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Risk factors for delirium during anesthesia recovery: A meta-analysis

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Abstract. Objectives: Although several risk factors for delirium during recovery from anesthesia have been identified, many risk factors remain unknown. The present study aimed to identify risk factors for delirium during recovery from anesthesia by meta-analysis. Methods: A systematic literature search of PubMed and Web of Science databases was conducted from inception until October 2021 without language restriction. All studies assessing the risk factors for delirium during recovery from anesthesia were reviewed, and the Newcastle–Ottawa Scale was used to assess the quality of included studies. Data were pooled and a meta-analysis was completed using RevMan 5.4. Results: A total of 21750 patients from 19 cohort studies were analyzed. Male gender, high American Society of Anesthesiologists (ASA) classification, and longer operation time were identified as risk factors for delirium. However, a trend for increased delirium risk was observed for high body mass index(BMI), smoking, alcohol abuse, hypertension, and longer anesthesia time, but these did not reach statistical significance. Summary: Meta analysis results showed that male gender, high ASA classification, and longer operative time were risk factors for delirium. The evidence quality in this meta-analysis was moderate, according to NOS.

Keywords: delirium; anesthesia recovery; risk factors.

1. Introduction

With the development of anesthesiology, the complications of anesthesia have become increasingly apparent. Delirium is one of the most serious complications during recovery from anesthesia and affects approximately 11-51% of patients [1]. This incidence is higher in the elderly [2]. Delirium during recovery from anesthesia can lead to self-injury and the accidental removal of medical devices and other malpractice risk [3]. Delirium is also associated with long-term behavioral and neurocognitive disturbances [4,5]; for example, previous studies suggested that delirium is responsible for approximately 10% of dementia cases[6]. Further, there is a strong and independent association between delirium and mortality [7].

Numerous clinical studies have been conducted in recent years regarding risk factors for delirium during recovery from anesthesia [2]. However, the limited number of samples across studies and variations in healthcare systems have led to paradoxical conclusions regarding the major risk factors for delirium during post-anesthesia recovery. Therefore, the aim of this meta-analysis was to confirm the association of possible major risk factors and delirium in adults by pooling the data of individual studies. We considered the following risk factors for delirium: male gender, high body mass index (BMI), smoking, alcohol abuse, high American Society of Anesthesiologists (ASA) classification, hypertension, long operation time, and long anesthesia time. We excluded age because the association of age with the occurrence of delirium during recovery from anesthesia has already been clearly demonstrated [2].

2. Methords

2.1 Search strategy and selection criteria

A comprehensive computerized literature search was carried out with PubMed and Web of Science databases from inception to October 2021 without language restrictions. The search terms were (Emergence delirium OR Emergence excitement OR Post-anesthestic excitement OR

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Emergence agitation) AND (Risk factors OR Relative factors OR Relative risk OR Reasons). The exclusion criteria were: (i) meta-analysis or review; (ii) data unavailable for the meta-analysis; (iii) inappropriate articles for the meta-analysis; and (iv) missing articles.

2.2 Literature screening and data extraction

Screening of titles, abstracts, and full-text articles; method quality assessment; and data extraction were independently performed by two investigators. The initial screening of the literature was made removing retrieval. After removing retrieval, two reviewers screened titles and abstracts, and if required, full texts to assess eligibility. The following variables were extracted from each study: (i) title, author's name, and publication year; and (ii) baseline data of patients including gender, BMI, smoking status, alcohol abuse, ASA classification, and hypertension and surgical conditions including operation time and duration of anesthesia.

2.3 Statistical considerations

RevMan 5.4 software was used for meta-analysis. We estimated the relative risk (RR) for categorical data and mean difference (MD) or standard mean difference (SMD) for continuous variables. Statistical heterogeneity was assessed using I2 values. The random effects model was used when I2 ≥ 50 %; otherwise, we used the fixed effect model. The risk of publication bias was assessed using the funnel plot, where asymmetry indicates the presence of bias. What is more, The Newcastle-Ottawa scale (NOS) was used for quality evaluation.

3. Results

3.1 Characteristics of the included studies

Nineteen studies that met the inclusion criteria were screened, including a total of 21750 patients. Of these, 4475 patients developed delirium and 17285 patients did not develop delirium. The incidence of delirium was 20.57%. The PRISMA flow diagram (Fig. 1) shows the results of the systematic literature search and research selection process. Table 1 summarizes the characteristics of the included studies.

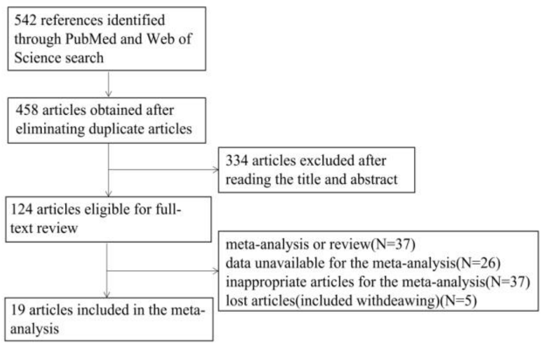

Fig. 1 PRISMA flow diagram

3.2 Quality/risk of bias assessment

The quality assessment of all included studies is shown in Table 1. NOS scores of the included cohort studies ranged from 7 to 9, indicating that these were high-quality studies. The presence of publication and reporting bias was investigated for each outcome using visual inspection of funnel plots (Fig. 2). Some funnel plots are asymmetric, indicating publication bias.

Table 1. Basic characteristics and NOS score of included studies

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Author and Year of publication	Setting	Outcomes	Surgical type	Sample size	NOS
Malik et al. (2018) [8]	USA	①③⑤	orthopaedic surgery	7859	8
Wang et al. (2020) [1]	China	①②③④⑤⑥	intracranial surgery	800	8
Yu et al. (2010) [9]	China	①	selective surgery	2000	7
Wiinholdt et al. (2019) [10]	Denmark	①⑤	orthopaedic and abdominal surgery	1000	8
Kim et al. (2015) [11]	Korea	①②③④⑤⑦⑧	Gastric surgery	400	9
Kim et al. (2015) [12]	Korea	①②③④⑦⑧	Nasal Surgery	792	9
Kim et al. (2015) [13]	Korea	①②③④⑤⑦⑧	urological surgery	488	8
Hino et al. (2017) [14]	Japan	①	selective surgery	120	8
Munk et al. (2016)[a] [15]	Denmark	①⑤⑦	selective surgery	1970	7
Ramroop et al. (2018) [16]	Trinidad and Tobago	①④⑤⑥⑦	selective surgery	417	8
Wada et al. (2018) [17]	Japan	①②⑤⑦⑧	cancer surgery	91	8
Assefa et al. (2019) [18]	Ethiopia	①⑤⑦	selective surgery	306	8
Reynolds et al. (2016) [19]	USA	①②⑦	Pediatric Ambulatory Surgery	1076	7
Kang et al. (2020) [20]	China	①③④⑤⑥	thoracoscopic lung Surgery	1950	9
Jiang et al. (2016) [21]	China	①②⑥⑦	spine surgery	451	9
Zhang et al. (2020) [22]	China	①②③④⑤⑥⑦⑧	selective surgery	915	9
Guo et al. (2016) [23]	China	①②⑥	orthopaedic surgery	572	8
Jooma et al. (2016) [24]	South Africa	①	dental surgery	91	7
Chu et al. (2021) [25]	China	①②⑥⑦	orthopaedic surgery	462	8

①gender, ②BMI, ③smoking, ④alcohol abuse, ⑤American Society of Anesthesiologists (ASA) classification, ⑥hypertension, ⑦operation time, ⑧duration of anesthesia

[a] In this study, the authors grouped trials based on RASS (Richmond Agitation–Sedation Scale) . We classified RASS >1 as delirium and RASS <1 as non-delirium.

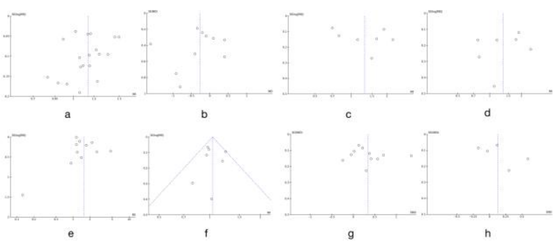

Fig. 2 Funnel plots for publication bias of gender(a), BMI(b), smoking(c), alcohol abuse(d), ASA classification(e), hypertension(f), operative time(g) and duration of anesthesia(h)

3.3 Pooled results for patient baseline data

Nineteen studies (N=21750) reported gender as a predictor of postoperative delirium [1,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25]. The random effects model was used. There was a significant association between gender and delirium incidence (RR=1.14; 95 %

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CI=1.05-1.23; P=0.002). Ten studies reported BMI data [1,11,12,13,17,19,21,23,25]. There was no statistically significant association of BMI and incidence of delirium(MD=-0.27; 95 % CI=-0.61-0.07; P=0.12). Smoking [1,8,11,12,13,20,22] and alcohol abuse [1,11,12,13,16,20,22] were each evaluated in 7 studies. Not statistically significant was observed (RR=1.30, 95 % CI=0.87-1.94, P=0.20; and RR=1.34, 95％CI=0.95-1.87, P=0.09, respectively). ASA classification was strongly associated with the incidence of delirium [1,8,10,11,13,15,16,17,18,20,22], and patients with higher ASA classification were more likely to develop delirium (RR=1.57; 95 % CI=1.21-2.03; P=0.0007). Seven studies reported the relationship between hypertension and delirium [1,16,20,21,22,23,25]. There was no statistically significant relationship between hypertension and the incidence of delirium (RR=1.04; 95 % CI=0.96-1.13; P=0.35). Results are presented in Fig. 3.

3.4 Pooled results for surgical conditions

Eleven studies reported the association between operation time and delirium, and operation time had a strong relationship with delirium[11,12,13,15,16,17,18,19,21,22,25]. Longer operation time was associated with a high incidence of delirium (SMD=0.34; 95％CI=0.11-0.57; P=0.004). The duration of anesthesia was not correlated with the incidence of delirium according to 5 studies (SMD=0.13; 95％CI=-0.10-0.35; P=0.27) [11,12,13,17,22]. Results are presented in Fig. 3.

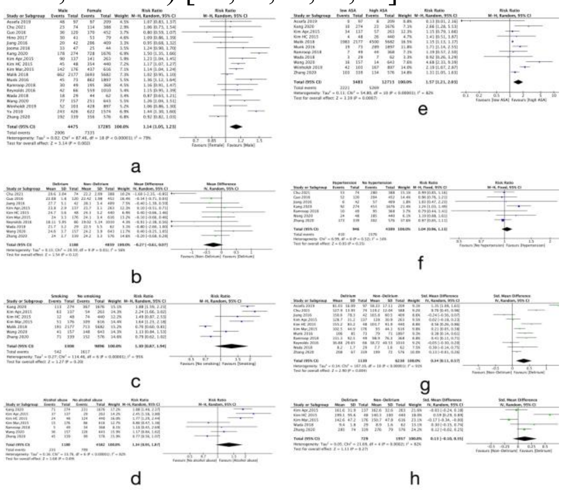

Fig. 3 Forest plots of gender(a), BMI(b), smoking(c), alcohol abuse(d), ASA classification(e), hypertension(f), operative time(g) and duration of anesthesia(h)

4. Discussion

This meta-analysis including 19 studies with 21750 patients revealed that gender (male), ASA classification, and operating time were significantly correlated with the incidence of delirium during anesthesia recovery.

Gender is an independent risk factor for delirium; however, the mechanisms underlying the association of gender and delirium are not fully understood. A possible explanation is that there is an association between lower pain tolerance in men and the incidence of delirium. Operation time was also related with the incidence of delirium. The operation time may be influenced by several factors; for example, operation time may be longer with more complex surgeries and due to the development of complications such as intraoperative blood loss. In this study, we did not analyze the effect of intraoperative blood loss on delirium because there was insufficient data to conduct a meta-analysis. Assefa and Sahile [18] and Zhang et al.[22] indicated that intraoperative blood loss was related to the incidence of delirium; however, Kim et al. reached a paradoxical conclusion [11]. Therefore, further studies are required to confirm the association between intraoperative blood loss and delirium incidence. ASA classification is also a measure of surgical complexity. Our

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meta-analysis indicated that patients with higher ASA classification (III-IV vs I-II) were more likely to develop delirium. Although the assignment of ASA classification is correct less than 70% clinically [26], ASA classification can effectively predict the risk of delirium.

Although an increasing number of studies have explored risk factors for delirium in recent years, consensus is lacking. Malik et al.[8] attempted to address this issue by conducting a large study of 7859 participants, but still yielded different results compared to previous studies. Several reasons may explain these inconsistencies including heterogeneity of the study populations and different healthcare environments between studies. Krewulak et al.[27] conducted a systematic review of risk factors for delirium; in contrast to our own study, the authors concluded that gender is not a risk factor for delirium. However, they only included four studies that evaluated gender, which was a limitation. In fact, there are numerous contributing factors to delirium[28,29,30,31,32,33,34], and it is difficult to evaluate the association of independent risk factors with delirium. We can only do research as accurate as possible from the aspect that most scholars are concerned with. Those risk factors which could be introduced with little literature were not analyzed for the accuracy of our article.

Delirium is associated with high mortality and morbidity rates and presents a substantial economic burden to society. The estimated cost of delirium in the United States is $152 billion each year[35]. Ritter et al.[36] reported that the accuracy of delirium assessment by physicians was only 81.8%; therefore, delirium prevention is of particular importance in high-risk individuals. To this end, it is important to identify high-risk individuals. Although delirium incidence is highest among the very young and elderly [37,38], we cannot ignore the risk of delirium in middle-aged adults. In particular, vigilance is warranted in people with obesity and higher ASA classification, even if they are middle-aged adults.

An understanding of the risk factors for delirium is essential to allow for the implementation of appropriate prevention and postoperative therapeutic strategies. Although no drug is currently approved for the treatment of delirium [39], commonly used preventative medications mainly include neuroleptic medications, dexamethasone, dexmedetomidine, statins. Meta-analyses indicated that neuroleptic drugs fail to reduce the incidence of delirium [40]. However, dexmedetomidine was shown to reduce the incidence of delirium during anesthesia recovery [41]. In general, there is inconclusive evidence for drug prevention of delirium, and further research is required given the potentially serious side effects of existing drugs [2]. Compared to pharmacological interventions for delirium, non-pharmacological interventions have achieved good results; these include activities and walking, avoiding physical constraints, adapting to the surrounding environment, sleep hygiene, sufficient oxygen, and adequate fluid intake and nutritional support [42]. Overall, there is no definitive optimal treatment for delirium, and most studies support the role of non-pharmacological interventions [43]. In the absence of effective treatment, prevention and detection are still the main measures to reduce the adverse consequences of delirium.

Our study demonstrated that male, high ASA classification, and long operation time are risk factors for delirium. Especially gender, it is a controversial aspect. Our meta-analysis provides important evidence that gender affects the incidence of delirium. Therefore, our study is clinically valuable and may help to implement strategies to prevent delirium during recovery from anesthesia. In the future, we will conduct additional clinical studies to further our understanding of the risk factors for delirium.

5. Summary

Meta-analysis results showed that male gender, high ASA classification, and longer operation time were risk factors for delirium. Smoking, alcohol abuse, hypertension, and longer time anesthesia did not reach statistical significance for occurrence of delirium. Clinicians should remain

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vigilant to the presence of independent and potential risk factors for delirium to ensure appropriate management and improve patient outcomes.

Ackonwledegment

F.T. and T.K. contributed equally to this study.

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