA was prone to occur after oral cavity and otolaryngological surgery. Another single-centre prospective study showed that otorhinolaryngology was an independent risk factor for EA in paediatric patients [17]. Osteoarthritis (OA) is the most frequent type of arthritis and affects 1 in 3 older people [18]. With the emergence of an ageing society, the incidence of OA is increasing annually. Presently, more than 240 million people worldwide have OA [19]. End-stage OA can be treated with total joint arthroplasty (TJA). Annually, in the United States, more than 1 million people undergo TJA, > 90% due to OA [19]. To date, the mechanisms of EA are unclear, and the risk factors for EA in elderly patients who have undergone TJA are also unknown. Therefore, it is important to explore and avoid the risk factors for EA. Elderly patients with EA will benefit greatly from identification of the risk factors and development of appropriate strategies.

In this study, we retrospectively collected the medical records of 421 elderly patients who underwent general anaesthesia for TJA and investigated the risk factors for EA. These results provided insights for further treatment.

Materials and methods

Ethics statement

This study was approved by the Biomedical Research Ethics Committee of our hospital (approval no. 201812001), and the trial was registered in the Chinese Clinical Registry (ChiCTR, 1800020193). All methods were performed according to relevant guidelines and regulations. Written informed consent was obtained from all patients.

Patients

We enrolled 421 patients who underwent TJA under general anaesthesia at our hospital between December 2019 and June 2021. The inclusion criteria included (1) preoperative diagnosis of OA, (2) age ≥ 60 years, (3) American Society of Anaesthesiologists (ASA) physical status I–III, and (4) having undergone scheduled elective primary TJA under general anaesthesia. Patients with any of the following conditions were excluded: revision TJA, spinal or epidural anaesthesia, general anaesthesia within the past 6 months, and preoperative diagnosis of neuropsychiatric disorder.

Routine practice of perioperative management

Anaesthesia was induced with intravenous midazolam, etomidate, sufentanil, and rocuronium. After 2 min, tracheal intubation was completed. Ultrasound-guided femoral nerve block was performed in patients undergoing total knee replacement,

and ultrasound-guided fascia iliac compartment block was performed in patients undergoing total hip replacement. All 20-ml (0.5%) ropivacaine solutions were infused into the nerve block. After induction of anaesthesia, urinary catheterisation was performed in all patients. Anaesthesia was maintained using intravenous remifentanil and propofol. After the operation, patients were transferred to the PACU.

All patients were assessed by specialty nurses in the PACU using a standardised protocol, including the visual analogue scale (VAS), RASS, and Steward recovery scores. VAS was used for pain assessment, and flurbiprofen was administered intravenously as an analgesic rescue if the VAS score was ≥ 5. EA was evaluated using the RASS [13]; the score criteria are presented in Table 1. Patients with RASS ≥ 1 were considered to have EA. For severe agitation (RASS = 4), dexmedetomidine was administered. Patients with ward recovery scores > 4 were transferred to the ward from the PACU.

Data collection

The following patient-related variables were recorded: (1) population data and medical history, including age, sex, body mass index (BMI), ASA classification, education level, history of heart disease, respiratory disease, hypertension, and diabetes; (2) perioperative clinical information, including operation type and time, body temperature at the end of the surgery, VAS score, catheter-related bladder discomfort (CRBD), preoperative fasting time, intraoperative blood loss, warm treatment, postoperative nausea and vomiting, duration in PACU, RASS, and severe

intraoperative hypotension (mean arterial pressure < 65 mmHg for at least 1 min); and (3) laboratory tests.

Statistical analysis and sample size

The sample size was calculated using GPower software version 3.1 (Franz Faul, University of Kiel, Kiel, Germany). The effect size was set to 0.3, α level to 0.05, and 1-β to 0.85. A sample size of 100 patients was the optimal sample size required to prove the difference between the 2 groups. Considering that electronic medical records were easy to acquire, we included patients according to the inclusion and exclusion criteria between December 2019 and June 2020.

Statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as the mean ± standard deviation, and categorical data are presented as numbers and percentages. Independent risk factors were identified using univariate and multivariate logistic regression analyses. The measurement data were assessed for normal and non-normal distribution. Two independent sample t-tests were used to determine the differences between groups of continuous variables with a normal distribution. The nonparametric Mann–Whitney U test was used to compare differences between groups of continuous variables with non-normal distributions. Chi-square tests were used to determine the differences between the groups of categorical data. Variables with $P < 0.2$ were entered in multivariate logistic regression analysis. A positive stepwise method was used to adjust for the multiple risk factors. Each variable was expressed as an odds ratio (OR), and the confidence interval (CI) was 95%. The predictive value of the risk factors for

EA was assessed using the receiver operating characteristic curve (ROC). The cut-off point was calculated based on the maximum Youden index value. P values < 0.05 were considered statistically significant.

Patient and public involvement

No patients were involved with design, data provision, analysis or publication of the study

Results

General information on the study population

A total of 421 patients met the inclusion and exclusion criteria. However, 11 patients were excluded from the study; 6 were transferred to the intensive care unit (ICU) postoperatively, and the surgical protocol of 5 patients was changed during the operation. Finally, 410 patients were included in the statistical analysis (Fig. 1). The incidence of EA was 37.6% (n = 154) in 410 patients. All patients (n = 410) were divided into 2 groups: the EA group and non-EA group. There were no significant differences between the 2 groups in terms of age, BMI, ASA classification, education level, and medical history (Table 2). The proportion of male patients in the EA group was significantly higher than that in the non-EA group ($P < 0.05$).

Perioperative clinical information and laboratory test

Univariate analysis showed significant differences between the EA and non-EA groups in VAS score, body temperature at the end of the surgery, CRBD, preoperative fasting time, and duration in the PACU.

Compared with the non-EA group, the VAS score was higher in the EA group ($P < 0.05$), body temperature at the end of surgery was lower in the EA group ($P < 0.05$), and the patients' duration in the PACU and preoperative fasting times were longer in the EA group ($P < 0.05$). Simultaneously, 119 of 154 patients in the EA group had CRBD, while 83 of 256 patients in the non-EA group experienced CRBD. This variable was significantly different between the 2 groups ($P < 0.05$). Additionally,

there were no significant differences between the 2 groups in terms of surgery type and time, intraoperative blood loss, intraoperative hypotension, warm treatment, and laboratory tests (Table 3).

Multivariate logistic regression analysis

Based on the univariate analysis, variables included in the multivariate logistic regression analysis were VAS score, male sex, body temperature at the end of surgery, duration of PACU, preoperative fasting time, and CRBD.

As shown in Fig. 2, the correlation between VAS score, male sex, preoperative fasting time, CRBD, and EA in the TOA could be determined based on multivariate logistic analysis. In particular, the VAS score (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), CRBD (OR = 7.847; 95% CI: 4.001–15.392), fasting time for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting time for fluids (OR = 1.728; 95% CI: 1.263–2.365) were independent risk factors. However, we could not confirm the independence of variables, such as body temperature at the end of surgery and PACU duration, in the multivariate logistic analysis.

Results of ROC curves for risk factors

The predictive value analysed using the ROC curve is demonstrated in Fig. 3. The area under the ROC curve (AUC) for the VAS score was 0.769, with a cut-off value of 4.0, sensitivity of 60%, and specificity of 87% (95% CI: 0.718–0.819, $P < 0.001$). The AUC of fasting time for solids was 0.753, with a cut-off value of 10.5, sensitivity of 62%, and specificity of 86% (95% CI: 0.699–0.807, $P < 0.001$). The

AUC of fasting time for fluids was 0.768, with a cut-off value of 8.5, sensitivity of 64%, and specificity of 74% (95% CI: 0.719–0.816, $P < 0.001$).

Discussion

The results of the present study indicated that EA was a common postoperative complication in patients who underwent general anaesthesia for TJA. Furthermore, this study identified 4 risk factors associated with the postoperative period in elderly patients who underwent TJA, including male sex, preoperative fasting time, CRBD, and postoperative pain.

The incidence of EA was 37.6% in elderly patients who underwent TJA. To our knowledge, this is the first report of EA in elderly patients who have undergone TJA. The incidence of EA could only be compared with other types of surgery and other assessment methods. However, previous studies have indicated that the incidence of EA varies. A recent prospective study showed that 158 of 1136 adult patients were determined to have EA according to the RASS [20]. Xi et al. [13] reported that the incidence of EA in elderly patients who underwent gastrointestinal surgery was 40% based on the Ricker Sedation-Agitation Scale (RSAS). Surprisingly, the incidence of EA was up to 90.5% because of the negative effects of succinylcholine [21]. These large differences may be attributed to the different types of surgery, anaesthetic management, patient characteristics, and assessment methods.

There are many scales for assessing EA, including the RASS, RSAS, motor activity assessment scale, and New Sheffield sedation scale. The RASS has been proven to have excellent reliability and validity in assessing sedation and agitation in the ICU [22]. Although the reliability and validity of the RASS in the PACU have not

been validated, the RASS is easy to use and administer and has discrete criteria [22]. Owing to these advantages, the RASS was chosen to assess EA in the PACU in this study. Similarly, Makarem et al. [20] and Xi et al. [13] also chose the RASS to assess EA in the PACU.

Almost all researchers agree that postoperative pain is an independent risk factor for EA. Many clinical practices suggest that postoperative pain is bound to cause uncomfortable emotional experiences and lead to a series of dysregulated behaviours. Our study showed that the VAS score of patients in the EA group was higher than that in the non-EA group, and postoperative pain VAS score ≥ 4 was the cut-off point for EA. Pain after TJA is common, and several studies have found that > 50% of patients have suboptimal pain management after total hip arthroplasty (THA), and 75% of patients undergoing total knee arthroplasty (TKA) complain of moderate-to-severe pain [23,24]. In the present study, 72% (n = 295) patients complained of pain, and 5% (n = 21) patients experienced severe pain, comparable to the results of previous reports. Yu et al. [16] found that nearly half of the patients had EA because of a lack of postoperative analgesia. It is well accepted that peripheral nerve blocks (PNBs) provide excellent analgesia. In our study, to improve postoperative analgesia, femoral nerve block was routinely used in patients undergoing TKA, and fascia iliaca compartment block was used for THA. In our clinical practice, every patient undergoes ultrasound-guided PNB. However, considering anatomic variations and individual characteristics, PNBs do not result in an absolute lack of pain in patients undergoing TJA; hence, some patients still experience EA due to postoperative pain.

Moreover, postoperative pain is not just wound related; sore throat and catheter-related pain should not be ignored. Based on these findings, we strongly suggest that multimodal analgesia should be performed although it greatly benefits patients with preventive analgesia.

Placement of an indwelling catheter is a common clinical operation in the perioperative period. The collected urine is used for urine measurements and blood volume evaluation. However, patients undergoing urinary catheterisation are prone to develop CRBD [25], characterised by discomfort confined to the suprapubic region, burning sensation, pain, urinary urgency, and frequency [26,27]. CRBD can occur in 47–90% of patients with a urinary catheter [4]. CRBD can enhance the incidence of EA and pain sensation after surgery [28]. A retrospective study reported that approximately 10% of patients experienced EA during urological surgery, which may be related to CRBD [29]. In our study, 119 of 410 patients experienced EA due to CRBD. The higher incidence of EA in our study may have been due to the age of the recruited patients because age ≥ 50 years was an independent predictor of CRBD [30]. Presently, many researchers have focused on EA associated with CRBD in patients undergoing urological surgery and rarely in patients undergoing TJA. It is necessary to remove urinary and indwelling catheters under topical anaesthesia early and avoid urinary catheterisation (if possible) to decrease EA associated with CRBD.

Regarding male patients, the conclusion of this study is similar to those of other studies; male sex was an independent risk factor for EA [30]. The fact that male patients were prone to EA can be explained by the following points: male patients

were high-risk patients with CRBD [30]. Half of all men aged ≥ 50 years and over 80% of men aged ≥80 years have prostatic hyperplasia [31]. They easily felt discomfort and pain when the tip of the catheter was in contact with the bladder triangle on the pubis. Notably, an indwelling catheter without discomfort was used after anaesthesia induction. However, during the awakening period, patients, especially male patients, find it difficult to bear unexpected catheter-related discomfort. Furthermore, postoperative pain tolerance in male patients is low, and male patients require more analgesics than female patients [32].

The relationship between emergence delirium (ED) and fasting time has also been demonstrated. Khanna et al. [33] reported that prolonged preoperative fasting (> 6 h) was a risk factor for postoperative ED in children. However, the relationship between preoperative fasting time and EA in elderly patients has not been reported. This study showed that patients in the EA group had a longer preoperative fasting time; meanwhile, 10.5 h (fasting time for solids) and 8.6 h (fasting time for fluids) are cut-off points for EA. Prolonged preoperative fasting can cause metabolic, physical, and psychological discomfort in patients, eventually leading to EA [34]. Prolonged preoperative fasting translates to a prolonged preoperative waiting time, leading to patient apprehension and anxiety. Preoperative anxiety is a risk factor for EA [29]. Owing to a large number of patients and the lack of medical resources, patients may undergo surgery later than expected, thereby prolonging the fasting time. Thus, it is necessary to reasonably schedule operations to decrease EA and reduce unnecessary fasting times.

This study has some limitations. First, because this was a single-centre study, the sample size was small, and the representative conclusions were insufficient. As the same surgical team performed all operations, the effect of operation time on EA could not be evaluated. Therefore, expanding the sample size and increasing the number of research centres is necessary. Second, all study patients received an indwelling catheter, and CRBD was a risk factor for EA. Thus, the conclusions of this study may not apply to patients undergoing TJA without catheterisation. Third, EA is different from ED. Delirium is an acute state of mental confusion characterised by hypoactivity or hyperactivity [35]. A proportion of patients with delirium present with agitation, making assessment of EA difficult during recovery from anaesthesia. Therefore, we evaluated only EA, which may have led to false-positive cases.

Conclusion

This retrospective study showed that the incidence rate of EA in elderly patients after TJA in the PACU was 37.6%. Postoperative pain, CRBD, male sex, and preoperative fasting duration were independent predictors of EA. To date, the pathophysiological mechanism of EA is unknown; hence, it is more important to prevent EA than to treat it, while the best choice should be to eliminate and avoid risk factors.

Strengths and limitations of this study

- Previous studies indicated that EA is common in children; however, more recent studies reported that elderly patients are also prone to EA after surgery. Therefore, this study was the first to explore the incidence and risk factors for EA

in elderly patients who underwent TJA under general anaesthesia and assess their predictive value.

- This study explored the incidence and risk factors for EA in elderly patients and assessed their predictive value, which could provide insights for further treatment.
- This was a single-centre study, the sample size was small. Moreover, since all patients in this study received an indwelling catheter, the finding of this study may not apply to patients who received TJA without catheter insertion.
- EA is different from emergence delirium. A proportion of patients with delirium present with agitation, making the assessment of EA difficult during recovery from anaesthesia. Therefore, we evaluated only EA, which may have led to false-positive cases.

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contributed equally to the manuscript and read and approved the final version of the manuscript.

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Tables

Table 1 Richmond agitation sedation scale

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Notes: Scores of 1 to 4 indicated different levels of agitation, 0 indicated calmness and alertness, and −1 to −5 indicated different levels of sedation.

472 **Table 2 Population data and medical history**

Variables	Agitation Groups(n=154)	Non-agitation Groups(n=256)	P-value
Age	69. 84±6. 53	69. 39±6. 82	0. 238
Male (n, %)	91 (59. 1%)	71 (27. 7%)	＜0. 001***
BMI (Kg. m^{-2})	22. 75±4. 31	23. 17±2. 56	0. 253
ASA classification (n, %)			0. 221
Ⅰ	0	0	
Ⅱ	118 (76. 6%)	182 (71. 1%)	
Ⅲ	36 (23. 4%)	74 (28. 9%)	
Education (n, %)			0. 412
Illiteracy	42 (27. 3%)	55 (21. 5%)	
Primary school	45 (29. 2%)	93 (36. 3%)	
Secondary school	59 (38. 3%)	96 (37. 5%)	
University and above	8 (5. 2%)	12 (4. 7%)	
Medical history (n, %)			
Heart disease			0. 816
Yes	72 (46. 8%)	113 (44. 1%)	
No	82 (53. 2%)	143 (55. 9%)	
Respiratory diseases			0. 760
Yes	80 (51. 9%)	129 (50. 4%)	
No	74 (48. 1%)	127 (49. 6%)	

Table2 (Continued)

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Hypertension			0. 981
Yes	78 (50. 6%)	131 (51. 2%)	
No	76 (49. 4%)	125 (48. 8%)	
Diabetes			0. 940
Yes	71 (46. 1%)	119 (46. 5%)	
No	83 (53. 9%)	137 (53. 5%)	

Notes: Clinical information of patients were analyzed by univariate analysis. Continuous data are presented as the mean ± standard deviation, and categorical data are presented as numbers and percentages. *P-value, differences between patients in two groups. *P<0. 05, ***P<0. 001. ASA: American Society of Anesthesiologists; BMI: body mass index.

Table 3 Patients' perioperative clinical information and agitation-related laboratory test indicators

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Operation type (n, %)			0. 524
TKA	85 (55. 2%)	133 (52. 0%)	
THA	69 (44. 8%)	123 (48. 0%)	
Operation time in TKA (min)	144. 42±59. 96	143. 91±46. 19	0. 236
Operation time in THA (min)	139. 96±64. 60	128. 48±58. 98	0. 213
Patients' VAS score	3. 50±2. 13	1. 67±1. 02	＜0. 001***
Body temperature at the end of the surgery (℃)	35. 87±0. 73	36. 03±0. 94	0. 037*
CRBD (n, %)			＜0. 001***
Yes	119(77. 3%)	83 (32. 4%)	
No	35(22. 7%)	173(67. 6%)	
Preoperative fasting time (h)			
Fasting time for solids	10. 19±1. 05	8. 76±0. 88	＜0. 001***
Fasting time for fluids	4. 81±1. 14	2. 99±0. 92	＜0. 001***
Intraoperative blood loss (ml)	217. 26±30. 18	200. 32±27. 48	0. 224

489 **Table3 (Continued)**

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Severe Intraoperative hypotension (n, %)			0. 261
Yes	14 (9. 1%)	15 (5. 9%)	
No	140 (90. 9%)	241 (94. 1%)	
Postoperative nausea and vomiting (n, %)			0. 332
Yes	67 (43. 5%)	124 (48. 4%)	
No	87 (56. 5%)	132 (51. 6%)	
The duration in PACU (min)	32. 83±14. 07	31. 00±8. 57	0. 025*
Warm treatment (n, %)			0. 880
Yes	68 (44. 2%)	115 (44. 9%)	
No	86 (55. 8%)	141 (55. 1%)	
Laboratory testing			
HCO_3^- (mmol/L)	22. 3±1. 86	24. 7±1. 33	0. 291
$PaCO_2$ (mmHg)	38. 61±1. 42	39. 44±1. 58	0. 318
PaO_2 (mmHg)	89. 52±1. 74	90. 17±1. 55	0. 282
pH	7. 447±0. 32	7. 426±0. 41	0. 263
Hb levels (g/L)	16. 6±1. 93	17. 1±1. 85	0. 274

Notes: Patients' perioperative clinical information and agitation-related laboratory test indicators were analyzed by univariate analysis. Continuous data are presented as the mean ± standard deviation, and categorical data are presented as numbers and percentages. *P-value, differences between patients in two groups. *P<0. 05, ***P<0. 001. TKA: total knee arthroplasty; THA: total hip arthroplasty; VAS: visual analog scale; CRBD: catheter-related bladder discomfort; PACU: post-anesthesia care unit.

Figure legends

Figure 1 Flow chart of study participants. A total of 421 patients met the inclusion and exclusion criteria. However, 11 patients were excluded from the study; 6 were transferred to the ICU postoperatively, and the surgical protocol of 5 patients was changed during the operation. Finally, 410 patients were included in the statistical analysis.

Figure 2 Risk factors of EA by metanalysis plot. The patients' VAS score (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), urinary catheter irritation (OR = 7.847; 95% CI: 4.001–15.392), fasting time for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting time for fluids (OR = 1.728; 95% CI: 1.263–2.365) were the independent risk factors. VAS: visual analogue scale

Figure 3 Risk factors of EA by the ROC curve. The predictive value of risk factors was assessed using the ROC curve. The patients' VAS score (AUC = 0.769, 95% CI: 0.718–0.819, P < 0.001), fasting time for solids (AUC = 0.753, 95% CI: 0.699–0.807, P < 0.001) and fasting time for fluids (AUC = 0.768, 95% CI: 0.719–0.816, P < 0.001) showed a good predictive effect.

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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Reporting Item	Page

			Number
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Objectives	#3	State specific objectives, including any prespecified hypotheses	6
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Study design	#4	Present key elements of study design early in the paper	NA

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Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	7
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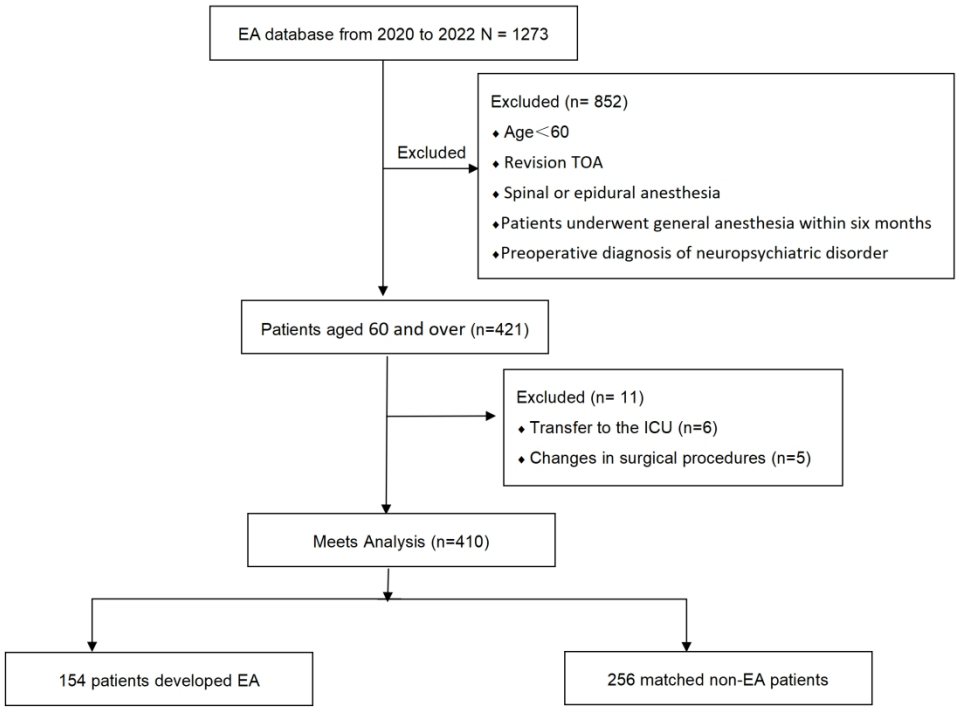
554

Figure 1 Flow chart of study participants.



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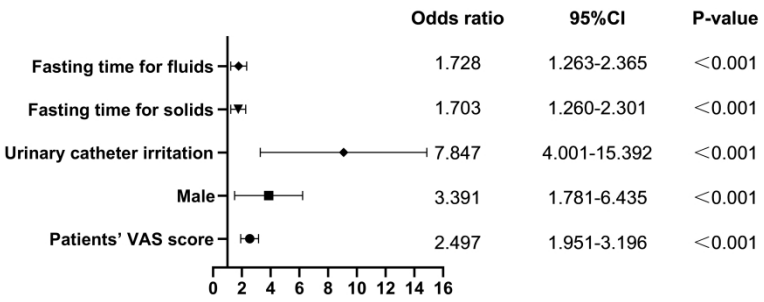

Figure 2 Risk factors of EA by metanalysis plot

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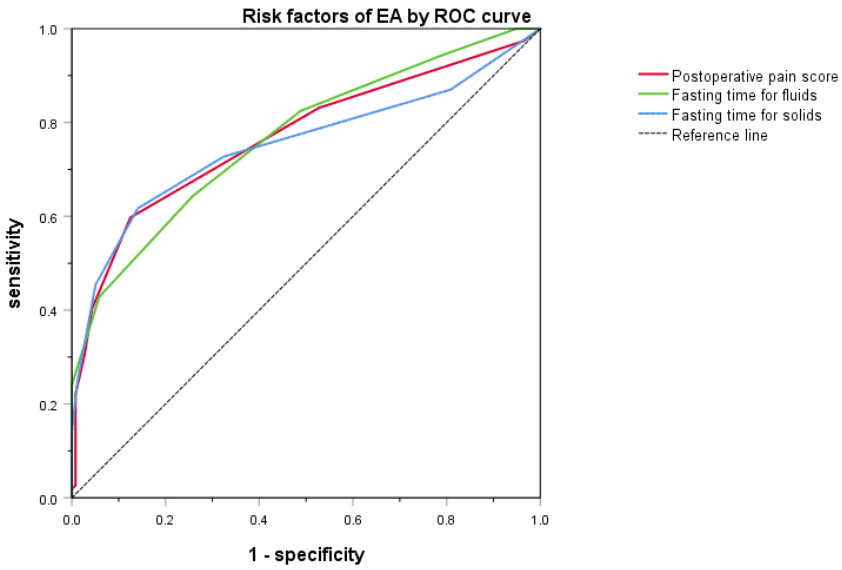

Figure 3 Risk factors of EA by the ROC curve

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Risk factors for emergence agitation during the awakening period in elderly patients after total joint arthroplasty: a retrospective cohort study

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Running title: EA risk factors after TJA

Keywords: Emergence agitation; Elderly patients; Risk factors; Total joint arthroplasty

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IRB number: 201812001 (Biomedical Research Ethics Committee of Honghui Hospital)

Clinical trial registration number: ChiCTR1800020193

Word count: 3198

Abstract

Objectives: This study aimed to explore the incidence and risk factors for emergence agitation (EA) in elderly patients who underwent total joint arthroplasty (TJA) under general anaesthesia and assess their predictive values.

Design: Single-centre retrospective cohort study.

Setting: A 1,600-bed general tertiary hospital in China.

Participants: This study enrolled 421 elderly patients scheduled for elective primary TJA under general anaesthesia.

Primary and Secondary Outcome Measures: EA was assessed using the Richmond Agitation Sedation Scale during the awakening period after surgery in the post-anaesthesia care unit. Risk factors for EA were identified using univariate and multivariable logistic analyses. The receiver operating characteristic curve (ROC) was used to assess the predictive values of the risk factors for EA.

Results: The incidence of EA in elderly patients who underwent TJA was 37.6%. According to the multivariable logistic analysis, postoperative pain (95% confidence interval [CI]: 1.951–3.196), male sex (95% CI: 1.781–6.435), catheter-related bladder discomfort (CRBD) (95% CI: 4.001–15.392), longer fasting times for solids(95% CI:1.260–2.301) and fluids (95% CI: 1.263–2.365) were independent risk factors for EA. As shown by the ROC analysis, postoperative pain,fasting times for solids and fluids had good predictive values ,with the area under the ROC curve (AUC) was 0.769, 0.753 and 0.768,respectively.

Conclusions: EA is a common complication in elderly patients after TJA. Reducing these risk factors is crucial in preventing or treating EA.

Keywords: Emergence agitation; Elderly patients; Risk factors; Total joint arthroplasty

Strengths and limitations:

- We investigated the incidence and risk factors for EA in elderly patients after total joint arthroplasty and assessed their predictive values.
- This study may provide novel insights for preventing and treating EA by identifying the risk factors for EA in elderly patients and assessing their predictive values.
- As a single-centre study, our sample size was relatively small.
- This was a single-centre retrospective cohort study; thus, some bias is unavoidable.

Trial Registration: ChiCTR1800020193

Introduction

Emergence agitation (EA), a common complication of the awakening period after general anaesthesia, refers to a temporary state of mental and motor excitement [1]. Clinical features of EA include disorientation, excitation, agitation, and combative behaviours [2,3]. EA can also increase the risk of wound bleeding or dehiscence, self-extubation, falling out of bed, and violent behaviour towards staff [4]. It may also prolong the patient's stay in the post-anaesthesia care unit (PACU) and increase the demand for medical staff [3], resulting in higher medical costs. The incidence of EA varies widely, ranging from 0.25% to 90.5%, depending on factors such as age, type of surgery, assessment tool, and anaesthesia method [5]. However, the exact aetiology and pathological mechanisms of EA remain unclear [5,6]. Hence, identifying the risk factors for EA is crucial in preventing and managing this condition.

EA has been reported in different age groups following general anaesthesia [5]. Many studies have demonstrated that EA is common in children [2,7-8]. However, other studies have demonstrated that the elderly are also at a high risk of developing EA [9]. Unfortunately, there are few reports on EA in the elderly compared with many studies on EA in children. Owing to the decline in physiological functions with age, the elderly may be predisposed to EA after surgery, leading to more serious consequences. Thus, more attention must be paid to EA in elderly patients.

Osteoarthritis (OA) is the most frequent type of arthritis and affects one in three older people [10]. As society ages, more and more older people experience OA. Total joint arthroplasty (TJA) is a successful treatment protocol for end-stage knee and hip OA [11]. Annually, more than 1 million people undergo TJA in the United States [12]. The demand for TJA surgery is expected to increase substantially in the coming years [13]. However, there are no reports on the incidence of EA after TJA.

In this study, we retrospectively collected the medical records of 421 elderly patients who underwent general anaesthesia for TJA. We aimed to evaluate the risk factors of postoperative EA in elderly patients, assess the predictive values, and provide guidance for preventing and treating EA during follow-up.

Materials and methods

Ethics statement

This study was approved by the Biomedical Research Ethics Committee of our hospital (approval no. 201812001), and the trial was registered in the Chinese Clinical Registry (ChiCTR, 1800020193). All methods were performed according to relevant guidelines and regulations. The study obtained consent to gather patients' medical record information through telephonic follow-up.

Patients

We enrolled 421 patients who underwent TJA under general anaesthesia at our hospital between December 2019 and June 2021. The inclusion criteria included (1) preoperative OA diagnosis, (2) age ≥ 60 years, (3) American Society of Anesthesiologists (ASA) physical status I–III, and (4) having undergone scheduled elective primary TJA under general anaesthesia. Patients with any of the following conditions were excluded: revision TJA, spinal or epidural anaesthesia, general anaesthesia within the past 6 months, and preoperative diagnosis of neuropsychiatric disorder.

Routine practice of perioperative management

Anaesthesia was induced with intravenous midazolam, etomidate, sufentanil, and rocuronium. Tracheal intubation was completed after 2 min. The ultrasound-guided femoral nerve block was performed in patients undergoing total knee replacement, while the ultrasound-guided fascia iliac compartment block was performed in patients undergoing total hip replacement. All 20-ml (0.5%) ropivacaine solutions were infused into the nerve block. Urinary catheterisation was performed in all patients after inducing anaesthesia. Anaesthesia was maintained using intravenous remifentanil and propofol. Patients were transferred to the PACU after the operation. These patients were extubated in the PACU.

Speciality nurses assessed all patients in the PACU using a standardised protocol, including the visual analogue scale (VAS), Richmond Agitation Sedation Scale (RASS), and Steward recovery scores. VAS was used for assessing postoperative pain, and intravenous flurbiprofen was administered as an analgesic rescue when the VAS score was >4. EA was evaluated using the RASS [14], and Table 1 presents the score criteria. Patients with a RASS score > 1 were considered to have EA[14]. Dexmedetomidine was administered in cases of severe agitation (RASS = 4). Patients with ward recovery scores > 4 were transferred to the ward from the PACU.

Data collection

The following patient-related variables were recorded: (1) population data and medical history, including age, sex, body mass index (BMI), ASA classification,

education level, and history of heart disease, respiratory disease, hypertension, and diabetes; (2) perioperative clinical information, including operation type and time, body temperature after the surgery, VAS score, catheter-related bladder discomfort (CRBD), preoperative fasting times, intraoperative blood loss, warm treatment, postoperative nausea and vomiting, duration in PACU, RASS score, and severe intraoperative hypotension (mean arterial pressure < 65 mmHg for at least 1 min); and (3) laboratory tests. Preoperative fasting times refers to the period from the last intake of liquids or solids to the beginning of the anaesthesia induction.

Statistical analysis and sample size

The sample size was calculated using GPower software version 3.1 (Franz Faul, University of Kiel, Kiel, Germany). The effect size was set to 0.3, α level to 0.05, and 1-β to 0.85. A sample size of 100 patients was the optimal sample size required to prove the difference between the two groups. Considering the easy acquisition of electronic medical records, we included patients who met the inclusion and exclusion criteria between December 2019 and June 2020.

Statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as the means ± standard deviations, and categorical data are presented as numbers and percentages. Independent risk factors were identified using univariate and multivariable logistic regression analyses. The measurement data were assessed for normal and non-normal distributions. Two independent sample t-tests were used to determine the differences between groups for

continuous variables with a normal distribution. The nonparametric Mann–Whitney U test was used to compare differences between groups for continuous variables with non-normal distributions. Chi-square tests were used to determine differences between groups for categorical data. Variables with $P < 0.2$ were entered in multivariable logistic regression analysis. A positive stepwise method was used to adjust for multiple risk factors. Each variable was expressed as an odds ratio (OR) with a 95% confidence interval (CI). The predictive value of the risk factors for EA was assessed using the receiver operating characteristic (ROC) curve. The cut-off point was calculated based on the maximum Youden index value. Statistical significance was set at a P value < 0.05.

Patient and public involvement

None of the patients were involved in the design, data provision, analysis, or publication of the study.

Results

General information on the study population

In total, 421 patients met the inclusion and exclusion criteria. However, 11 patients were excluded from the study; six were transferred to the intensive care unit (ICU) postoperatively, and the surgical protocols of five patients were changed during the operation. Finally, the statistical analysis included 410 patients (Fig. 1). The incidence of EA was 37.6% (n = 154) in 410 patients. All patients (n = 410) were divided into two groups: EA and non-EA. No significant differences were observed between the two groups in age, BMI, ASA classification, education level, and medical history (Table 2). The EA group had a significantly higher proportion of male patients than the non-EA group ($P < 0.05$).

Perioperative clinical information and laboratory test

Univariate analysis demonstrated significant differences between the EA and non-EA groups in the VAS score for postoperative pain, body temperature after the surgery, CRBD, preoperative fasting times, and length of stay in the PACU.

Compared with the non-EA group, the VAS score was higher ($P < 0.05$), body temperature after the surgery was lower ($P < 0.05$), and the patient's length-of-stay in the PACU and preoperative fasting times were longer in the EA group ($P < 0.05$). Simultaneously, 119 of 154 patients in the EA group had CRBD, while 83 of 256

patients in the non-EA group experienced CRBD. This variable differed significantly between the two groups ($P < 0.05$). Additionally, no significant differences were observed between the two groups regarding surgery type and time, intraoperative blood loss, intraoperative hypotension, warm treatment, and laboratory tests (Table 3).

Multivariable logistic regression analysis

Based on the univariate analysis, variables included in the multivariable logistic regression analysis include the VAS score for postoperative pain, male sex, body temperature after the surgery, length-of-stay in the PACU, preoperative fasting times, and CRBD.

The correlation between the VAS score for postoperative pain, male sex, preoperative fasting times, CRBD, and EA in the TJA could be determined based on multivariable logistic analysis (Fig. 2). The VAS score for postoperative pain (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), CRBD (OR = 7.847; 95% CI: 4.001–15.392), fasting times for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting times for fluids (OR = 1.728; 95% CI: 1.263–2.365) were independent risk factors. However, we could not confirm the independence of variables, such as body temperature after the surgery and length-of-stay in the PACU, in the multivariable logistic analysis.

Results of ROC curves for risk factors

The predictive value analysed using the ROC curve is demonstrated in Fig. 3. The area under the ROC curve (AUC) for the VAS score was 0.769, with a cut-off value of 4.0, sensitivity of 60%, and specificity of 87% (95% CI: 0.718–0.819, P < 0.001). The AUC of fasting time for solids was 0.753, with a cut-off value of 10.5, sensitivity of 62%, and specificity of 86% (95% CI: 0.699–0.807, P < 0.001). The AUC of fasting time for fluids was 0.768, with a cut-off value of 8.5, sensitivity of 64%, and specificity of 74% (95% CI: 0.719–0.816, P < 0.001).

Discussion

This study's results indicated that EA is a common postoperative complication in patients who underwent general anaesthesia for TJA. Furthermore, this study identified four risk factors associated with the postoperative period in elderly patients who underwent TJA, including male sex, preoperative fasting times, CRBD, and postoperative pain.

The incidence of EA was 37.6% in elderly patients who underwent TJA. To our knowledge, this is the first report on EA in elderly patients who have undergone TJA. The incidence of EA could only be compared with other types of surgery and other assessment methods. However, previous studies have indicated that the incidence of EA varies. A recent prospective study demonstrated that 158 of 1136 adult patients had EA using the RASS [15]. Xi et al. [9] reported that the incidence of EA in elderly patients who underwent gastrointestinal surgery was 40% based on the Ricker

Sedation-Agitation Scale (RSAS). The incidence of EA was approximately 90.5% because of the negative effects of succinylcholine [16]. These large differences may be attributed to the types of surgery, anaesthetic management, patient characteristics, and assessment methods.

There are many scales for assessing EA, including the RASS, RSAS, motor activity assessment scale, and New Sheffield sedation scale. However, the RASS has excellent reliability and validity in assessing sedation and agitation in the ICU [14]. The reliability and validity of the RASS in the PACU have not been validated; however, the RASS is easy to use and administer and has discrete criteria [14]. Owing to these advantages, the RASS was chosen to assess EA in the PACU in this study. Similarly, Makarem et al. [15] and Xi et al. [9] also chose the RASS to assess EA in the PACU.

Almost all researchers agree that postoperative pain is an independent risk factor for EA. Many clinical practices suggest that postoperative pain can cause uncomfortable emotional experiences and lead to several dysregulated behaviours. Our study demonstrated that the VAS scores of patients in the EA group were higher than those in the non-EA group, and a postoperative pain VAS score ≥ 4 was the cut-off point for EA. Pain after TJA is common, and several studies have discovered that more than 50% of patients have suboptimal pain management after total hip arthroplasty (THA), and 75% of patients undergoing total knee arthroplasty (TKA) complain of moderate-to-severe pain [17,18]. In this study, 72% (n = 295) of patients complained of pain, and 5% (n = 21) of patients experienced severe pain, comparable

to the results of previous reports. Yu et al. [6] found that nearly half of the patients had EA because of insufficient postoperative analgesia. Peripheral nerve blocks (PNBs) provide excellent analgesia. In our study, the femoral nerve block was routinely used in patients undergoing TKA, while the fascia iliaca compartment block was used for THA to improve postoperative analgesia. In our clinical practice, every patient undergoes ultrasound-guided PNB. However, considering anatomic variations and individual characteristics, PNBs may not eliminate pain in patients undergoing TJA, leading to some patients experiencing EA due to postoperative pain. Moreover, sore throat and catheter-related pain should not be ignored because postoperative pain is not only wound related. Based on these findings, we strongly suggest that multimodal analgesia should be performed to benefit patients, especially with preventive analgesia.

The placement of an indwelling catheter is a common clinical operation in the perioperative period. The collected urine is used for urine measurements and blood volume evaluation. However, patients undergoing urinary catheterisation are prone to CRBD [19], characterised by discomfort confined to the suprapubic region, burning sensation, pain, and urinary urgency and frequency [20,21]. CRBD can occur in 47–90% of patients with a urinary catheter [4]. CRBD can increase the incidence of EA and pain sensation after surgery [22]. A retrospective study reported that approximately 10% of patients experienced EA during urological surgery, possibly related to CRBD [23]. In our study, 119 of 410 patients experienced EA due to CRBD. Moreover, the higher incidence of EA may be due to the age of the recruited

patients because age ≥ 50 years was an independent predictor of CRBD [24]. Many researchers have focused on EA associated with CRBD in patients undergoing urological surgery and rarely in patients undergoing TJA. Urinary and indwelling catheters under topical anaesthesia must be removed early, and urinary catheterisation (if possible) avoided to decrease EA associated with CRBD.

Regarding male patients, this study's conclusion is similar to that of other studies where the male sex was identified as an independent risk factor for EA [24]. This observation could be explained by several factors. Firstly, male patients were high-risk patients with CRBD [24]. Half of all men aged ≥ 50 years and over 80% of men aged ≥80 years have prostatic hyperplasia, which can easily cause discomfort and pain when the catheter tip contacts the bladder triangle on the pubis [25]. However, during the awakening period of anaesthesia, male patients especially have difficulty tolerating the discomfort associated with catheters. Furthermore, male patients have low postoperative pain tolerance, requiring more analgesics than female patients [26].

The relationship between emergence delirium (ED) and fasting times has also been demonstrated. Khanna et al. [27] reported that prolonged preoperative fasting (> 6 h) was a risk factor for postoperative ED in children. However, the relationship between preoperative fasting times and EA in elderly patients has not been reported. This study showed that patients in the EA group had a longer preoperative fasting times. Moreover, 10.5 h (fasting times for solids) and 8.6 h (fasting times for fluids) are cut-off points for EA. Prolonged preoperative fasting can cause metabolic,

physical, and psychological discomfort in patients, eventually leading to EA [28]. Prolonged preoperative fasting translates to prolonged preoperative waiting time, leading to patient apprehension and anxiety. Preoperative anxiety is a risk factor for EA [23]. Owing to the numerous patients and the lack of medical resources, patients may undergo surgery later than expected, thereby prolonging the fasting times. Thus, operations to decrease EA and reduce unnecessary fasting timess must be reasonably scheduled.

This study had some limitations. Firstly, we only included elderly patients who had undergone intravenous anaesthesia. Future studies may utilize other methods and anaesthetics. Secondly, this was a single-centre study; therefore, the generalisability of the results was not fully verified. Future multi-centre studies must assess external validity. Lastly, this is a retrospective cohort study; some bias is unavoidable. Future prospective studies must be conducted for further research.

Conclusion

This retrospective study showed that the incidence rate of EA in elderly patients after TJA in the PACU was 37.6%. Postoperative pain, CRBD, male sex, and preoperative fasting duration were independent predictors of EA. The pathophysiological mechanism of EA is unknown; hence, preventing EA is more important than treating it. However, the best choice should be to eliminate and avoid risk factors.

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Author Contributions: Zhenguo Luo and Jianhong Hao have made substantial contributions to the conception or design of the manuscript. Naigeng Wang wrote this manuscript and made some changes after review. Furthermore, he worked with Jing Du and Jie Zhang to acquire, analyse, and interpret the data. All authors have participated in drafting the manuscript, and Zhenguo Luo revised it critically. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Conflict of interest: No potential conflict of interest relevant to this article was reported.

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Tables

Table 1 Richmond agitation sedation scale

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement; fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awake with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Notes: Scores of 1 to 4 indicated different levels of agitation, 0 indicated calmness and alertness, and −1 to −5 indicated different levels of sedation.

451 **Table 2 Population data and medical history**

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Age	69. 84±6. 53	69. 39±6. 82	0. 238
Male (n, %)	91 (59. 1%)	71 (27. 7%)	＜0. 001***
BMI (Kg. m^{-2})	22. 75±4. 31	23. 17±2. 56	0. 253
ASA classification (n, %)			0. 221
Ⅰ	0	0	
Ⅱ	118 (76. 6%)	182 (71. 1%)	
Ⅲ	36 (23. 4%)	74 (28. 9%)	
Education (n, %)			0. 412
Illiteracy	42 (27. 3%)	55 (21. 5%)	
Primary school	45 (29. 2%)	93 (36. 3%)	
Secondary school	59 (38. 3%)	96 (37. 5%)	
University and above	8 (5. 2%)	12 (4. 7%)	
Medical history (n, %)			
Heart disease			0. 816
Yes	72 (46. 8%)	113 (44. 1%)	
No	82 (53. 2%)	143 (55. 9%)	

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Respiratory diseases			0. 760
Yes	80 (51. 9%)	129 (50. 4%)	
No	74 (48. 1%)	127 (49. 6%)	
Hypertension			0. 981
Yes	78 (50. 6%)	131 (51. 2%)	
No	76 (49. 4%)	125 (48. 8%)	
Diabetes			
Yes	71 (46. 1%)	119 (46. 5%)	0. 940
No	83 (53. 9%)	137 (53. 5%)	

Notes: Clinical information of patients were analysed using univariate analysis. Continuous data are presented as the means ± standard deviations, while categorical data are presented as numbers and percentages. *P-value, differences between patients in the two groups. *P<0. 05, ***P<0. 001. ASA: American Society of Anesthesiologists; BMI: body mass index.

462 **Table 3 Patients' perioperative clinical information and agitation-related**

463 **laboratory test indicators**

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Operation type (n, %)			0. 524
TKA	85 (55. 2%)	133 (52. 0%)	
THA	69 (44. 8%)	123 (48. 0%)	
Operation time in TKA (min)	144. 42±59. 96	143. 91±46. 19	0. 236
Operation time in THA (min)	139. 96±64. 60	128. 48±58. 98	0. 213
VAS score for postoperative pain	3. 50±2. 13	1. 67±1. 02	＜0. 001***
Body temperature at the end of the surgery (℃)	35. 87±0. 73	36. 03±0. 94	0. 037*
CRBD (n, %)			＜0. 001***
Yes	119(77. 3%)	83 (32. 4%)	
No	35(22. 7%)	173(67. 6%)	
Preoperative fasting times (h)			
fasting times for solids	10. 19±1. 05	8. 76±0. 88	＜0. 001***
fasting times for fluids	4. 81±1. 14	2. 99±0. 92	＜0. 001***
Intraoperative blood loss (ml)	217. 26±30. 18	200. 32±27. 48	0. 224

464

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Severe Intraoperative hypotension (n, %)			0. 261
Yes	14 (9. 1%)	15 (5. 9%)	
No	140 (90. 9%)	241 (94. 1%)	
Postoperative nausea and vomiting (n, %)			0. 332
Yes	67 (43. 5%)	124 (48. 4%)	
No	87 (56. 5%)	132 (51. 6%)	
The duration in PACU (min)	32. 83±14. 07	31. 00±8. 57	0. 025*
Warm treatment (n, %)			0. 880
Yes	68 (44. 2%)	115 (44. 9%)	
No	86 (55. 8%)	141 (55. 1%)	
Laboratory testing			
HCO_3^- (mmol/L)	22. 3±1. 86	24. 7±1. 33	0. 291
$PaCO_2$ (mmHg)	38. 61±1. 42	39. 44±1. 58	0. 318
PaO_2 (mmHg)	89. 52±1. 74	90. 17±1. 55	0. 282
pH	7. 447±0. 32	7. 426±0. 41	0. 263
Hb levels (g/L)	16. 6±1. 93	17. 1±1. 85	0. 274

Notes: Patients' perioperative clinical information and agitation-related laboratory

test indicators were analysed using univariate analysis. Continuous data are presented as means ± standard deviations, while categorical data are presented as numbers and percentages. *P-value, differences between patients in the two groups. *P<0. 05, ***P<0. 001. TKA: total knee arthroplasty; THA: total hip arthroplasty; VAS: visual analogue scale; CRBD: catheter-related bladder discomfort; PACU: post-anaesthesia care unit.

Figure legends

Figure 1 Flow chart of study participants. In total, 421 patients met the inclusion and exclusion criteria. However, 11 patients were excluded from the study; six were transferred to the ICU postoperatively, and the surgical protocols of five were changed during the operation. Finally, the statistical analysis included 410 patients.

Figure 2 Risk factors for EA using metanalysis plot. The VAS score for postoperative pain (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), urinary catheter irritation (OR = 7.847; 95% CI: 4.001–15.392), fasting times for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting times for fluids (OR = 1.728; 95% CI: 1.263–2.365) were the independent risk factors.

Figure 3 Risk factors for EA using the ROC curve. Predictive values of risk factors were assessed using the ROC curve. The VAS score for postoperative pain (AUC = 0.769, 95% CI: 0.718–0.819, P < 0.001), fasting times for solids (AUC = 0.753, 95% CI: 0.699–0.807, P < 0.001) and fasting times for fluids (AUC = 0.768, 95% CI: 0.719–0.816, P < 0.001) demonstrated good predictive effects.

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

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In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3

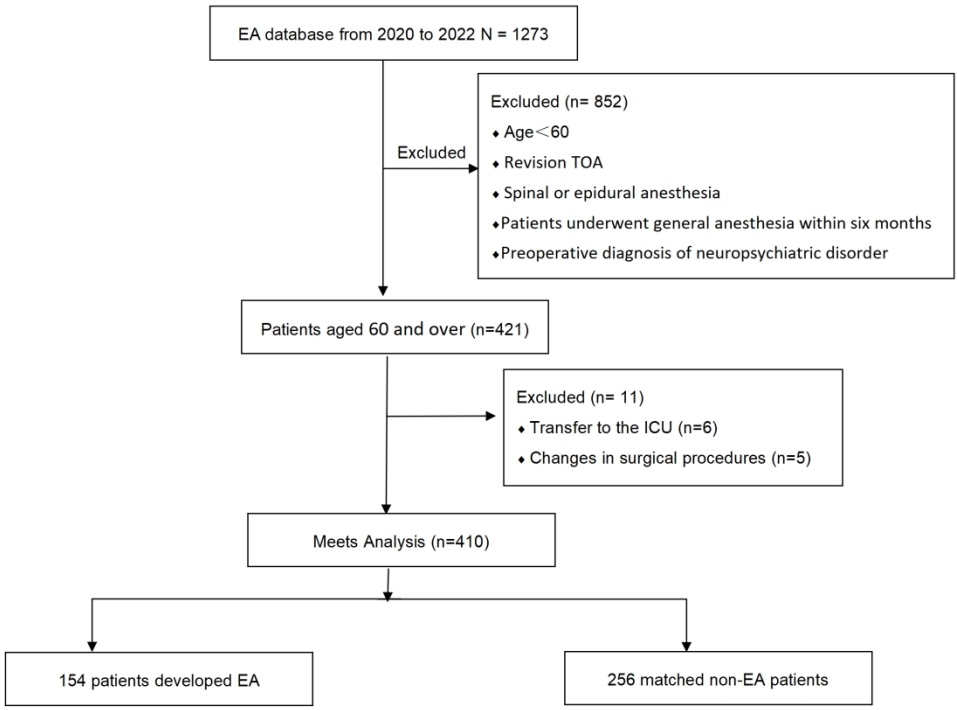
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	NA
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8
Bias	#9	Describe any efforts to address potential	8-9

		sources of bias	
Study size	#10	Explain how the study size was arrived at	9
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9-10
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9-10
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
Statistical methods	#12e	Describe any sensitivity analyses	9-10
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	11
Participants	#13b	Give reasons for non-participation at each stage	11
Participants	#13c	Consider use of a flow diagram	32

Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	11
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	11
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	11-13
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
Main results	#16b	Report category boundaries when continuous variables were categorized	NA
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	#18	Summarise key results with reference to study objectives	14

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	18-19
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	18
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

Figure 1 Flow chart of study participants.



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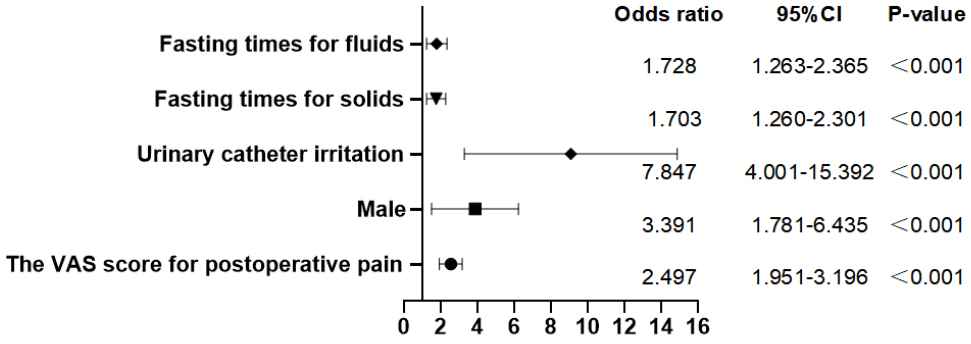

Figure 2 Risk factors of EA by metanalysis plot

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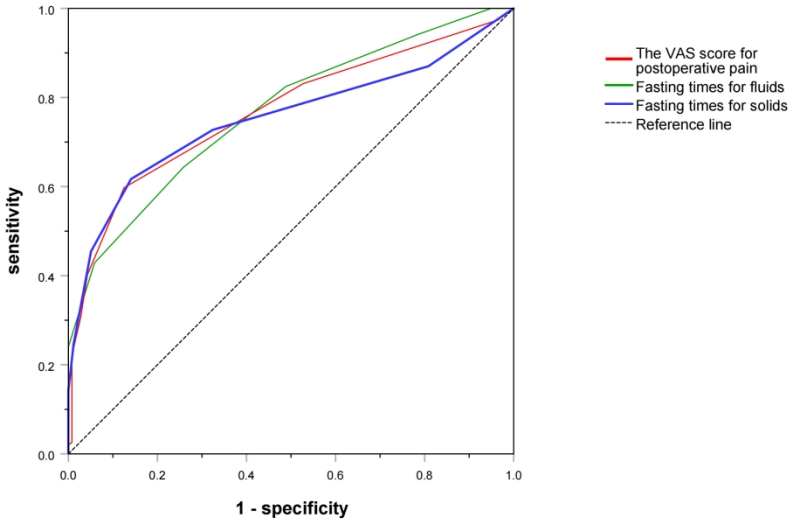

Figure 3 Risk factors of EA by the ROC curve

1178x667mm (57 x 57 DPI)

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Bias	#9	Describe any efforts to address potential sources of bias	8-9

Study size	#10	Explain how the study size was arrived at	9
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9-10
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9-10
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
Statistical methods	#12e	Describe any sensitivity analyses	9-10
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	11
Participants	#13b	Give reasons for non-participation at each stage	11
Participants	#13c	Consider use of a flow diagram	32
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and	11

		information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	11
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	11-13
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
Main results	#16b	Report category boundaries when continuous variables were categorized	NA
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	#18	Summarise key results with reference to study objectives	14
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or	18-19

		imprecision. Discuss both direction and magnitude of any potential bias.	
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	18
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

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Risk factors for emergence agitation during the awakening period in elderly patients after total joint arthroplasty: a retrospective cohort study

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Abstract

Objectives: This study aimed to explore the incidence and risk factors for emergence agitation (EA) in elderly patients who underwent total joint arthroplasty (TJA) under general anaesthesia, and to assess their predictive values.

Design: Single-centre retrospective cohort study.

Setting: A 1,600-bed general tertiary hospital in China.

Participants: This study enrolled 421 elderly patients scheduled for elective primary TJA under general anaesthesia.

Primary and Secondary Outcome Measures: EA was assessed using the Richmond Agitation Sedation Scale during the awakening period after surgery in the postanaesthesia care unit(PACU). Risk factors for EA were identified using univariate and multivariable logistic analyses. The receiver operating characteristic curve (ROC) was used to assess the predictive values of the risk factors for EA.

Results: The incidence of EA in elderly patients who underwent TJA was 37.6%. According to the multivariable logistic analysis, postoperative pain (95% confidence interval [CI]: 1.951–3.196), male sex (95% CI: 1.781–6.435), catheter-related bladder discomfort (CRBD) (95% CI: 4.001–15.392), and longer fasting times for solids (95% CI: 1.260–2.301) and fluids (95% CI: 1.263–2.365) were independent risk factors for EA. As shown by the ROC analysis, postoperative pain and fasting times for solids and fluids had good predictive values,with areas under the ROC curve (AUCs) equalling 0.769, 0.753 and 0.768,respectively.

Conclusions: EA is a common complication after TJA in elderly patients.Some risk factors, including postoperative pain, male sex, CRBD, and longer fasting times, can increase the incidence of EA. These risk factors may contribute to identifying high-risk patients, which facilitates the development of effective strategies to prevent and treat EA.

Keywords: Emergence agitation; Elderly patients; Risk factors; Total joint arthroplasty

Strengths and limitations:

- We performed a retrospective study of risk factors for EA in elderly patients after TJA.
- This work was a single-centre retrospective study, and the generalizability of the results is weak.
- Only patients with one category of arthritis were studied.

Introduction

Emergence agitation (EA), a common complication during the awakening period after general anaesthesia, refers to a temporary state of mental and motor excitement [1]. Clinical features of EA include disorientation, excitation, agitation, and combative behaviours [2,3]. The incidence of EA in adults varies from 4.7% to 74% [4]. EA can also increase the risk of wound bleeding or dehiscence, self-extubation, falling out of bed, and violent behaviour towards staff [5]. It may also prolong the patient's stay in the PACU and increase the demand for medical staff , resulting in higher medical costs [6]. Elderly individuals are one of the main population groups affected by EA [7]. Cardiovascular and cerebrovascular diseases are common in elderly individuals [8]. EA may have more serious adverse consequences for elderly patients[5]..

Total joint arthroplasty (TJA) is a successful treatment protocol for end-stage knee and hip OA [9]. Annually, more than 1 million people undergo TJA in the United States [10]. As the population ages, the demand for TJA surgery is expected to increase substantially in the coming years [11]. Most patients suffer from moderate-to-severe pain after TJA[12], which is one of the risk factors for EA in adult patients[3,13-14]. The incidence and risk factors for EA in adults vary depending on the surgery[15-17]; however, reports on the incidence and risk factors for EA after TJA are lacking.

In this study, we retrospectively collected the medical records of 421 elderly patients who underwent general anaesthesia for TJA. We aimed to determine the incidence and risk factors of postoperative EA in elderly patients, in order to assess the predictive values, and provide guidance for preventing and treating EA.

Materials and methods

Ethics statement

This study was approved by the Biomedical Research Ethics Committee of our hospital (approval no. 201812001), and the trial was registered in the Chinese Clinical Registry (ChiCTR, 1800020193). All methods were performed according to relevant guidelines and regulations. The study obtained consent to gather patients' medical record information through telephone follow-up.

Patients

We enrolled 421 patients who underwent TJA under general anaesthesia at our hospital from December 2019 to June 2021.Inclusion criteria included (1) preoperative OA diagnosis, (2) age ≥ 60 years, (3) American Society of Anaesthesiologists (ASA) physical status I–III, and (4) having undergone scheduled elective primary TJA under general anaesthesia. Patients with any of the following conditions were excluded: revision TJA, spinal or epidural anaesthesia, general anaesthesia within the past 6 months, and preoperative diagnosis of neuropsychiatric disorder.

Routine practice of perioperative management

Anaesthesia was induced with intravenous midazolam, etomidate, sufentanil, and rocuronium. Tracheal intubation was completed after 2 min. Ultrasound-guided

femoral nerve block (FNB) was performed in patients undergoing total knee replacement (TKA), while ultrasound-guided fascia iliac compartment block (FICB) was performed in patients undergoing total hip replacement (THA). All 20-ml (0.5%) ropivacaine solutions were infused into the nerve block. Urinary catheterisation was performed in all patients after inducing anaesthesia. Anaesthesia was maintained using intravenous remifentanil and propofol. Patients were transferred to the PACU after the operation. These patients were extubated in the PACU.

Speciality nurses assessed all patients in the PACU using a standardised protocol, including the visual analogue scale (VAS), Richmond Agitation Sedation Scale (RASS), and Steward recovery scores. VAS was used to assess postoperative pain, and intravenous flurbiprofen was administered as an analgesic rescue when the VAS score was > 4. EA was evaluated using the RASS [18], and Table 1 presents the score criteria. Patients with a RASS score > 1 were considered to have EA [18]. Dexmedetomidine was administered in cases of severe agitation (RASS = 4). Patients with ward recovery scores > 4 were transferred to the ward from the PACU.

Data collection

The following patient-related variables were recorded: (1) population data and medical history, including age, sex, body mass index (BMI), ASA classification, education level, history of heart disease, respiratory disease, hypertension, and diabetes; (2) perioperative clinical information, including operation type and times, body temperature after the surgery, VAS score, catheter-related bladder discomfort

(CRBD), preoperative fasting times, intraoperative blood loss, warm treatment, postoperative nausea and vomiting, duration in PACU, RASS score, and severe intraoperative hypotension (mean arterial pressure < 65 mmHg for at least 1 min); and (3) laboratory tests. Preoperative fasting time refers to the period from the last intake of liquids or solids to the beginning of anaesthesia induction.

Statistical analysis and sample size

The sample size was calculated using GPower software version 3.1 (Franz Faul, University of Kiel, Kiel, Germany). The effect size was set to 0.3, α level to 0.05, and 1-β to 0.85. A sample size of 100 patients was the optimal sample size needed to prove the difference between the two groups. Considering the easy acquisition of electronic medical records, we included patients who met the inclusion and exclusion criteria between December 2019 and June 2020.

Statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as the means ± standard deviations, and categorical data are presented as numbers and percentages. Independent risk factors were identified using univariate and multivariable logistic regression analyses. The measurement data were assessed for normal and nonnormal distributions. Two independent sample t tests were used to determine the differences between groups for continuous variables with a normal distribution. The nonparametric Mann–Whitney U test was used to compare differences between groups for continuous variables with nonnormal distributions. Chi-square tests were used to determine differences between

groups for categorical data. Variables with $P < 0.2$ were entered in multivariable logistic regression analysis. A positive stepwise method was used to adjust for multiple risk factors. Each variable was expressed as an odds ratio (OR) with a 95% confidence interval (CI). The predictive value of the risk factors for EA was assessed using the receiver operating characteristic (ROC) curve. The cut-off point was calculated based on the maximum Youden index value. Statistical significance was set at a P value < 0.05.

Patient and public involvement

None of the patients were involved in the design, data provision, analysis, or publication of the study.

Results

General information on the study population

In total, 421 patients met the inclusion and exclusion criteria. However, 11 patients were excluded from the study; six were transferred to the intensive care unit (ICU) postoperatively, and the surgical protocols of five patients were changed during the operation. Finally, the statistical analysis included 410 patients (Fig. 1). The incidence of EA was 37.6% (n = 154) in 410 patients. All patients (n = 410) were divided into two groups: EA and non-EA. Age, BMI, ASA classification, education level, and medical history did not significantly differ between the two groups (Table 2). The EA group had a significantly higher proportion of male patients than the non-EA group ($P < 0.05$).

Perioperative clinical information and laboratory tests

Univariate analysis demonstrated significant differences between the EA and non-EA groups in the VAS score for postoperative pain, body temperature after the surgery, CRBD, preoperative fasting times, and length of stay in the PACU.

Compared with the non-EA group, the VAS score was higher ($P < 0.05$), body temperature after the surgery was lower ($P < 0.05$), and the patient's length of stay in the PACU and preoperative fasting times were longer in the EA group ($P < 0.05$). Moreover, 77.3% (119/154) of patients in the EA group had CRBD, while 83 of 256 patients in the non-EA group experienced CRBD. This variable differed significantly

between the two groups ($P < 0.05$). Additionally, no significant differences were observed between the two groups regarding surgery type and times, intraoperative blood loss, intraoperative hypotension, warm treatment, and laboratory tests (Table 3).

Multivariable logistic regression analysis

Based on the univariate analysis, variables included in the multivariable logistic regression analysis included the VAS score for postoperative pain, male sex, body temperature after the surgery, length of stay in the PACU, preoperative fasting times, and CRBD.

The correlation between the VAS score for postoperative pain, male sex, preoperative fasting times, CRBD, and EA after TJA could be determined based on multivariable logistic analysis (Fig. 2). The VAS score for postoperative pain (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), CRBD (OR = 7.847; 95% CI: 4.001–15.392), fasting times for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting times for fluids (OR = 1.728; 95% CI: 1.263–2.365) were independent risk factors. However, we could not confirm the independence of variables, such as body temperature after the surgery and length of stay in the PACU, in the multivariable logistic analysis.

Results of ROC curves for risk factors

The predictive value analysed using the ROC curve is demonstrated in Fig. 3. The area under the ROC curve (AUC) for the VAS score was 0.769, with a cut-off

value of 4.0, sensitivity of 60%, and specificity of 87% (95% CI: 0.718–0.819, P < 0.001). The AUC of fasting times for solids was 0.753, with a cut-off value of 10.5, sensitivity of 62%, and specificity of 86% (95% CI: 0.699–0.807, P < 0.001). The AUC of fasting times for fluids was 0.768, with a cut-off value of 8.5, sensitivity of 64%, and specificity of 74% (95% CI: 0.719–0.816, P < 0.001).

Discussion

The results of this study indicated that EA was a common postoperative complication in patients who underwent general anaesthesia for TJA. Furthermore, this study identified four risk factors associated with with EA in elderly patients who underwent TJA, including postoperative pain, CRBD, male sex, and preoperative fasting times.

The incidence of EA was 37.6% in elderly patients who underwent TJA. To our knowledge, this report is the first on the incidence of EA in elderly patients who have undergone TJA. Previous research has shown that the incidence of EA varies widely. A prospective study demonstrated that 13.9% (158/1136) of adult patients had EA in the PACU [19]. Xi et al. [7] reported that the incidence of EA in elderly patients who underwent gastrointestinal surgery was 40%. Moreover, an extremely high proportion of patients, 90.5% (19/21), experienced EA because of the effects of succinylcholine [20]. These large differences may be attributed to the types of surgery, anaesthetic management, patient characteristics, and assessment methods.

Many scales are available to assess EA in adults, including the RASS, Ricker Sedation-Agitation Scale (RSAS), Aono's 4-point scale and so on. Unlike the excellent reliability and validity in assessing sedation and agitation in the ICU [18], the reliability and validity of the RASS in the PACU have not been validated; Nevertheless, the RASS is easy to use and administer and has discrete criteria [18]. Thus, we believe that RASS is a effective and efficient method of assessing EA in the PACU. Similarly, Makarem et al. [19] and Xi et al. [7] also chose the RASS to assess EA in the PACU.

Almost all researchers agree that postoperative pain is an independent risk factor for EA. Pain, an uncomfortable emotional experiences, can lead to some complex neurobehavioural behaviours, such as agitation [21]. Our study demonstrated that the VAS scores of patients in the EA group were higher than those in the non-EA group, and a postoperative pain VAS score ≥ 4 was the cut-off point for EA. Pain after TJA is common, and several studies have discovered that more than 50% of patients have suboptimal pain management afterTHA, and 75% of patients undergoing TKA complain of moderate-to-severe pain [12,22]. In this study, 72% (295/410) of patients complained of pain, and 5% (21/410) of patients experienced severe pain, comparable to the results of previous reports. Yu et al. [23] found that nearly half of patients had EA because of insufficient postoperative analgesia. Peripheral nerve blocks (PNBs) can provide excellent analgesia [24]. In our study, FNB was routinely used in patients undergoing TKA, and FICB was used for THA to improve postoperative analgesia. However, due to anatomic variations and individual characteristics, PNBs may not

absolutely eliminate pain in patients undergoing TJA, leading to some patients experiencing EA due to postoperative pain in the study. Moreover, sore throat and catheter-related pain should not be ignored because postoperative pain is not limited to wound pain. Based on these findings, we strongly suggest that multimodal analgesia should be performed to benefit patients, especially with preventive analgesia.

The placement of an indwelling catheter is a common clinical procedure in the perioperative period. The collected urine is used for urine measurements and blood volume evaluation. However, patients with indwelling catheters are prone to CRBD [25]. CRBD is characterised by discomfort confined to the suprapubic region, burning sensation, pain, and urinary urgency and frequency [26,27]. CRBD can occur in 47–90% of patients with a indwelling catheter [5] and CRBD can increase the incidence of EA and pain sensation after surgery [28]. A retrospective study reported that approximately 10% of patients experienced EA during urological surgery, possibly related to CRBD [16]. In our study, 28.0% (119 of 410) of patients experienced EA due to CRBD, and the higher incidence of EA may be due to the age of the recruited patients.This is because age ≥ 50 years was an independent predictor of CRBD [29]. Indwelling catheters as a risk factor for EA have been reported previously in the literature [30]. Early removal of indwelling catheters is helpful in decreasing EA associated with CRBD.

Regarding the effect of sex on EA, the results of the study are similar to those of reported in other literatures in which male sex was identified as an independent risk

factor for EA [29]. This observation could be explained by several factors. First, male patients were high-risk patients with CRBD [29]. Half of all men aged ≥ 50 years and over 80% of men aged ≥80 years have prostatic hyperplasia, which can easily cause discomfort and pain when the catheter tip contacts the bladder triangle on the pubis [31].Thus, male patients especially have difficulty tolerating the discomfort associated with catheters during the awakening period of anaesthesia. Furthermore, male patients have low postoperative pain tolerance, requiring more analgesics than female patients [32].

Preoperative fasting is one of the preoperative instructions for patients. whether preoperative fasting is a risk factor for EA has not been reported in previous studies.. Prolonged preoperative fasting can cause metabolic, physical, and psychological discomfort in patients, eventually leading to abnormal neurobehavioural changes, such as postoperative delirium (PD) [33]. However, EA was not analysed. In this study,the fasting times of the EA group were significantly longer than those of the non-EA group and exceeded conventional fasting times (no more than 8 hours for solids and no more than 6 hours for liquids before surgery)[34],furthermore,10.5 h (fasting times for solids) and 8.6 h (fasting times for fluids) are cut-off points for EA. Prolonged preoperative fasting times led to patient anxiety, and the degree of anxiety was related to the length of fasting time [34], While preoperative anxietyhas been reported as a risk factor for EA [16]. Due to the numerous patients and the lack of medical resources, patients may often experienced longer fasting times than they were

advised .To reduce the incidence of EA, effective preoperative education and scientific operation schedule lists should be developed.

This study had some limitations. Firstly, we only included elderly patients who had undergone intravenous anaesthesia. Future studies may utilize other methods and anaesthetics. Secondly, this was a single-centre study; therefore, the generalisability of the results was not fully verified. Future multi-centre studies must assess external validity. Lastly, this is a retrospective cohort study; some bias is unavoidable. Future prospective studies must be conducted for further research.

Conclusions

In short, this retrospective study showed that EA is a common complication in elderly patients after TJA .EA occurred in 37.6% of the elderly patients who underwent TJA. Postoperative pain, CRBD, male sex, and preoperative fasting times were independent predictors of EA.These risk factors can contribute to identifying high-risk patients to develop effective strategies to prevent and treat EA. Agitation has many causes [35]; therefore, the best clinical strategies should be multimodal.

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Tables

Table 1 Richmond agitation sedation scale

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement; fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awake with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Notes: Scores of 1 to 4 indicated different levels of agitation, 0 indicated calmness and alertness, and −1 to −5 indicated different levels of sedation.

466 **Table 2 Population data and medical history**

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Age	69. 84±6. 53	69. 39±6. 82	0. 238
Male (n, %)	91 (59. 1%)	71 (27. 7%)	＜0. 001***
BMI (Kg. m^{-2})	22. 75±4. 31	23. 17±2. 56	0. 253
ASA classification (n, %)			0. 221
Ⅰ	0	0	
Ⅱ	118 (76. 6%)	182 (71. 1%)	
Ⅲ	36 (23. 4%)	74 (28. 9%)	
Education (n, %)			0. 412
Illiteracy	42 (27. 3%)	55 (21. 5%)	
Primary school	45 (29. 2%)	93 (36. 3%)	
Secondary school	59 (38. 3%)	96 (37. 5%)	
University and above	8 (5. 2%)	12 (4. 7%)	
Medical history (n, %)			
Heart disease			0. 816
Yes	72 (46. 8%)	113 (44. 1%)	
No	82 (53. 2%)	143 (55. 9%)	

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Respiratory diseases			0. 760
Yes	80 (51. 9%)	129 (50. 4%)	
No	74 (48. 1%)	127 (49. 6%)	
Hypertension			0. 981
Yes	78 (50. 6%)	131 (51. 2%)	
No	76 (49. 4%)	125 (48. 8%)	
Diabetes			
Yes	71 (46. 1%)	119 (46. 5%)	0. 940
No	83 (53. 9%)	137 (53. 5%)	

Notes: Clinical information of patients were analysed using univariate analysis. Continuous data are presented as the means ± standard deviations, while categorical data are presented as numbers and percentages. *P-value, differences between patients in the two groups. *P<0. 05, ***P<0. 001. ASA: American Society of Anesthesiologists; BMI: body mass index.

477

478 **Table 3 Patients' perioperative clinical information and agitation-related**

479 **laboratory test indicators**

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Operation type (n, %)			0. 524
TKA	85 (55. 2%)	133 (52. 0%)	
THA	69 (44. 8%)	123 (48. 0%)	
Operation times in TKA (min)	144. 42±59. 96	143. 91±46. 19	0. 236
Operation times in THA (min)	139. 96±64. 60	128. 48±58. 98	0. 213
VAS score for postoperative pain	3. 50±2. 13	1. 67±1. 02	＜0. 001***
Body temperature at the end of the surgery (℃)	35. 87±0. 73	36. 03±0. 94	0. 037*
CRBD (n, %)			＜0. 001***
Yes	119(77. 3%)	83 (32. 4%)	
No	35(22. 7%)	173(67. 6%)	
Preoperative fasting times (h)			
fasting times for solids	10. 19±1. 05	8. 76±0. 88	＜0. 001***
fasting times for fluids	4. 81±1. 14	2. 99±0. 92	＜0. 001***
Intraoperative blood loss (ml)	217. 26±30. 18	200. 32±27. 48	0. 224

480

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Severe Intraoperative hypotension (n, %)			0. 261
Yes	14 (9. 1%)	15 (5. 9%)	
No	140 (90. 9%)	241 (94. 1%)	
Postoperative nausea and vomiting (n, %)			0. 332
Yes	67 (43. 5%)	124 (48. 4%)	
No	87 (56. 5%)	132 (51. 6%)	
The duration in PACU (min)	32. 83±14. 07	31. 00±8. 57	0. 025*
Warm treatment (n, %)			0. 880
Yes	68 (44. 2%)	115 (44. 9%)	
No	86 (55. 8%)	141 (55. 1%)	
Laboratory testing			
HCO_3^- (mmol/L)	22. 3±1. 86	24. 7±1. 33	0. 291
$PaCO_2$ (mmHg)	38. 61±1. 42	39. 44±1. 58	0. 318
PaO_2 (mmHg)	89. 52±1. 74	90. 17±1. 55	0. 282
pH	7. 447±0. 32	7. 426±0. 41	0. 263
Hb levels (g/L)	16. 6±1. 93	17. 1±1. 85	0. 274

Notes: Patients' perioperative clinical information and agitation-related laboratory test indicators were analysed using univariate analysis. Continuous data are presented as means ± standard deviations, while categorical data are presented as numbers and percentages. *P-value, differences between patients in the two groups. *P<0. 05, ***P<0. 001.

Figure legends

Figure 1 Flow chart of study participants. In total, 421 patients met the inclusion and exclusion criteria. However, 11 patients were excluded from the study; six were transferred to the ICU postoperatively, and the surgical protocols of five were changed during the operation. Finally, the statistical analysis included 410 patients.

Figure 2 Risk factors for EA using metanalysis plot. The VAS score for postoperative pain (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), urinary catheter irritation (OR = 7.847; 95% CI: 4.001–15.392), fasting times for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting times for fluids (OR = 1.728; 95% CI: 1.263–2.365) were the independent risk factors.

Figure 3 Risk factors for EA using the ROC curve. Predictive values of risk factors were assessed using the ROC curve. The VAS score for postoperative pain (AUC = 0.769, 95% CI: 0.718–0.819, P < 0.001), fasting times for solids (AUC = 0.753, 95% CI: 0.699–0.807, P < 0.001) and fasting times for fluids (AUC = 0.768, 95% CI: 0.719–0.816, P < 0.001) demonstrated good predictive effects.

Reporting checklist for cross sectional study.

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Methods			
Study design	#4	Present key elements of study design early in the paper	NA
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	7
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Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8

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Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
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Key results	#18	Summarise key results with reference to study objectives	13
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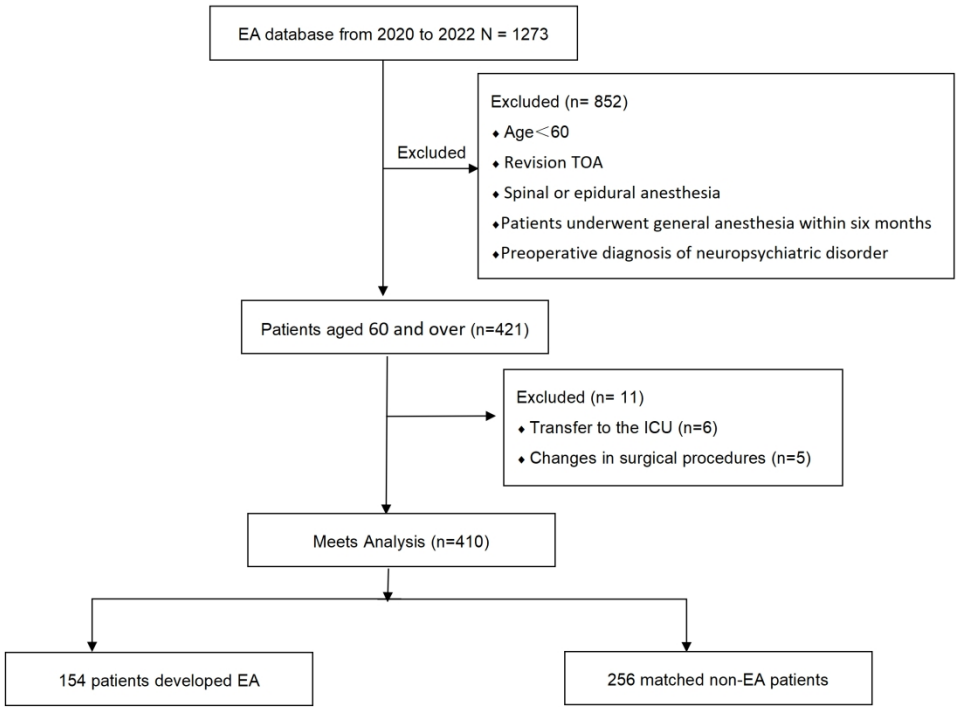

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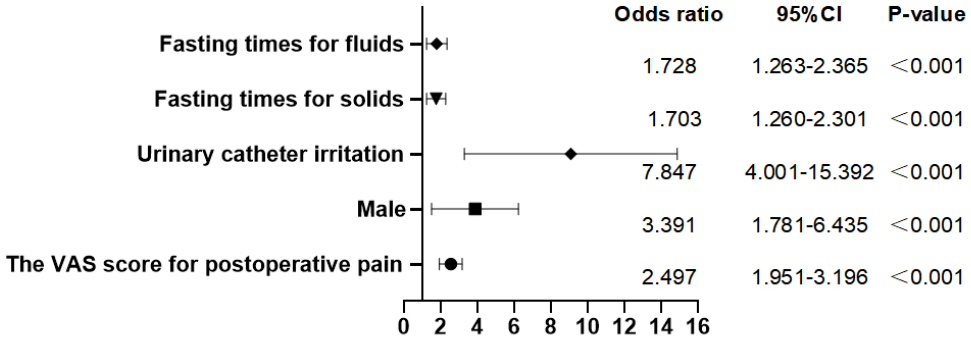

Figure 2 Risk factors of EA by metanalysis plot

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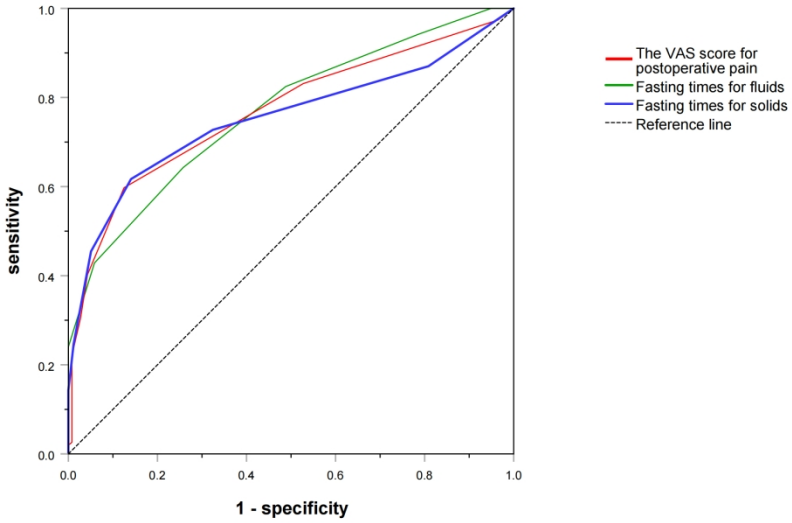

Figure 3 Risk factors of EA by the ROC curve

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Risk factors for emergence agitation during the awakening period in elderly patients after total joint arthroplasty: a retrospective cohort study

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Running title: EA risk factors after TJA

Keywords: Emergence agitation; Elderly patients; Risk factors; Total joint arthroplasty

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IRB number: 201812001 (Biomedical Research Ethics Committee of Honghui Hospital)

Clinical trial registration number: ChiCTR1800020193

Word count: 3151

Abstract

Objectives: This study aimed to explore the incidence and risk factors for emergence agitation (EA) in elderly patients who underwent total joint arthroplasty (TJA) under general anaesthesia, and to assess their predictive values.

Design: Single-centre retrospective cohort study.

Setting: A 1,600-bed general tertiary hospital in China.

Participants: This study enrolled 421 elderly patients scheduled for elective primary TJA under general anaesthesia.

Primary and Secondary Outcome Measures: EA was assessed using the Richmond Agitation Sedation Scale during the awakening period after surgery in the postanaesthesia care unit(PACU). Risk factors for EA were identified using univariate and multivariable logistic analyses. The receiver operating characteristic curve (ROC) was used to assess the predictive values of the risk factors for EA.

Results: The incidence of EA in elderly patients who underwent TJA was 37.6%. According to the multivariable logistic analysis, postoperative pain (95% confidence interval [CI]: 1.951–3.196), male sex (95% CI: 1.781–6.435), catheter-related bladder discomfort (CRBD) (95% CI: 4.001–15.392), and longer fasting times for solids (95% CI: 1.260–2.301) and fluids (95% CI: 1.263–2.365) were independent risk factors for EA. As shown by the ROC analysis, postoperative pain and fasting times for solids and fluids had good predictive values,with areas under the ROC curve (AUCs) equalling 0.769, 0.753 and 0.768,respectively.

Conclusions: EA is a common complication after TJA in elderly patients.Some risk factors, including postoperative pain, male sex, CRBD, and longer fasting times, can increase the incidence of EA. These risk factors may contribute to identifying high-risk patients, which facilitates the development of effective strategies to prevent and treat EA.

Keywords: Emergence agitation; Elderly patients; Risk factors; Total joint arthroplasty

Strengths and Limitations:

- .In this study, the medical records of 421 patients who underwent TJA were reviewed. Univariate and multivariable logistic analyses were used to identify the risk factors of EA, and the ROC was used to evaluate the predictive values of the risk factors.
- This work was a single-centre retrospective study, and the generalizability of the results is weak.
- Only patients with one category of arthritis were studied.

Introduction

Emergence agitation (EA), a common complication during the awakening period after general anaesthesia, refers to a temporary state of mental and motor excitement [1]. Clinical features of EA include disorientation, excitation, agitation, and combative behaviours [2,3]. The incidence of EA in adults varies from 4.7% to 74% [4]. EA can also increase the risk of wound bleeding or dehiscence, self-extubation, falling out of bed, and violent behaviour towards staff [5]. It may also prolong the patient's stay in the PACU and increase the demand for medical staff , resulting in higher medical costs [6]. Elderly individuals are one of the main population groups affected by EA [7]. Cardiovascular and cerebrovascular diseases are common in elderly individuals [8].Thus, EA may have more serious adverse consequences for elderly patients[5].

Total joint arthroplasty (TJA) is a successful treatment protocol for end-stage knee and hip osteoarthritis (OA) [9]. Annually, more than 1 million people undergo TJA in the United States [10]. As the population ages, the demand for TJA surgery is expected to increase substantially in the coming years [11]. Most patients suffer from moderate-to-severe pain after TJA[12], which is one of the risk factors for EA in adult patients[3,13-14]. The incidence and risk factors for EA in adults vary depending on the surgery[15-17]; however, reports on the incidence and risk factors for EA after TJA are lacking.

In this study, we retrospectively collected the medical records of 421 elderly patients who underwent general anaesthesia for TJA. We aimed to determine the incidence and risk factors of postoperative EA in elderly patients, to assess the predictive values, and provide guidance for preventing and treating EA.

Materials and methods

Ethics statement

This study was approved by the Biomedical Research Ethics Committee of our hospital (approval no. 201812001), and the trial was registered in the Chinese Clinical Registry (ChiCTR, 1800020193). All methods were performed according to relevant guidelines and regulations. The study obtained consent to gather patients' medical record information through telephone follow-up.

Patients

We enrolled 421 patients who underwent TJA under general anaesthesia at our hospital from December 2019 to June 2021.Inclusion criteria included (1) preoperative OA diagnosis, (2) age ≥ 60 years, (3) American Society of Anaesthesiologists (ASA) physical status I–III, and (4) having undergone scheduled elective primary TJA under general anaesthesia. Patients with any of the following conditions were excluded: revision TJA, spinal or epidural anaesthesia, general anaesthesia within the past 6 months, and preoperative diagnosis of neuropsychiatric disorder.

Routine practice of perioperative management

Anaesthesia was induced with intravenous midazolam, etomidate, sufentanil, and rocuronium. Tracheal intubation was completed after 2 min. Ultrasound-guided

femoral nerve block (FNB) was performed in patients undergoing total knee replacement (TKA), while ultrasound-guided fascia iliac compartment block (FICB) was performed in patients undergoing total hip replacement (THA). All 20-ml (0.5%) ropivacaine solutions were infused into the nerve block. Urinary catheterisation was performed in all patients after inducing anaesthesia. Anaesthesia was maintained using intravenous remifentanil and propofol. Patients were transferred to the PACU after the operation. These patients were extubated in the PACU.

Speciality nurses assessed all patients in the PACU using a standardised protocol, including the visual analogue scale (VAS), Richmond Agitation Sedation Scale (RASS), and Steward recovery scores. VAS was used to assess postoperative pain, and intravenous flurbiprofen was administered as an analgesic rescue when the VAS score was > 4. EA was evaluated using the RASS [18], and Table 1 presents the score criteria. Patients with a RASS score > 1 were considered to have EA [18]. Dexmedetomidine was administered in cases of severe agitation (RASS = 4). Patients with ward recovery scores > 4 were transferred to the ward from the PACU.

Data collection

The following patient-related variables were recorded: (1) population data and medical history, including age, sex, body mass index (BMI), ASA classification, education level, history of heart disease, respiratory disease, hypertension, and diabetes; (2) perioperative clinical information, including operation type and times, body temperature after the surgery, VAS score, catheter-related bladder discomfort

(CRBD), preoperative fasting times, intraoperative blood loss, warm treatment, postoperative nausea and vomiting, duration in PACU, RASS score, and severe intraoperative hypotension (mean arterial pressure < 65 mmHg for at least 1 min); and (3) laboratory tests. Preoperative fasting time refers to the period from the last intake of liquids or solids to the beginning of anaesthesia induction.

Statistical analysis and sample size

The sample size was calculated using GPower software version 3.1 (Franz Faul, University of Kiel, Kiel, Germany). The effect size was set to 0.3, α level to 0.05, and 1-β to 0.85. A sample size of 100 patients was the optimal sample size needed to prove the difference between the two groups. Considering the easy acquisition of electronic medical records, we included patients who met the inclusion and exclusion criteria between December 2019 and June 2020.

Statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). Continuous data were presented as the means ± standard deviations, and categorical data were presented as numbers and percentages. Independent risk factors were identified using univariate and multivariable logistic regression analyses. The measurement data were assessed for normal and nonnormal distributions. Two independent sample t tests were used to determine the differences between groups for continuous variables with a normal distribution. The nonparametric Mann–Whitney U test was used to compare differences between groups for continuous variables with nonnormal distributions. Chi-square tests were

used to determine differences between groups for categorical data. Variables with P < 0.2 were entered in multivariable logistic regression analysis. A positive stepwise method was used to adjust for multiple risk factors. Each variable was expressed as an odds ratio (OR) with a 95% confidence interval (CI). The predictive value of the risk factors for EA was assessed using the receiver operating characteristic (ROC) curve. The cut-off point was calculated based on the maximum Youden index value. Statistical significance was set at a P value < 0.05.

Patient and public involvement

None of the patients were involved in the design, data provision, analysis, or publication of the study.

Results

General information on the study population

In total, 421 patients met the inclusion and exclusion criteria. However, 11 patients were excluded from the study; six were transferred to the intensive care unit (ICU) postoperatively, and the surgical protocols of five patients were changed during the operation. Finally, the statistical analysis included 410 patients (Fig. 1). The incidence of EA was 37.6% (n = 154) in 410 patients. All patients (n = 410) were divided into two groups: EA and non-EA. Age, BMI, ASA classification, education level, and medical history did not significantly differ between the two groups (Table 2). The EA group had a significantly higher proportion of male patients than the non-EA group ($P < 0.05$).

Perioperative clinical information and laboratory tests

Univariate analysis demonstrated significant differences between the EA and non-EA groups in the VAS score for postoperative pain, body temperature after the surgery, CRBD, preoperative fasting times, and length of stay in the PACU.

Compared with the non-EA group, the VAS score was higher ($P < 0.05$), body temperature after the surgery was lower ($P < 0.05$), and the patient's length of stay in the PACU and preoperative fasting times were longer in the EA group ($P < 0.05$). Moreover, 77.3% (119/154) of patients in the EA group had CRBD, while 32.4% (83/256) of patients in the non-EA group experienced CRBD. This variable differed

significantly between the two groups ($P < 0.05$). Additionally, no significant differences were observed between the two groups regarding surgery type and times, intraoperative blood loss, intraoperative hypotension, warm treatment, and laboratory tests (Table 3).

Multivariable logistic regression analysis

Based on the univariate analysis, variables included in the multivariable logistic regression analysis included the VAS score for postoperative pain, male sex, body temperature after the surgery, length of stay in the PACU, preoperative fasting times, and CRBD.

The correlation between the VAS score for postoperative pain, male sex, preoperative fasting times, CRBD, and EA after TJA could be determined based on multivariable logistic analysis (Fig. 2). The VAS score for postoperative pain (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), CRBD (OR = 7.847; 95% CI: 4.001–15.392), fasting times for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting times for fluids (OR = 1.728; 95% CI: 1.263–2.365) were independent risk factors. However, we could not confirm the independence of variables, such as body temperature after the surgery and length of stay in the PACU, in the multivariable logistic analysis.

Results of ROC curves for risk factors

The predictive value analysed using the ROC curve is demonstrated in Fig. 3. The area under the ROC curve (AUC) for the VAS score was 0.769, with a cut-off value of 4.0, sensitivity of 60%, and specificity of 87% (95% CI: 0.718–0.819, P < 0.001). The AUC of fasting times for solids was 0.753, with a cut-off value of 10.5, sensitivity of 62%, and specificity of 86% (95% CI: 0.699–0.807, P < 0.001). The AUC of fasting times for fluids was 0.768, with a cut-off value of 8.5, sensitivity of 64%, and specificity of 74% (95% CI: 0.719–0.816, P < 0.001).

Discussion

The results of this study indicated that EA was a common postoperative complication in patients who underwent general anaesthesia for TJA. Furthermore, this study identified four risk factors associated with with EA in elderly patients who underwent TJA, including postoperative pain, CRBD, male sex, and preoperative fasting times.

The incidence of EA was 37.6% in elderly patients who underwent TJA. To our knowledge, this report is the first on the incidence of EA in elderly patients who have undergone TJA. Previous research has shown that the incidence of EA varies widely. A prospective study demonstrated that 13.9% (158/1136) of adult patients had EA in the PACU [19]. Xi et al. [7] reported that the incidence of EA in elderly patients who underwent gastrointestinal surgery was 40%. Moreover, an extremely high proportion of patients, 90.5% (19/21), experienced EA because of the effects of succinylcholine

[20]. These large differences may be attributed to the types of surgery, anaesthetic management, patient characteristics, and assessment methods.

Many scales are available to assess EA in adults, including the RASS, Ricker Sedation-Agitation Scale (RSAS), Aono's 4-point scale and so on. Unlike the excellent reliability and validity in assessing sedation and agitation in the ICU [18], the reliability and validity of the RASS in the PACU have not been validated; Nevertheless, the RASS is easy to use and administer and has discrete criteria [18]. Thus, we believe that RASS is a effective and efficient method of assessing EA in the PACU. Similarly, Makarem et al. [19] and Xi et al. [7] also chose the RASS to assess EA in the PACU.

Almost all researchers agree that postoperative pain is an independent risk factor for EA. Pain, an uncomfortable emotional experiences, can lead to some complex neurobehavioural effects, such as agitation [21]. Our study demonstrated that the VAS scores of patients in the EA group were higher than those in the non-EA group, and a postoperative pain VAS score ≥ 4 was the cut-off point for EA. Pain after TJA is common, and several studies have discovered that more than 50% of patients have suboptimal pain management afterTHA, and 75% of patients undergoing TKA complain of moderate-to-severe pain [12,22]. In this study, 72% (295/410) of patients complained of pain, and 5% (21/410) of patients experienced severe pain, comparable to the results of previous reports. Yu et al. [23] found that nearly half of patients had EA because of insufficient postoperative analgesia. Peripheral nerve blocks (PNBs) can provide excellent analgesia [24]. In our study, FNB was routinely used in patients

undergoing TKA, and FICB was used for THA to improve postoperative analgesia. However, due to anatomic variations and individual characteristics, PNBs may not absolutely eliminate pain in patients undergoing TJA, leading to some patients experiencing EA due to postoperative pain in the study. Moreover, sore throat and catheter-related pain should not be ignored because postoperative pain is not limited to wound pain. Based on these findings, we strongly suggest that multimodal analgesia should be performed to benefit patients, especially with preventive analgesia.

The placement of an indwelling catheter is a common clinical procedure in the perioperative period. The collected urine is used for urine measurements and blood volume evaluation. However, patients with indwelling catheters are prone to CRBD [25]. CRBD is characterised by discomfort confined to the suprapubic region, burning sensation, pain, and urinary urgency and frequency [26,27]. CRBD can occur in 47–90% of patients with an indwelling catheter [5] and CRBD can increase the incidence of EA and pain sensation after surgery [28]. A retrospective study reported that approximately 10% of patients experienced EA during urological surgery, possibly related to CRBD [16]. In our study, 28.0% (119 of 410) of patients experienced EA due to CRBD, and the higher incidence of EA may be due to the age of the recruited patients.This is because age ≥ 50 years was an independent predictor of CRBD [29]. Indwelling catheters as a risk factor for EA have been reported previously in the literature [30]. Early removal of indwelling catheters is helpful in decreasing EA associated with CRBD.

Regarding the effect of sex on EA, the results of the study are similar to those of reported in other literatures in which male sex was identified as an independent risk factor for EA [29]. This observation could be explained by several factors. First, male patients were high-risk patients with CRBD [29]. Half of all men aged ≥ 50 years and over 80% of men aged ≥80 years have prostatic hyperplasia, which can easily cause discomfort and pain when the catheter tip contacts the bladder triangle on the pubis [31].Thus, male patients especially have difficulty tolerating the discomfort associated with catheters during the awakening period of anaesthesia. Furthermore, male patients have low postoperative pain tolerance, requiring more analgesics than female patients [32].

Preoperative fasting is one of the preoperative instructions for patients. Whether preoperative fasting is a risk factor for EA has not been reported in previous studies.. Prolonged preoperative fasting can cause metabolic, physical, and psychological discomfort in patients, eventually leading to abnormal neurobehavioural changes, such as postoperative delirium (PD) [33]. However, EA was not analysed. In this study,the fasting times of the EA group were significantly longer than those of the non-EA group and exceeded conventional fasting times (no more than 8 hours for solids and no more than 6 hours for liquids before surgery) [34]. Furthermore,10.5 h (fasting times for solids) and 8.6 h (fasting times for fluids) are cut-off points for EA. Prolonged preoperative fasting times led to patient anxiety, and the degree of anxiety was related to the length of fasting time [34], While preoperative anxietyhas been reported as a risk factor for EA [16]. Due to the numerous patients and the lack of

medical resources, patients may often experienced longer fasting times than they were advised .To reduce the incidence of EA, effective preoperative education and scientific operation schedule lists should be developed.

This study had some limitations. Firstly, we only included elderly patients who had undergone intravenous anaesthesia. Future studies may utilize other methods and anaesthetics. Secondly, this was a single-centre study; therefore, the generalisability of the results was not fully verified. Future multi-centre studies must assess external validity. Lastly, this is a retrospective cohort study; some bias is unavoidable. Future prospective cohort studies should evaluate and validate the risk factors for EA identified by our study.

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Conclusions

In short, this retrospective study showed that EA is a common complication in elderly patients after TJA .EA occurred in 37.6% of the elderly patients who underwent TJA. Postoperative pain, CRBD, male sex, and preoperative fasting times were independent predictors of EA.These risk factors may contribute to identifying high-risk patients to develop effective strategies to prevent and treat EA. Agitation has many causes [35]; therefore, the optimal clinical strategies should be multimodal.

Contributorship statements: Zhenguo Luo and Jianhong Hao have made substantial contributions to the conception or design of the manuscript. Naigeng Wang wrote this

manuscript and made some changes after review. Furthermore, he worked with Jing Du and Jie Zhang to acquire, analyse, and interpret the data. All authors have participated in drafting the manuscript, and Zhenguo Luo revised it critically. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Competing interest: No potential conflict of interest relevant to this article was reported.

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Data sharing statement ： No additional data are available.

Ethics statements ： This study was approved by the Biomedical Research Ethics Committee of our hospital (approval no. 201812001).The study obtained consent to gather patients' medical record information through telephone follow-up.

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Tables

Table 1 Richmond agitation sedation scale

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement; fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awake with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Notes: Scores of 1 to 4 indicated different levels of agitation, 0 indicated calmness and alertness, and −1 to −5 indicated different levels of sedation.

471 **Table 2 Population data and medical history**

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Age	69. 84±6. 53	69. 39±6. 82	0. 238
Male (n, %)	91 (59. 1%)	71 (27. 7%)	＜0. 001***
BMI (Kg. m^{-2})	22. 75±4. 31	23. 17±2. 56	0. 253
ASA classification (n, %)			0. 221
Ⅰ	0	0	
Ⅱ	118 (76. 6%)	182 (71. 1%)	
Ⅲ	36 (23. 4%)	74 (28. 9%)	
Education (n, %)			0. 412
Illiteracy	42 (27. 3%)	55 (21. 5%)	
Primary school	45 (29. 2%)	93 (36. 3%)	
Secondary school	59 (38. 3%)	96 (37. 5%)	
University and above	8 (5. 2%)	12 (4. 7%)	
Medical history (n, %)			
Heart disease			0. 816
Yes	72 (46. 8%)	113 (44. 1%)	
No	82 (53. 2%)	143 (55. 9%)	

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Respiratory diseases			0. 760
Yes	80 (51. 9%)	129 (50. 4%)	
No	74 (48. 1%)	127 (49. 6%)	
Hypertension			0. 981
Yes	78 (50. 6%)	131 (51. 2%)	
No	76 (49. 4%)	125 (48. 8%)	
Diabetes			
Yes	71 (46. 1%)	119 (46. 5%)	0. 940
No	83 (53. 9%)	137 (53. 5%)	

Notes: Clinical information of patients were analysed using univariate analysis. Continuous data are presented as the means ± standard deviations, while categorical data are presented as numbers and percentages. *P-value, differences between patients in the two groups. *P<0. 05, ***P<0. 001. ASA: American Society of Anesthesiologists; BMI: body mass index.

482

483 **Table 3 Patients' perioperative clinical information and agitation-related**

484 **laboratory test indicators**

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Operation type (n, %)			0. 524
TKA	85 (55. 2%)	133 (52. 0%)	
THA	69 (44. 8%)	123 (48. 0%)	
Operation times in TKA (min)	144. 42±59. 96	143. 91±46. 19	0. 236
Operation times in THA (min)	139. 96±64. 60	128. 48±58. 98	0. 213
VAS score for postoperative pain	3. 50±2. 13	1. 67±1. 02	＜0. 001***
Body temperature at the end of the surgery (℃)	35. 87±0. 73	36. 03±0. 94	0. 037*
CRBD (n, %)			＜0. 001***
Yes	119(77. 3%)	83 (32. 4%)	
No	35(22. 7%)	173(67. 6%)	
Preoperative fasting times (h)			
fasting times for solids	10. 19±1. 05	8. 76±0. 88	＜0. 001***
fasting times for fluids	4. 81±1. 14	2. 99±0. 92	＜0. 001***
Intraoperative blood loss (ml)	217. 26±30. 18	200. 32±27. 48	0. 224

485

Variables	**Agitation Groups (n=154)**	**Non-agitation Groups (n=256)**	**P-value**
Severe Intraoperative hypotension (n, %)			0. 261
Yes	14 (9. 1%)	15 (5. 9%)	
No	140 (90. 9%)	241 (94. 1%)	
Postoperative nausea and vomiting (n, %)			0. 332
Yes	67 (43. 5%)	124 (48. 4%)	
No	87 (56. 5%)	132 (51. 6%)	
The duration in PACU (min)	32. 83±14. 07	31. 00±8. 57	0. 025*
Warm treatment (n, %)			0. 880
Yes	68 (44. 2%)	115 (44. 9%)	
No	86 (55. 8%)	141 (55. 1%)	
Laboratory testing			
HCO_3^- (mmol/L)	22. 3±1. 86	24. 7±1. 33	0. 291
$PaCO_2$ (mmHg)	38. 61±1. 42	39. 44±1. 58	0. 318
PaO_2 (mmHg)	89. 52±1. 74	90. 17±1. 55	0. 282
pH	7. 447±0. 32	7. 426±0. 41	0. 263
Hb levels (g/L)	16. 6±1. 93	17. 1±1. 85	0. 274

Notes: Patients' perioperative clinical information and agitation-related laboratory test indicators were analysed using univariate analysis. Continuous data are presented as means ± standard deviations, while categorical data are presented as numbers and percentages. *P-value, differences between patients in the two groups. *P<0. 05, ***P<0. 001.

Figure legends

Figure 1 Flow chart of study participants. In total, 421 patients met the inclusion and exclusion criteria. However, 11 patients were excluded from the study; six were transferred to the ICU postoperatively, and the surgical protocols of five were changed during the operation. Finally, the statistical analysis included 410 patients.

Figure 2 Risk factors for EA using metanalysis plot. The VAS score for postoperative pain (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), urinary catheter irritation (OR = 7.847; 95% CI: 4.001–15.392), fasting times for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting times for fluids (OR = 1.728; 95% CI: 1.263–2.365) were the independent risk factors.

Figure 3 Risk factors for EA using the ROC curve. Predictive values of risk factors were assessed using the ROC curve. The VAS score for postoperative pain (AUC = 0.769, 95% CI: 0.718–0.819, P < 0.001), fasting times for solids (AUC = 0.753, 95% CI: 0.699–0.807, P < 0.001) and fasting times for fluids (AUC = 0.768, 95% CI: 0.719–0.816, P < 0.001) demonstrated good predictive effects.

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and	3

		what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	NA
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8

Bias	#9	Describe any efforts to address potential sources of bias	8-9
Study size	#10	Explain how the study size was arrived at	9
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9-10
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9-10
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
Statistical methods	#12e	Describe any sensitivity analyses	9-10
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	11
Participants	#13b	Give reasons for non-participation at each stage	11

Participants	#13c	Consider use of a flow diagram	32
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	11
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	11
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	11-13
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
Main results	#16b	Report category boundaries when continuous variables were categorized	NA
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			

Key results	#18	Summarise key results with reference to study objectives	13
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	17
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	17
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

Figure 1 Flow chart of study participants.

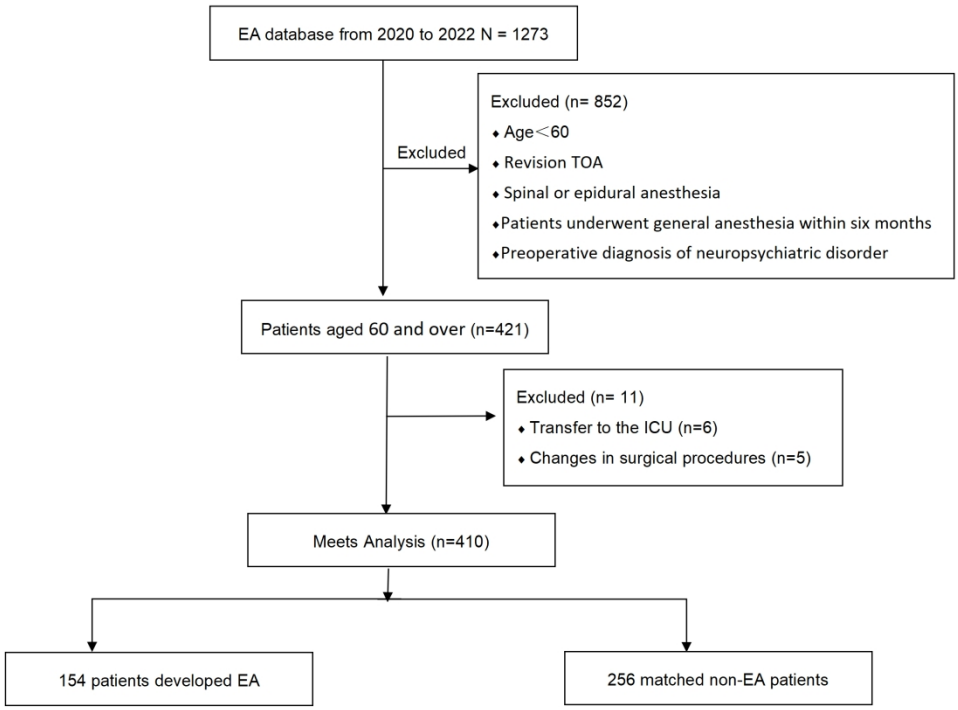

Figure 1 Flow chart of study participants

419x390mm (144 x 144 DPI)

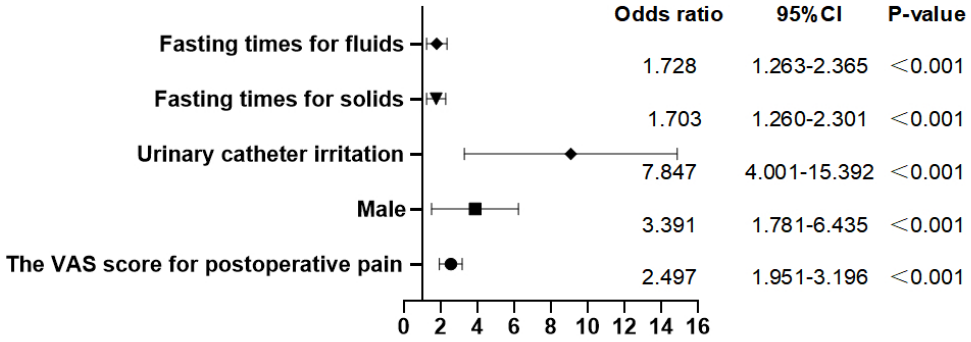

Figure 2 Risk factors of EA by metanalysis plot

436x179mm (57 x 57 DPI)

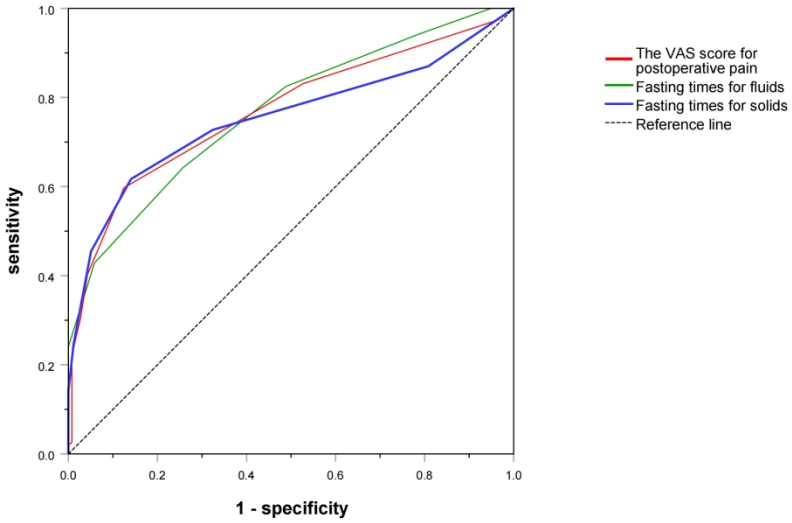

Figure 3 Risk factors of EA by the ROC curve

1178x667mm (57 x 57 DPI)

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and	3

		what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	NA
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8
Bias	#9	Describe any efforts to address potential	8-9

		sources of bias	
Study size	#10	Explain how the study size was arrived at	9
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9-10
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9-10
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
Statistical methods	#12e	Describe any sensitivity analyses	9-10
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	11
Participants	#13b	Give reasons for non-participation at each stage	11
Participants	#13c	Consider use of a flow diagram	32
Descriptive data	#14a	Give characteristics of study participants	11

		(eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	11
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	11-13
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
Main results	#16b	Report category boundaries when continuous variables were categorized	NA
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	#18	Summarise key results with reference to study objectives	13
Limitations	#19	Discuss limitations of the study, taking	17

		into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	17
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17