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

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14 **Running title:** EA risk factors after TJA

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

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22 **IRB number:** 201812001 (Biomedical Research Ethics Committee of Honghui

23 Hospital)

24 **Clinical trial registration number:** ChiCTR1800020193

25 **Word count:** 2971

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43 Abstract

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

47 **Design:** Single-centre retrospective observational study.

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

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

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

56 **Results:** The incidence of EA in elderly patients who underwent TJA was 37.6%.
57 According to the multivariate logistic analysis, patients' visual analogue scale (VAS)
58 score (95% confidence interval [CI]: 1.951–3.196), male sex (95% CI: 1.781–6.435),
59 catheter-related bladder discomfort (CRBD) (95% CI: 4.001–15.392), fasting time for
60 solids (95% CI: 1.260–2.301), and fasting time for fluids (95% CI: 1.263–2.365) were
61 independent risk factors for EA. As shown by the ROC analysis, patients' VAS score
62 (95% CI: 0.718–0.819), CRBD (95% CI: 0.673–0.775), fasting time for solids (95%
63 CI: 0.699–0.807), and fasting time for fluids (95% CI: 0.719–0.816) showed a good
64 predictive value.

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4 65 **Conclusions:** EA was a common complication in elderly patients after TJA. The

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7 66 reduction of risk factors contributes to prevention and treatment of EA.

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9 67 **Keywords:** Emergence agitation; Elderly patients; Risk factors; Total joint

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14 69 **Trial Registration:** ChiCTR1800020193

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72 Introduction

73 Emergence agitation (EA) is a common complication of the awakening period
74 after general anaesthesia and refers to a temporary state of mental and motor
75 excitement [1]. There are several clinical features of EA, including disorientation,
76 excitation, agitation, and combative behaviours [2,3]. EA can also lead to an increased
77 risk of wound bleeding or splitting, self-extubation, falling out of bed, and violence
78 against staff [4]. It may also increase the patient's stay in the PACU and demand on
79 medical staff [3], and simultaneously, more medical costs are incurred. The incidence
80 of EA in paediatric patients ranges from 10% to 80% [5]. EA has many risk factors in
81 paediatric patients, including pain, strange recovery surroundings, anaesthesia
82 techniques, anaesthetics, patient features, and operative factors [6,7]. Lehmann et al.
83 [8] reported that propofol was the first choice for preventing and treating EA in
84 paediatric patients. In addition, α 2-antagonists (clonidine and dexmedetomidine) have
85 been shown to reduce the occurrence of EA in paediatric patients significantly
86 [1,9,10].

87 Previous studies indicated that EA is common in children [11,12]; however,
88 more recent studies reported that elderly patients are also prone to EA after surgery
89 [13]. Currently, numerous studies have focused on EA in children, and few have
90 examined elderly patients. EA in elderly adults may cause more serious consequences
91 owing to decreased physiological functions and various complications; therefore, it is
92 necessary to pay more attention to EA in elderly patients.

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4 93 The incidence of EA varies according to the type of surgery performed. Card et al.
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6 94 [14] reported that the incidence of EA in adults after non-cardiac surgery was 19%.
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9 95 The incidence of EA in adult patients undergoing nasal and thoracic surgery varies
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11 96 from 2.5% to 22% [3,15]. In a retrospective observational study, Yu et al. [16] found
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14 97 that the incidence of EA in adults was 21.3% and that EA was prone to occur after
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16 98 oral cavity and otolaryngological surgery. Another single-centre prospective study
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19 99 showed that otorhinolaryngology was an independent risk factor for EA in paediatric
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22 100 patients [17]. Osteoarthritis (OA) is the most frequent type of arthritis and affects 1 in
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25 101 3 older people [18]. With the emergence of an ageing society, the incidence of OA is
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27 102 increasing annually. Presently, more than 240 million people worldwide have OA
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30 103 [19]. End-stage OA can be treated with total joint arthroplasty (TJA). Annually, in the
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33 104 United States, more than 1 million people undergo TJA, > 90% due to OA [19]. To
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35 105 date, the mechanisms of EA are unclear, and the risk factors for EA in elderly patients
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38 106 who have undergone TJA are also unknown. Therefore, it is important to explore and
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41 107 avoid the risk factors for EA. Elderly patients with EA will benefit greatly from
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43 108 identification of the risk factors and development of appropriate strategies.

45 109 In this study, we retrospectively collected the medical records of 421 elderly
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48 110 patients who underwent general anaesthesia for TJA and investigated the risk factors
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51 111 for EA. These results provided insights for further treatment.

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113 **Materials and methods**

114 *Ethics statement*

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

119 *Patients*

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

128 *Routine practice of perioperative management*

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

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4 132 and ultrasound-guided fascia iliac compartment block was performed in patients
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6 133 undergoing total hip replacement. All 20-ml (0.5%) ropivacaine solutions were
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9 134 infused into the nerve block. After induction of anaesthesia, urinary catheterisation
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12 135 was performed in all patients. Anaesthesia was maintained using intravenous
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14 136 remifentanyl and propofol. After the operation, patients were transferred to the PACU.

17 137 All patients were assessed by specialty nurses in the PACU using a standardised
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19 138 protocol, including the visual analogue scale (VAS), RASS, and Steward recovery
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22 139 scores. VAS was used for pain assessment, and flurbiprofen was administered
23
24 140 intravenously as an analgesic rescue if the VAS score was ≥ 5 . EA was evaluated
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27 141 using the RASS [13]; the score criteria are presented in Table 1. Patients with RASS \geq
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30 142 1 were considered to have EA. For severe agitation (RASS = 4), dexmedetomidine
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33 143 was administered. Patients with ward recovery scores > 4 were transferred to the ward
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35 144 from the PACU.

37 145 ***Data collection***

40 146 The following patient-related variables were recorded: (1) population data and
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43 147 medical history, including age, sex, body mass index (BMI), ASA classification,
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45 148 education level, history of heart disease, respiratory disease, hypertension, and
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48 149 diabetes; (2) perioperative clinical information, including operation type and time,
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51 150 body temperature at the end of the surgery, VAS score, catheter-related bladder
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53 151 discomfort (CRBD), preoperative fasting time, intraoperative blood loss, warm
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56 152 treatment, postoperative nausea and vomiting, duration in PACU, RASS, and severe
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4 153 intraoperative hypotension (mean arterial pressure < 65 mmHg for at least 1 min); and
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7 154 (3) laboratory tests.

9 155 ***Statistical analysis and sample size***

11 156 The sample size was calculated using GPower software version 3.1 (Franz Faul,
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14 157 University of Kiel, Kiel, Germany). The effect size was set to 0.3, α level to 0.05, and
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17 158 1- β to 0.85. A sample size of 100 patients was the optimal sample size required to
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20 159 prove the difference between the 2 groups. Considering that electronic medical
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23 160 records were easy to acquire, we included patients according to the inclusion and
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25 161 exclusion criteria between December 2019 and June 2020.

27 162 Statistical analysis was performed using SPSS version 26.0 (SPSS Inc.,
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30 163 Chicago, IL, USA). Continuous data are presented as the mean \pm standard deviation,
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33 164 and categorical data are presented as numbers and percentages. Independent risk
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36 165 factors were identified using univariate and multivariate logistic regression analyses.
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38 166 The measurement data were assessed for normal and non-normal distribution. Two
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41 167 independent sample t-tests were used to determine the differences between groups of
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44 168 continuous variables with a normal distribution. The nonparametric Mann–Whitney U
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47 169 test was used to compare differences between groups of continuous variables with
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50 170 non-normal distributions. Chi-square tests were used to determine the differences
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53 171 between the groups of categorical data. Variables with $P < 0.2$ were entered in
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56 172 multivariate logistic regression analysis. A positive stepwise method was used to
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59 173 adjust for the multiple risk factors. Each variable was expressed as an odds ratio (OR),
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174 and the confidence interval (CI) was 95%. The predictive value of the risk factors for

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4 175 EA was assessed using the receiver operating characteristic curve (ROC). The cut-off
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6 176 point was calculated based on the maximum Youden index value. P values < 0.05
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9 177 were considered statistically significant.
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12 178 ***Patient and public involvement***
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14 179 No patients were involved with design, data provision, analysis or publication of the
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181 **Results**

182 *General information on the study population*

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

192 *Perioperative clinical information and laboratory test*

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

196 Compared with the non-EA group, the VAS score was higher in the EA group (P
197 < 0.05), body temperature at the end of surgery was lower in the EA group (P < 0.05),
198 and the patients' duration in the PACU and preoperative fasting times were longer in
199 the EA group (P < 0.05). Simultaneously, 119 of 154 patients in the EA group had
200 CRBD, while 83 of 256 patients in the non-EA group experienced CRBD. This
201 variable was significantly different between the 2 groups (P < 0.05). Additionally,

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4 202 there were no significant differences between the 2 groups in terms of surgery type
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6 203 and time, intraoperative blood loss, intraoperative hypotension, warm treatment, and
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9 204 laboratory tests (Table 3).

11 205 ***Multivariate logistic regression analysis***

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14 206 Based on the univariate analysis, variables included in the multivariate logistic
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17 207 regression analysis were VAS score, male sex, body temperature at the end of
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20 208 surgery, duration of PACU, preoperative fasting time, and CRBD.

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22 209 As shown in Fig. 2, the correlation between VAS score, male sex, preoperative
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25 210 fasting time, CRBD, and EA in the TOA could be determined based on multivariate
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28 211 logistic analysis. In particular, the VAS score (OR = 2.497; 95% CI: 1.951–3.196),
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31 212 male sex (OR = 3.391; 95% CI: 1.781–6.435), CRBD (OR = 7.847; 95% CI: 4.001–
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34 213 15.392), fasting time for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting time
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37 214 for fluids (OR = 1.728; 95% CI: 1.263–2.365) were independent risk factors.

38 215 However, we could not confirm the independence of variables, such as body
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41 216 temperature at the end of surgery and PACU duration, in the multivariate logistic
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44 217 analysis.

45 218 ***Results of ROC curves for risk factors***

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48 219 The predictive value analysed using the ROC curve is demonstrated in Fig. 3.
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51 220 The area under the ROC curve (AUC) for the VAS score was 0.769, with a cut-off
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54 221 value of 4.0, sensitivity of 60%, and specificity of 87% (95% CI: 0.718–0.819, P <
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57 222 0.001). The AUC of fasting time for solids was 0.753, with a cut-off value of 10.5,
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60 223 sensitivity of 62%, and specificity of 86% (95% CI: 0.699–0.807, P < 0.001). The

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4 224 AUC of fasting time for fluids was 0.768, with a cut-off value of 8.5, sensitivity of
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6 225 64%, and specificity of 74% (95% CI: 0.719–0.816, $P < 0.001$).
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227 **Discussion**

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

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

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

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4 248 been validated, the RASS is easy to use and administer and has discrete criteria [22].
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7 249 Owing to these advantages, the RASS was chosen to assess EA in the PACU in this
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10 250 study. Similarly, Makarem et al. [20] and Xi et al. [13] also chose the RASS to assess
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12 251 EA in the PACU.

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14 252 Almost all researchers agree that postoperative pain is an independent risk factor
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17 253 for EA. Many clinical practices suggest that postoperative pain is bound to cause
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20 254 uncomfortable emotional experiences and lead to a series of dysregulated behaviours.
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22 255 Our study showed that the VAS score of patients in the EA group was higher than that
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25 256 in the non-EA group, and postoperative pain VAS score ≥ 4 was the cut-off point for
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27 257 EA. Pain after TJA is common, and several studies have found that $> 50\%$ of patients
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30 258 have suboptimal pain management after total hip arthroplasty (THA), and 75% of
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33 259 patients undergoing total knee arthroplasty (TKA) complain of moderate-to-severe
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35 260 pain [23,24]. In the present study, 72% (n = 295) patients complained of pain, and 5%
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38 261 (n = 21) patients experienced severe pain, comparable to the results of previous
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41 262 reports. Yu et al. [16] found that nearly half of the patients had EA because of a lack
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44 263 of postoperative analgesia. It is well accepted that peripheral nerve blocks (PNBs)
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46 264 provide excellent analgesia. In our study, to improve postoperative analgesia, femoral
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49 265 nerve block was routinely used in patients undergoing TKA, and fascia iliaca
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51 266 compartment block was used for THA. In our clinical practice, every patient
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54 267 undergoes ultrasound-guided PNB. However, considering anatomic variations and
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57 268 individual characteristics, PNBs do not result in an absolute lack of pain in patients
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59 269 undergoing TJA; hence, some patients still experience EA due to postoperative pain.

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4 270 Moreover, postoperative pain is not just wound related; sore throat and
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6 271 catheter-related pain should not be ignored. Based on these findings, we strongly
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9 272 suggest that multimodal analgesia should be performed although it greatly benefits
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12 273 patients with preventive analgesia.

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14 274 Placement of an indwelling catheter is a common clinical operation in the
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17 275 perioperative period. The collected urine is used for urine measurements and blood
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20 276 volume evaluation. However, patients undergoing urinary catheterisation are prone to
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22 277 develop CRBD [25], characterised by discomfort confined to the suprapubic region,
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24 278 burning sensation, pain, urinary urgency, and frequency [26,27]. CRBD can occur in
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27 279 47–90% of patients with a urinary catheter [4]. CRBD can enhance the incidence of
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30 280 EA and pain sensation after surgery [28]. A retrospective study reported that
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32 281 approximately 10% of patients experienced EA during urological surgery, which may
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35 282 be related to CRBD [29]. In our study, 119 of 410 patients experienced EA due to
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37
38 283 CRBD. The higher incidence of EA in our study may have been due to the age of the
39
40 284 recruited patients because age ≥ 50 years was an independent predictor of CRBD [30].
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43 285 Presently, many researchers have focused on EA associated with CRBD in patients
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45 286 undergoing urological surgery and rarely in patients undergoing TJA. It is necessary
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48 287 to remove urinary and indwelling catheters under topical anaesthesia early and avoid
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51 288 urinary catheterisation (if possible) to decrease EA associated with CRBD.

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53 289 Regarding male patients, the conclusion of this study is similar to those of other
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56 290 studies; male sex was an independent risk factor for EA [30]. The fact that male
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59 291 patients were prone to EA can be explained by the following points: male patients
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4 292 were high-risk patients with CRBD [30]. Half of all men aged ≥ 50 years and over
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6 293 80% of men aged ≥ 80 years have prostatic hyperplasia [31]. They easily felt
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9 294 discomfort and pain when the tip of the catheter was in contact with the bladder
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11 295 triangle on the pubis. Notably, an indwelling catheter without discomfort was used
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14 296 after anaesthesia induction. However, during the awakening period, patients,
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17 297 especially male patients, find it difficult to bear unexpected catheter-related
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19 298 discomfort. Furthermore, postoperative pain tolerance in male patients is low, and
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22 299 male patients require more analgesics than female patients [32].
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25 300 The relationship between emergence delirium (ED) and fasting time has also
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27 301 been demonstrated. Khanna et al. [33] reported that prolonged preoperative fasting (>
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29 302 6 h) was a risk factor for postoperative ED in children. However, the relationship
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32 303 between preoperative fasting time and EA in elderly patients has not been reported.
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35 304 This study showed that patients in the EA group had a longer preoperative fasting
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37 305 time; meanwhile, 10.5 h (fasting time for solids) and 8.6 h (fasting time for fluids) are
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40 306 cut-off points for EA. Prolonged preoperative fasting can cause metabolic, physical,
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43 307 and psychological discomfort in patients, eventually leading to EA [34]. Prolonged
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46 308 preoperative fasting translates to a prolonged preoperative waiting time, leading to
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48 309 patient apprehension and anxiety. Preoperative anxiety is a risk factor for EA [29].
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51 310 Owing to a large number of patients and the lack of medical resources, patients may
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53 311 undergo surgery later than expected, thereby prolonging the fasting time. Thus, it is
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56 312 necessary to reasonably schedule operations to decrease EA and reduce unnecessary
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58 313 fasting times.
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4 314 This study has some limitations. First, because this was a single-centre study, the
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6 315 sample size was small, and the representative conclusions were insufficient. As the
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9 316 same surgical team performed all operations, the effect of operation time on EA could
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11 317 not be evaluated. Therefore, expanding the sample size and increasing the number of
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14 318 research centres is necessary. Second, all study patients received an indwelling
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17 319 catheter, and CRBD was a risk factor for EA. Thus, the conclusions of this study may
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20 320 not apply to patients undergoing TJA without catheterisation. Third, EA is different
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22 321 from ED. Delirium is an acute state of mental confusion characterised by hypoactivity
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24
25 322 or hyperactivity [35]. A proportion of patients with delirium present with agitation,
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28 323 making assessment of EA difficult during recovery from anaesthesia. Therefore, we
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30 324 evaluated only EA, which may have led to false-positive cases.

325 **Conclusion**

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

332 ***Strengths and limitations of this study***

333 ➤ Previous studies indicated that EA is common in children; however, more recent
334 studies reported that elderly patients are also prone to EA after surgery.

335 Therefore, this study was the first to explore the incidence and risk factors for EA

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4 336 in elderly patients who underwent TJA under general anaesthesia and assess their
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7 337 predictive value.

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9 338 ➤ This study explored the incidence and risk factors for EA in elderly patients and
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12 339 assessed their predictive value, which could provide insights for further
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14 340 treatment.

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17 341 ➤ This was a single-centre study, the sample size was small. Moreover, since all
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20 342 patients in this study received an indwelling catheter, the finding of this study
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22 343 may not apply to patients who received TJA without catheter insertion.

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24 344 ➤ EA is different from emergence delirium. A proportion of patients with delirium
25
26
27 345 present with agitation, making the assessment of EA difficult during recovery
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30 346 from anaesthesia. Therefore, we evaluated only EA, which may have led to
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33 347 false-positive cases.

34
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36
37
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41
42
43 351 language editing.

44
45 352 **Data Statement:** No additional data are available.

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49
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51 354 contributions to the conception or the design of the manuscript. Naigeng Wang wrote
52
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54 355 this manuscript and made some changes after review. At the same time, he worked
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57 356 with Jing Du and Jie Zhang to acquire, analyse and interpret the data. All authors have
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60 357 participated to drafting the manuscript, Zhenguo Luo revised it critically. All authors

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

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

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For peer review only

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465 **Tables**466 **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

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468 **Notes:** Scores of 1 to 4 indicated different levels of agitation, 0 indicated calmness

469 and alertness, and -1 to -5 indicated different levels of sedation.

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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%)	

473 **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%)	

474 **Notes:** Clinical information of patients were analyzed by univariate analysis.

475 Continuous data are presented as the mean \pm standard deviation, and categorical data

476 are presented as numbers and percentages. *P-value, differences between patients

477 in two groups. *P<0. 05, ***P<0. 001. ASA: American Society of

478 Anesthesiologists; BMI: body mass index.

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486 **Table 3 Patients' perioperative clinical information and agitation-related**
 487 **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 (°C)	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

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60489 **Table3 (Continued)**

Variables	Agitation Groups (n=154)	Non-agitation Groups (n=256)	P-value
Severe Intraoperative hypotension			0. 261
(n, %)			
Yes	14 (9. 1%)	15 (5. 9%)	
No	140 (90. 9%)	241 (94. 1%)	
Postoperative nausea and vomiting			0. 332
(n, %)			
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

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4 490 **Notes:** Patients' perioperative clinical information and agitation-related laboratory
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6 491 test indicators were analyzed by univariate analysis. Continuous data are presented
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9 492 as the mean \pm standard deviation, and categorical data are presented as numbers and
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11 493 percentages. *P-value, differences between patients in two groups. *P<0. 05,
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14 494 ***P<0. 001. TKA: total knee arthroplasty; THA: total hip arthroplasty; VAS:
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17 495 visual analog scale; CRBD: catheter-related bladder discomfort; PACU:
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19 496 post-anesthesia care unit.
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4 512 **Figure legends**

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6 513 **Figure 1 Flow chart of study participants.** A total of 421 patients met the inclusion
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9 514 and exclusion criteria. However, 11 patients were excluded from the study; 6 were
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12 515 transferred to the ICU postoperatively, and the surgical protocol of 5 patients was
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15 516 changed during the operation. Finally, 410 patients were included in the statistical
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17 517 analysis.
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22 519 **Figure 2 Risk factors of EA by metanalysis plot.** The patients' VAS score (OR =
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24 520 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), urinary
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27 521 catheter irritation (OR = 7.847; 95% CI: 4.001–15.392), fasting time for solids (OR =
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30 522 1.703; 95% CI: 1.260–2.301), and fasting time for fluids (OR = 1.728; 95% CI:
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32 523 1.263–2.365) were the independent risk factors. VAS: visual analogue scale
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37 525 **Figure 3 Risk factors of EA by the ROC curve.** The predictive value of risk factors
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39 526 was assessed using the ROC curve. The patients' VAS score (AUC = 0.769, 95% CI:
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41 527 0.718–0.819, $P < 0.001$), fasting time for solids (AUC = 0.753, 95% CI: 0.699–0.807,
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43 528 $P < 0.001$) and fasting time for fluids (AUC = 0.768, 95% CI: 0.719–0.816, $P <$
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45 529 0.001) showed a good predictive effect.
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5 534 **Reporting checklist for cross sectional**
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13 536 Based on the STROBE cross sectional guidelines.
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17 537 **Instructions to authors**
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20 538 Complete this checklist by entering the page numbers from your manuscript
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47 547 JP. The Strengthening the Reporting of Observational Studies in
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			Number
Title and abstract			
Title	<u>#1a</u>	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	<u>#1b</u>	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	<u>#2</u>	Explain the scientific background and rationale for the investigation being reported	5
Objectives	<u>#3</u>	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	<u>#4</u>	Present key elements of study design early in the paper	NA

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5	Setting	<u>#5</u>	Describe the setting, locations, and	7
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5	Study size	<u>#10</u>	Explain how the study size was arrived at	9
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		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.	
Participants	<u>#13b</u>	Give reasons for non-participation at each stage	11
Participants	<u>#13c</u>	Consider use of a flow diagram	32
Descriptive data	<u>#14a</u>	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	<u>#14b</u>	Indicate number of participants with missing data for each variable of interest	11
Outcome data	<u>#15</u>	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	11-13

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5	Main results	<u>#16a</u> Give unadjusted estimates and, if	NA
6		applicable, confounder-adjusted	
7		estimates and their precision (eg, 95%	
8		confidence interval). Make clear which	
9		confounders were adjusted for and why	
10		they were included	
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21	Main results	<u>#16b</u> Report category boundaries when	NA
22		continuous variables were categorized	
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27	Main results	<u>#16c</u> If relevant, consider translating estimates	NA
28		of relative risk into absolute risk for a	
29		meaningful time period	
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36	Other analyses	<u>#17</u> Report other analyses done—e.g.,	NA
37		analyses of subgroups and interactions,	
38		and sensitivity analyses	
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44	Discussion		
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48	Key results	<u>#18</u> Summarise key results with reference to	14
49		study objectives	
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54	Limitations	<u>#19</u> Discuss limitations of the study, taking	18-19
55		into account sources of potential bias or	
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4 imprecision. Discuss both direction and
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6 magnitude of any potential bias.
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10 Interpretation #20 Give a cautious overall interpretation 14-17
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12 considering objectives, limitations,
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14 multiplicity of analyses, results from
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16 similar studies, and other relevant
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18 evidence.
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24 Generalisability #21 Discuss the generalisability (external NA
25
26 validity) of the study results
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28

30 Other

32 Information

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36 Funding #22 Give the source of funding and the role of 19
37
38 the funders for the present study and, if
39
40 applicable, for the original study on which
41
42 the present article is based
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51 552 using <https://www.goodreports.org/>, a tool made by the EQUATOR Network in
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53 553 collaboration with Penelope.ai
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Figure 1 Flow chart of study participants.

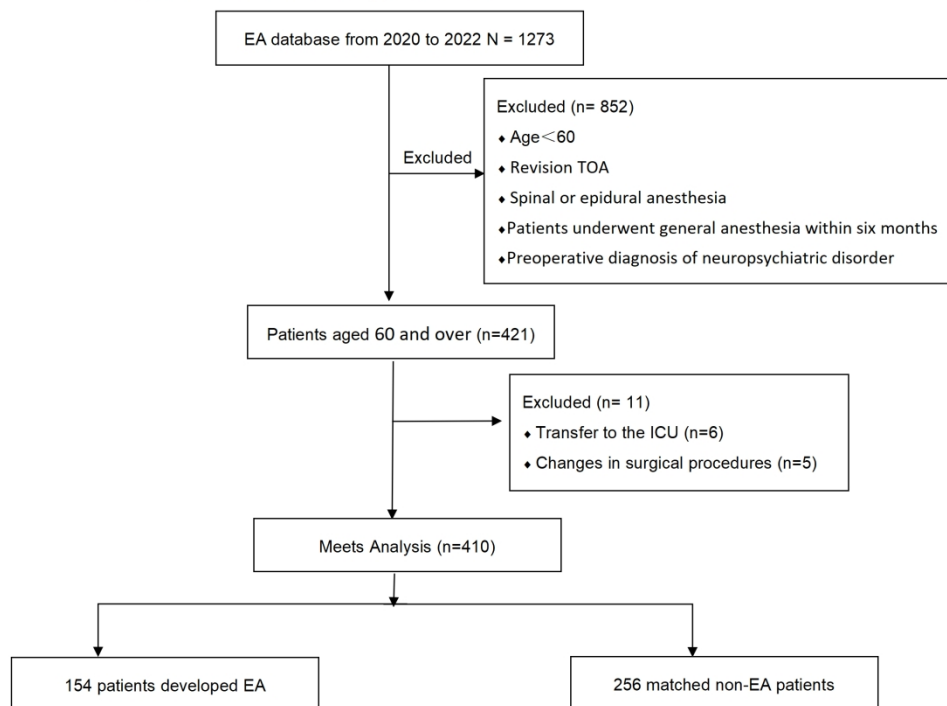


Figure 1 Flow chart of study participants

419x390mm (144 x 144 DPI)

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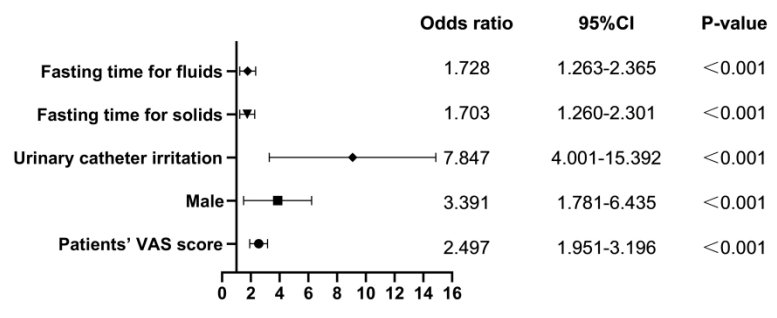


Figure 2 Risk factors of EA by metanalysis plot
220x73mm (600 x 600 DPI)

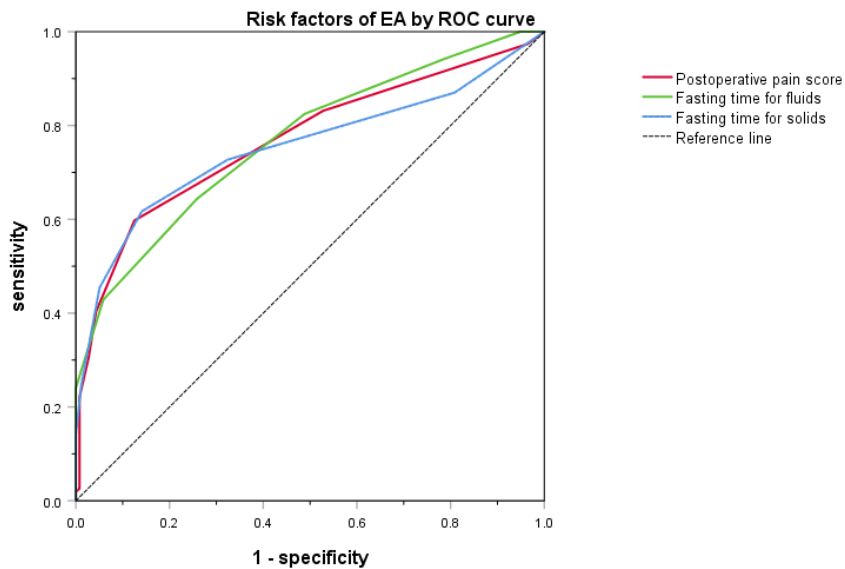


Figure 3 Risk factors of EA by the ROC curve

149x88mm (144 x 144 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.

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

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche 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 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			

1	Study design	#4	Present key elements of study design early in the paper	NA
2				
3	Setting	#5	Describe the setting, locations, and relevant dates, including	7
4			periods of recruitment, exposure, follow-up, and data collection	
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6				
7	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of	7
8			selection of participants.	
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11		#7	Clearly define all outcomes, exposures, predictors, potential	8
12			confounders, and effect modifiers. Give diagnostic criteria, if	
13			applicable	
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16	Data sources /	#8	For each variable of interest give sources of data and details of	8
17	measurement		methods of assessment (measurement). Describe	
18			comparability of assessment methods if there is more than one	
19			group. Give information separately for for exposed and	
20			unexposed groups if applicable.	
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24	Bias	#9	Describe any efforts to address potential sources of bias	NA
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27	Study size	#10	Explain how the study size was arrived at	9
28				
29	Quantitative	#11	Explain how quantitative variables were handled in the	8
30	variables		analyses. If applicable, describe which groupings were chosen,	
31			and why	
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34	Statistical	#12a	Describe all statistical methods, including those used to control	9-10
35	methods		for confounding	
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38	Statistical	#12b	Describe any methods used to examine subgroups and	9-10
39	methods		interactions	
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42	Statistical	#12c	Explain how missing data were addressed	NA
43	methods			
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46	Statistical	#12d	If applicable, describe analytical methods taking account of	NA
47	methods		sampling strategy	
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50	Statistical	#12e	Describe any sensitivity analyses	9-10
51	methods			
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54	Results			
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56	Participants	#13a	Report numbers of individuals at each stage of study—eg	11
57			numbers potentially eligible, examined for eligibility, confirmed	
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eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.

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5	Participants	#13b	Give reasons for non-participation at each stage 11
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11			clinical, social) and information on exposures and potential
12			confounders. Give information separately for exposed and
13			unexposed groups if applicable.
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22			Give information separately for exposed and unexposed
23			groups if applicable.
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26	Main results	#16a	Give unadjusted estimates and, if applicable, confounder- NA
27			adjusted estimates and their precision (eg, 95% confidence
28			interval). Make clear which confounders were adjusted for and
29			why they were included
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33	Main results	#16b	Report category boundaries when continuous variables were NA
34			categorized
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37	Main results	#16c	If relevant, consider translating estimates of relative risk into NA
38			absolute risk for a meaningful time period
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41	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and NA
42			interactions, and sensitivity analyses
43			
44	Discussion		
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46	Key results	#18	Summarise key results with reference to study objectives 14
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49	Limitations	#19	Discuss limitations of the study, taking into account sources of 18-19
50			potential bias or imprecision. Discuss both direction and
51			magnitude of any potential bias.
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54	Interpretation	#20	Give a cautious overall interpretation considering objectives, 14-17
55			limitations, multiplicity of analyses, results from similar studies,
56			and other relevant evidence.
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1 Generalisability [#21](#) Discuss the generalisability (external validity) of the study NA
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4
5 **Other**
6 **Information**
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9 Funding [#22](#) Give the source of funding and the role of the funders for the 19
10 present study and, if applicable, for the original study on which
11 the present article is based
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16 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

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

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Date Submitted by the Author:	28-Feb-2023
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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Anaesthesia in orthopaedics < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY

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

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15 **Running title:** EA risk factors after TJA

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

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25
26 **IRB number:** 201812001 (Biomedical Research Ethics Committee of Honghui
27 Hospital)

28 **Clinical trial registration number:** ChiCTR1800020193

29 **Word count: 3198**

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4 43 **Abstract**

5
6 44 **Objectives:** This study aimed to explore the incidence and risk factors for emergence
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8
9 45 agitation (EA) in elderly patients who underwent total joint arthroplasty (TJA) under
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12 46 general anaesthesia and assess their predictive values.

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14 47 **Design:** Single-centre retrospective cohort study.

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17 48 **Setting:** A 1,600-bed general tertiary hospital in China.

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19 49 **Participants:** This study enrolled 421 elderly patients scheduled for elective primary
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22 50 TJA under general anaesthesia.

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24 51 **Primary and Secondary Outcome Measures:** EA was assessed using the Richmond
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27 52 Agitation Sedation Scale during the awakening period after surgery in the
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30 53 post-anaesthesia care unit. Risk factors for EA were identified using univariate and
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33 54 multivariable logistic analyses. The receiver operating characteristic curve (ROC) was
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36 55 used to assess the predictive values of the risk factors for EA.

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38 56 **Results:** The incidence of EA in elderly patients who underwent TJA was 37.6%.
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41 57 According to the multivariable logistic analysis, postoperative pain (95% confidence
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43 58 interval [CI]: 1.951–3.196), male sex (95% CI: 1.781–6.435), catheter-related bladder
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45 59 discomfort (CRBD) (95% CI: 4.001–15.392), longer fasting times for solids(95%
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48 60 CI:1.260–2.301) and fluids (95% CI: 1.263–2.365) were independent risk factors for
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51 61 EA. As shown by the ROC analysis, postoperative pain,fasting times for solids and
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54 62 fluids had good predictive values ,with the area under the ROC curve (AUC) was
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57 63 0.769, 0.753 and 0.768,respectively.

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4 64 **Conclusions:** EA is a common complication in elderly patients after TJA. Reducing
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7 65 these risk factors is crucial in preventing or treating EA.
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11 67 **Keywords:** Emergence agitation; Elderly patients; Risk factors; Total joint
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14 68 arthroplasty
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20 70 **Strengths and limitations:**

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22 71 ➤ We investigated the incidence and risk factors for EA in elderly patients after
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24 72 total joint arthroplasty and assessed their predictive values.
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26 73 ➤ This study may provide novel insights for preventing and treating EA by
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28 74 identifying the risk factors for EA in elderly patients and assessing their
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31 75 predictive values.
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34 76 ➤ As a single-centre study, our sample size was relatively small.
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36 77 ➤ This was a single-centre retrospective cohort study; thus, some bias is
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39 78 unavoidable.
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41 79 **Trial Registration:** ChiCTR1800020193
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78 **Introduction**
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10 Emergence agitation (EA), a common complication of the awakening period after
11 general anaesthesia, refers to a temporary state of mental and motor excitement [1].
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15 Clinical features of EA include disorientation, excitation, agitation, and combative
16 behaviours [2,3]. EA can also increase the risk of wound bleeding or dehiscence,
17 self-extubation, falling out of bed, and violent behaviour towards staff [4]. It may also
18 prolong the patient's stay in the post-anaesthesia care unit (PACU) and increase the
19 demand for medical staff [3], resulting in higher medical costs. The incidence of EA
20 varies widely, ranging from 0.25% to 90.5%, depending on factors such as age, type
21 of surgery, assessment tool, and anaesthesia method [5]. However, the exact aetiology
22 and pathological mechanisms of EA remain unclear [5,6]. Hence, identifying the risk
23 factors for EA is crucial in preventing and managing this condition.
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39 EA has been reported in different age groups following general anaesthesia [5].
40 Many studies have demonstrated that EA is common in children [2,7-8]. However,
41 other studies have demonstrated that the elderly are also at a high risk of developing
42 EA [9]. Unfortunately, there are few reports on EA in the elderly compared with
43 many studies on EA in children. Owing to the decline in physiological functions with
44 age, the elderly may be predisposed to EA after surgery, leading to more serious
45 consequences. Thus, more attention must be paid to EA in elderly patients.
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4 102• Osteoarthritis (OA) is the most frequent type of arthritis and affects one in
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6 103 three older people [10]. As society ages, more and more older people experience OA.
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9 104 Total joint arthroplasty (TJA) is a successful treatment protocol for end-stage knee
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11 105 and hip OA [11]. Annually, more than 1 million people undergo TJA in the United
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14 106 States [12]. The demand for TJA surgery is expected to increase substantially in the
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17 107 coming years [13]. However, there are no reports on the incidence of EA after TJA.

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19 108 In this study, we retrospectively collected the medical records of 421 elderly
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22 109 patients who underwent general anaesthesia for TJA. We aimed to evaluate the risk
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25 110 factors of postoperative EA in elderly patients, assess the predictive values, and
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28 111 provide guidance for preventing and treating EA during follow-up.
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56 114 **Materials and methods**
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10 115 *Ethics statement*
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14 116 This study was approved by the Biomedical Research Ethics Committee of our
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16 117 hospital (approval no. 201812001), and the trial was registered in the Chinese Clinical
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18 118 Registry (ChiCTR, 1800020193). All methods were performed according to relevant
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20 119 guidelines and regulations. The study obtained consent to gather patients' medical
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22 120 record information through telephonic follow-up.
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28 121 *Patients*
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31 122 We enrolled 421 patients who underwent TJA under general anaesthesia at our
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33 123 hospital between December 2019 and June 2021. The inclusion criteria
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35 124 included (1) preoperative OA diagnosis, (2) age \geq 60 years, (3) American Society of
36
37 125 Anesthesiologists (ASA) physical status I–III, and (4) having undergone scheduled
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39 126 elective primary TJA under general anaesthesia. Patients with any of the following
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41 127 conditions were excluded: revision TJA, spinal or epidural anaesthesia, general
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43 128 anaesthesia within the past 6 months, and preoperative diagnosis of neuropsychiatric
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45 129 disorder.
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53 130 *Routine practice of perioperative management*
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4 131 Anaesthesia was induced with intravenous midazolam, etomidate, sufentanil, and
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7 132 rocuronium. Tracheal intubation was completed after 2 min. The ultrasound-guided
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10 133 femoral nerve block was performed in patients undergoing total knee replacement,
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12 134 while the ultrasound-guided fascia iliac compartment block was performed in patients
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14 135 undergoing total hip replacement. All 20-ml (0.5%) ropivacaine solutions were
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17 136 infused into the nerve block. Urinary catheterisation was performed in all patients
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20 137 after inducing anaesthesia. Anaesthesia was maintained using intravenous
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22 138 remifentanyl and propofol. Patients were transferred to the PACU after the operation.
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25 139 These patients were extubated in the PACU.

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27 140 Speciality nurses assessed all patients in the PACU using a standardised
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30 141 protocol, including the visual analogue scale (VAS), Richmond Agitation Sedation
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32 142 Scale (RASS), and Steward recovery scores. VAS was used for assessing
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35 143 postoperative pain, and intravenous flurbiprofen was administered as an analgesic
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38 144 rescue when the VAS score was >4 . EA was evaluated using the RASS [14], and
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41 145 Table 1 presents the score criteria. Patients with a RASS score > 1 were considered to
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43 146 have EA[14]. Dexmedetomidine was administered in cases of severe agitation (RASS
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46 147 = 4). Patients with ward recovery scores > 4 were transferred to the ward from the
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48 148 PACU.

150 ***Data collection***

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

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4 153 education level, and history of heart disease, respiratory disease, hypertension, and
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6 154 diabetes; (2) perioperative clinical information, including operation type and time,
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9 155 body temperature after the surgery, VAS score, catheter-related bladder discomfort
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11 156 (CRBD), preoperative fasting times, intraoperative blood loss, warm treatment,
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14 157 postoperative nausea and vomiting, duration in PACU, RASS score, and severe
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17 158 intraoperative hypotension (mean arterial pressure < 65 mmHg for at least 1 min); and
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19 159 (3) laboratory tests. Preoperative fasting times refers to the period from the last intake
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22 160 of liquids or solids to the beginning of the anaesthesia induction.
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26 27 162 *Statistical analysis and sample size*

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30 163 The sample size was calculated using GPower software version 3.1 (Franz Faul,
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32 164 University of Kiel, Kiel, Germany). The effect size was set to 0.3, α level to 0.05, and
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34
35 165 $1-\beta$ to 0.85. A sample size of 100 patients was the optimal sample size required to
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37
38 166 prove the difference between the two groups. Considering the easy acquisition of
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41 167 electronic medical records, we included patients who met the inclusion and exclusion
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43 168 criteria between December 2019 and June 2020.

44
45 169 Statistical analysis was performed using SPSS version 26.0 (SPSS Inc.,
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47
48 170 Chicago, IL, USA). Continuous data are presented as the means \pm standard deviations,
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51 171 and categorical data are presented as numbers and percentages. Independent risk
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53 172 factors were identified using univariate and multivariable logistic regression analyses.
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56 173 The measurement data were assessed for normal and non-normal distributions. Two
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58 174 independent sample t-tests were used to determine the differences between groups for
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4 175 continuous variables with a normal distribution. The nonparametric Mann–Whitney U
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6 176 test was used to compare differences between groups for continuous variables with
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8
9 177 non-normal distributions. Chi-square tests were used to determine differences
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11 178 between groups for categorical data. Variables with $P < 0.2$ were entered in
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14 179 multivariable logistic regression analysis. A positive stepwise method was used to
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17 180 adjust for multiple risk factors. Each variable was expressed as an odds ratio (OR)
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19 181 with a 95% confidence interval (CI). The predictive value of the risk factors for EA
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22 182 was assessed using the receiver operating characteristic (ROC) curve. The cut-off
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25 183 point was calculated based on the maximum Youden index value. Statistical
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27 184 significance was set at a P value < 0.05 .

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31 32 186 ***Patient and public involvement***

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35 187 None of the patients were involved in the design, data provision, analysis, or
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38 188 publication of the study.

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78 **190 Results**9
10 **191 *General information on the study population***

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13 192 In total, 421 patients met the inclusion and exclusion criteria. However, 11
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15 193 patients were excluded from the study; six were transferred to the intensive care unit
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18 194 (ICU) postoperatively, and the surgical protocols of five patients were changed during
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21 195 the operation. Finally, the statistical analysis included 410 patients (Fig. 1). The
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23 196 incidence of EA was 37.6% (n = 154) in 410 patients. All patients (n = 410) were
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25
26 197 divided into two groups: EA and non-EA. No significant differences were observed
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28
29 198 between the two groups in age, BMI, ASA classification, education level, and medical
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31 199 history (Table 2). The EA group had a significantly higher proportion of male patients
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34 200 than the non-EA group (P < 0.05).

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3940 **202 *Perioperative clinical information and laboratory test***

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42 203 Univariate analysis demonstrated significant differences between the EA and
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44 204 non-EA groups in the VAS score for postoperative pain, body temperature after the
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47 205 surgery, CRBD, preoperative fasting times, and length of stay in the PACU.

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49 206 Compared with the non-EA group, the VAS score was higher (P < 0.05), body
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52 207 temperature after the surgery was lower (P < 0.05), and the patient's length-of-stay in
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55 208 the PACU and preoperative fasting times were longer in the EA group (P < 0.05).

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57 209 Simultaneously, 119 of 154 patients in the EA group had CRBD, while 83 of 256
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4 210 patients in the non-EA group experienced CRBD. This variable differed significantly
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6 211 between the two groups ($P < 0.05$). Additionally, no significant differences were
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9 212 observed between the two groups regarding surgery type and time, intraoperative
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11 213 blood loss, intraoperative hypotension, warm treatment, and laboratory tests (Table 3).
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16 17 215 ***Multivariable logistic regression analysis***

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19 216 Based on the univariate analysis, variables included in the multivariable logistic
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21 217 regression analysis include the VAS score for postoperative pain, male sex, body
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23 218 temperature after the surgery, length-of-stay in the PACU, preoperative fasting times,
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25 219 and CRBD.
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30 220 The correlation between the VAS score for postoperative pain, male sex,
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32 221 preoperative fasting times, CRBD, and EA in the TJA could be determined based on
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34 222 multivariable logistic analysis (Fig. 2). The VAS score for postoperative pain (OR =
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36 223 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), CRBD
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38 224 (OR = 7.847; 95% CI: 4.001–15.392), fasting times for solids (OR = 1.703; 95% CI:
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40 225 1.260–2.301), and fasting times for fluids (OR = 1.728; 95% CI: 1.263–2.365) were
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42 226 independent risk factors. However, we could not confirm the independence of
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44 227 variables, such as body temperature after the surgery and length-of-stay in the PACU,
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46 228 in the multivariable logistic analysis.
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54 55 56 230 ***Results of ROC curves for risk factors***

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4 231 The predictive value analysed using the ROC curve is demonstrated in Fig. 3.
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6 232 The area under the ROC curve (AUC) for the VAS score was 0.769, with a cut-off
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9 233 value of 4.0, sensitivity of 60%, and specificity of 87% (95% CI: 0.718–0.819, $P <$
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11 234 0.001). The AUC of fasting time for solids was 0.753, with a cut-off value of 10.5,
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14 235 sensitivity of 62%, and specificity of 86% (95% CI: 0.699–0.807, $P <$ 0.001). The
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17 236 AUC of fasting time for fluids was 0.768, with a cut-off value of 8.5, sensitivity of
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20 237 64%, and specificity of 74% (95% CI: 0.719–0.816, $P <$ 0.001).

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239 **Discussion**

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

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

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

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

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

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4 274 to the results of previous reports. Yu et al. [6] found that nearly half of the patients
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6 275 had EA because of insufficient postoperative analgesia. Peripheral nerve blocks
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9 276 (PNBs) provide excellent analgesia. In our study, the femoral nerve block was
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11 277 routinely used in patients undergoing TKA, while the fascia iliaca compartment
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14 278 block was used for THA to improve postoperative analgesia. In our clinical practice,
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17 279 every patient undergoes ultrasound-guided PNB. However, considering anatomic
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19 280 variations and individual characteristics, PNBs may not eliminate pain in patients
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22 281 undergoing TJA, leading to some patients experiencing EA due to postoperative pain.
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25 282 Moreover, sore throat and catheter-related pain should not be ignored because
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27 283 postoperative pain is not only wound related. Based on these findings, we strongly
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30 284 suggest that multimodal analgesia should be performed to benefit patients, especially
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33 285 with preventive analgesia.

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35 286 The placement of an indwelling catheter is a common clinical operation in the
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37 287 perioperative period. The collected urine is used for urine measurements and blood
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40 288 volume evaluation. However, patients undergoing urinary catheterisation are prone to
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43 289 CRBD [19], characterised by discomfort confined to the suprapubic region, burning
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46 290 sensation, pain, and urinary urgency and frequency [20,21]. CRBD can occur in
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49 291 47–90% of patients with a urinary catheter [4]. CRBD can increase the incidence of
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51 292 EA and pain sensation after surgery [22]. A retrospective study reported that
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54 293 approximately 10% of patients experienced EA during urological surgery, possibly
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57 294 related to CRBD [23]. In our study, 119 of 410 patients experienced EA due to
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59 295 CRBD. Moreover, the higher incidence of EA may be due to the age of the recruited

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4 296 patients because age ≥ 50 years was an independent predictor of CRBD [24]. Many
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6 297 researchers have focused on EA associated with CRBD in patients undergoing
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9 298 urological surgery and rarely in patients undergoing TJA. Urinary and indwelling
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11 299 catheters under topical anaesthesia must be removed early, and urinary catheterisation
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14 300 (if possible) avoided to decrease EA associated with CRBD.

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17 301 Regarding male patients, this study's conclusion is similar to that of other studies
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19 302 where the male sex was identified as an independent risk factor for EA [24]. This
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21 303 observation could be explained by several factors. Firstly, male patients were
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23 304 high-risk patients with CRBD [24]. Half of all men aged ≥ 50 years and over 80% of
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25 305 men aged ≥ 80 years have prostatic hyperplasia, which can easily cause discomfort
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27 306 and pain when the catheter tip contacts the bladder triangle on the pubis [25].
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29 307 However, during the awakening period of anaesthesia, male patients especially have
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31 308 difficulty tolerating the discomfort associated with catheters. Furthermore, male
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33 309 patients have low postoperative pain tolerance, requiring more analgesics than female
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35 310 patients [26].

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38 311 The relationship between emergence delirium (ED) and fasting times has also
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40 312 been demonstrated. Khanna et al. [27] reported that prolonged preoperative fasting ($>$
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42 313 6 h) was a risk factor for postoperative ED in children. However, the relationship
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44 314 between preoperative fasting times and EA in elderly patients has not been reported.
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46 315 This study showed that patients in the EA group had a longer preoperative fasting
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48 316 times. Moreover, 10.5 h (fasting times for solids) and 8.6 h (fasting times for fluids)
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50 317 are cut-off points for EA. Prolonged preoperative fasting can cause metabolic,
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4 318 physical, and psychological discomfort in patients, eventually leading to EA [28].
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6 319 Prolonged preoperative fasting translates to prolonged preoperative waiting time,
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9 320 leading to patient apprehension and anxiety. Preoperative anxiety is a risk factor for
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11 321 EA [23]. Owing to the numerous patients and the lack of medical resources, patients
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14 322 may undergo surgery later than expected, thereby prolonging the fasting times. Thus,
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17 323 operations to decrease EA and reduce unnecessary fasting times must be reasonably
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20 324 scheduled.

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22 325• This study had some limitations. Firstly, we only included elderly patients
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25 326 who had undergone intravenous anaesthesia. Future studies may utilize other methods
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28 327 and anaesthetics. Secondly, this was a single-centre study; therefore, the
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31 328 generalisability of the results was not fully verified. Future multi-centre studies must
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34 329 assess external validity. Lastly, this is a retrospective cohort study; some bias is
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37 330 unavoidable. Future prospective studies must be conducted for further research.
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40 332 **Conclusion**

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43 333 This retrospective study showed that the incidence rate of EA in elderly patients
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46 334 after TJA in the PACU was 37.6%. Postoperative pain, CRBD, male sex, and
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49 335 preoperative fasting duration were independent predictors of EA. The
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52 336 pathophysiological mechanism of EA is unknown; hence, preventing EA is
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55 337 more important than treating it. However, the best choice should be to eliminate and
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58 338 avoid risk factors.

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347
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352 participated in drafting the manuscript, and Zhenguo Luo revised it critically. All
353 authors contributed equally to the manuscript and read and approved the final version
354 of the manuscript.

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444 **Tables**445 **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

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447 **Notes:** Scores of 1 to 4 indicated different levels of agitation, 0 indicated calmness

448 and alertness, and -1 to -5 indicated different levels of sedation.

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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%)	

452 **Notes:** Clinical information of patients were analysed using univariate analysis.

453 Continuous data are presented as the means \pm standard deviations, while categorical

454 data are presented as numbers and percentages. *P-value, differences between

455 patients in the two groups. *P<0. 05, ***P<0. 001. ASA: American Society of

456 Anesthesiologists; BMI: body mass index.

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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 (°C)	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

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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

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

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

For peer review only

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4 488 **Figure legends**

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6 489 **Figure 1 Flow chart of study participants.** In total, 421 patients met the inclusion
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9 490 and exclusion criteria. However, 11 patients were excluded from the study; six were
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12 491 transferred to the ICU postoperatively, and the surgical protocols of five were
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15 492 changed during the operation. Finally, the statistical analysis included 410 patients.
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19 494 **Figure 2 Risk factors for EA using metanalysis plot.** The VAS score for
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22 495 postoperative pain (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95%
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24
25 496 CI: 1.781–6.435), urinary catheter irritation (OR = 7.847; 95% CI: 4.001–15.392),
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28 497 fasting times for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting times for
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30
31 498 fluids (OR = 1.728; 95% CI: 1.263–2.365) were the independent risk factors.
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35 500 **Figure 3 Risk factors for EA using the ROC curve.** Predictive values of risk factors
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38 501 were assessed using the ROC curve. The VAS score for postoperative pain (AUC =
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41 502 0.769, 95% CI: 0.718–0.819, $P < 0.001$), fasting times for solids (AUC = 0.753, 95%
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44 503 CI: 0.699–0.807, $P < 0.001$) and fasting times for fluids (AUC = 0.768, 95% CI:
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47 504 0.719–0.816, $P < 0.001$) demonstrated good predictive effects.
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4 510 **Reporting checklist for cross sectional study.**

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7 511 Based on the STROBE cross sectional guidelines.

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10 512 **Instructions to authors**

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13 513 Complete this checklist by entering the page numbers from your manuscript
14 514 where readers will find each of the items listed below.

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18 515 Your article may not currently address all the items on the checklist. Please
19 516 modify your text to include the missing information. If you are certain that an
20 517 item does not apply, please write "n/a" and provide a short explanation.

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24 518 Upload your completed checklist as an extra file when you submit to a journal.

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27 519 In your methods section, say that you used the STROBE cross
28 520 sectionalreporting guidelines, and cite them as:

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31 521 von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandembroucke
32 522 JP. The Strengthening the Reporting of Observational Studies in Epidemiology
33 523 (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	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

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4 **Introduction**
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7 Background / #2 Explain the scientific background and 5
8 rationale for the investigation being
9 reported

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12 Objectives #3 State specific objectives, including any 6
13 prespecified hypotheses
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17 Methods

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19 Study design #4 Present key elements of study design NA
20 early in the paper
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24 Setting #5 Describe the setting, locations, and 7
25 relevant dates, including periods of
26 recruitment, exposure, follow-up, and
27 data collection
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31 Eligibility criteria #6a Give the eligibility criteria, and the 7
32 sources and methods of selection of
33 participants.
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37 #7 Clearly define all outcomes, exposures, 8
38 predictors, potential confounders, and
39 effect modifiers. Give diagnostic criteria, if
40 applicable
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45 Data sources / #8 For each variable of interest give sources 8
46 measurement of data and details of methods of
47 assessment (measurement). Describe
48 comparability of assessment methods if
49 there is more than one group. Give
50 information separately for for exposed
51 and unexposed groups if applicable.
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57 Bias #9 Describe any efforts to address potential 8-9
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			sources of bias	
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6	Study size	#10	Explain how the study size was arrived at	9
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8	Quantitative	#11	Explain how quantitative variables were	8
9	variables		handled in the analyses. If applicable,	
10			describe which groupings were chosen,	
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16	Statistical	#12a	Describe all statistical methods, including	9-10
17	methods		those used to control for confounding	
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24	Statistical	#12c	Explain how missing data were	NA
25	methods		addressed	
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28	Statistical	#12d	If applicable, describe analytical methods	NA
29	methods		taking account of sampling strategy	
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33	Statistical	#12e	Describe any sensitivity analyses	9-10
34	methods			
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37	Results			
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40	Participants	#13a	Report numbers of individuals at each	11
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4	Descriptive data	#14a	Give characteristics of study participants 11
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18			groups if applicable.
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20	Main results	#16a	Give unadjusted estimates and, if 12
21			applicable, confounder-adjusted
22			estimates and their precision (eg, 95%
23			confidence interval). Make clear which
24			confounders were adjusted for and why
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27	Main results	#16b	Report category boundaries when NA
28			continuous variables were categorized
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38	Discussion		
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42	Key results	#18	Summarise key results with reference to 14
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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

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Figure 1 Flow chart of study participants.

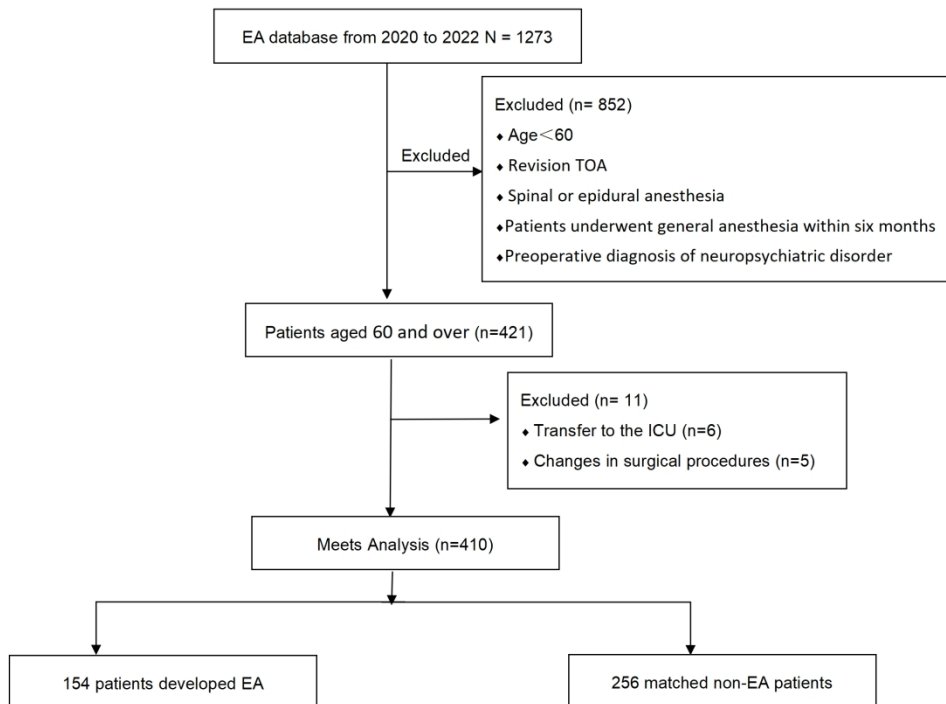


Figure 1 Flow chart of study participants

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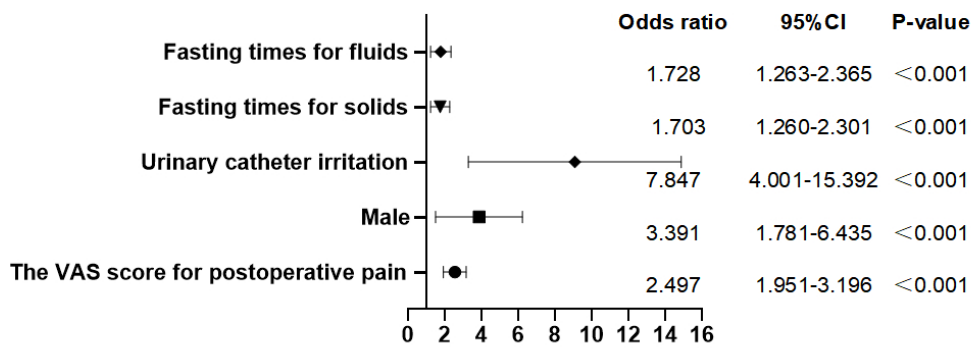


Figure 2 Risk factors of EA by metanalysis plot

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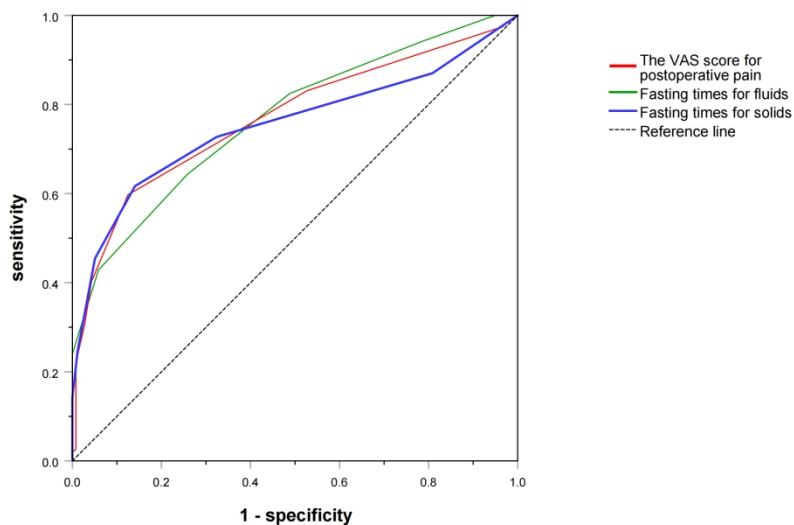


Figure 3 Risk factors of EA by the ROC curve

1178x667mm (57 x 57 DPI)

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

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BMJ Open

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

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

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15 **Running title:** EA risk factors after TJA

16
17 **Keywords:** Emergence agitation; Elderly patients; Risk factors; Total joint
18 arthroplasty

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14 26 **IRB number:** 201812001 (Biomedical Research Ethics Committee of Honghui
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17 Hospital)
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19 28 **Clinical trial registration number:** ChiCTR1800020193
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4 43 **Abstract**

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6 44 **Objectives:** This study aimed to explore the incidence and risk factors for emergence
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9 45 agitation (EA) in elderly patients who underwent total joint arthroplasty (TJA) under
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12 46 general anaesthesia, and to assess their predictive values.

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14 47 **Design:** Single-centre retrospective cohort study.

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17 48 **Setting:** A 1,600-bed general tertiary hospital in China.

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19 49 **Participants:** This study enrolled 421 elderly patients scheduled for elective primary
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22 50 TJA under general anaesthesia.

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24 51 **Primary and Secondary Outcome Measures:** EA was assessed using the Richmond
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27 52 Agitation Sedation Scale during the awakening period after surgery in the
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30 53 postanaesthesia care unit(PACU). Risk factors for EA were identified using univariate
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33 54 and multivariable logistic analyses. The receiver operating characteristic curve (ROC)
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36 55 was used to assess the predictive values of the risk factors for EA.

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38 56 **Results:** The incidence of EA in elderly patients who underwent TJA was 37.6%.
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41 57 According to the multivariable logistic analysis, postoperative pain (95% confidence
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43 58 interval [CI]: 1.951–3.196), male sex (95% CI: 1.781–6.435), catheter-related bladder
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45 59 discomfort (CRBD) (95% CI: 4.001–15.392), and longer fasting times for solids (95%
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48 60 CI: 1.260–2.301) and fluids (95% CI: 1.263–2.365) were independent risk factors for
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51 61 EA. As shown by the ROC analysis, postoperative pain and fasting times for solids
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54 62 and fluids had good predictive values,with areas under the ROC curve (AUCs)
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57 63 equalling 0.769, 0.753 and 0.768,respectively.

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4 64 **Conclusions:** EA is a common complication after TJA in elderly patients. Some
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6 65 risk factors, including postoperative pain, male sex, CRBD, and longer fasting times,
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9 66 can increase the incidence of EA. These risk factors may contribute to identifying
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11 67 high-risk patients, which facilitates the development of effective strategies to prevent
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14 68 and treat EA.
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22 71 **Keywords:** Emergence agitation; Elderly patients; Risk factors; Total joint
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24 72 arthroplasty
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30 74 **Strengths and limitations:**
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- 32 75 ➤ We performed a retrospective study of risk factors for EA in elderly patients after
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34 76 TJA.
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36 77 ➤ This work was a single-centre retrospective study, and the generalizability of the
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38 78 results is weak.
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40 79 ➤ Only patients with one category of arthritis were studied.
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83 Introduction

84 Emergence agitation (EA), a common complication during the awakening period
85 after general anaesthesia, refers to a temporary state of mental and motor excitement
86 [1]. Clinical features of EA include disorientation, excitation, agitation, and
87 combative behaviours [2,3]. The incidence of EA in adults varies from 4.7% to 74%
88 [4]. EA can also increase the risk of wound bleeding or dehiscence, self-extubation,
89 falling out of bed, and violent behaviour towards staff [5]. It may also prolong the
90 patient's stay in the PACU and increase the demand for medical staff, resulting in
91 higher medical costs [6]. Elderly individuals are one of the main population groups
92 affected by EA [7]. Cardiovascular and cerebrovascular diseases are common in
93 elderly individuals [8]. EA may have more serious adverse consequences for elderly
94 patients[5]..

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

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4 103 In this study, we retrospectively collected the medical records of 421 elderly
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6 104 patients who underwent general anaesthesia for TJA. We aimed to determine the
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9 105 incidence and risk factors of postoperative EA in elderly patients, in order to assess
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12 106 the predictive values, and provide guidance for preventing and treating EA.
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For peer review only

108 **Materials and methods**

109 *Ethics statement*

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

115 *Patients*

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

124 *Routine practice of perioperative management*

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

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4 127 femoral nerve block (FNB) was performed in patients undergoing total knee
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6 128 replacement (TKA), while ultrasound-guided fascia iliac compartment block (FICB)
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9 129 was performed in patients undergoing total hip replacement (THA). All 20-ml (0.5%)
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11 130 ropivacaine solutions were infused into the nerve block. Urinary catheterisation was
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14 131 performed in all patients after inducing anaesthesia. Anaesthesia was maintained
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17 132 using intravenous remifentanyl and propofol. Patients were transferred to the PACU
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20 133 after the operation. These patients were extubated in the PACU.

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22 134 Speciality nurses assessed all patients in the PACU using a standardised
23
24 135 protocol, including the visual analogue scale (VAS), Richmond Agitation Sedation
25
26 136 Scale (RASS), and Steward recovery scores. VAS was used to assess postoperative
27
28 137 pain, and intravenous flurbiprofen was administered as an analgesic rescue when the
29
30 138 VAS score was > 4 . EA was evaluated using the RASS [18], and Table 1 presents the
31
32 139 score criteria. Patients with a RASS score > 1 were considered to have EA [18].
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35 140 Dexmedetomidine was administered in cases of severe agitation (RASS = 4). Patients
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37 141 with ward recovery scores > 4 were transferred to the ward from the PACU.
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44 143 ***Data collection***

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47 144 The following patient-related variables were recorded: (1) population data and
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49 145 medical history, including age, sex, body mass index (BMI), ASA classification,
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51 146 education level, history of heart disease, respiratory disease, hypertension, and
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54 147 diabetes; (2) perioperative clinical information, including operation type and times,
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57 148 body temperature after the surgery, VAS score, catheter-related bladder discomfort
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4 149 (CRBD), preoperative fasting times, intraoperative blood loss, warm treatment,
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6 150 postoperative nausea and vomiting, duration in PACU, RASS score, and severe
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9 151 intraoperative hypotension (mean arterial pressure < 65 mmHg for at least 1 min); and
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12 152 (3) laboratory tests. Preoperative fasting time refers to the period from the last intake
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14 153 of liquids or solids to the beginning of anaesthesia induction.
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19 155 *Statistical analysis and sample size*

22 156 The sample size was calculated using GPower software version 3.1 (Franz Faul,
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24 157 University of Kiel, Kiel, Germany). The effect size was set to 0.3, α level to 0.05, and
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27 158 1- β to 0.85. A sample size of 100 patients was the optimal sample size needed to
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30 159 prove the difference between the two groups. Considering the easy acquisition of
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33 160 electronic medical records, we included patients who met the inclusion and exclusion
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35 161 criteria between December 2019 and June 2020.
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37 162 Statistical analysis was performed using SPSS version 26.0 (SPSS Inc.,
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40 163 Chicago, IL, USA). Continuous data are presented as the means \pm standard deviations,
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43 164 and categorical data are presented as numbers and percentages. Independent risk
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45 165 factors were identified using univariate and multivariable logistic regression analyses.
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48 166 The measurement data were assessed for normal and nonnormal distributions. Two
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51 167 independent sample t tests were used to determine the differences between groups for
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54 168 continuous variables with a normal distribution. The nonparametric Mann–Whitney U
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56 169 test was used to compare differences between groups for continuous variables with
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59 170 nonnormal distributions. Chi-square tests were used to determine differences between
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4 171 groups for categorical data. Variables with $P < 0.2$ were entered in multivariable
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6 172 logistic regression analysis. A positive stepwise method was used to adjust for
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9 173 multiple risk factors. Each variable was expressed as an odds ratio (OR) with a 95%
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11 174 confidence interval (CI). The predictive value of the risk factors for EA was assessed
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14 175 using the receiver operating characteristic (ROC) curve. The cut-off point was
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17 176 calculated based on the maximum Youden index value. Statistical significance was set
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19 177 at a P value < 0.05 .

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23 24 179 ***Patient and public involvement***

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27 180 None of the patients were involved in the design, data provision, analysis, or
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30 181 publication of the study.
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182 **Results**

183 *General information on the study population*

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

194 *Perioperative clinical information and laboratory tests*

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

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

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4 203 between the two groups ($P < 0.05$). Additionally, no significant differences were
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6 204 observed between the two groups regarding surgery type and times, intraoperative
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9 205 blood loss, intraoperative hypotension, warm treatment, and laboratory tests (Table 3).
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12 13 14 207 ***Multivariable logistic regression analysis***

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17 208 Based on the univariate analysis, variables included in the multivariable logistic
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19 209 regression analysis included the VAS score for postoperative pain, male sex, body
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21 210 temperature after the surgery, length of stay in the PACU, preoperative fasting times,
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25 211 and CRBD.

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27 212 The correlation between the VAS score for postoperative pain, male sex,
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30 213 preoperative fasting times, CRBD, and EA after TJA could be determined based on
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32 214 multivariable logistic analysis (Fig. 2). The VAS score for postoperative pain (OR =
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34 215 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), CRBD
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36 216 (OR = 7.847; 95% CI: 4.001–15.392), fasting times for solids (OR = 1.703; 95% CI:
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38 217 1.260–2.301), and fasting times for fluids (OR = 1.728; 95% CI: 1.263–2.365) were
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41 218 independent risk factors. However, we could not confirm the independence of
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44 219 variables, such as body temperature after the surgery and length of stay in the PACU,
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46 220 in the multivariable logistic analysis.
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49 50 51 222 ***Results of ROC curves for risk factors***

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54 223 The predictive value analysed using the ROC curve is demonstrated in Fig. 3.

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57 224 The area under the ROC curve (AUC) for the VAS score was 0.769, with a cut-off
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4 225 value of 4.0, sensitivity of 60%, and specificity of 87% (95% CI: 0.718–0.819, P <
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6 226 0.001). The AUC of fasting times for solids was 0.753, with a cut-off value of 10.5,
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9 227 sensitivity of 62%, and specificity of 86% (95% CI: 0.699–0.807, P < 0.001). The
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11 228 AUC of fasting times for fluids was 0.768, with a cut-off value of 8.5, sensitivity of
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14 229 64%, and specificity of 74% (95% CI: 0.719–0.816, P < 0.001).
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20 231 **Discussion**

22 232 The results of this study indicated that EA was a common postoperative
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24 233 complication in patients who underwent general anaesthesia for TJA. Furthermore,
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26 234 this study identified four risk factors associated with with EA in elderly patients who
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28 235 underwent TJA, including postoperative pain, CRBD, male sex, and preoperative
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31 236 fasting times.
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36 237 The incidence of EA was 37.6% in elderly patients who underwent TJA. To our
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38 238 knowledge, this report is the first on the incidence of EA in elderly patients who have
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40 239 undergone TJA. Previous research has shown that the incidence of EA varies widely.
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43 240 A prospective study demonstrated that 13.9% (158/1136) of adult patients had EA in
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45 241 the PACU [19]. Xi et al. [7] reported that the incidence of EA in elderly patients who
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47 242 underwent gastrointestinal surgery was 40%. Moreover, an extremely high proportion
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49 243 of patients, 90.5% (19/21), experienced EA because of the effects of succinylcholine
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51 244 [20]. These large differences may be attributed to the types of surgery, anaesthetic
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54 245 management, patient characteristics, and assessment methods.
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4 246 Many scales are available to assess EA in adults, including the RASS, Ricker
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6 247 Sedation-Agitation Scale (RSAS), Aono's 4-point scale and so on. Unlike the
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9 248 excellent reliability and validity in assessing sedation and agitation in the ICU [18],
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11 249 the reliability and validity of the RASS in the PACU have not been validated;
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14 250 Nevertheless, the RASS is easy to use and administer and has discrete criteria [18].
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17 251 Thus, we believe that RASS is a effective and efficient method of assessing EA in the
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19 252 PACU. Similarly, Makarem et al. [19] and Xi et al. [7] also chose the RASS to assess
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22 253 EA in the PACU.

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25 254 Almost all researchers agree that postoperative pain is an independent risk factor
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27 255 for EA. Pain, an uncomfortable emotional experiences, can lead to some complex
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30 256 neurobehavioural behaviours, such as agitation [21]. Our study demonstrated that the
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33 257 VAS scores of patients in the EA group were higher than those in the non-EA group,
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35 258 and a postoperative pain VAS score ≥ 4 was the cut-off point for EA. Pain after TJA
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38 259 is common, and several studies have discovered that more than 50% of patients have
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41 260 suboptimal pain management afterTHA, and 75% of patients undergoing TKA
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43 261 complain of moderate-to-severe pain [12,22]. In this study, 72% (295/410) of patients
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46 262 complained of pain, and 5% (21/410) of patients experienced severe pain, comparable
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49 263 to the results of previous reports. Yu et al. [23] found that nearly half of patients had
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51 264 EA because of insufficient postoperative analgesia. Peripheral nerve blocks (PNBs)
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54 265 can provide excellent analgesia [24]. In our study, FNB was routinely used in patients
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57 266 undergoing TKA, and FICB was used for THA to improve postoperative analgesia.
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59 267 However, due to anatomic variations and individual characteristics, PNBs may not
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4 268 absolutely eliminate pain in patients undergoing TJA, leading to some patients
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7 269 experiencing EA due to postoperative pain in the study. Moreover, sore throat and
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10 270 catheter-related pain should not be ignored because postoperative pain is not limited
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12 271 to wound pain. Based on these findings, we strongly suggest that multimodal
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14 272 analgesia should be performed to benefit patients, especially with preventive
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17 273 analgesia.

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20 274 The placement of an indwelling catheter is a common clinical procedure in the
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22 275 perioperative period. The collected urine is used for urine measurements and blood
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25 276 volume evaluation. However, patients with indwelling catheters are prone to CRBD
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27 277 [25]. CRBD is characterised by discomfort confined to the suprapubic region, burning
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30 278 sensation, pain, and urinary urgency and frequency [26,27]. CRBD can occur in 47–
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33 279 90% of patients with a indwelling catheter [5] and CRBD can increase the incidence
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35 280 of EA and pain sensation after surgery [28]. A retrospective study reported that
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38 281 approximately 10% of patients experienced EA during urological surgery, possibly
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41 282 related to CRBD [16]. In our study, 28.0% (119 of 410) of patients experienced EA
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44 283 due to CRBD, and the higher incidence of EA may be due to the age of the recruited
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47 284 patients. This is because age ≥ 50 years was an independent predictor of CRBD [29].
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50 285 Indwelling catheters as a risk factor for EA have been reported previously in the
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53 286 literature [30]. Early removal of indwelling catheters is helpful in decreasing EA
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56 287 associated with CRBD.

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59 288 Regarding the effect of sex on EA, the results of the study are similar to those of
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289 reported in other literatures in which male sex was identified as an independent risk

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4 290 factor for EA [29]. This observation could be explained by several factors. First, male
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6 291 patients were high-risk patients with CRBD [29]. Half of all men aged ≥ 50 years and
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9 292 over 80% of men aged ≥ 80 years have prostatic hyperplasia, which can easily cause
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11 293 discomfort and pain when the catheter tip contacts the bladder triangle on the pubis
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14 294 [31]. Thus, male patients especially have difficulty tolerating the discomfort associated
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17 295 with catheters during the awakening period of anaesthesia. Furthermore, male patients
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19 296 have low postoperative pain tolerance, requiring more analgesics than female patients
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22 297 [32].

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25 298 Preoperative fasting is one of the preoperative instructions for patients. whether
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27 299 preoperative fasting is a risk factor for EA has not been reported in previous studies..
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30 300 Prolonged preoperative fasting can cause metabolic, physical, and psychological
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32 301 discomfort in patients, eventually leading to abnormal neurobehavioural changes,
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35 302 such as postoperative delirium (PD) [33]. However, EA was not analysed. In this
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38 303 study, the fasting times of the EA group were significantly longer than those of the
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41 304 non-EA group and exceeded conventional fasting times (no more than 8 hours for
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43 305 solids and no more than 6 hours for liquids before surgery)[34], furthermore, 10.5 h
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45 306 (fasting times for solids) and 8.6 h (fasting times for fluids) are cut-off points for EA.
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48 307 Prolonged preoperative fasting times led to patient anxiety, and the degree of anxiety
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51 308 was related to the length of fasting time [34], While preoperative anxiety has been
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54 309 reported as a risk factor for EA [16]. Due to the numerous patients and the lack of
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56 310 medical resources, patients may often experienced longer fasting times than they were
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4 311 advised .To reduce the incidence of EA, effective preoperative education and
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6 312 scientific operation schedule lists should be developed.
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9 313• This study had some limitations. Firstly, we only included elderly patients
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11 314 who had undergone intravenous anaesthesia. Future studies may utilize other methods
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13 315 and anaesthetics. Secondly, this was a single-centre study; therefore, the
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15 316 generalisability of the results was not fully verified. Future multi-centre studies must
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17 317 assess external validity. Lastly, this is a retrospective cohort study; some bias is
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19 318 unavoidable. Future prospective studies must be conducted for further research.
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320 **Conclusions**

321 In short, this retrospective study showed that EA is a common complication in
322 elderly patients after TJA .EA occurred in 37.6% of the elderly patients who
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34 323 underwent TJA. Postoperative pain, CRBD, male sex, and preoperative fasting times
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36 324 were independent predictors of EA.These risk factors can contribute to identifying
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38 325 high-risk patients to develop effective strategies to prevent and treat EA. Agitation
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40 326 has many causes [35]; therefore, the best clinical strategies should be multimodal.
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49 328 **Contributorship statements:** Zhenguo Luo and Jianhong Hao have made substantial
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51 329 contributions to the conception or design of the manuscript. Naigeng Wang wrote this
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53 330 manuscript and made some changes after review. Furthermore, he worked with Jing
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55 331 Du and Jie Zhang to acquire, analyse, and interpret the data. All authors have
56
57 332 participated in drafting the manuscript, and Zhenguo Luo revised it critically. All
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333 authors contributed equally to the manuscript and read and approved the final version
334 of the manuscript.

335

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338

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341

342 **Data sharing statement :** No additional data are available.

343

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

347

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45 452 2015;21;5(4):e007542

458 **Tables**459 **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

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461 **Notes:** Scores of 1 to 4 indicated different levels of agitation, 0 indicated calmness
 462 and alertness, and -1 to -5 indicated different levels of sedation.

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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%)	

467 **Notes:** Clinical information of patients were analysed using univariate analysis.

468 Continuous data are presented as the means \pm standard deviations, while categorical

469 data are presented as numbers and percentages. *P-value, differences between

470 patients in the two groups. *P<0.05, ***P<0.001. ASA: American Society of

471 Anesthesiologists; BMI: body mass index.

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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 (°C)	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

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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

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4 481 **Notes:** Patients' perioperative clinical information and agitation-related laboratory
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6 482 test indicators were analysed using univariate analysis. Continuous data are presented
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9 483 as means \pm standard deviations, while categorical data are presented as numbers and
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11 484 percentages. *P-value, differences between patients in the two groups. *P<0. 05,
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14 485 ***P<0. 001.
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7 504 **Figure legends**8
9 505 **Figure 1 Flow chart of study participants.** In total, 421 patients met the inclusion
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11 506 and exclusion criteria. However, 11 patients were excluded from the study; six were
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13 507 transferred to the ICU postoperatively, and the surgical protocols of five were
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15 508 changed during the operation. Finally, the statistical analysis included 410 patients.
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22 510 **Figure 2 Risk factors for EA using metanalysis plot.** The VAS score for
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24 511 postoperative pain (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95%
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26 512 CI: 1.781–6.435), urinary catheter irritation (OR = 7.847; 95% CI: 4.001–15.392),
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28 513 fasting times for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting times for
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30 514 fluids (OR = 1.728; 95% CI: 1.263–2.365) were the independent risk factors.
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37 516 **Figure 3 Risk factors for EA using the ROC curve.** Predictive values of risk factors
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39 517 were assessed using the ROC curve. The VAS score for postoperative pain (AUC =
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41 518 0.769, 95% CI: 0.718–0.819, $P < 0.001$), fasting times for solids (AUC = 0.753, 95%
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43 519 CI: 0.699–0.807, $P < 0.001$) and fasting times for fluids (AUC = 0.768, 95% CI:
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45 520 0.719–0.816, $P < 0.001$) demonstrated good predictive effects.
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8 526 **Reporting checklist for cross sectional study.**9
10 527 Based on the STROBE cross sectional guidelines.11
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14 528 **Instructions to authors**15
16
17 529 Complete this checklist by entering the page numbers from your manuscript
18 530 where readers will find each of the items listed below.19
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21 531 Your article may not currently address all the items on the checklist. Please
22 532 modify your text to include the missing information. If you are certain that an
23 533 item does not apply, please write "n/a" and provide a short explanation.24
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26 534 Upload your completed checklist as an extra file when you submit to a journal.27
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29 535 In your methods section, say that you used the STROBE cross
30 536 sectionalreporting guidelines, and cite them as:31
32
33 537 von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandembroucke
34 538 JP. The Strengthening the Reporting of Observational Studies in Epidemiology
35 539 (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	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

8	Background /	#2	Explain the scientific background and	5
9	rationale		rationale for the investigation being	
10			reported	
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14	Objectives	#3	State specific objectives, including any	6
15			prespecified hypotheses	
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18	Methods			
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21	Study design	#4	Present key elements of study design	NA
22			early in the paper	
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25	Setting	#5	Describe the setting, locations, and	7
26			relevant dates, including periods of	
27			recruitment, exposure, follow-up, and	
28			data collection	
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33	Eligibility criteria	#6a	Give the eligibility criteria, and the	7
34			sources and methods of selection of	
35			participants.	
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39		#7	Clearly define all outcomes, exposures,	8
40			predictors, potential confounders, and	
41			effect modifiers. Give diagnostic criteria, if	
42			applicable	
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46	Data sources /	#8	For each variable of interest give sources	8
47	measurement		of data and details of methods of	
48			assessment (measurement). Describe	
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4	Bias	#9	Describe any efforts to address potential sources of bias	8-9
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8	Study size	#10	Explain how the study size was arrived at	9
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11	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
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18	Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9-10
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22	Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9-10
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27	Statistical methods	#12c	Explain how missing data were addressed	NA
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31	Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
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35	Statistical methods	#12e	Describe any sensitivity analyses	9-10
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39	Results			
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42	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
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54	Participants	#13b	Give reasons for non-participation at each stage	11
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4	Participants	#13c Consider use of a flow diagram	32
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7	Descriptive data	#14a Give characteristics of study participants	11
8		(eg demographic, clinical, social) and	
9		information on exposures and potential	
10		confounders. Give information separately	
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12		applicable.	
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17	Descriptive data	#14b Indicate number of participants with	11
18		missing data for each variable of interest	
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22	Outcome data	#15 Report numbers of outcome events or	11-13
23		summary measures. Give information	
24		separately for exposed and unexposed	
25		groups if applicable.	
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29	Main results	#16a Give unadjusted estimates and, if	12
30		applicable, confounder-adjusted	
31		estimates and their precision (eg, 95%	
32		confidence interval). Make clear which	
33		confounders were adjusted for and why	
34		they were included	
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40	Main results	#16b Report category boundaries when	NA
41		continuous variables were categorized	
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44	Main results	#16c If relevant, consider translating estimates	NA
45		of relative risk into absolute risk for a	
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50	Other analyses	#17 Report other analyses done—e.g.,	NA
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56	Discussion		
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4	Key results	#18	Summarise key results with reference to 13
5			study objectives
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8	Limitations	#19	Discuss limitations of the study, taking 17
9			into account sources of potential bias or
10			imprecision. Discuss both direction and
11			magnitude of any potential bias.
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16	Interpretation	#20	Give a cautious overall interpretation 13-17
17			considering objectives, limitations,
18			multiplicity of analyses, results from
19			similar studies, and other relevant
20			evidence.
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25	Generalisability	#21	Discuss the generalisability (external 17
26			validity) of the study results
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29	Other		
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34	Funding	#22	Give the source of funding and the role of 17
35			the funders for the present study and, if
36			applicable, for the original study on which
37			the present article is based
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 542 using <https://www.goodreports.org/>, a tool made by the EQUATOR Network in
 543 collaboration with Penelope.ai

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Figure 1 Flow chart of study participants.

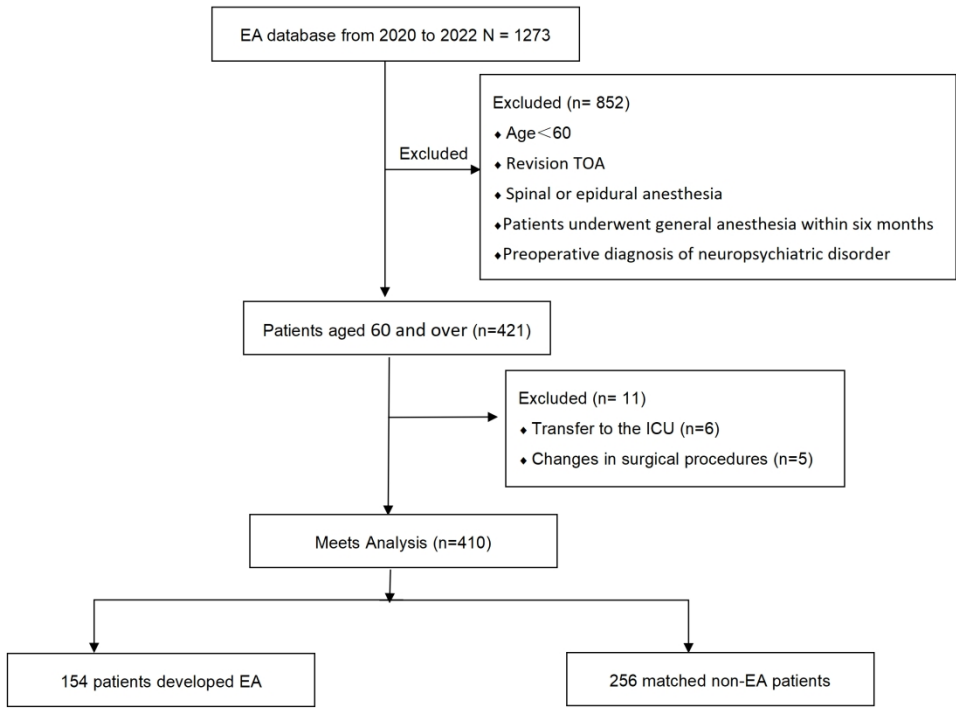


Figure 1 Flow chart of study participants

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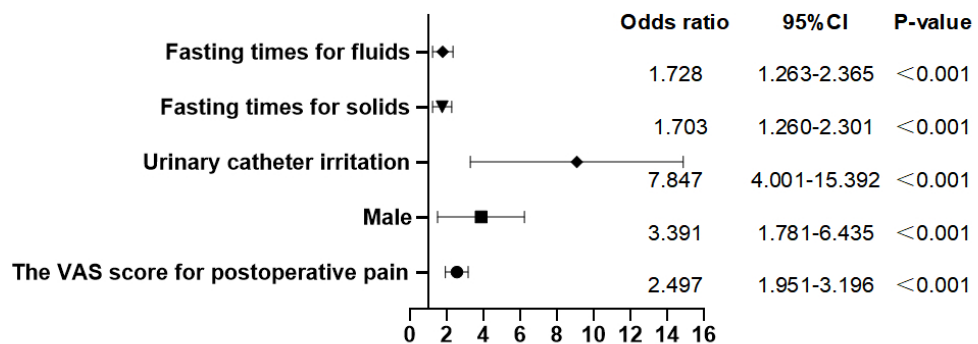


Figure 2 Risk factors of EA by metanalysis plot

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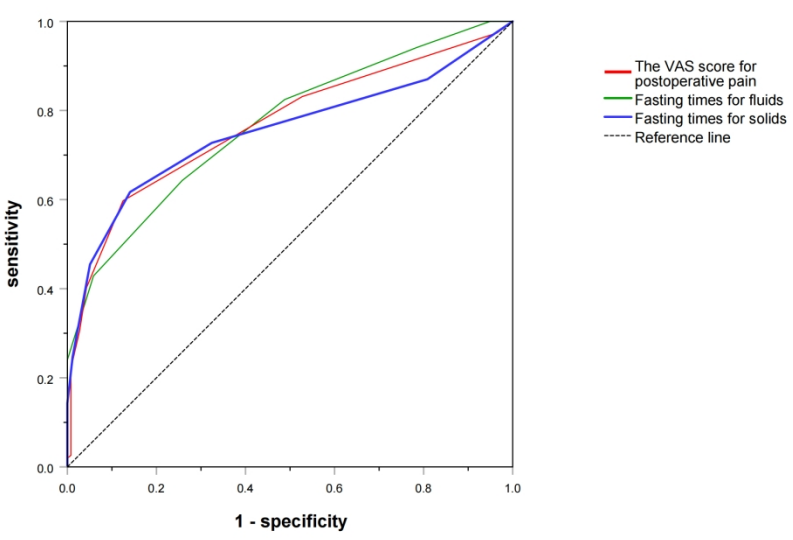


Figure 3 Risk factors of EA by the ROC curve
1178x667mm (57 x 57 DPI)

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 sectional reporting guidelines, and cite them as:

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

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15			prespecified hypotheses	
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18	Methods			
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21	Study design	#4	Present key elements of study design	NA
22			early in the paper	
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24				
25	Setting	#5	Describe the setting, locations, and	7
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34			sources and methods of selection of	
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52			and unexposed groups if applicable.	
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59	Bias	#9	Describe any efforts to address potential	8-9
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			sources of bias	
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6	Study size	#10	Explain how the study size was arrived at	9
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8	Quantitative	#11	Explain how quantitative variables were	8
9	variables		handled in the analyses. If applicable,	
10			describe which groupings were chosen,	
11			and why	
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16	Statistical	#12a	Describe all statistical methods, including	9-10
17	methods		those used to control for confounding	
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20	Statistical	#12b	Describe any methods used to examine	9-10
21	methods		subgroups and interactions	
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24	Statistical	#12c	Explain how missing data were	NA
25	methods		addressed	
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28	Statistical	#12d	If applicable, describe analytical methods	NA
29	methods		taking account of sampling strategy	
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33	Statistical	#12e	Describe any sensitivity analyses	9-10
34	methods			
35				
36				
37	Results			
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40	Participants	#13a	Report numbers of individuals at each	11
41			stage of study—eg numbers potentially	
42			eligible, examined for eligibility, confirmed	
43			eligible, included in the study, completing	
44			follow-up, and analysed. Give information	
45			separately for for exposed and	
46			unexposed groups if applicable.	
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52	Participants	#13b	Give reasons for non-participation at	11
53			each stage	
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56	Participants	#13c	Consider use of a flow diagram	32
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59	Descriptive data	#14a	Give characteristics of study participants	11
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(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

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		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

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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-068284.R3
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1 **Risk factors for emergence agitation during the awakening**
2 **period in elderly patients after total joint arthroplasty: a**
3 **retrospective cohort study**

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

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17 Hospital)
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4 43 **Abstract**

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6 44 **Objectives:** This study aimed to explore the incidence and risk factors for emergence
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9 45 agitation (EA) in elderly patients who underwent total joint arthroplasty (TJA) under
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12 46 general anaesthesia, and to assess their predictive values.

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14 47 **Design:** Single-centre retrospective cohort study.

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17 48 **Setting:** A 1,600-bed general tertiary hospital in China.

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19 49 **Participants:** This study enrolled 421 elderly patients scheduled for elective primary
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22 50 TJA under general anaesthesia.

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24 51 **Primary and Secondary Outcome Measures:** EA was assessed using the Richmond
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27 52 Agitation Sedation Scale during the awakening period after surgery in the
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30 53 postanaesthesia care unit(PACU). Risk factors for EA were identified using univariate
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33 54 and multivariable logistic analyses. The receiver operating characteristic curve (ROC)
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36 55 was used to assess the predictive values of the risk factors for EA.

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38 56 **Results:** The incidence of EA in elderly patients who underwent TJA was 37.6%.
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41 57 According to the multivariable logistic analysis, postoperative pain (95% confidence
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43 58 interval [CI]: 1.951–3.196), male sex (95% CI: 1.781–6.435), catheter-related bladder
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45 59 discomfort (CRBD) (95% CI: 4.001–15.392), and longer fasting times for solids (95%
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47
48 60 CI: 1.260–2.301) and fluids (95% CI: 1.263–2.365) were independent risk factors for
49
50
51 61 EA. As shown by the ROC analysis, postoperative pain and fasting times for solids
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53
54 62 and fluids had good predictive values,with areas under the ROC curve (AUCs)
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56
57 63 equalling 0.769, 0.753 and 0.768,respectively.

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4 64 **Conclusions:** EA is a common complication after TJA in elderly patients. Some risk
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6 65 factors, including postoperative pain, male sex, CRBD, and longer fasting times, can
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9 66 increase the incidence of EA. These risk factors may contribute to identifying
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11 67 high-risk patients, which facilitates the development of effective strategies to prevent
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14 68 and treat EA.
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22 71 **Keywords:** Emergence agitation; Elderly patients; Risk factors; Total joint
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24 72 arthroplasty
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30 74 **Strengths and Limitations:**
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- 32 75 ➤ .In this study, the medical records of 421 patients who underwent TJA were
33
34 76 reviewed. Univariate and multivariable logistic analyses were used to identify the
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36 77 risk factors of EA, and the ROC was used to evaluate the predictive values of the
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38 78 risk factors.
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40 79 ➤ This work was a single-centre retrospective study, and the generalizability of the
41
42 80 results is weak.
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44 81 ➤ Only patients with one category of arthritis were studied.
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85 **Introduction**

86 Emergence agitation (EA), a common complication during the awakening period
87 after general anaesthesia, refers to a temporary state of mental and motor excitement
88 [1]. Clinical features of EA include disorientation, excitation, agitation, and
89 combative behaviours [2,3]. The incidence of EA in adults varies from 4.7% to 74%
90 [4]. EA can also increase the risk of wound bleeding or dehiscence, self-extubation,
91 falling out of bed, and violent behaviour towards staff [5]. It may also prolong the
92 patient's stay in the PACU and increase the demand for medical staff, resulting in
93 higher medical costs [6]. Elderly individuals are one of the main population groups
94 affected by EA [7]. Cardiovascular and cerebrovascular diseases are common in
95 elderly individuals [8]. Thus, EA may have more serious adverse consequences for
96 elderly patients[5].

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

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4 105 In this study, we retrospectively collected the medical records of 421 elderly
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6 106 patients who underwent general anaesthesia for TJA. We aimed to determine the
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9 107 incidence and risk factors of postoperative EA in elderly patients, to assess the
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12 108 predictive values, and provide guidance for preventing and treating EA.
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For peer review only

110 **Materials and methods**

111 *Ethics statement*

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

117 *Patients*

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

126 *Routine practice of perioperative management*

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

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4 129 femoral nerve block (FNB) was performed in patients undergoing total knee
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6 130 replacement (TKA), while ultrasound-guided fascia iliac compartment block (FICB)
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9 131 was performed in patients undergoing total hip replacement (THA). All 20-ml (0.5%)
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11 132 ropivacaine solutions were infused into the nerve block. Urinary catheterisation was
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14 133 performed in all patients after inducing anaesthesia. Anaesthesia was maintained
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17 134 using intravenous remifentanyl and propofol. Patients were transferred to the PACU
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20 135 after the operation. These patients were extubated in the PACU.

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22 136 Speciality nurses assessed all patients in the PACU using a standardised
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24 137 protocol, including the visual analogue scale (VAS), Richmond Agitation Sedation
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27 138 Scale (RASS), and Steward recovery scores. VAS was used to assess postoperative
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30 139 pain, and intravenous flurbiprofen was administered as an analgesic rescue when the
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32 140 VAS score was > 4 . EA was evaluated using the RASS [18], and Table 1 presents the
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35 141 score criteria. Patients with a RASS score > 1 were considered to have EA [18].
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38 142 Dexmedetomidine was administered in cases of severe agitation (RASS = 4). Patients
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40 143 with ward recovery scores > 4 were transferred to the ward from the PACU.
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45 145 ***Data collection***

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48 146 The following patient-related variables were recorded: (1) population data and
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51 147 medical history, including age, sex, body mass index (BMI), ASA classification,
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54 148 education level, history of heart disease, respiratory disease, hypertension, and
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57 149 diabetes; (2) perioperative clinical information, including operation type and times,
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59 150 body temperature after the surgery, VAS score, catheter-related bladder discomfort

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4 151 (CRBD), preoperative fasting times, intraoperative blood loss, warm treatment,
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6 152 postoperative nausea and vomiting, duration in PACU, RASS score, and severe
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9 153 intraoperative hypotension (mean arterial pressure < 65 mmHg for at least 1 min); and
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12 154 (3) laboratory tests. Preoperative fasting time refers to the period from the last intake
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14 155 of liquids or solids to the beginning of anaesthesia induction.
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19 157 *Statistical analysis and sample size*

22 158 The sample size was calculated using GPower software version 3.1 (Franz Faul,
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24 159 University of Kiel, Kiel, Germany). The effect size was set to 0.3, α level to 0.05, and
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27 160 1- β to 0.85. A sample size of 100 patients was the optimal sample size needed to
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30 161 prove the difference between the two groups. Considering the easy acquisition of
31
32 162 electronic medical records, we included patients who met the inclusion and exclusion
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35 163 criteria between December 2019 and June 2020.
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37 164 Statistical analysis was performed using SPSS version 26.0 (SPSS Inc.,
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40 165 Chicago, IL, USA). Continuous data were presented as the means \pm standard
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43 166 deviations, and categorical data were presented as numbers and percentages.
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46 167 Independent risk factors were identified using univariate and multivariable logistic
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48 168 regression analyses. The measurement data were assessed for normal and nonnormal
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51 169 distributions. Two independent sample t tests were used to determine the differences
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54 170 between groups for continuous variables with a normal distribution. The
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56 171 nonparametric Mann–Whitney U test was used to compare differences between
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59 172 groups for continuous variables with nonnormal distributions. Chi-square tests were
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4 173 used to determine differences between groups for categorical data. Variables with $P <$
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6 174 0.2 were entered in multivariable logistic regression analysis. A positive stepwise
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9 175 method was used to adjust for multiple risk factors. Each variable was expressed as an
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12 176 odds ratio (OR) with a 95% confidence interval (CI). The predictive value of the risk
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14 177 factors for EA was assessed using the receiver operating characteristic (ROC) curve.
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17 178 The cut-off point was calculated based on the maximum Youden index value.
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19 179 Statistical significance was set at a P value < 0.05 .

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23 24 181 ***Patient and public involvement***

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27 182 None of the patients were involved in the design, data provision, analysis, or
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30 183 publication of the study.
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184 **Results**

185 *General information on the study population*

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

196 *Perioperative clinical information and laboratory tests*

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

200 Compared with the non-EA group, the VAS score was higher (P < 0.05), body
201 temperature after the surgery was lower (P < 0.05), and the patient's length of stay in
202 the PACU and preoperative fasting times were longer in the EA group (P < 0.05).
203 Moreover, 77.3% (119/154) of patients in the EA group had CRBD, while 32.4%
204 (83/256) of patients in the non-EA group experienced CRBD. This variable differed

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4 205 significantly between the two groups ($P < 0.05$). Additionally, no significant
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6 206 differences were observed between the two groups regarding surgery type and times,
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9 207 intraoperative blood loss, intraoperative hypotension, warm treatment, and laboratory
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11 208 tests (Table 3).

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15 16 17 210 ***Multivariable logistic regression analysis***

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19 211 Based on the univariate analysis, variables included in the multivariable logistic
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21 212 regression analysis included the VAS score for postoperative pain, male sex, body
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23 213 temperature after the surgery, length of stay in the PACU, preoperative fasting times,
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25 214 and CRBD.

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29 215 The correlation between the VAS score for postoperative pain, male sex,
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31 216 preoperative fasting times, CRBD, and EA after TJA could be determined based on
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33 217 multivariable logistic analysis (Fig. 2). The VAS score for postoperative pain (OR =
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35 218 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95% CI: 1.781–6.435), CRBD
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37 219 (OR = 7.847; 95% CI: 4.001–15.392), fasting times for solids (OR = 1.703; 95% CI:
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39 220 1.260–2.301), and fasting times for fluids (OR = 1.728; 95% CI: 1.263–2.365) were
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41 221 independent risk factors. However, we could not confirm the independence of
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43 222 variables, such as body temperature after the surgery and length of stay in the PACU,
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45 223 in the multivariable logistic analysis.

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52 53 54 225 ***Results of ROC curves for risk factors***

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4 226 The predictive value analysed using the ROC curve is demonstrated in Fig. 3.
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6 227 The area under the ROC curve (AUC) for the VAS score was 0.769, with a cut-off
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9 228 value of 4.0, sensitivity of 60%, and specificity of 87% (95% CI: 0.718–0.819, $P <$
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12 229 0.001). The AUC of fasting times for solids was 0.753, with a cut-off value of 10.5,
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15 230 sensitivity of 62%, and specificity of 86% (95% CI: 0.699–0.807, $P <$ 0.001). The
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17 231 AUC of fasting times for fluids was 0.768, with a cut-off value of 8.5, sensitivity of
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20 232 64%, and specificity of 74% (95% CI: 0.719–0.816, $P <$ 0.001).
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26 234 **Discussion**

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29 235 The results of this study indicated that EA was a common postoperative
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31 236 complication in patients who underwent general anaesthesia for TJA. Furthermore,
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34 237 this study identified four risk factors associated with with EA in elderly patients who
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37 238 underwent TJA, including postoperative pain, CRBD, male sex, and preoperative
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39 239 fasting times.

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42 240 The incidence of EA was 37.6% in elderly patients who underwent TJA. To our
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45 241 knowledge, this report is the first on the incidence of EA in elderly patients who have
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47 242 undergone TJA. Previous research has shown that the incidence of EA varies widely.
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50 243 A prospective study demonstrated that 13.9% (158/1136) of adult patients had EA in
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52 244 the PACU [19]. Xi et al. [7] reported that the incidence of EA in elderly patients who
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55 245 underwent gastrointestinal surgery was 40%. Moreover, an extremely high proportion
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57 246 of patients, 90.5% (19/21), experienced EA because of the effects of succinylcholine
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4 247 [20]. These large differences may be attributed to the types of surgery, anaesthetic
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6 248 management, patient characteristics, and assessment methods.
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9 249 Many scales are available to assess EA in adults, including the RASS, Ricker
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11 250 Sedation-Agitation Scale (RSAS), Aono's 4-point scale and so on. Unlike the
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14 251 excellent reliability and validity in assessing sedation and agitation in the ICU [18],
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17 252 the reliability and validity of the RASS in the PACU have not been validated;
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20 253 Nevertheless, the RASS is easy to use and administer and has discrete criteria [18].
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22 254 Thus, we believe that RASS is a effective and efficient method of assessing EA in the
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25 255 PACU. Similarly, Makarem et al. [19] and Xi et al. [7] also chose the RASS to assess
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27 256 EA in the PACU.
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30 257 Almost all researchers agree that postoperative pain is an independent risk factor
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32 258 for EA. Pain, an uncomfortable emotional experiences, can lead to some complex
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35 259 neurobehavioural effects, such as agitation [21]. Our study demonstrated that the VAS
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38 260 scores of patients in the EA group were higher than those in the non-EA group, and a
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41 261 postoperative pain VAS score ≥ 4 was the cut-off point for EA. Pain after TJA is
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44 262 common, and several studies have discovered that more than 50% of patients have
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47 263 suboptimal pain management afterTHA, and 75% of patients undergoing TKA
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50 264 complain of moderate-to-severe pain [12,22]. In this study, 72% (295/410) of patients
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53 265 complained of pain, and 5% (21/410) of patients experienced severe pain, comparable
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56 266 to the results of previous reports. Yu et al. [23] found that nearly half of patients had
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59 267 EA because of insufficient postoperative analgesia. Peripheral nerve blocks (PNBs)
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268 can provide excellent analgesia [24]. In our study, FNB was routinely used in patients

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4 269 undergoing TKA, and FICB was used for THA to improve postoperative analgesia.
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7 270 However, due to anatomic variations and individual characteristics, PNBs may not
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9 271 absolutely eliminate pain in patients undergoing TJA, leading to some patients
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11 272 experiencing EA due to postoperative pain in the study. Moreover, sore throat and
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14 273 catheter-related pain should not be ignored because postoperative pain is not limited
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17 274 to wound pain. Based on these findings, we strongly suggest that multimodal
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19 275 analgesia should be performed to benefit patients, especially with preventive
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22 276 analgesia.

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25 277 The placement of an indwelling catheter is a common clinical procedure in the
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27 278 perioperative period. The collected urine is used for urine measurements and blood
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30 279 volume evaluation. However, patients with indwelling catheters are prone to CRBD
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32 280 [25]. CRBD is characterised by discomfort confined to the suprapubic region, burning
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35 281 sensation, pain, and urinary urgency and frequency [26,27]. CRBD can occur in 47–
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37
38 282 90% of patients with an indwelling catheter [5] and CRBD can increase the incidence
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41 283 of EA and pain sensation after surgery [28]. A retrospective study reported that
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43 284 approximately 10% of patients experienced EA during urological surgery, possibly
44
45 285 related to CRBD [16]. In our study, 28.0% (119 of 410) of patients experienced EA
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47
48 286 due to CRBD, and the higher incidence of EA may be due to the age of the recruited
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51 287 patients. This is because age ≥ 50 years was an independent predictor of CRBD [29].
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53 288 Indwelling catheters as a risk factor for EA have been reported previously in the
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55 289 literature [30]. Early removal of indwelling catheters is helpful in decreasing EA
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58 290 associated with CRBD.

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291 Regarding the effect of sex on EA, the results of the study are similar to those of
292 reported in other literatures in which male sex was identified as an independent risk
293 factor for EA [29]. This observation could be explained by several factors. First, male
294 patients were high-risk patients with CRBD [29]. Half of all men aged ≥ 50 years and
295 over 80% of men aged ≥ 80 years have prostatic hyperplasia, which can easily cause
296 discomfort and pain when the catheter tip contacts the bladder triangle on the pubis
297 [31]. Thus, male patients especially have difficulty tolerating the discomfort associated
298 with catheters during the awakening period of anaesthesia. Furthermore, male patients
299 have low postoperative pain tolerance, requiring more analgesics than female patients
300 [32].

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

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4 313 medical resources, patients may often experienced longer fasting times than they were
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6 314 advised .To reduce the incidence of EA, effective preoperative education and
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9 315 scientific operation schedule lists should be developed.
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11 316 This study had some limitations. Firstly, we only included elderly patients who
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14 317 had undergone intravenous anaesthesia. Future studies may utilize other methods and
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17 318 anaesthetics. Secondly, this was a single-centre study; therefore, the generalisability
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19 319 of the results was not fully verified. Future multi-centre studies must assess external
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22 320 validity. Lastly, this is a retrospective cohort study; some bias is unavoidable. Future
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25 321 prospective cohort studies should evaluate and validate the risk factors for EA
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27 322 identified by our study.
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35 325 **Conclusions**

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37 326 In short, this retrospective study showed that EA is a common complication in
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40 327 elderly patients after TJA .EA occurred in 37.6% of the elderly patients who
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43 328 underwent TJA. Postoperative pain, CRBD, male sex, and preoperative fasting times
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46 329 were independent predictors of EA.These risk factors may contribute to identifying
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48 330 high-risk patients to develop effective strategies to prevent and treat EA. Agitation
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50 331 has many causes [35]; therefore, the optimal clinical strategies should be multimodal.
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56 333 **Contributorship statements:** Zhenguo Luo and Jianhong Hao have made substantial
57
58 334 contributions to the conception or design of the manuscript. Naigeng Wang wrote this
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4 335 manuscript and made some changes after review. Furthermore, he worked with Jing
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6
7 336 Du and Jie Zhang to acquire, analyse, and interpret the data. All authors have
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10 337 participated in drafting the manuscript, and Zhenguo Luo revised it critically. All
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12 338 authors contributed equally to the manuscript and read and approved the final version
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14 339 of the manuscript.

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35 347 **Data sharing statement :** No additional data are available.

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40 349 **Ethics statements :** This study was approved by the Biomedical Research Ethics
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43 350 Committee of our hospital (approval no. 201812001). The study obtained consent to
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46 351 gather patients' medical record information through telephone follow-up.

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463 **Tables**464 **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

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466 **Notes:** Scores of 1 to 4 indicated different levels of agitation, 0 indicated calmness

467 and alertness, and -1 to -5 indicated different levels of sedation.

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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%)	

472 **Notes:** Clinical information of patients were analysed using univariate analysis.

473 Continuous data are presented as the means \pm standard deviations, while categorical

474 data are presented as numbers and percentages. *P-value, differences between

475 patients in the two groups. *P<0.05, ***P<0.001. ASA: American Society of

476 Anesthesiologists; BMI: body mass index.

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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 (°C)	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

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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

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4 486 **Notes:** Patients' perioperative clinical information and agitation-related laboratory
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6 487 test indicators were analysed using univariate analysis. Continuous data are presented
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9 488 as means \pm standard deviations, while categorical data are presented as numbers and
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11 489 percentages. *P-value, differences between patients in the two groups. *P<0. 05,
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14 490 ***P<0. 001.
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7 509 **Figure legends**8
9 510 **Figure 1 Flow chart of study participants.** In total, 421 patients met the inclusion
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11 511 and exclusion criteria. However, 11 patients were excluded from the study; six were
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14 512 transferred to the ICU postoperatively, and the surgical protocols of five were
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17 513 changed during the operation. Finally, the statistical analysis included 410 patients.
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22 515 **Figure 2 Risk factors for EA using metanalysis plot.** The VAS score for
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25 516 postoperative pain (OR = 2.497; 95% CI: 1.951–3.196), male sex (OR = 3.391; 95%
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27 517 CI: 1.781–6.435), urinary catheter irritation (OR = 7.847; 95% CI: 4.001–15.392),
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30 518 fasting times for solids (OR = 1.703; 95% CI: 1.260–2.301), and fasting times for
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33 519 fluids (OR = 1.728; 95% CI: 1.263–2.365) were the independent risk factors.
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38 521 **Figure 3 Risk factors for EA using the ROC curve.** Predictive values of risk factors
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40 522 were assessed using the ROC curve. The VAS score for postoperative pain (AUC =
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43 523 0.769, 95% CI: 0.718–0.819, $P < 0.001$), fasting times for solids (AUC = 0.753, 95%
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45 524 CI: 0.699–0.807, $P < 0.001$) and fasting times for fluids (AUC = 0.768, 95% CI:
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48 525 0.719–0.816, $P < 0.001$) demonstrated good predictive effects.
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8 531 **Reporting checklist for cross sectional study.**9
10 532 Based on the STROBE cross sectional guidelines.11
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13 533 **Instructions to authors**14
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17 534 Complete this checklist by entering the page numbers from your manuscript
18 535 where readers will find each of the items listed below.19
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21 536 Your article may not currently address all the items on the checklist. Please
22 537 modify your text to include the missing information. If you are certain that an
23 538 item does not apply, please write "n/a" and provide a short explanation.24
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27 539 Upload your completed checklist as an extra file when you submit to a journal.28
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30 540 In your methods section, say that you used the STROBE cross
31 541 sectionalreporting guidelines, and cite them as:32
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35 542 von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandembroucke
36 543 JP. The Strengthening the Reporting of Observational Studies in Epidemiology
37 544 (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

8	Background /	#2	Explain the scientific background and	5
9	rationale		rationale for the investigation being	
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14	Objectives	#3	State specific objectives, including any	6
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21	Study design	#4	Present key elements of study design	NA
22			early in the paper	
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33	Eligibility criteria	#6a	Give the eligibility criteria, and the	7
34			sources and methods of selection of	
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40			predictors, potential confounders, and	
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46	Data sources /	#8	For each variable of interest give sources	8
47	measurement		of data and details of methods of	
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4	Bias	#9	Describe any efforts to address potential sources of bias	8-9
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8	Study size	#10	Explain how the study size was arrived at	9
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11	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
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18	Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9-10
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27	Statistical methods	#12c	Explain how missing data were addressed	NA
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31	Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
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39	Results			
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54	Participants	#13b	Give reasons for non-participation at each stage	11
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4	Participants	#13c Consider use of a flow diagram	32
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7	Descriptive data	#14a Give characteristics of study participants	11
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29	Main results	#16a Give unadjusted estimates and, if	12
30		applicable, confounder-adjusted	
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40	Main results	#16b Report category boundaries when	NA
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4	Key results	#18	Summarise key results with reference to	13
5			study objectives	
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8	Limitations	#19	Discuss limitations of the study, taking	17
9			into account sources of potential bias or	
10			imprecision. Discuss both direction and	
11			magnitude of any potential bias.	
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16	Interpretation	#20	Give a cautious overall interpretation	13-17
17			considering objectives, limitations,	
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19			similar studies, and other relevant	
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25	Generalisability	#21	Discuss the generalisability (external	17
26			validity) of the study results	
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34	Funding	#22	Give the source of funding and the role of	17
35			the funders for the present study and, if	
36			applicable, for the original study on which	
37			the present article is based	
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41	545	None	The STROBE checklist is distributed under the terms of the Creative	
42	546	Commons Attribution License CC-BY. This checklist can be completed online		
43	547	using https://www.goodreports.org/ , a tool made by the EQUATOR Network in		
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Figure 1 Flow chart of study participants.

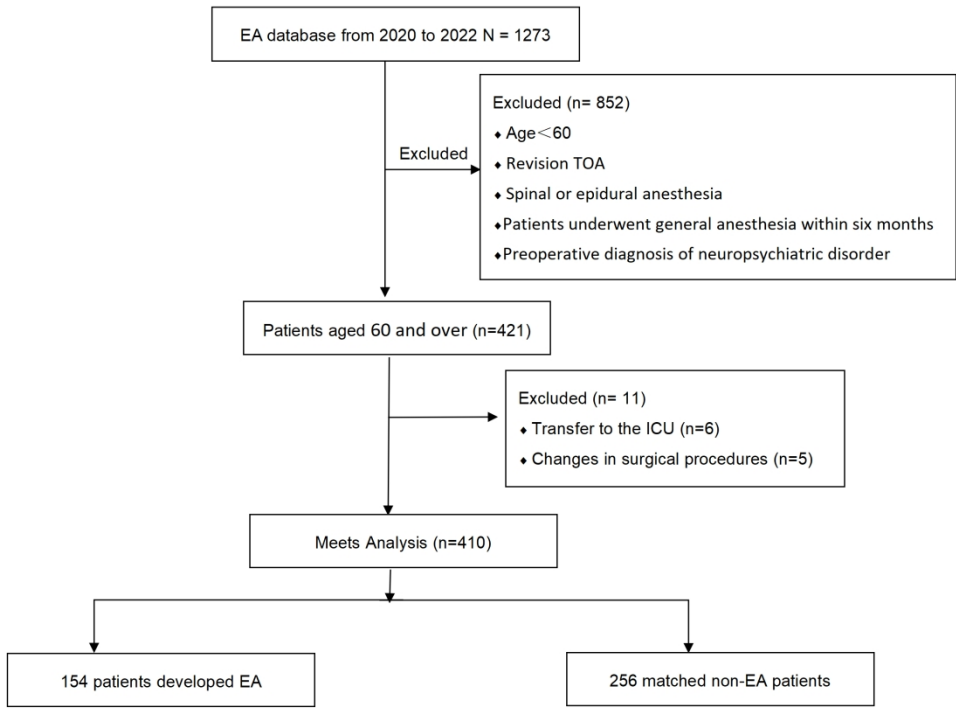


Figure 1 Flow chart of study participants

419x390mm (144 x 144 DPI)

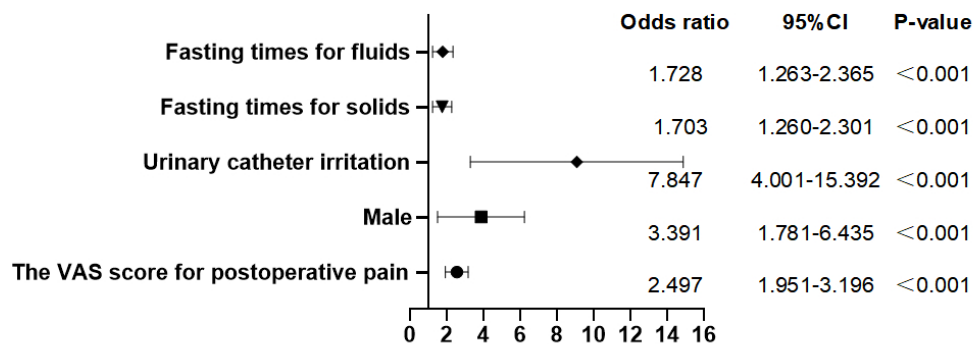


Figure 2 Risk factors of EA by metanalysis plot

436x179mm (57 x 57 DPI)

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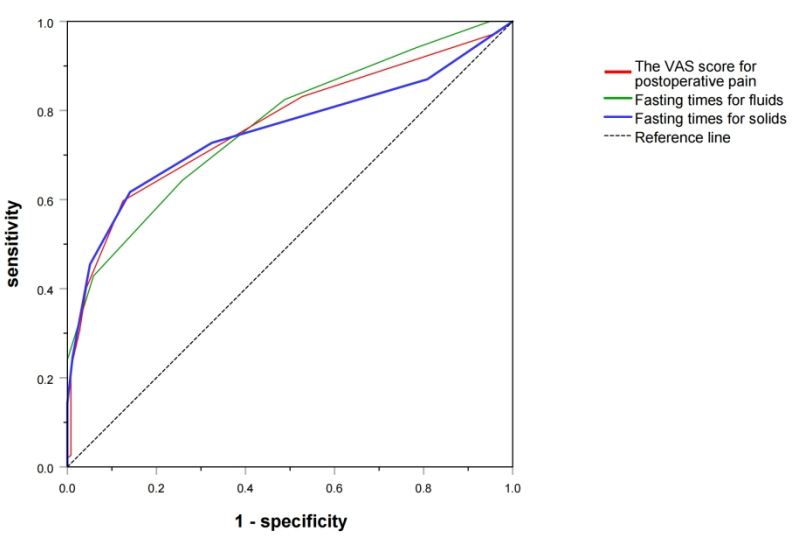


Figure 3 Risk factors of EA by the ROC curve
1178x667mm (57 x 57 DPI)

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 sectional reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche 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

8	Background /	#2	Explain the scientific background and	5
9	rationale		rationale for the investigation being	
10			reported	
11				
12				
13				
14	Objectives	#3	State specific objectives, including any	6
15			prespecified hypotheses	
16				
17				
18	Methods			
19				
20				
21	Study design	#4	Present key elements of study design	NA
22			early in the paper	
23				
24				
25	Setting	#5	Describe the setting, locations, and	7
26			relevant dates, including periods of	
27			recruitment, exposure, follow-up, and	
28			data collection	
29				
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31				
32				
33	Eligibility criteria	#6a	Give the eligibility criteria, and the	7
34			sources and methods of selection of	
35			participants.	
36				
37				
38				
39		#7	Clearly define all outcomes, exposures,	8
40			predictors, potential confounders, and	
41			effect modifiers. Give diagnostic criteria, if	
42			applicable	
43				
44				
45				
46	Data sources /	#8	For each variable of interest give sources	8
47	measurement		of data and details of methods of	
48			assessment (measurement). Describe	
49			comparability of assessment methods if	
50			there is more than one group. Give	
51			information separately for for exposed	
52			and unexposed groups if applicable.	
53				
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59	Bias	#9	Describe any efforts to address potential	8-9
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			sources of bias	
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6	Study size	#10	Explain how the study size was arrived at	9
7				
8	Quantitative	#11	Explain how quantitative variables were	8
9	variables		handled in the analyses. If applicable,	
10			describe which groupings were chosen,	
11			and why	
12				
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14				
15				
16	Statistical	#12a	Describe all statistical methods, including	9-10
17	methods		those used to control for confounding	
18				
19				
20	Statistical	#12b	Describe any methods used to examine	9-10
21	methods		subgroups and interactions	
22				
23				
24	Statistical	#12c	Explain how missing data were	NA
25	methods		addressed	
26				
27				
28	Statistical	#12d	If applicable, describe analytical methods	NA
29	methods		taking account of sampling strategy	
30				
31				
32				
33	Statistical	#12e	Describe any sensitivity analyses	9-10
34	methods			
35				
36				
37	Results			
38				
39				
40	Participants	#13a	Report numbers of individuals at each	11
41			stage of study—eg numbers potentially	
42			eligible, examined for eligibility, confirmed	
43			eligible, included in the study, completing	
44			follow-up, and analysed. Give information	
45			separately for for exposed and	
46			unexposed groups if applicable.	
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52	Participants	#13b	Give reasons for non-participation at	11
53			each stage	
54				
55				
56	Participants	#13c	Consider use of a flow diagram	32
57				
58				
59	Descriptive data	#14a	Give characteristics of study participants	11
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(eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.

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4		(eg demographic, clinical, social) and	
5		information on exposures and potential	
6		confounders. Give information separately	
7		for exposed and unexposed groups if	
8		applicable.	
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13	Descriptive data	#14b Indicate number of participants with	11
14		missing data for each variable of interest	
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16			
17	Outcome data	#15 Report numbers of outcome events or	11-13
18		summary measures. Give information	
19		separately for exposed and unexposed	
20		groups if applicable.	
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24	Main results	#16a Give unadjusted estimates and, if	12
25		applicable, confounder-adjusted	
26		estimates and their precision (eg, 95%	
27		confidence interval). Make clear which	
28		confounders were adjusted for and why	
29		they were included.	
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35	Main results	#16b Report category boundaries when	NA
36		continuous variables were categorized	
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40	Main results	#16c If relevant, consider translating estimates	NA
41		of relative risk into absolute risk for a	
42		meaningful time period	
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46	Other analyses	#17 Report other analyses done—e.g.,	NA
47		analyses of subgroups and interactions,	
48		and sensitivity analyses	
49			
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51	Discussion		
52			
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54	Key results	#18 Summarise key results with reference to	13
55		study objectives	
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58	Limitations	#19 Discuss limitations of the study, taking	17
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		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

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